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STUDIES IN THE ACIDITIES AND MECHANISM OF DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC AND SALICYLIC ACIDS IN NONAQUEOUS SOLVENTS

by

Murray Amerigo Morello

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"Whether you eat or drink, or whatever you do, do all to the glory of God."

1 Corinthians 10:31

Ph. D. Thesis

by

Murray Amerigo Morello

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TO MY WIFE, CATHY

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ABSTRACT OF PhD. THESIS

The rates of decarboxylation of a series of 4- and 5-substituted anthranilic acids in quinoline solution have been determined at 230.6°C. The reaction was found to be first order with respect to the acid and to be aided by electron-releasing nuclear substituents. An application of the Hammett equation utilizing sigma-plus substituent constants was successful. The result contrasted with that obtained in the decarboxylation of substituted salicylic acids in quinoline (5). The apparent insensitivity of substituent effects to ionization in the anthranilic acid-quinoline system has been discussed. A concerted multi-centre mechanism is proposed in which a solvent molecule assists in an intramolecular proton transfer from the carboxyl group to carbon 1. It appears that both C-C bond breaking and C-H bond making are important with the latter predominating at the transition step. An ionization pre-equilibrium does not have to be invoked for the decomposition

of anthranilic acids in quinoline.

Evidence from acidity studies of anthranilic and salicylic acids in pryidine and quinoline at room temperature corroborated the results of decarboxylation. In these basic solvents the family of anthranilic acids is considerably weaker than the salicylic acids. Evidence was obtained using proton magnetic resonance, ultraviolet absorption spectrophotometry and potentiometric titrimetry. The relative acidities of 4- and 5-substituted anthranilic acids were determined in pyridine at 25.0°C. using the latter technique. The differential half-neutralization potentials ($\triangle$HNP) were correlated with an extended form of the Hammett equation which reflected the substituent effects on acid strength both directly to the carboxyl group and indirectly via an intramolecular hydrogen bond. The nature and possible presence of different species of anthranilic and salicylic acids in the basic solvents is also discussed in detail.

The decarboxylation of 4- and 5-substituted anthranilic acids in nitrobenzene solution(200.2°C.)was re-examined in order to confirm an earlier study (2). Electron-releasing substituents again accelerated the decomposition. The second-order reaction-rate constants were correlated in a Hammett equation using sigma-plus substituent constants. Two unionized acid molecules are involved in the reaction in which proton transfer may occur intra or intermolecularly.

In the first case a second anthranilic acid molecule would function as a basic site similar to quinoline. A more likely mechanism would involve concurrent bond breaking and making over an extended cyclic system embodying carbon 1, both hydroxyl groups and one ortho-amino group. The relative importance of the microscopic processes occurring are discussed in the light of the Hammett equation and other evidence.

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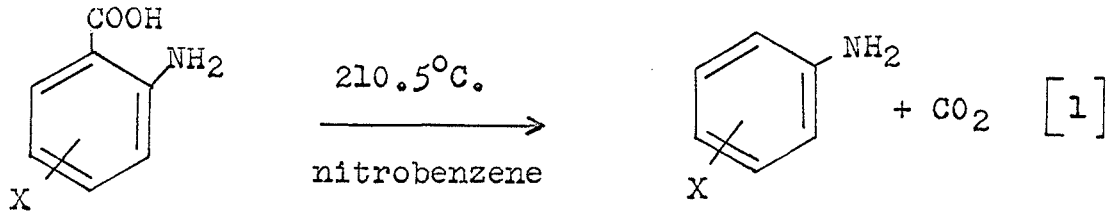
INTRODUCTION

Decarboxylative studies began in this laboratory some ten years ago. The aromatic acids principally under investigation have been suitably substituted anthranilic and salicylic acids. In the case of anthranilic acids, studies have included a deuterium isotope investigation in melt decarboxylation (1) and decompositions in aprotic solvents (2) and in aqueous solution (3). Quinoline, a common solvent in organic acid decarboxylations, has been utilized as the medium for studying salicylic acid decompositions (4,5).

Dunn and Prysiazniuk were among the first to apply the Hammett equation and its extensions to decarboxylations in order to study the effects of nuclear substituents in the decomposition of anthranilic acids in nitrobenzene and 1-methylnaphthalene (2).



[1]

It was concluded that the rate-determining step involved attack by a proton from one anthranilic acid molecule on carbon 1 of a second molecule. The data used to correlate the rates and substituent constants, however, were not found to fit the various equations that were tested particularly well. Furthermore, Prysiazniuk, at that time, did not have available (except for 4-aminoanthranilic) acids with substituents capable of strong electron release to adequately test a correlation

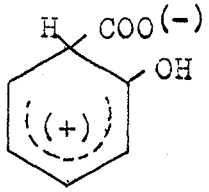
with Brown's sigma plus (σ^+) substituent constants. It was proposed, therefore, to undertake in the present inquiry a confirmative study of the earlier work so as to take advantage of a refined experimental technique, which had been developed since the original research, and to include a number of extra substituted acids that might lend support to a more adequate representation of the Hammett relationship.

A study into the nature of decarboxylation of substituted salicylic acids in quinoline solution was begun by Janzen (4). With respect to salicylic acid the reaction was first order, being significantly accelerated by strong electron-releasing substituents in the para position. Apparent inconsistencies in the data limited the amount of information obtainable from an application of the Hammett expression. Rodewald (5) continued the investigation with an extensive examination of activation parameters, the order of the reaction with respect to quinoline, the enthalpy-entropy relation, the extended Hammett equation and the basicity and steric requirements of the solvent in the process of decarboxylation. A first order dependence with respect to quinoline in quinoline-nitrobenzene mixtures was established. The rates were found to correlate significantly with a form of two-parameter Hammett equation,

$$\log \frac{k}{k_o} = \rho_1 \sigma^+ + \rho_2 \sigma \qquad [2]$$

which accounted for processes that were oppositely influenced by substituents. The rate constants, k and k_o referred to the

substituted salicylic acid and salicylic acid itself respectively. The first term, $\rho_1\sigma^+$, is related to processes such as C-H bond making and C-C bond breaking occurring at carbon 1 in which Brown's sigma plus substituent constants should apply. The latter term emphasized the relative importance of ionization in the reaction. The signs of the values of ρ_1 and ρ_2 were in keeping with respective requirements of electron release and withdrawal for the proposed mechanism. Until a carboxyl- ^{13}carbon kinetic isotope effect was carried out, it was not possible to unequivocally decide on a concerted or two-step process -- the latter explaining the results by formation of a zwitterionic intermediate (I),



I

which formed reversibly from an ion pair. Support for such an intermediate was presented by Buccini in his kinetic-isotope effect investigation (6).

It was of interest to extend this inquiry by examining the decarboxylative behaviour of substituted anthranilic acids in quinoline. The examination was to include an investigation of the kinetic order of the reaction and the influence of varying nuclear substituents on the reactivity. An application of the Hammett relation could then be made, inferences as to mechanism presented, and comparisons extended to other studies, particularly to those dealing with salicylic

acid decompositions in the same solvent.

One of the difficulties encountered in satisfactorily interpreting rates of decarboxylation in nonaqueous sytems is very often the lack of quantitative information about the nature of ionization and dissociation phenomena of carboxylic acids in these media. A number of investigators have postulated, in their mechanisms, some form of preliminary or concomitant acid dissociation and/or ion-pair formation (5,7,8). The intention, therefore, was to begin an examination of acid-base behaviour in basic solvents such as quinoline and pyridine. After a brief preliminary exploration using proton magnetic resonance and spectrophotometric techniques, it was decided not to pursue, for the present, any further attempt at quantitatively measuring the extent of ionization or dissociation. What was proposed, however, was to study the relative acidity of substituted anthranilic and certain salicylic acids by a potentiometric method which had found much favour by workers in recent years (9,10,11). It was hoped that a study of relative acidities by this method would enable one to determine the relative position of anthranilic acid strength compared to salicylic acid in these basic solvents. Comparisons could also be made to aqueous sytems in which anthranilic acid ionization is complicated by the presence of zwitterionic molecules (12). Besides, by introducing substituents into anthranilic acid their influence on acidity might furnish some information

on the nature of the ionization process occurring particularly as to what effect the ortho-amino group has in the equilibria. The majority of the work was carried out with acids dissolved in pyridine although in the decarboxylative studies quinoline had been used. It was felt the adoption of this procedure was justified because of comparable basicities and dielectric constants possessed by the two solvents but, more importantly, because direct comparison could be made of past studies in the relative acidities of substituted benzoic acids in pyridine (9,10). Nevertheless, it was proposed to conduct an adequate number of titrations in quinoline so that comparison of results would confirm the similarity in behaviour.

The above description has followed closely the manner in which the experimental work developed during the course of this investigation. In the succeeding sections or chapters of this dissertation, however, it was found more convenient to treat those aspects related to acid-base behaviour in nonaqueous solvents first and then to examine the studies in decarboxylation. In the Review, which follows immediately, both these major topics are preceded by a survey of the Hammett relationship.

REVIEW OF THE LITERATURE

A. THE HAMMETT RELATIONSHIP

One of the most successful attempts at formulating a quantitative correlation between molecular structure and reactivity in organic chemistry was developed by Hammett (13,14,15,16). For a large number of reactions of meta- and para-substituted benzene derivatives Hammett found that a plot of the logarithms of the rate (k) or the equilibrium constant (K) for one reaction (reference) series against the log k' or log K' for another reaction series gave reasonably straight lines.

When one considers an equilibrium situation, this linearity can be expressed as follows:

$$\log K' = \rho \log K + C , \qquad [3]$$

where rho, ρ, is the slope of the line and C is the intercept. This equation may be used for compounds bearing any substituent including those with no substituent, that is, bearing hydrogen only. In the latter case K_o and K_o' denote equilibrium constants for the nonsubstituted compounds. Hence,

$$\log K_o' = \rho \log K_o + C , \qquad [4]$$

Subtracting equation [4] from expression [3] gives

$$\log \frac{K'}{K_o'} = \rho \log \frac{K}{K_o} \qquad [5]$$

In the above equation any given equilibrium may be chosen as a reference equilibrium with which to compare all others.

Accurate data was available for the ionization of benzoic acids in aqueous solutions at 25°C. and this equilibrium was thereby chosen as the standard reaction. A new constant, sigma (σ), was defined by the equation

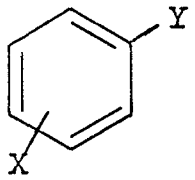
$$\sigma = \log \left(\frac{K_{X\text{-}C_6H_4\text{-}COOH}}{K_{C_6H_5COOH}} \right) \qquad [6]$$

where $K_{XC_6H_4COOH}$ and $K_{C_6H_5COOH}$ were the thermodynamic ionization constants for the substituted and unsubstituted benzoic acids respectively. Equation [5] could now be written in the form

$$\log \frac{K'}{K_o}, = \rho\sigma . \qquad [7]$$

The constant, σ, (also called Hammett's substituent constant) characterizes the change in the strength of the benzoic acid caused by the substituent. The action of the substituents changes the charge density at the point of acid dissociation and the constants are, therefore, a measure of the electron-donating or electron-withdrawing power of such substituents. A substituent, which bears a positive sigma value, is deemed a stronger electron attractor than hydrogen whereas substituents with negative sigma values are weaker electron attractors than hydrogen. The second parameter, ρ, is known as the reaction constant and is characteristic of the reaction series in question. It is a measure of how sensitive the equilibrium, in this case, is to changes in charge density at the reaction

centre caused by transmission of electronic effects through ring substitution. Rho, therefore, depends upon the general reaction type, the reaction conditions (i.e., temperature, solvent, etc.) and the nature of the side chain or reaction centre Y.

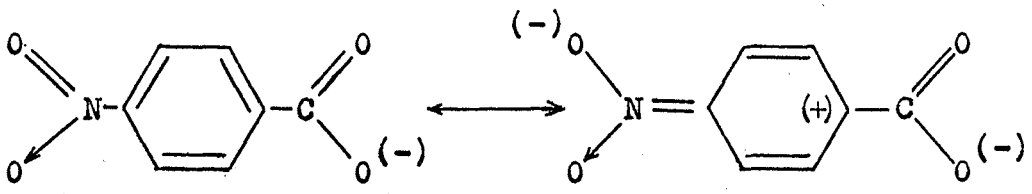


For the standard reaction, the ionization of benzoic acids in water at 25°C., rho has been defined as unity.

The Hammett equation was derived on the assumption that substituents in the meta and para positions would have no effect on the entropy of activation or reaction. Steric effects are generally added to the reactivity by a substituent ortho to the reaction site and, because this situation is reflected in entropy effects, the reaction series would not as a rule conform to the Hammett relationship. Taft has, however, presented information establishing a set of constants for ortho substituents (17,18). The effect of ortho substituents has also been examined by Farthing and Nam (19). Furthermore, the necessity or desirability of accepting the conclusion that constancy in entropies of reaction or activation is an essential feature of the Hammett relationship has been called into question (20).

A number of significant modifications have been made to the Hammett equation as originally formulated. One of the earliest dealt with those reactions in which certain structural features invalidated the sigma values as derived from

the ionization constants of benzoic acids. Modified sigma values were required in instances where the substituent group entered into resonance with the reaction site (14,21). Hammett first noted that enhanced sigma values were required for the ionization of anilines and phenols where such para electron-withdrawing substituents as nitro, cyano, carboxyl, formyl and methylsulfonyl groups were present in the molecule. The following example will help to contrast or at least point out the distinction between the two ways in which the resonance effect of a substituent in the para position may influence reactivity.



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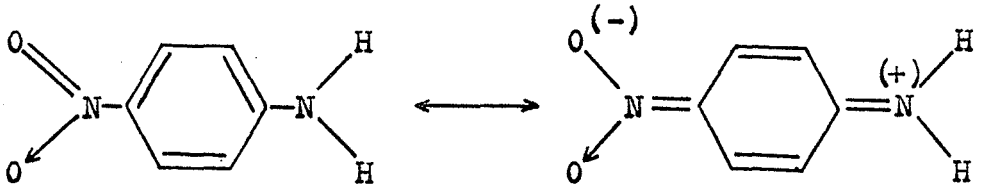


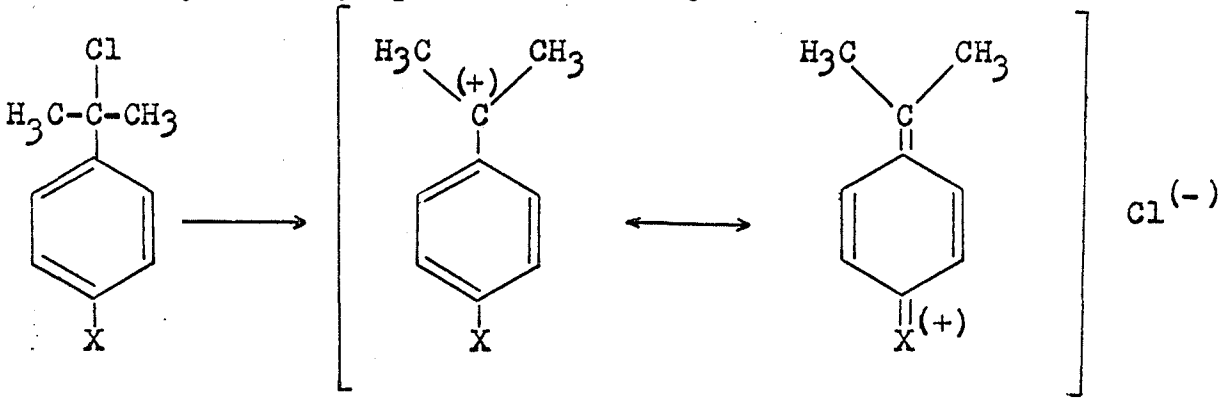
III

In the anion (or acid itself) of p-nitrobenzoic acid (II), the electron-withdrawing effect of the nitro group is transmitted to the para-carbon atom of the ring by conjugation

and must be relayed then to the oxygens of the carboxylate group (or carboxyl group) via the carboxyl carbon by induction. Para-nitroaniline (III), on the other hand, possesses an amino group which is in direct conjugation with the nitro group. Contribution from such structures have no counterpart among the contributing structures of the anilinium ions or those of the carboxylic acid. It has been found, therefore, that the p-nitro group, which has a regular Hammett sigma constant value of +0.778 when considering reaction centres such as the ionization of carboxylic acids, should instead require a value of +1.27 because of its nature and position as a resonance electron-withdrawing para substituent to such strong resonance electron-donating groups as $-NH_2$, $-O^{(-)}$, $-S^{(-)}$, etc. acting as the reaction centre. Jaffe (22) and, more recently, Biggs (23) have evaluated these enhanced sigma values, denoted as sigma minus (σ^-), for several more para substituents. These same values have also been proposed for nucleophilic aromatic substitution in which electron-withdrawing substituents are in the para position (24,25).

Another instance where modification of the Hammett equation was required was in the treatment of directive effects in electrophilic aromatic substitution (26,27) or side chain reactions which involved the formation of cationic or electron-deficient reaction centres (28,29). In this case, the reaction centre which is capable of strong electron with-

drawal can be stabilized (reactant or transition state) by resonance interaction with electron-donating substituents such as p-alkoxy, p-hydroxy and p-amino groups. Brown (20, 30,31) prepared a number of phenyldimethylcarbinyl (tert-cumyl) chlorides with appropriate substituents in the meta and para positions of the benzene ring (IV) and determined their rates of solvolysis in 90 percent acetone.

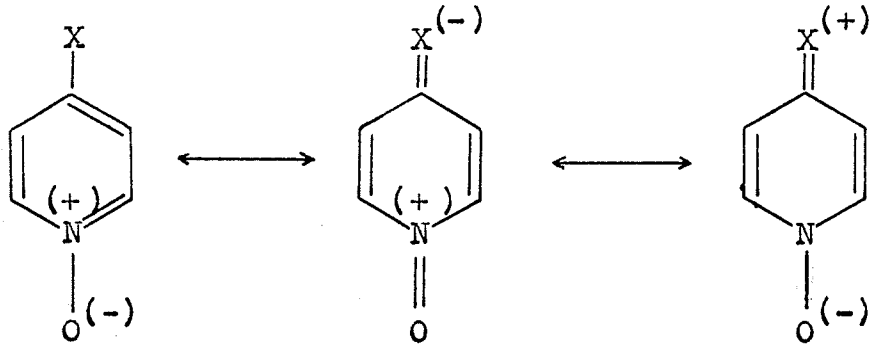


IV V

The results gave valuable insights into the nature and importance of the interaction of various substituents in electron-deficient systems, the carbonium ion (V) or transition state of the tert-cumyl system being such an arrangement. They also permitted the development of a set of electrophilic substituent constants denoted as sigma plus (σ^+). These constants have proved useful in correlating quantitatively the directive effects in electrophilic substitution of aromatic derivatives (30,31) and of electrophilic side-chain reactions (32).

An interesting example of a reaction series in which both σ^+ and σ^- substituent constants were required along with normal Hammett σ's to correlate the data was the

study on the basicities of substituted pyridine-1-oxides. Jaffe (33) recognized that resonance between structures (VI), (VII) and (VIII) was important.



VI VII VIII

It was expected that VII would make a particularly important contribution when substituent X was electron-withdrawing by a tautomeric effect (e.g., $-NO_2$, -COOR) and thereby he used σ^- values for these substituents. Similarly a large contribution to the resonance hybrid would be made by VIII when X was capable of strong electron release by a tautomeric effect (e.g., -OR, $-NR_2$) and hence σ^+ values were used for such substituents. The plot of pKa's for the 1-hydroxypyridinium ions against the proper substituent constants gave a rather good fit to the data and the calculated rho value resembled closely the value applicable to the pKa's of phenols.

For purposes of comparison of their sign and magnitude, reaction constants that have been derived for some typical reaction types are listed in Table I.

TABLE I

A COMPARISON OF REACTION CONSTANTS (RHO) DEDUCED FROM COMMON REACTION SERIES

Nature of reaction	Rho
Ionization equilibrium of benzoic acids in water at 25°C.	+ 1.00[a]
Ionization equilibrium of anilinium ions in water at 25°C.	+ 2.77[a]
Nucleophilic substitution of methoxide ion on substituted fluorobenzenes in methanol at 0°C.	+ 9.20[b]
Solvolysis of tert-cumyl chlorides in 90 percent aqueous acetone at 25°C.	- 4.62[c]
Bromination of monosubstituted benzenes by bromine in acetic acid at 25°C.	-12.14[d]

[a]Reference (22).
[b]Reference (25).
[c]Reference (32).
[d]Reference (31).

The rho value for the anilinium ion ionization equilibrium illustrates how more sensitive the reaction series is to substituent effects as compared with the benzoic acid ionization when the proton is lost from an atom adjacent to the ring. The large positive rho value for the nucleophilic reaction points out the importance of electron withdrawal from the reaction centre in the transition state whereas the large negative values for the last two rho values listed, indicate the great electron demand in the transition states in reactions of these types.

Over the past ten years several workers have seriously questioned the concept of three distinct sigma scales and have put forward rather convincing evidence that a multiplicity of sigma values would be required, corresponding to the range of configuration and polarization of molecules, to correlate existing data in cases where it is expected that substituents are capable of direct resonance interaction with reaction sites. van Bekkum and co-workers (34) have made a re-evaluation of a number of Hammett equation correlations. By utilizing a set of 'primary' sigma values, ones of substituents for which extra conjugation seemed to be impossible, they calculated rho constants which in turn served to calculate sigma values for other substituents in each reaction under consideration. A continuous range of substituent constant values, in the cases where conjugation was observed, pointed out that the σ^+ and σ^- values could be considered as simply limiting values of these ranges. Indeed, the number of sigma scales has increased greatly since the Hammett equation was first formulated, leading to some confusion in definition and significance. Nevertheless, substituent constants such as the original Hammett σ, σ^-, or σ^+ values will continue to be of importance, empirically at least, despite the fact that conjugative effects in certain reactions may be more or less than that for which the 'limiting' values would be applicable, thus depriving these substituent constant values of much of the theoretical

significance which has been assigned to them.

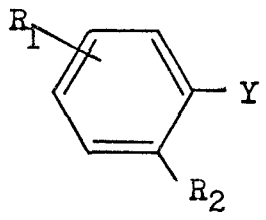
The introduction of two or more substituents in the meta and para positions of an aromatic compound often allows their combined effect to be represented by the sum of their individual sigma values as indicated in equation [8].

$$\log \frac{k}{k_o} = \rho \sum \sigma \qquad [8]$$

Reactions including the ionization of benzoic acids, the saponification of ethyl benzoates and the reaction of phenyl isothiocyanates with ethanol are examples in which this simple additive relationship is confirmed (22,35). An excellent additive sigma correlation was obtained by Simon et al. in their study of the relative acidities of 3,4- and 4,5-disubstituted benzoic acids in methylcellosolve-water (80:20 weight percent) (36). Deviations from the additivity of substituent effects can be expected if during the course of a reaction the interaction of the substituents with each other is changed. Dippy has tended to be skeptical of the additivity principle. From his examination of the acid strengths of di- and trisubstituted benzoic acids (37) and the alkaline hydrolysis of disubstituted esters (38), he concluded that regularities in the cumulative effects were few and only partial support for the additivity principle was forthcoming from systems in which it might have been expected to apply.

An interesting extension of the additivity of substituent constants for multiple substitution is found for compounds

having the structure shown by IX.

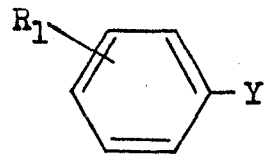


IX

The reaction series bears a constant ortho substituent, R_2, and a variable substituent, R_1, in the 4 or 5 position relative to the reaction centre, Y (22,35). The Hammett equation, in the case of ionizing equilibria then takes the form

$$\log \frac{K}{K_o} = \rho\sigma + X \qquad [9]$$

The constant, X, is a measure of log K ($o\text{-}R_2C_6H_4Y$) - log K (C_6H_5Y) but since the Hammett equation does not apply to ortho substituents, this quantity cannot be evaluated in terms of substituent and reaction constants. The reaction constant for compounds such as IX should be the same as for the similar reaction of a series of compounds having structure (X) since only R_1 is being varied.



X

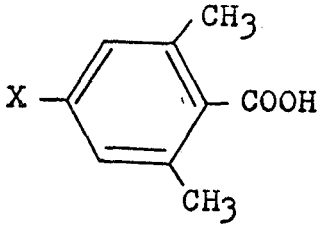
Jaffe (22) has outlined at least two necessary restrictions for use of equation [9]. The constant ortho substituent,

R_2, should not affect the reaction mechanism followed by the series containing no ortho substituent. Also, the equation does not usually hold if the substituent, R_1, is in the 3 position since any steric interaction of R_2 and Y could be affected and the resonance contribution of R_2 may be inhibited by a substituent in the 3 position. Cohen and Jones have discussed and given examples of situations in which variations in rho should occur in the case of phenolic ionization (39).

Jaffe (35) made reference to the work of Roberts and Yancy (40) when he formulated the Hammett equation for the 'constant ortho' substituent. These workers found the reaction constant for the ionization of 4- and 5- substituted-2-methylbenzoic acids (+1.67) was significantly larger than for the 4- and 5-substituted benzoic acids (+1.46), a fact they attributed to differences in stabilization of species from the two reaction series by solvent molecules. On the other hand the steric influence of a methyl group ortho to the reactive carboxyl group was found to be constant when the acids for each series were made to react with diphenyldiazomethane in absolute ethanol. The similar rho's obtained from the rate constants for the 2-methyl and the 2-unsubstituted acids were explained by observing that the influence of a given substituent on the rate of the diphenyldiazomethane reaction would be exerted in the slow step in which the O-H bond of the acid is only partially ionized. As a consequence

ionic solvation effects on the reaction would be expected to be of relatively minor importance.

Roberts and Regan extended this inquiry to include the determination of apparent ionization constants of 4-substituted-2, 6-dimethylbenzoic acids (XI) in 50:50 water-ethanol (by volume) as before (41).

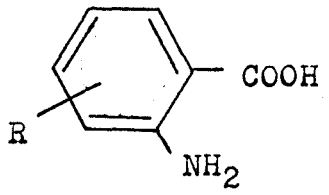


XI

The reaction constant in this case had a value of +1.40. Goering and co-workers (42) advanced an interpretation of the effect of the ortho-methyl group on the rho value for the ionization of this series of acids as compared to those reported earlier (40). A polar and an opposing solvation effect, each of which is affected by steric factors, were assumed to rationalize the results. Similar comparative studies have been made in the ionization (39) and infrared frequencies and intensities of the hydroxyl group (43) of hindered and unhindered phenols.

There have been a number of other interesting investigations into the applicability of equation [9] since the review by Jaffe (22) was published. Kellie and co-workers selected substituted anthranilic acids (XII) for study, a

series of compounds in which strong interaction might be expected between the adjacent amino and carboxyl groups (44).



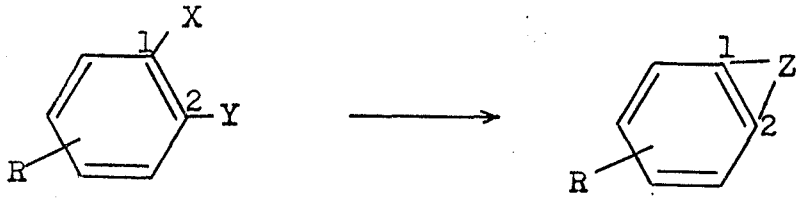
XII

Infrared spectra of anthranilic acids were determined in chloroform and in potassium bromide discs and examined for symmetric and asymmetric amino and carbonyl frequencies. No evidence was uncovered for the presence of a zwitterionic structure of XII although both intra- and intermolecular hydrogen bonding occurred in chloroform solution. The authors did not consider the possible effect of transmission of the electronic influences by the various substituents via both the amino and carboxyl groups. Apparently, however, the intramolecular hydrogen bond was not as significant since a reasonable regression line for the data correlating the carbonyl frequences of the anthranilic acids with sigma substituent constants considered in relation to the carboxyl group was obtained (correlation coefficient = 0.887). The slope was similar to that found for benzoic acid monomers in carbon tetrachloride (45).

Other references dealing with investigations with compounds bearing a fixed ortho substituent are given by

Cohen and Jones (39), Jaffe (22) and Jaffe and Jones (46). The latter review those situations which apply to heterocyclic systems.

As mentioned briefly above, a suitably placed substituent may also influence the reaction site by means of transmitting its effect by two different paths (22,47). Such a possibility can be represented as follows:



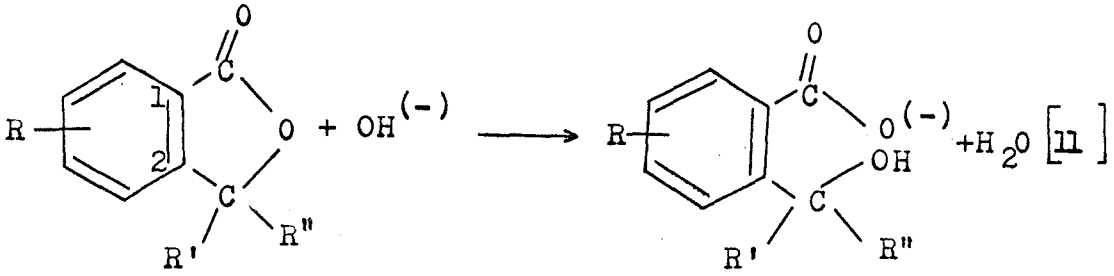
XIII XIV

The reacting side chain depicted in XIII consists of two groups placed ortho to each other undergoing cyclization (XIV) or some other form of interaction. The equation describing this would take the form

$$\log \frac{k}{k_o} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \qquad [10]$$

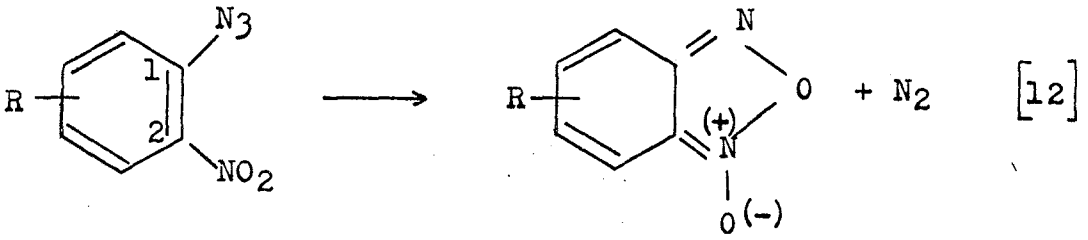
where σ_1 refers to the substituent constant relative to one point of attachment of the reacting side chain as shown in XIII and σ_2 refers to the constant relative to the position of the other point of attachment. Since the rate-affecting substituents can transmit their effect by two electronic pathways to the reaction site, separate reaction constants should apply as equation [10] implies. It has been

suggested that the alkaline hydrolysis of substituted phthalides and their derivatives could be accommodated by this equation (22,47).



[11]

A more recent correlation of rate constants by the two-parameter Hammett equation, [10] , for the intramolecular reaction of o-nitrophenylazides has been proposed by Anderson et al. (48).



[12]

Hancock and co-workers applied the results of acidity measurements of 4-substituted-2-nitrophenols (49) and 5-substituted-2-nitrophenols (50) to a correlation with substituent constants. Recorded in Table II are the pertinent data. The reaction constant for the ionization of 4-substituted-2-nitrophenols acquired from the simple Hammett relation (-2.16) was found not to differ significantly from those for the ionization of m- and p-substituted phenols from the literature (-2.11 or -2.23). Experimental validation

TABLE II

A COMPARATIVE STUDY FOR THE APPLICATION OF THE HAMMETT EQUATION TO THE IONIZATION OF SEVERAL SERIES OF PHENOLS IN AQUEOUS SOLUTION AT 25°C.[a]

Acid Series	Rho[b]	pK_A^o (expt.)[f]	pK_A^o (calc'd)[g]	r[h]
4- and 5-XC_6H_4OH	-2.11[c]; -2.23[d]			
4-X-2-$NO_2C_6H_3OH$	-2.16	7.08	6.89	-0.992
5-X-2-$NO_2C_6H_3OH$	-3.01	7.13	7.22	-0.974
	(ρ_1=-2.53, ρ_2=-0.307)[e]	7.13	7.09	0.986[i]

[a] References (49,50).

[b] Calculated from the Hammett equation in the form $pK_A = pK_A^o - \rho\sigma$ unless otherwise noted. Sigma is the substituent constant relative to the phenolic group in each case. Sigma minus constants are applicable for electron-withdrawing groups with multiple bonds which are para to the hydroxyl group.

[c] Reference (22).

[d] Reference (23).

[e] Calculated from the extended Hammett equation in the form $pK_A = pK_A^o - \rho_1\sigma_m - \rho_2\sigma_p^+$ where σ_m is the substituent constant relative to the phenolic group and σ_p^+ is Brown's sigma plus substituent constant which takes into account enhanced interaction of strong electron-donating groups para to the nitro group.

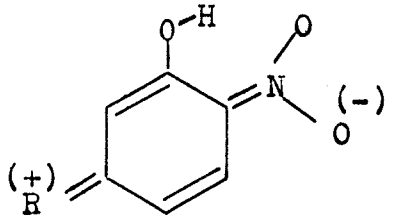
[f] Experimentally determined apparent pK_A^o for unsubstituted 2-nitrophenol from absorption spectra.

[g] Regression pK_A^o value.

[h] Correlation coefficient.

[i] Multiple correlation coefficient.

for the constant ortho effect principle as depicted by equation [9] was thus afforded since the evidence suggested that in the ground state there was no interaction between the 4 substituent and the nitro group and, one may add, no apparent strong hydrogen bonding between the two ortho groups. In their second paper (50) they obtained a much more negative rho (-3.01) for the ionization of 5-substituted-2-nitrophenols, a fact which did not conform to the idea of constancy of rho for this type of series. Transmission of the electronic characteristics of the 5 substituent to the reaction site was being done more effectively in 5-substituted-2-nitrophenols. In order to explain the apparent deviation some significance was attached to the position of the variable 5 substituent (particularly of a resonance electron-releasing type) which was para to the strongly electron-withdrawing nitro group. Structure XV was thought to represent the type of resonance interaction involved.



XV

The ionization constants of the phenols would be expected to be affected by any modification of the electronic properties of the nitro group caused by the para substituent. The summation of three individual effects were considered to

describe the over-all result.

(i) Electron density on the ring was greater since the para substituent was showing a greater tendency to release electrons than usual. The result was to make the departure of a proton from the phenolic group less facile.

(ii) There was a reduction in the deactivating influence of the nitro group, an effect operating in the same direction as (i).

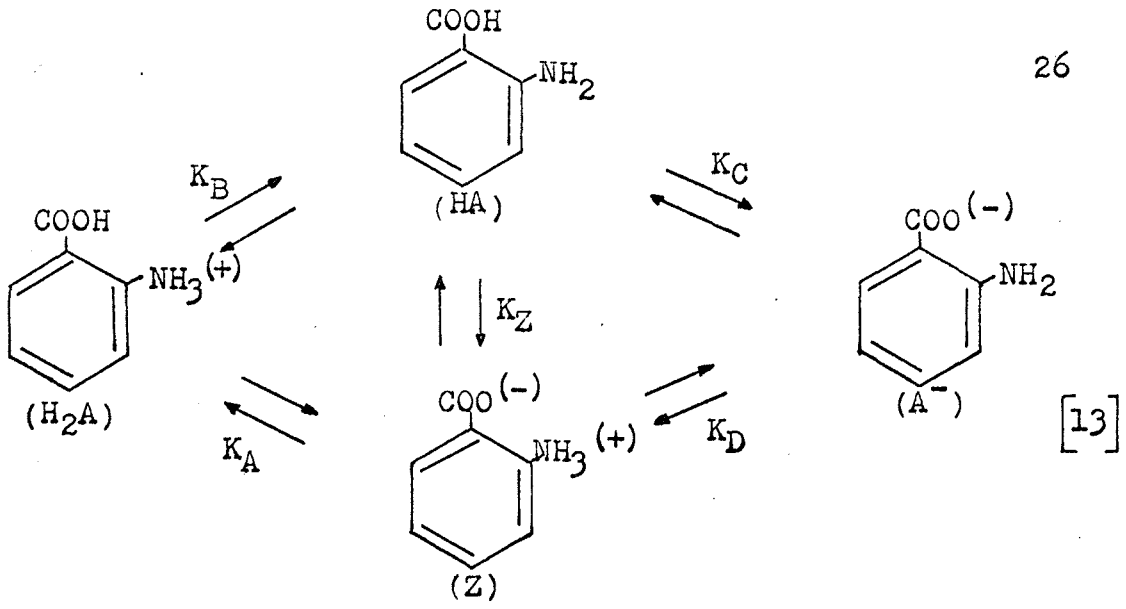
(iii) A change in the strength of an intramolecular hydrogen bond could be effected by the contribution of two opposing influences the direction of which was difficult to predict. Any hydrogen bond could be strengthened as the oxygen atoms of the nitro group became more basic while a weakening of the hydrogen bond would occur because of the decreased acidity of the phenolic hydrogen.

Concentrating their attention on the first two effects which tended to lower the ionization constants of phenols, Hancock and Clague introduced into the Hammett equation a quantity, $\rho_2\sigma_p^+$, which was a measure of the enhanced ability of a substituent to donate electrons by resonance over that normally displayed in the ionization of benzoic acids. The equation (Table II, footnote e), in fact, took the form of expression [10] which described transmission of a substituent

effect via two different paths. The contribution from this para term, although small, was significant. The negative ρ_2 indicated that pK_A increased (acidity decreased) as the 5 substituent became more strongly electron-donating. The suggestion was made that this increase in pK_A probably resulted from an increase in the strength of the intramolecular hydrogen bond and a concomitant decrease in the ease of dissociation of the proton. The authors felt that the extended form of the Hammett relationship was preferred over a simple Hammett equation since the pK_A^o (calc'd) (7.09) approximated more closely the pK_A^o (expt.) and that ρ_m increased to -2.53 which more closely approached the value for the ionization of 2-unsubstituted phenols as anticipated according to the assumption made by Jaffe (22).

Jaffe had also proposed equation [10] for the case in which ortho interaction included hydrogen-bond formation (47). Very recently an important example of such a situation was found by Dunn and Penner in an examination of the relative acidities of substituted salicylic acids in benzene (11).

Leggate and Dunn (12) have shown that a special form of the extended Hammett relationship applies to the ionization of carboxyl and amino groups in substituted anthranilic acids in aqueous solution. It was assumed that in aqueous solution the equilibria



[13]

described the system in which the experimentally determined ionization constants K_1 and K_2 were related to the 'true' constants, K_A, K_B, K_C, K_D by the equations

$$K_1 = K_A + K_B, \qquad [14]$$

$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D} \quad , \qquad [15]$$

$$K_1K_2 = K_AK_D = K_BK_C \qquad [16]$$

and K_Z, the equilibrium constant for the ionization of neutral anthranilic acid to zwitterion, could be related through the expression

$$K_Z = \frac{K_A}{K_B} = \frac{K_C}{K_D} \quad . \qquad [17]$$

The extended Hammett relation,

$$\log \frac{K_1K_2}{K_1^{\circ}K_2^{\circ}} = \rho_1 \sigma_A + \rho_2 \sigma_B \quad , \qquad [18]$$

was derived where A and B referred respectively to the ionization of the carboxyl and amino groups. The reaction

constants, ρ_1 and ρ_2, were abbreviated representations of additive terms taking into account the possibility of both direct and indirect (chelation) substituent effects. An excellent fit to the two-parameter Hammett equation [18] was obtained from the experimental data giving the indication that substituted anthranilic acids at the isoelectric point were better represented as a mixture of zwitterion and neutral acid than as a single hybrid species. The method allowed for an unusual opportunity to estimate the zwitterionic content of an aromatic amino acid and also to give an indication that transmission of substituent effects by chelation was of little significance.

Further examples of the application of the two-parameter Hammett equation have been recorded by Jaffe (47) and Jaffe and Jones (46).

The literature within the last ten years abounds in studies pertinent to the Hammett relationship and particularly in a re-examination of this rather successful structure-reactivity relationship. Introductory and more general treatments of the Hammett equation as well as other linear free-energy relationships can be found in the textbooks of Gould (51), Hine (52), Wiberg (53) and Ferguson (54). The review of Jaffe (22) was the earliest most extensive re-examination of the relationship and dealt with reaction and substituent constants, precision of the equation, the range of application and a discussion of a number of its extensions.

More recent studies have treated the Hammett equation in conjunction with other structure-reactivity relationships (18,55,56[a],57,58,59,60,61). Substituent parameters were reviewed particularly by Taft et al. (62) and van Bekkum and co-workers (34). The reviews of Ritchie and Sager (63) and Taft (21) give an extensive discussion of the thermodynamic basis of linear free-energy relationships and of attempts at separation of polar, steric and conjugative effects in such systems. Taft especially has done much work regarding this latter aspect. Ehrenson in a recent study has discussed the theoretical interpretation of the Hammett and derivative relationships (64). Specific treatments of directive effects in aromatic substitution have been given by de la Mare and Ridd (65), Norman (66,67a) and Stock and Brown (68). Jaffe and Jones have examined the Hammett equation as applied to heterocyclic compounds (46), and more recently its application in radical reactions has been outlined (69).

Further consideration will be given to the Hammett relationship and its extensions in the application to acidity and decarboxylative studies under the appropriate headings in the review to follow.

B. ACID-BASE BEHAVIOUR IN NONAQUEOUS SOLVENTS

INTRODUCTION

The Swedish chemist, Svante Arrhenius, proposed in 1887 that the characteristic properties of acids and bases in

water solution were a consequence of the existence of the hydrogen ion, $H^{(+)}$, and hydroxide ion, $OH^{(-)}$, respectively (70). A substance, HX, whose water solution contained an excess of $H^{(+)}$ ions arising from an equilibrium such as

$$HX \rightleftharpoons H^{(+)} + X^{(-)} \qquad [19]$$

was considered to be an acid, and a base, BOH, was taken to be one whose aqueous solution had a preponderance of hydroxide ions because of the dissociation

$$BOH \rightleftharpoons B^{(+)} + OH^{(-)}. \qquad [20]$$

Other notions about the nature of the ionization process taking place on dissolution and solvation of the ionic species were not adequately treated at that time and had to await later developments. It became apparent that the Arrhenius concept of acid-base behaviour was exceedingly limited as it applied only to aqueous solution.

Early in this century reports were made describing the occurrence of certain acid-base reactions in benzene solution which resembled those of ions in aqueous solution (71,72,73). Chemists, equipped with the electrolytic theory of dissociation known up to that time, could not offer any logical explanation of the physico-chemical basis for such phenomena in nonaqueous solvents. It remained for Bronsted (74) and Lowry (75) to propose a theory which shed new light on the nature of these nonaqueous acid-base

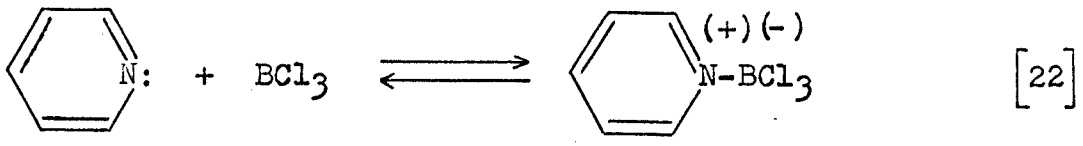
reactions. The concept of acids and bases was broadened by regarding an acid as a substance which had the tendency to dissociate to yield protons and donate them to another substance which was capable of accepting a proton and thereby act as a base. The proton theory intimately linked the nature of acidity and basicity in that no substance was capable of acting as an acid unless some other substance was present to accept the proton donated by the first substance. Earlier work (72) in the non-ionizing solvent, benzene, could now be explained. Hydrochloric acid would not likely be ionized significantly in benzene but, as soon as a substance like aniline was added, proton transfer was possible and the following reaction occurred.

$$HCl + C_6H_5NH_2 \rightleftharpoons C_6H_5NH_3^{(+)}Cl^{(-)} \qquad [21]$$

Although the theory took into account the fact that other substances besides hydroxide ions could exhibit basic properties it only attributed acidic behaviour to the proton.

Lewis (76,77) extended the concept of acids and bases by substituting the idea of electron-pair transfer for Bronsted and Lowry's theory of proton transfer. An acid was thus considered to be a species containing any atom which could accept a share in an electron pair and a base was any species which could share its electron pair with any electron-pair acceptor. An acid-base reaction in this sense, therefore, was the sharing of an electron pair through

co-ordination with an acid by a base. For example, boron trichloride could be titrated against the base, pyridine, in chlorobenzene solution with crystal violet as indicator (78).



[22]

The Lewis concept has been valuable not only as a new theoretical insight into acid-base behaviour but also for its revolutionary ideas and practice of acid catalysis.

For the following discussion in these pages, particularly because of its relation to the experimental work, solvents and acid-base systems will be considered on the basis of the Bronsted-Lowry theory because of its emphasis on the proton and because it has done much to clarify the role of the solvent in acid-base reactions. A more thorough treatment of the development of acid-base theories including new concepts and contributions from other workers can be located in a number of sources (51b,78,79,80,81,82a,83a,84, 85,86a).

Solvents are generally classified as aprotic, protophilic and protogenic. Those exhibiting both protophillic and protogenic properties are called amphiprotic solvents (82b, 86b,87,88,89a,90). Aprotic solvents are those which are not capable of accepting or donating protons. Aliphatic and aromatic hydrocarbons and their halogenated derivatives are characteristic of this class. The protogenic or acidic

solvent acts predominately as a proton donor, examples of which would be hydrofluoric, formic and acetic acids. Proton acceptors, which are basic or protophilic solvents, can be represented by such liquids as ammonia, pyridine and ether. Certain workers prefer alternate classifications (89a,90,91,92,93,94).

The extent to which acid-base reactions occur in solvents such as those noted immediately above is dependent on at least three important properties: the solvent's dielectric constant, its acidity or basicity and its ability to solvate ions and molecules of the acid or base (95a,96). The dielectric constant (ϵ) of a solvent is a rough measure of the relative ability of the solvent to effect a separation of positive and negative ions in solution. Thus, in considering the following equilibrium between the solvent (SH) and a solute acid (HX),

$$SH + HX \rightleftharpoons SH_2^{(+)} + X^{(-)}, \qquad [23]$$

the work of separation of $SH_2^{(+)}$ and $X^{(-)}$ ions will vary inversely with the dielectric constant of SH. It would be expected that reaction [23] would occur to a lesser extent in ethanol (ϵ = 24.3 at 25°C. (97)) than in water (ϵ = 78.5 at 25°C. (97)). The ions produced by such equilibria in solvents of low dielectric constant may not separate at all but persist as ion pairs $SH_2^{(+)}X^{(-)}$ or even as higher ionic or molecular aggregates. It is, therefore, necessary to

distinguish between 'ionization' and 'dissociation' processes in acid-base behaviour in certain instances. The care that is needed in the interpretation of equilibria in nonaqueous solvents was recognized early. Abegg, a student of Arrhenius, expressed such an observation in 1907.

> "Accordingly, with decreasing power of dissociation, we must have, in nonaqueous solvents, as compared with water, not only a decrease of the dissociation into ions but also a decrease of the dissociation of polymerized molecules into simple ones, or, conversely expressed, the association into polymerized molecules must be favoured.(98)"

Equilibria expressed by equation [23] in which the proton is transferred from acid to solvent or in those systems in which a base is added to a solvent, which acts as an acid, are dependent on the basic and acidic nature of the components. In a strongly basic solvent (such as butylamine) mineral acids, carboxylic acids and certain phenols would in all likelihood be leveled to the solvated cation. Therefore, such a solvent would afford little or no differentation in acid strength compared to that found in water or acetic acid. Solvent interactions may also be of a more specific nature. Parker (99) has given a brief but pertinent discussion of solvation of polar solvent molecules in their interaction between ions and solvent dipoles in helping to stabilize the ions. An important aspect of solvent interaction is the ability of the solvent to function as a hydrogen-bond donor.

Generally speaking, it is the wide variation or interplay of these properties in nonaqueous solvents that make acid-base behaviour characteristically different from that displayed in aqueous solutions. The use of water as a solvent medium has so predominated studies of acidity and basicity as well as other chemical reactions in the past that the influences that the extraordinary properties of water exert on dissolved species are easily overlooked. The role of the solvent has become better delineated by studies of acid-base reactions in nonaqueous systems. This is not to say that understanding the idea of acidity or basicity in nonaqueous solvents is without its difficulties. For instance, in a system in which an acid solute is dissolved in a basic solvent, its conjugate base and solvent species are involved in numerous and often unknown modes of association, dissociation, solvation and ion pairing, all of which may change with solvent, concentration and temperature. Arnett has discussed the state of our ignorance about the exact nature of the entities being studied particularly with reference to basicity (100). Izmailov has attempted to resolve equilibrium constants into a number of separate equilibria in which dissociation is pictured as occurring as a result of a number of consecutive stages (101,102). Shedlovsky has in fact proposed composite equilibria to explain electromotive force and conductance data in the behaviour of carboxylic acids in aqueous methyl and ethyl

alcohol solutions (103).

Efforts to clarify the complex equilibria which are involved in nonaqueous solvents are continually being extended -- particularly within the last ten years. Excellent discussions, dealing with solvent effects on acid-base behaviour are to be found as chapters in a number of books or reviews (82b,83b,89b,95b,99,104,105,106). The biennial reviews in Analytical Chemistry provide a valuable survey of leading references on theoretical studies in acid-base equilibria in nonaqueous solvents carried out in the previous two-year period (107,108,109,110,111).

One of the most encouraging signs that is frequently apparent in rapidly developing fields of chemical endeavour is the varied attack that is used to solving the problem. The nature of acid-base reactions in nonaqueous solvents is certainly no exception. It is of interest, therefore, to give an indication of the application of spectrophotometry, conductivity, potentiometry, proton magnetic resonance and a number of miscellaneous techniques to a study of equilibria in protophillic solvents composed of nitrogen bases. These solvents are chosen because of their relevancy to the decarboxylative studies and the determination of relative acid strengths of substituted anthranilic acids in quinoline and pyridine.

ACID-BASE BEHAVIOUR IN NITROGENOUS SOLVENTS

Conductivity Studies

The earliest major studies on the nature of acid-base

behaviour and dissociation processes in nonaqueous solvents were undertaken by examining the electrical conductivity of such solutions. Caldwell and co-worker presented early reports on the conductances of acids and pseudo acids in pyridine (112,113) and piperidine (113). The authors pointed out, that since little was known at that time about salt formation and dissociation of pyridine salts in pyridine solution, only approximate comparisons could be made by conductance. It was demonstrated, however, that pyridine acted as a differentiating solvent toward typically strong acids. Conductance measurements determined the order of relative acidity in pyridine to be

$$HI > HNO_3 > HBr > HCl > C_6H_5COOH .$$

Pearce gave a rather detailed account of conductivity measurements in basic solvents of low dielectric constant. Among the systems studied were anilinium chloride in aniline and anilinium bromide in aniline and quinoline (114).

Excellent reviews on the conductance of hydrogen halides in anhydrous polar organic solvents have been prepared by Janz and Danyluk (93,115). A survey of studies made in basic solvents such as nitriles, pyridine compounds and other amines is outlined. Miskidzhyan's brief review of electrically conducting nonaqueous systems formed from non-conducting components includes a survey of organic acid-amine systems (116).

Using a method of successive approximations, which had

been described earlier by Fuoss and Kraus, Davies (117) calculated the dissociation constants in pyridine of pyridinium perchlorate, iodide and nitrate to be 7.55×10^{-4}, 5.9×10^{-4} and 4.96×10^{-5} respectively in the concentration range of $4\text{-}100 \times 10^{-5}$ gram-equivalents per litre. In the case of benzoic acid the conductivity relative to that of the solvent was too small and the estimated dissociation constant of 1.6×10^{-10} for this weak acid should only be accepted for its qualitative significance. More recent conductance data, acquired by Burgess and Kraus, were used to determine limiting conductances and dissociation constants of electrolytes in pyridine at 25°C. Respective values of 1.8×10^{-5} and 5.1×10^{-5} for the dissociation constants of piperidinum and pyridinium nitrate were determined (118). The latter estimate is in good agreement with the earlier figure of Davies noted above. Hlasko (119) investigated the conductance behaviour of hydrohalides in pyridine and found the following constants of dilution (dissociation constants) at 25°C: $K_{HF.C_5H_5N}=3\times10^{-9}$, $K_{HCl.C_5H_5N}= 4\times10^{-6}$, $K_{HBr.C_5H_5N}= 10^{-4}$, $K_{HI\cdot C_5H_5N}= 3\times10^{-3}$.

Ethylenediamine represents an organic solvent which is a slightly stronger base than ammonia when dissolved in water, and therefore, significantly more basic than pyridine. Its dielectric constant (ϵ = 12.5 at 25°C. (105)) is, however, comparable to that of pyridine (ϵ =12.3 at 25°C.(97)). Schaap

et al. have reinvestigated some early conductance work (which had lacked agreement) for mineral acids in ethylenediamine and found hydrochloric, hydrobromic and nitric acids to possess ion-pair association constants of 9.52×10^3, 4.18×10^3 and 3.00×10^3 (105) respectively. Fowles and McGregor (120) made conductance measurements in ethylenediamine and propylenediamine and found, using the procedure of Fuoss and Kraus, a dissociation constant of 1.16×10^{-4} for ethylenediamine monohydrochloride in ethylenediamine.

Hydrazine is a basic solvent with a relatively high dielectric constant ($\epsilon = 51.7$ at 25°C.(121)). Vieland and Seward were able to apply Shedlovsky's method for incompletely dissociated electrolytes in determining dissociation constants of substituted phenols in this solvent (122). Values ranged from 1.79×10^{-4} for *p*-cresol to 6.42×10^{-3} for *p*-chlorophenol. The authors cautioned that although phenol in hydrazine may be completely ionized to form the salt, a complete description of the phenol-hydrazine system must include interactions other than of a simple coulombic nature. It would seem that in these solutions the ions and molecules are more complex than those indicated by the equation

$$N_2H_4 + HOC_6H_5 \rightleftharpoons N_2H_5^{(+)} + {}^{(-)}OC_6H_5 \quad . \qquad [24]$$

Relatively few studies of acid-base equilibria in nonaqueous systems have been carried out at elevated temperatures. Jander and Winkler have found, however, that acids

such as perchloric, nitric, hydrobromic, hydrochloric, picric and p-toluolsulfonic are essentially completely dissociated in molten acetamide at 94°C (123). Thermodynamic dissociation constants were determined for the weaker acids, 2,4-dinitrobenzoic, o-nitrobenzoic, salicylic and benzoic; respective values obtained were 11.9×10^{-4}, 1.18×10^{-4}, 1.91×10^{-4} and 0.0217×10^{-4}. Dawson et al. (124) have examined the conductance behaviour at 40°C. for univalent electrolytes in N-methylacetamide, a basic solvent which is characterized by an unusually high dielectric constant (ϵ = 165.5 at 40°C.(124)). N-methylacetamide acts as a levelling solvent to acids in contrast to the differentiating action of isomeric N,N-dimethylformamide. In dilute solution in the former solvent 2,4,6-trinitrophenol and hydrogen chloride are completely dissociated but not in the latter amide. It is apparent that the extent of substitution on the amide nitrogen effects the proton-accepting properties of the medium to a great extent. In a later study Dawson and co-workers found that acetic acid behaved like a typically weak electrolyte in N-methylacetamide at 40°C.(125). Their estimate for the dissociation constant of acetic acid was of the order of 10^{-8}. They rationalized this rather small value, relative to the ionization constant in water ($K_a(H_2O) = 1.76 \times 10^{-5}$ at 25°C.(126a)), by considering the basicity of the solvents in question. N-methylacetamide is less basic than the acetate ion. Because of this the proton

is held more tightly by the acetate ion such that N-methylacetamide is not as effective in removing it.

Acetonitrile has proven to be a valuable medium for the investigation of the more subtle intrinsic properties of acidic solutes which are often masked in aqueous solution (127,128,129). It has both acidic and basic properties, the latter slightly stronger, and can thereby be classified as amphiprotic. The proton-accepting power is not as marked as in the case of the aromatic base pyridine. Because of the lower dielectric constant of acetonitrile (ϵ =37.5 at 20°C.(97)) as compared to water (ϵ =80.4 at 20°C.(97)), the dissociation step (b) of the reaction,

$$HX + S \overset{a}{\rightleftharpoons} SH^{(+)}X^{(-)} \overset{b}{\rightleftharpoons} SH^{(+)} + X^{(-)}, \qquad [25]$$

where the acid is HX and S represents acetonitrile may prove more sensitive to variations in the effective radii of ions in acetonitrile than in water. As a consequence of the very weakly acidic or hydrogen-bonding properties, acetonitrile has a limited capacity to solvate and stabilize anions ($X^{(-)}$) derived from Bronsted acids. Anions may be stabilized by resorting to hydrogen bonding with undissociated acid instead, thereby producing complexes such as $X^{(-)}...HX$.

A rather extensive conductometric study of hydrohalides in acetonitrile was undertaken by Janz and Danyluk (127). They observed that the conductance of solutions containing hydrochloric, hydrobromic or hydroiodic acids increased

with time. This conductance-time effect was attributed to the slow attainment of ionization equilibria due to solvent-solute interaction. It would appear that the polarizability of the acid molecule and the electron donor properties of acetonitrile were the chief factors involved in this change. Utilizing the donor-acceptor classification of Mulliken (84), Janz and Danyluk noted that acetonitrile could function in a dual manner, that is, as an onium electron donor (a nitrogen base containing a lone unshared pair of electrons), and as a π-ketoid acceptor (interaction leading to the formation of one sigma bond and the rupture of one pi bond). Two mechanisms were, therefore, proposed to account for acetonitrile-hydrogen halide interaction. In the first case, in which the solvent acted as an onium donor, the equilibria presented were

$$CH_3CN + HX \rightleftharpoons CH_3CN \cdot HX, \qquad [26]$$

$$CH_3CN \cdot HX \rightleftharpoons CH_3CNH^{(+)}X^{(-)}, \qquad [27]$$

$$CH_3CNH^{(+)}X^{(-)} \rightleftharpoons CH_3CNH^{(+)} + X^{(-)}. \qquad [28]$$

An 'outer' charge-transfer complex or 1:1 addition compound is formed initially as in [26]. A rearrangement or ionization then occurs to an 'inner' complex [27] followed by dissociation of this 'inner' complex to yield solvated ions in solution [28]. A further complication may ensue in that the anion could interact with another acid acceptor

to form the bihalide triple ion.

$$HX + X^{(-)} \rightleftharpoons HX_2^{(-)} \qquad [29]$$

The formation of nitrilium-type salts of empirical formula, $CH_3CN \cdot 2HX$, could equivalently describe the over-all interaction.

If the solute-solvent interaction is considered to involve the pi-electron system of the nitrile, then it is necessary to examine the canonical structures of the compound(s) formed as in equations [26] and [27].

$$CH_3C \equiv NH^{(+)}X^{(-)} \longleftrightarrow CH_3C^{(+)} = NHX^{(-)} \qquad [30]$$

The electronegative halide ion from a second molecule of acid could then attack the electron deficient carbon atom of the nitrile group.

$$CH_3C^{(+)}=NHX^{(-)} + HX \rightleftharpoons CH_3\overset{X}{\overset{|}{C}} = NH_2^{(+)}X^{(-)} , \qquad [31]$$

followed by dissociation of the imino hydrohalide

$$CH_3\text{-}\overset{X}{\overset{|}{C}} = NH_2^{(+)}X^{(-)} \rightleftharpoons CH_3\text{-}\overset{X}{\overset{|}{C}} = NH_2^{(+)} + X^{(-)} \qquad [32]$$

The imino-type interactions were favoured by the increased polarizabilities of hydrobromic and hydroiodic acids. In the earlier series of charge-transfer interactions the slow step was postuled as the rearrangement from the 'outer' to an 'inner' complex in order to account for the conductance-

time effect, whereas in the latter scheme, a finite rate of formation of the imino type of compound and subsequent ionization helped to explain this phenomenon.

In their second paper of the series Janz and Danyluk obtained corroborative evidence for their earlier observations by examining the nature of solid substrates isolable from solutions of the three halo acids in anhydrous acetonitrile. Their attention was then turned to a study of the electrical conductance of 'aged' solutions of the three acids in the nitrile. It had been hoped that their molar conductivities could be analyzed in the light of theoretical treatments for weak electrolytes and ion association. Since molecular-type solvent-solute interactions contributed to the ionic processes, however, systems such as CH_3CN-HX could not be explained adequately by such treatments.

More recently Janz and co-workers have examined the electrical conductance of hydrobromic (130) and hydrochloric (131) acids in anhydrous benzonitrile. Coetzee and Kolthoff also have contributed significantly to our understanding of solvent interaction in an acetonitrile medium. The former worker, in a paper co-authored with Cunningham, reported the reaction of ortho-substituted benzoic acids with amines in acetonitrile by conductometric titration (132). Several equilibria were considered and it was shown that the greater stability, derived from intramolecular hydrogen bonding of the 2,6-dihydroxybenzoate ion over that of the salicylate

ion, accounted for the marked decrease in the former of:

(i) the solvation of the anion,

(ii) the stability of the ion pair with ammonium ions, and

(iii) the stability of its homoconjugate complex, $(X...HX)^{(-)}$, with the free acid.

Colorimetric and Spectrophotometric Studies

The visual colorimetric study of Krohen and La Mer (133) was an early attempt by this method at a semi-quantitative analysis of the behaviour of acids and bases in pyridine. By using a Hellige comparator and indicators dissolved in pyridine they established an 'apparent pH' which meant that the indicator in pyridine gave a colour identical with that given by the same indicator in water solution of that pH. They did not, however, imply that the acidity in pyridine was identical with that in the aqueous solution. Indicator comparisons were made in the case of diethylamine and trichloroacetic acid and dilution curves of apparent pH *versus* concentration obtained for the concentration range of 10^{0} - 10^{-4} molar. It was concluded that changes in apparent pH were a consequence of changes in the activity coefficients of the acid and base studied since variations with concentration were independent of the indicator used.

Lagowski *et al.* have found that weak acids such as *o*- and *p*-nitroacetanilide undergo incomplete ionization and

dissociation in liquid ammonia at -55.6°C. (ϵ =22.4 at -33.4°C.(126c)) (134,135). These workers determined equilibrium constants for the ionization, K_i, that is, the equilibrium between the weakly acidic electrolyte (HX, o- or p-nitroacetanilide) and its ion pair,

$$HX + NH_3 \overset{K_i}{\rightleftharpoons} (NH_4^{(+)}X^{(-)}), \qquad [33]$$

and for the dissociation, K_d, which involves the equilibrium between the ion pair and its dissociated ions,

$$(NH_4^{(+)}X^{(-)}) \overset{K_d}{\rightleftharpoons} NH_4^{(+)} + X^{(-)}, \qquad [34]$$

for the first time by an ultraviolet and visible spectrophotometric technique. Both isomers displayed a low-wavelength band attributed to the un-ionized molecules. The higher band corresponded to the anion and/or ion pairs containing the anions of o- and p-nitroacetanilide. An indication, that ionic aggregates containing the nitroacetanilide anion and the free anion could not be distinguished spectrophotometrically, was given by the fact that the shapes and positions of these bands remained constant for solutions with varying amounts of potassium iodide and bromide added. However, the relative intensities of the low- and high-wavelength bands, that is, those associated with the molecular and ionic forms, changed markedly as the inert electrolyte was added. These observations suggested that the equilibrium position in this system was altered with

a change in the activity of the species in solution because of the presence of the inert electrolyte. A method for evaluating the equilibrium constants was described in their paper (135) and the results noted in Table III.

TABLE III

IONIZATION (K_i) AND DISSOCIATION (K_d) CONSTANTS OF o- AND p-NITROACETANILIDE IN LIQUID AMMONIA SOLUTIONS AT -55.6°C*

Acid	$K_i \times 10^2$	$K_d \times 10^4$
o-Nitroacetanilide	2.2	2.2
p-Nitroacetanilide	9.3	0.89

* Reference (135).

Lagowski and his co-workers also stressed that direct comparison between the ionization constants determined in liquid ammonia solutions and those in high dilectric solvents such as water is often difficult. They recommended that a more meaningful comparison would involve the degree of ionization (α) which was defined as

$$\alpha = \frac{\left(\left[X^{(-)}\right] + \left[NH_4^{(+)}X^{(-)}\right] \right)}{\left[HX\right]} \qquad [35]$$

in the ammonia system. At the temperature and concentration (ca. 10^{-4}) used the value of α was about 25 percent which corresponded to an acid with an ionization constant of about

9×10^{-6} in water solution.

A spectrophotometric method was also used to determine the over-all dissociation

$$HCl \rightleftharpoons H^{(+)} + Cl^{(-)} \qquad [36]$$

in ethylenediamine (136). The use of an indicator acid, 3-methyl-4-phenylazophenol (HI) which dissociated in ethylenediamine according to equations [33] and [34], was necessary because the nonabsorbing acid, HCl, was being studied. The dissociation constant of hydrochloric acid, K_{HCl}, was not arrived at directly but was calculated from the best values of K_{HI} and K_{HI}/K_{HCl} to be 7.06×10^{-5}.

Corey (137) examined the behaviour of certain phenols and carboxylic acids in pyridine. This work was, in fact, the first quantitative attempt at determining the nature and relative amounts of species which result when weakly acidic substances are dissolved in pyridine. Of the acids (HA) studied p-nitrophenol showed no appreciable ionization whereas 2,4,6-trinitrophenol was essentially completely ionized. Confirmation of this latter fact has been given by Izmailov and Gurevich in their observation that at a concentration of 5×10^{-5} moles per litre picric acid and sodium picrate had the same absorption spectrum in pyridine (138). In between these two extremes Corey found that 2,6-dinitro-3,4-xylenol and 2,5-dinitrophenol exhibited partial ionization. Solutions of the latter two phenols contained ionic species both in the form of dissociated

ions and pyridinium-phenoxide ion pairs. Spectra were taken (ca. 10^{-4} moles per litre) in neutral solvent and in basic (N-ethylpiperidine added) and acidic (pyridinium nitrate) solutions. The intensity of the phenoxide band of 2,6-dinitro-3,4-xylenol was reduced by the addition of the pyridinium nitrate but reached a definite constant value. The residual phenoxide absorption, which appeared as a shoulder on the phenol band, was attributed to the presence of phenoxide-pyridinium ion pairs or higher aggregates. Calculated values for the equilibria K and K' as outlined in the following scheme,

$$\begin{array}{ccc} nHA + C_5H_5N & \overset{K'}{\rightleftharpoons} & (C_5H_5NH^{(+)}A^{(-)})_n \\ \uparrow\downarrow K & & \uparrow\downarrow K'' \\ nC_5H_5NH^{(+)} & + & nA^{(-)} \end{array} \quad , \qquad [37]$$

where n = 1 is assumed, are given in Table IV. Utilizing some previously published data Corey also estimated equilibrium constants for ethyl hydrogen isopropylidenemalonate (XVI)($pK(H_2O)$ = 3.36 (137)) in pyridine.

$$(CH_3)_2C = \underset{\displaystyle X}{\overset{\displaystyle |}{C}} - COOH$$

XVI, X = $COOC_2H_5$

XVII, X = CN

TABLE IV

OVER-ALL DISSOCIATION CONSTANTS (K) AND IONIZATION CONSTANTS (K') OF 2,6-DINITRO-3,4-XYLENOL (I) AND 2,5-DINITROPHENOL (II) IN PYRIDINE[a]

	I	II
K^b	$1.1 \times 10^{-3} - 3 \times 10^{-1}$	$0.8 \times 10^{-3} - 3 \times 10^{-3}$
K^c	3.0×10^{-3}	7.5×10^{-4}
K'	3×10^{-1}	3.3×10^{-2}
Concentration range moles/litre x 10^3	0.188-0.942	0.500-1.74

[a] Reference (137).

[b] Calculation made on the basis that dissociated ions are only ionic species present, that is, no ion pairs ($K >> K'$).

[c] Calculation made by assuming that both ion pairs and dissociated ions existed in solution.

He found values of $\sim 2 \times 10^{-8}$ and *ca.* 10^{-4} for K and K' respectively. An infrared spectral examination of pyridine solutions of XVI, the cyano acid (XVII)($pK(H_2O) = 3.04$ (137)) and acetic acid ($pK(H_2O) = 4.75$ at 25°C.(126a)) showed little or no absorption at 1600 cm^{-1} -- the frequency at which strong absorption by carboxylate ions usually occurs. These results are in agreement with equilibrium values estimated for XVI.

An examination of the infrared absorption frequencies of nitrate ion has proven of value in distinguishing species in saturated solutions of pyridinium and other nitrate salts in pyridine and aqueous pyridine (139). Hadzi has made a major contribution to an understanding of hydrogen-bonding present in binary systems of carboxylic acids in pyridine by infrared spectroscopy (140,141). In the latter reference results were used to clarify types of association encountered in solid forms of pyridine carboxylic acids. The infrared spectrum of a liquid film, prepared with an equimolecular mixture of benzoic acid and pyridine, displayed a band at 1690 cm^{-1} but no strong band near 1600 cm^{-1} demonstrating that the carboxylate ions were not present to any significant amount. Two bands positioned at 1900 and 2450 cm^{-1} were reasoned to be due to a splitting of the vibrational energy level because of tunnelling of the proton between two minima of potential energy (which

gave rise to two hydroxyl bands). The bands due to pyridine were not discussed except for noting that the one at 1530 cm^{-1} in the spectrum of pyridinium ion was absent from the acid mixtures which was additional proof that ionization had not occurred appreciably.

Chiorboli has used Raman spectra to study perturbations caused by solute-solvent interactions. Systems examined included mixtures of o-chlorophenol, p-chlorophenol, acetic acid and formic acids in pyridine (142). Raman and infrared vibrational frequencies of quinoline, quinolinium chloride and quinoline in phenol, acetic acid and formic acid were also assigned (143). Bands due to the quinolinium ion were shown to be present in each of the three mentioned systems, being particularly strong in the case of formic acid. Spectra also showed bands attributed to quinoline which were modified because of hydrogen bonding with the solvent.

Nuclear Magnetic Resonance Studies

The application of nuclear magnetic resonance to the study of hydrogen bonding, tautomerism, proton exchange and association phenomena in nonaqueous solvents has gained wide use and is the fastest growing technique for such studies (144,145a,146a,147,148).

Early in the development of nuclear magnetic resonance rather large proton shifts were recognized as resulting from hydrogen bonding phenomena. In such measurements it

is usually not possible to observe both the associated and nonassociated species simultaneously in the same medium. One observes rather a spectrum characteristic of an averaged out environment of the proton which will depend on the number and kind of donor species present. What would be required, in order to observe both states simultaneously, is that the lifetime of each state be longer than the reciprocal of the chemical shift (in cycles per second). There are some examples involving stronger hydrogen bonds where at lower temperatures two separate signals appear and on raising the temperature coalesce to a single broad peak which becomes sharp at still higher temperatures (149). A study of acid-base phenomena between trifluoroacetic acid and quinoline in acetonitrile at low temperatures afforded distinct peaks for the $\gtrless N^{(+)}-H$ proton of the quinolinium ion and carboxyl proton although considerable exchange broadening was evident (150).

The principal contributions to the cause of a chemical shift of the proton involved in hydrogen-bond formation have been suggested some time ago (146a). When a hydrogen bond, X-H...Y, is formed, where Y is the donor atom of a second molecule, the hydrogen-bond shift is observed because the magnetic field experienced by the proton is modified.

(i) The electronic structure of the chemical bond in which the proton is participating (X-H) is distorted and thereby contributes to proton screening (always in a negative or deshielding sense)

(ii) Any magnetic anistropy of the molecule to which the proton is hydrogen-bonded may contribute (negatively or positively) also to the proton screening.

The hydrogen bond between methyl alcohol and pyridine was studied by ^{14}N nuclear magnetic resonance (151). Compared to the ^{14}N signal of neat pyridine the peaks in pyridine-methanol solution were shifted to higher field and were interpreted in terms of a hydrogen bond between pyridine and methyl alcohol. The electronegativity of neighbouring atoms and the changes in ionic character of the nitrogen atom were reasons given for the magnitude of such shifts (145b,146b). The hydroxyl proton shift for the system (referred to the methyl proton) showed that the maximum hydrogen bond was realized in 0.5 mole fraction methanol. The hydrogen bond, O-H...N, would seem, therefore, to be stronger than that represented by O-H...O. These results were used in applying the valence bond theory to an estimation of the contribution of the following structures to a hydrogen-bonded system, X-H...Y:

XVIII X-H Y (purely covalent)

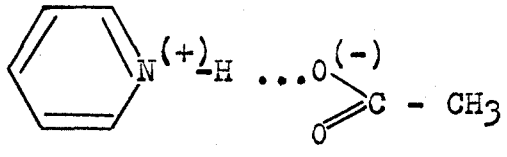
XIX $X^{(-)}$ $H^{(+)}$ Y (ionic)

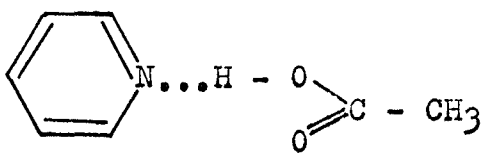
XX $X^{(-)}$ $H\text{-}Y^{(+)}$ (charge-transfer)

The observed chemical shift was attributed to structure (XX) which was approximated by that of the pyridinium ion. A calculation using experimental values was made and XX was

found to contribute 7 ± 3 percent to the total amount of the hydrogen-bonded state, a value quite comparable to the theoretical model which gave 9.2 percent.

Proton magnetic resonance experiments have been carried out in the binary systems, acetic acid-, phenol- and water-pyridine (152). The lowest resonance field of the -OH proton was exhibited in every case by the mixture of 50 mole percent pyridine. This and other observations helped to confirm the existence of pyridinium ion in the binary system accompanied with a fast proton exchange reaction. Tests were also made on the chemical shift of the hydroxyl proton in a mixture of acetic acid-sodium acetate in the acid-rich region of the solution. In this case a similar tendency was exhibited but at a little higher resonance field than that of pyridine-acetic acid. The existence of a strong hydrogen bond, $O\text{-}H\ldots O^{(-)}$, for the acetic acid-acetate system was confirmed by infrared spectra which indicated a strong -OH band at about 2400 cm^{-1}. A double minimum potential for the proton of the following type:

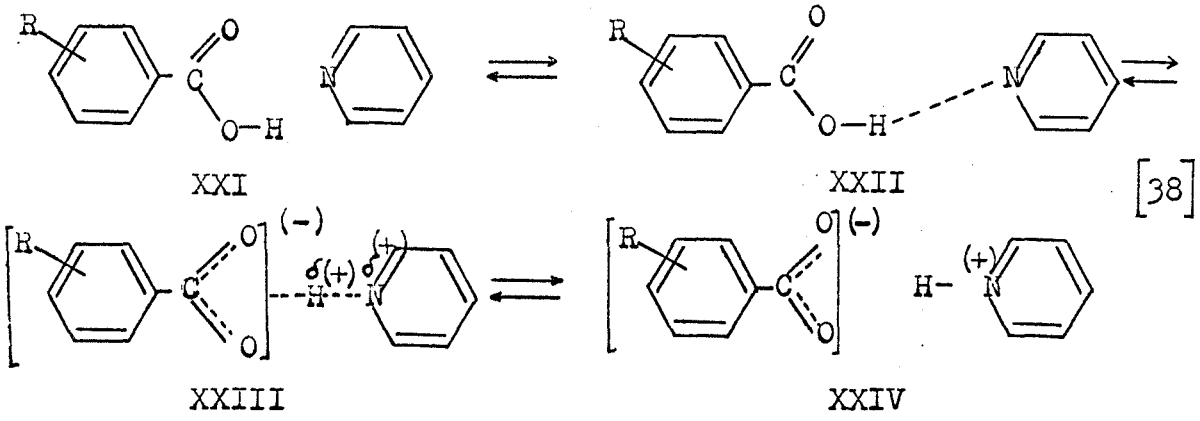




was presumed for the acetic acid-pyridine system.

The importance of proton magnetic resonance in providing evidence on complex formation and on the site of solvent attachment in the decarboxylation of malonic acid in quinoline has been reported (153).

The chemical shifts of meta- and para-substituted benzoic acids (substituent = OCH_3, CH_3, Cl, Br, I, NO_2, or CN) at infinite dilution in pyridine were measured and correlated well with Hammett's sigma substituent constants (154). The interaction between each acid and pyridine was pictured as involving the following equilibria:

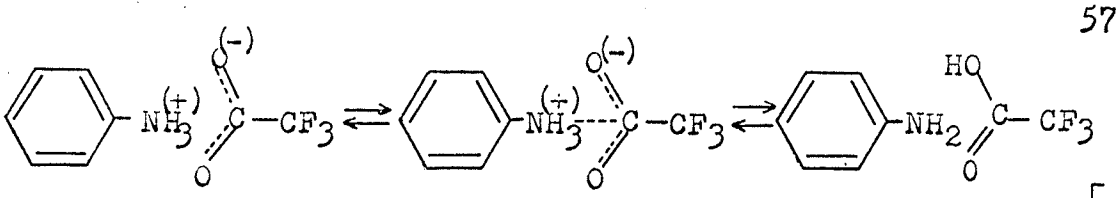


XXI XXII XXIII XXIV [38]

The over-all chemical shift of the hydroxyl proton in pyridine will be dependent on the time average of the chemical shift for the proton in the environments from each of XXI to XXIV. Equilibria for acids bearing ortho substituents as a rule do not conform to the Hammett relationship so that it was of interest to note that the infinite dilution chemical shifts of proton signals for a series of ortho-

substituted benzoic acids were also well correlated with Hammett's sigma para or Taft's σ^* substituent constants. The reaction constant, rho, for the acids with meta and para substituents was estimated to be 1.5 from the graph while that for the ortho-substituted series using sigma para substituent constants was estimated as 2.4. The authors attributed this difference to the influence of the electric field possessed by the ortho-substituted benzoic acids. Nevertheless, it would seem that the ortho effect was not apparent in the case of ortho-substituted benzoic acids. Unfortunately, data for salicylic and anthranilic acid were not included. The authors did note that in earlier work, the infinite dilution chemical shift of the hydroxyl proton of ortho-substituted phenols in pyridine solution had shifted to higher field when compared to meta- and para-substituted phenols. It was suggested that steric factors were more important in these phenol-base systems.

Proton-exchange reactions of aniline, halo-substituted anilines and N,N-dimethylaniline in trifluoroacetic acid have been studied by Reynolds and Schaefer in solutions containing from 1 to 3 mole percent of the substituted aniline (155). The acid proton-exchange rates were determined by measuring the acid proton width. The reaction was proposed to proceed through the formation of ion pairs which then transferred protons internally.



XXV XXVI XXVII [39]

The experimental work gave an indication that the molar ion-pair dissociation constant,

$$K_D = \frac{[XXV]\ [XXVI]}{[XXVII]} \quad , \qquad [40]$$

was of the order of 10^{0} to 10^{-2}.

Krakower and Reeves (150) extended the study of protonation of bases by nuclear magnetic resonance by examining the chemical shift changes with concentration in quinoline-trifluoroacetic acid mixtures. The formation of a strongly hydrogen-bonded ion pair was indicated both in pure acid-base composition and in acetonitrile as solvent. In the two-component system at room temperature an exchange-averaged signal of the trifluoroacetic acid carboxyl proton (-COOH) and the quinolinium ion proton ($\gtrless N^{(+)}\text{-}H$) existed for all concentrations. The results were in contrast to those obtained with a 5 mole percent solution of pyridine in trifluoroacetic acid (156). In this latter case a signal from the carboxyl group proton of the trifluoroacetic acid was observed along with a triplet signal characteristic of a proton bonded to a nitrogen atom. Krakower and Reeves thought that this difference in behaviour in the two acid-base sys-

tems was a reflection of the reduced basicity of quinoline. Because of solubility difficulties the whole concentration range (0-1 mole fraction acid) in quinoline was not obtained but a similar set of results were secured as various concentrations of pure acid and base were dissolved in 50 mole percent acetonitrile. A very large low-field chemical-shift limit was reached in the concentration versus shift curve at 50:50 mole ratio of acid to base. Distinct peaks for the $\rangle\!\!=\!\!N^{(+)}$-H and -COOH protons were observed for acid-base mixtures in dichloromethane at -18°C. although they were considerably exchange broadened. At lowest field was the $\rangle\!\!=\!\!N^{(+)}$-H signal, which was broader than the -OH peak but was not resolved into the triplet structure expected for coupling to ^{14}N.

The following two simplified equilibria, both of which were rapidly reached on the time scale of the inverse of the chemical shifts of the various proton environments, were proposed to explain the position of the exchange-averaged peak in solutions containing trifluoroacetic acid, (HA), and quinoline, (Q).

$$Q + HA \rightleftharpoons \left[QH^{(+)}\ldots A^{(-)}\right] \qquad [41]$$

$$\left[QH^{(+)}\ldots A^{(-)}\right] \rightleftharpoons QH^{(+)} + A^{(-)} \qquad [42]$$

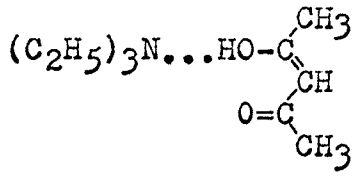
The species, $\left[QH^{(+)}\ldots A^{(-)}\right]$, represents the strongly hydrogen-bonded ion pair of the conjugate acid and base. An exchange-

averaged proton resonance between a trifluoroacetic acid proton and a quinolinium ion which was largely hydrogen bonded to an anion was observed for solutions with acid to base ratios greater than one. The position of the trifluoroacetic acid proton resonance lay to the high field of the exchange-averaged peak while the ion pairs, $\left[QH^{(+)}...A^{(-)}\right]$, developed a proton resonance to the low field of the averaged peak. The authors further argued that, in solutions which were quinoline rich, the very large concentration-dependent shift to high field could be associated with the rupture of hydrogen bonds in the ion pairs as the salt was diluted in the basic solvent. Experimental values of the infinite dilution chemical shift of the quinolinium ion in quinoline and the chemical shift of the fully associated species, $\left[QH^{(+)}...A^{(-)}\right]$, were derived from the data. From the linear dependence of chemical shift on the concentration in the region 0.12 to 0.04 mole fraction, an equilibrium constant of 6.5×10^{-2} mole fraction units was estimated for equilibrium [42].

Martin has conducted a major proton magnetic resonance study into the effect of various solvents on the dissociation, complexation and ionization phenomena of alcohols and phenols (157). Basic solvents included triethylamine and pyridine. The displacement of the resonance signal of the hydroxyl proton constituted a good measure of relative acidities of alcohols and phenols.

Tautomerism may be considered as a combination of hydrogen bonding and slow inter- or intramolecular proton transfer. Reeves examined interactions which could disturb the equilibrium between the tautomeric forms of acetylacetone (158). Acetic acid and cyclohexane as solvents were without this effect. It was assumed that acetic acid molecules by virtue of their self association were largely inert. The keto-enol equilibrium was affected in cyclohexane only in that the lower dielectric constant favoured the less polar enol form of the two tautomers. With pyrrole as solvent, a large change in chemical shift was observed for the N-H proton and a smaller change in the keto-CH_2-. These effects were explained in the breaking of intramolecular association of acetylacetone and formation of 1:1 and/or 2:1 complexes through the N-H proton with the carbonyl groups. In strongly basic solvents such as triethylamine there was an absence of any keto form up to 87 mole percent of acetylacetone together with a large dilution shift of the enolic - OH proton to high field. The implication was that enolization proceeded, followed by specific interaction of the lone pair of electrons on the nitrogen with the enolic proton. The change in chemical shift could then be explained as a composite effect of breaking the intramolecular hydrogen bond, which would cause the signal to move to high field, and formation of the hydrogen-bonded complex to ethylamine which

would favour a low-field shift for the enolic proton. Such an interpretation was consistent with a fast exchange between free and complexed enolic hydroxyl groups (XXVIII).



XXVIII

Potentiometric Studies

Adequate progress in the utilization of potentiometric techniques in studying acid-base behaviour in nonaqueous solvents has depended chiefly on the development of suitable electrode systems in which requirements of stability, reversibility and reproducibility are of paramount importance. The classic work of Conant, Hall and co-workers (159) and Kolthoff and Bruckenstein (160) on equilibria in acetic acid is well known. The latter authors, particularly, helped to lay the groundwork for interpretation of the frequently complex equilibria present in acid-base systems of nonaqueous solvents of low dielectric constant. Work in basic media has progressed more slowly but the number of nitrogenous solvents studied is continually growing. In the following paragraphs a brief account of some quantitative studies in determining acidity constants in basic media will be given. The development of particular electrode combinations

and titrants, solvent systems, electrode response and studies in relative acidity related to the present work will be described in later sections of this review.

The weakly basic solvent, acetonitrile, and the relatively strongly basic ethylenediamine have received by far the closest attention. Coetzee and Padmanabhan used a conventional general-purpose glass electrode reversible to hydrogen ion activity in picric acid-tetraethylammonium picrate and 1,3-diphenylguanidine-diphenylguanidinium perchlorate buffers in anhydrous acetonitrile (161). From earlier results of conductometric and spectrophotometric studies of the dissociation constants of picric acid and 1,3-diphenylguanidine in acetonitrile and from the potentiometric measurements described in the above paper they were able to determine the autoprotolysis constant of acetonitrile. These same authors undertook an exploratory potentiometric study of five phenols in acetonitrile (129). Formation constants of the homoconjugate complex formed by the free acid (HX) and anion ($X^{(-)}$) were calculated (see equation [29] on page 42) for all phenols except picric acid. The unsubstituted phenol also formed a 2:1 complex, $(HX)_2X^{(-)}$. Homoconjugation was reduced significantly by substitution of phenol with an ortho-nitro group. Substitution of p-nitrophenol in both ortho positions, as in picric acid, eliminated entirely any complex formation. Stabilization of the acid form by intramolecular hydrogen

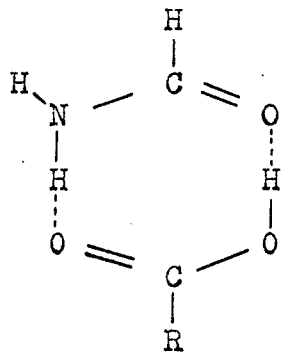
bonding was given as the chief reason for this effect. Further indication of such stabilization was given by the fact that o-nitrophenol was weaker than p-nitrophenol in acetonitrile whereas both these acids had similar dissociation constants in water.

Mandel and Decroly chose formamide for their studies on the dissociation constants of carboxylic acids because of the very high dielectric constant possessed by this solvent and for the fact that certain other physical properties show some resemblance to those of water (162,163, 164). They first measured the standard potential of the Ag-AgCl electrode with respect to the normal hydrogen electrode and then calculated the dissociation constants of formic and acetic acids from the potential of the following cell without liquid-liquid junction (162,163),

$$Pt,H_2/AH(m_1),\ ANa(m_2),\ NaCl(m_3)(HCONH_2)/AgCl,Ag\ , \qquad [43]$$

where AH stands for the acid, ANa for the sodium salt and m_1, m_2, and m_3 represent the molalities of the acid, its sodium salt and the sodium chloride in formamide solution respectively. The values in formamide were lower than in water although the dielectric constant of the former (ϵ =109.5 at 25°C. (163)) is much higher than that of water. Dissociation constants were determined at temperatures varying from 15 - 45°C. and their variation in formamide could be represented by a parabolic curve for log K_a = f(T). K_a was found to change faster with temperature in formamide

than in water. These findings were discussed in the light of energy of proton transfer and electrostatic interaction of the carboxyl group and the strongly polar solvent. In an attempt to qualitatively explain the behaviour of carboxylic acids in this nonaqueous solvent Mandel and Decroly proposed that besides purely electrostatic interactions between the formed ions one should take into account the existence of complexes between the undissociated acid molecules and formamide, the most stable one envisaged to involve a cyclic structure (XXIX)(165).



XXIX

No real dissociation occurs if the proton when transferred from the carboxyl group to the solvent molecule, is trapped inside the complex. What is needed for proper dissociation is that the cyclic structure be disrupted and the protonized solvent molecule made to separate from the acid anion.

Bruckenstein and Mukherjee (166) used the cell

Reference electrode (S.C.S.E.)	$HX(C_{HX})$ and/or $NaX(C_{NaX})$ in EDA	H_2(latm.) Pt	[44]

where S.C.S.E. refers to the saturated corrosive sublimate electrode and EDA to ethylenediamine. The other symbols have their usual significance. In dilute solution the equilibrium,

$$HX \rightleftharpoons H^{(+)} + X^{(-)} \quad , \qquad [45]$$

described the behaviour of hydrochloric acid and four different phenols but in more concentrated phenolic solutions the additional reaction

$$HX + X^{(-)} \rightleftharpoons HX_2^{(-)} \quad , \qquad [46]$$

needed to be considered in order to interpret the experimental results adequately. In a strongly basic and hydrogen-bonding solvent such as ethylenediamine it was somewhat surprising that the stability of these homoconjugate ions ($HX_2^{(-)}$) was such that complete hydrogen bonding to the undissociated phenol by the solvent in preference to the phenolate ions was precluded. Absolute pK values of acids were determined in ethylenediamine by Bruckenstein and co-workers after measuring the potential of the saturated corrosive sublimate electrode and a pH scale in that solvent was established (136).

A potentiometric study in buffers consisting of acids and their tetrabutylammonium salts enabled Juillard to determine ionization constants of several phenols in N,N-dimethylformamide (167). A pH scale was set up relative to a reference solution made from picric acid and its salt. Potentials were measured with the aid of a glass electrode filled with dimethylformamide and a calomel electrode in which the junction

was made up of a saturated solution of potassium chloride in the solvent used. The pK or $pH_{\frac{1}{2}}$ values of the phenols, including salicylic acid, in N,N-dimethylformamide were linearly related to the pK_a's in water with the exception of p-nitrophenol and 2,5-dinitrophenol. The existence of acid-acid anion association complexes for these two acids was invoked as the cause for the discrepancy. The work helped to confirm a prevailing opinion (168) that the capacity for acid-anion association is determined chiefly by the electron density at the phenolic oxygen.

An electrochemical investigation of hydrochloric acid in pyridine was carried out by Argenstein (169). Both conductance measurements and electromotive force values from the cell

$$H_2 \mid C_5H_5N{\cdot}HCl \mid BaCl_{2(s)} \mid Ba\text{-}Hg \qquad [47]$$

were used to determine the degree of dissociation and the dissociation constant of pyridinium chloride in the basic solvent. Similar to its behaviour with respect to hydronium ions in aqueous solutions, the hydrogen electrode was found to be reversible with respect to $C_5H_5NH^{(+)}$ ions. The value for the dissociation constant obtained was 7.15×10^{-7}.

Miscellaneous Studies

A number of miscellaneous methods have been used by workers to clarify the nature of acid-base behaviour and/or species in binary systems containing basic solvents.

A rather interesting polarographic study was presented by Spritzer et al. (170). The following acids were studied in pyridine solution: trifluoroacetic, benzoic, acetic, pyridinium nitrate, 2,4-dichlorophenol, phenol, salicylic, sulfuric and phthalic. With the exception of phenol all the named compounds gave similar half-wave potentials. Among the species that could possibly undergo reduction, the presence of free hydrogen ions was considered unlikely in the basic solvent. Neither the undissociated acid nor pyridine were reducible at the dropping mercury electrode within the potential range involved and the reduction of the acid anion does not occur. The polarographic wave pattern was attributed to the pyridinium ion. Since the pyridine solution containing phenol gave no wave, it was concluded that acids with a pK_a (aqueous) greater than about 9 were too weak to form the pyridinium ion in pyridine solution.

Cryoscopic measurements have been demonstrated to be useful in studying dissociation of the type represented by equation [36] on page 47 in ethylenediamine (136). Baliah and Ramakrishnan undertook to study the behaviour of substituted phenols in ethanolamine in order to gather information on the extent to which dissociation of ion pairs, formed by the interaction of a phenol and the ethanolamine, occurred in that solvent and to discover how molecular structure affected the dissociation (171). These authors reasoned, that since ethanolamine was a fairly strong base

($pK_b(H_2O)$ = 4.55 at 25°C.(172)), the levelling effect would enable virtually complete reaction with the acid solute. The van't Hoff i-factors were, therefore, interpreted as indicating only the extent of dissociation of the ion pairs as visualized by the equation,

$$ArOH+H_2NCH_2CH_2OH \longrightarrow ArO^{(-)} \ldots H_3^{(+)}NCH_2CH_2OH \rightleftharpoons ArO^{(-)}+H_3^{(+)}NCH_2CH_2OH. \quad [48]$$

Ar ≡ aryl

Further support for the idea that equation [48] did in fact describe the system in ethanolamine was given by the observation that phenol-solvent ion pairs did not dissociate in bases of low dielectric constant. In N,N-dimethylaniline, for instance, phenol, p-cresol and p-chlorophenol gave i-factors which were nearly equal to unity in contrast to values in ethanolamine.

Benzoic acid has been shown to self-associate significantly in nitromethane by a differential vapour-pressure technique but not in acetonitrile which has the same dielectric constant (173). The authors proposed that the lack of self-association in this latter solvent resulted from hydrogen bonding between acid and solvent producing species such as XXX and stabilizing the monomeric form.

$$CH_3CN \ldots HO-\overset{\overset{O}{\|}}{C}-C_6H_5$$

XXX

Magnetic susceptibility experiments were conducted on

acetic acid, pyridine and then mixtures by Deshpande and Pathi (174). Positive deviations from the additivity law were recorded at all concentrations with maximum departures occurring at 30, 60 and 80 mole percent acid concentration. Rather than interpret the results solely on formation of complexes the deviations were discussed by the authors also in terms of the effects produced by changes in the states of aggregation of the two components and in particular the stabilizing of monomers in preference to closed acid polymers. Sriraman et al. (175) have attempted to elucidate the nature of association of acetic acid in binary systems with triethylamine, pyridine and aniline using diamagnetic susceptibilities. The results were explained on the basis of ion-pair formation which tended to increase diamagnetism because of release of constraints. Maximum deviations from Wiedemann's additive law were taken as indications of maximum ionization at the particular acid-base concentration.

Viscosity determinations on binary mixtures of pyridine and acetic (176,177) and butyric (176) acids have been used to explain occurrences of compound formation. Swearington and Heck also studied the effect of changes of temperature on viscosity (177). Mixtures of the two components (acetic acid and pyridine) were made to cover the entire range of composition and then viscosities were measured at temperatures from 35-80°C. The maximum viscosity, which was recorded

for a solution containing approximately 85 mole percent acetic acid, occurred at this fixed composition for all the temperatures studied. A more detailed examination of the pyridine-acetic acid system was carried out by Venkatesan and Suryanarayana (178). Among their physico-chemical study they included contraction in volume, refractive index and densities. All the properties examined exhibited a maximum at a composition of 83 mole percent acetic acid. Whereas former workers, who had investigated this system ascribed the maximum to formation of a complex, Venkatesan and co-worker explained it on the basis of an attainment of maximum ionization within the system and postulated the existence of free hydrogen ions in addition to pyridinium ions. They reasoned that the ratio of free hydrogen ions to pyridinium ions must attain a maximum at this percent composition.

The examples of the work in this section at least point out clearly the great strides that are being made in trying to delineate the behaviour of acid solutes in basic nitrogenous solvents. The exact nature of the species studied in these solutions is often difficult to uncover. The wide variation in properties of solvents such as their dielectric constant, basicity or acidity and their ability to solvate ions and molecules helps to set up numerous and often unknown modes of association, ion-pairing, etc., which may further change with temperature and concen-

tration. In solvents which solvate anions only very weakly another complication arises, that is, the tendency to form acid-anion species. However, it seems well established by now (and many workers utilize this assumption) that ionization and dissociation are to be treated concurrently in nonaqueous solvents especially in those of lower dielectric constant.

There are very few acid-base systems in which quantitative evaluation of equilibrium constants have been made, that have been studied by more than one technique in order to confirm and establish agreement between the various procedures. When sufficient results have been accumulated, for instance in ethylenediamine (136) and acetonitrile (179), the agreement is quite good. There is need also for studies to be directed to examine the effect of varying the temperature on association and dissociation processes in nonaqueous solvents. Temperature effects are usually not marked but since many organic reactions, including kinetic studies, are carried out at relatively high temperatures it is quite possible that rather unusual effects could occur at these higher temperatures such that acidity studies at room or near room temperature may not adequately describe the system.

THE DEVELOPMENT OF POTENTIOMETRIC TITRIMETRY IN NONAQUEOUS (NITROGENOUS) MEDIA

The scope of titrimetry, particularly for analytical

purposes, was broadened considerably with the introduction and widespread use of nonaqueous solvents. A minimum of equipment is required for this relatively simple technique and accuracy in the titration is very often improved by their use. The intense interest in acid-base titrations in nonaqueous solvents is attested to by the innumerable papers that are surveyed in biennial reviews (107,108,109, 110,111,180,181,182). Particular attention has been paid to the development and use of various electrode systems, titrants and solvents. It is also noticed that difficulties met in obtaining aqueous solutions of a large number of organic substances are largely overcome by using nonaquous titrimetry. The number of reviews and monographs on the subject appearing in the literature is growing rapidly (79,87,88,90,91,183,184,185,186,187,188,189,190,191). Kucharsky and Safarick have presented a critical survey in book form (82).

The first analytical method of titrating in nonaqueous media was published by Folin and Wentworth (73). Sharp end points (indicator) were obtained for the titration of higher fatty acids, extracted from fat in feces, with sodium alcoholate in solvents such as chloroform, carbon-tetrachloride, benzene or toluene. Riddick (107) stated, that an electrometric procedure for the determination of acidity in oils published in the Proceedings of the American Society for Testing Materials (ASTM) in 1925, appeared to be

the first official recognition of a titration in nonaqueous media. He added, however, that the potentiometric and indicator method for the determination of amino acids in glacial acetic acid, as outlined by Nadeau and Branchen (192), was the earliest procedure of an acid-base titration in a nonaqueous solvent to find wide acceptance. Among the first workers to titrate acids and bases potentiometrically in an aprotic solvent were LaMer and Downes (193). Using the Pt-quinhydrone electrode, these authors titrated trichloroacetic acid dissolved in benzene with diethylamine in benzene as titrant. The important paper of Lykken et al. (194) was a major contribution to the field of nonaqueous titrimetry for a number of reasons. They discussed in great detail the important characteristics and conditions needed for the potentiometric method and included leading references to previous work. Their development of the ASTM titration solvent (equal volume mixture of benzene and isopropyl alcohol containing ca.one percent water) had a most successful practical application in the determination of free acids using a glass-calomel electrode system. Their paper was among the first to report the innovations of the glass electrode and the correlation between nonaqueous and aqueous acidities.

Moss, Elliot and Hall created much interest in presenting a new approach to the problem of potentiometric titration of phenols and other weak acids (in water) by introducing the

strongly basic and anhydrous solvent, ethylenediamine (195). The titrant used was sodium aminoethoxide in ethylenediamine. Successful electrode arrangements included the hydrogen-calomel and antimony-antimony combinations. The latter arrangement was more convenient. The antimony reference electrode could be immersed in the titrant and connected electrically with the solution being titrated through the buret tip. In this way diffusion was prevented as the reference electrode was continually being flushed with fresh titrant and the liquid junction, occurring at the end of the buret tip and serving as a salt bridge, was removed with the addition of each new increment of titrant. Gran and Althin did not obtain satisfactory results, however, with the electrode arrangements of Moss and co-workers and developed a calomel reference electrode charged with ethylenediamine and saturated with calomel and lithium chloride (196). Katz and Glenn (197) used the procedure of Moss et al. successfully in the determination of the phenolic content of coal hydrogenation products. In certain instances they modified the method by replacing the antimony-antimony electrode combination by glass-autimony or glass-platinum electrodes. In either case both electrodes were placed inside the titration flask.

Ethylenediamine was chosen as solvent by Moss and co-workers with the hope that carboxylic acids would behave as strong acids while phenols, having lower acid strengths,

would act as weak acids and hence two inflection points could be obtained in the potential vs. volume-of-titrant added curve for acidic mixtures or in compounds containing two acidic components in the molecule. This situation was, in fact, realized when two abrupt potential drops were observed for the titration of resorcinol or salicylic acid corresponding to each of their acidic hydrogens. The reactions occurring in the titration of carboxylic acids in this solvent with sodium aminoethoxide could be represented by the following equations:

$$RCO_2H + H_2NC_2H_4NH_2 \longrightarrow H_2NC_2H_4NH_3^{(+)} + RCO_2^{(-)} \qquad [49]$$

$$H_2NC_2H_4ONa \longrightarrow Na^{(+)} + H_2NC_2H_4O^{(-)} \qquad [50]$$

$$H_2NC_2H_4NH_3^{(+)} + H_2NC_2H_4O^{(-)} \longrightarrow H_2NC_2H_4OH + H_2NC_2H_4NH_2 \qquad [51]$$

The neutralization reaction was pictured, therefore, as involving a proton transfer from the conjugate acid of ethylenediamine with the sodium ethoxide anion (the stronger base in solution) and a regeneration of the two free bases.

The use of ethylenediamine was also desirable from the point of view of electrode stability and faster attainment of electrode equilibrium as compared to electrometric measurements that are carried out in media of lower dielectric constant. The unattractive features of ethylenediamine as a basic solvent in nonaqueous titrations are its

corrosive nature and its tendency to pick up carbon dioxide from the atmosphere very readily. Moss and co-workers also tried diamylamine, pyridine and ethanolamine as solvents but none gave end points as distinct as those obtained in ethylenediamine.

Fritz and Lisicki (198) showed that many types of organic compounds could be determined by titration as acids in n-butylamine using both a visual end point and potentiometrically with the use of a pH meter and an antimony-glass electrode combination. Carboxylic acids, phenols, nitro compounds, enols, imides and mercaptans were adequately determined. The titrant in these experiments was sodium methoxide dissolved in benzene-methanol. It was interesting to note, that, in such a basic solvent as butylamine, the antimony electrode appeared to serve as the indicator electrode while the glass electrode was so insensitive that it acted as the reference electrode. Fritz stated that the antimony-glass electrode arrangement could not be used in benzene or benzene-methanol.

Alcoholic potassium hydroxide in anhydrous isopropyl alcohol was used by Deal and Wyld in conjunction with a glass-calomel electrode system to titrate acids in ethylene-diamine and N,N-dimethylformamide (199). The latter solvent could be used to differentiate mineral acids, carboxylic acids and hydroxybenzenes. The glass electrode had been found to be unstable and insensitive in ethylenediamine (195,200) and insensitive in butylamine (198) when titrants

containing sodium were used. The use of potassium hydroxide by Deal and Wyld resulted in reproducible potentials but difficulties were experienced in certain titrations in dimethylformamide where precipitation occurred prior to completion of the titration of dibasic or polybasic acids. Rough uncertain titration curves were a consequence of the system's behaviour. For this application a solution of tetra-n-butylammonium hydroxide (TBAOH) in isopropyl alcohol containing ten percent water was found to be superior since ammonium salts of these acids were more soluble in the organic media used and it also gave inflections in the titration curve of very weak acids which were similar in appearance to those obtained with potassium hydroxide in anhydrous isopropyl alcohol. Wyld and co-workers had reason to believe that the relatively high water content in the quaternary ammonium hydroxide titrant was counteracting any advantage of greater electrode sensitivity when this titrant was used instead of potassium hydroxide and, therefore, developed a nearly anhydrous (ca. 0.5 percent water content) form of the hydroxide by passing a solution of tetra-n-butylammonium iodide in isopropyl alcohol through an anion exchange column which had originally been converted to the hydroxide form with potassium hydroxide (201). Their speculation was well founded in that the glass electrode responded well

in ethylendiamine and pyridine with no pronounced loss of sensitivity in the highly alkaline region. An unsuccessful attempt was made to prepare the hydroxide titrant in pyridine.

Cundiff and Markunas made an extensive examination of TBAOH as titrant in several solvents for acids in a variety of nonaqueous solutions (202). They made a number of important innovations including the preparation of the titrant by reaction of tetra-n-butylammonium iodide in absolute methanol with silver oxide. The final solution consisted of benzene-methanol (9:1 by volume). A much improved electrode system was obtained through a modification of the calomel electrode by replacing the saturated aqueous solution of potassium chloride in the outer jacket with a saturated solution of the chloride in methanol. Of the basic solvents tested, pyridine was the best for use with 0.1 N TBAOH. In this solvent, the cell potentials were steadier and were reached more readily than in otherstested. In a later paper these authors found that strong or mineral acids were titrated satisfactorily only in pyridine since solvents such as certain ketones, dimethylformamide, acetonitrile and isopropyl alcohol reacted in varying degrees with the acids causing errors particularly when differentiating titrations of acid mixtures were attempted (203).

Tetramethylguanidine, a much less volatile solvent

(b.p.*ca.* 160°C.), has proved useful as a new basic solvent for the titration of weak acids (204). Good potential breaks were obtained for a series of phenols when a glass electrode was used as indicator.

A third method for the preparation of quaternary ammonium hydroxides was developed by Harlow and Wyld. The particular quaternary ammonium chloride was mixed with potassium hydroxide in isopropyl alcohol. The reaction was forced to completion because of the insolubility of potassium chloride in the solvent (205).

Some progress has been made in developing titrants in which the titrant solute is dissolved in solvents which bear resemblance to the basic medium in which the particular acid is being titrated. In this way alteration of acidic or basic properties of the medium is minimized during the titration. Van der Heijde and Dahmen (189a) prepared solutions of TBAOH and tri-n-butylmethylammonium hydroxide in pyridine but found that these bases were not stable at room temperature because of decomposition *via* a Hoffmann degradation. Storage in a refrigerator at -20°C., however, prevented any noticeable decomposition for many months. Heijde later found trimethylisobutylammonium hydroxide to be completely stable in pyridine at room temperature. He noted that this fact was in accordance with the view that substitution of alkyl chains at the β-position with an electron-releasing radical increases the stability towards bimolecular elimination of olefin (189c). Trimethylbenzylammonium hydroxide

in pyridine has been used by Patchornik and Rogozinski for acid-base titrations (206). Piperidine in dimethylformamide has been tested for titration of salicylic and p-toluene-sulfonic acids in dimethylformamide (189a).

Within the last ten years the major attention has been directed to a rather intensive inspection of quaternary ammonium hydroxides as titrants in potentiometric titrations. Included in this study have been examinations into the nature of such titrants, impurities which lead to errors in titration results, improvements in hydroxide preparation, affect of potassium ion on the shape of potential titration curves and stability of titrants.

Cluett (207) re-examined the titrant as prepared by Cundiff and Markunas (202) and concluded that it was most likely a one to one mixture of the hydroxide and the methylate.

$$2R_4N^{(+)}I^{(-)} + Ag_2O + CH_3OH \xrightarrow{CH_3OH} \underline{2AgI} + R_4N^{(+)}OH^{(-)} + R_4N^{(+)}OCH_3^{(-)} \quad [52]$$

Harlow has contributed significantly by reporting that the structure of the quaternary ammonium cation may have an influence on the titratability and apparent strength of negatively charged acids as determined by nonaqueous potentiometric titration (208).

An early indication of the impurities present in TBAOH was reported by Harlow et al. when the presence of a weaker base, probably the tertiary amine, was detected (201).

Cundiff and Markunas (209) improved the resolution of acid mixtures containing a strong acid by eliminating an impurity (unidentified) in the titrant as a result of passing the titrant through a short section of a strongly basic anion-exchange column. A very pure TBAOH reagent was prepared by Marple and Fritz by using the silver oxide process and an elaborate procedure to remove impurities which were a result of the presence of tetrabutylammonium carbonate, tri-n-butylamine and silver in anionic complex form (210). The carbonate formed as a result of silver carbonate present in the oxide but could also be introduced from exposure of the titrant to air. Its removal could be affected by either recrystallization from an aqueous solution or by passing an aqueous solution through a column of strong base anion-exchange resin. The source of the tri-n-butylamine impurity could have arisen from the use of relatively impure tetrabutyl-ammonium halides or by the decomposition of the hydroxide under certain conditions. An extraction of the amine from an aqueous solution of the hydroxide with benzene proved to be adequate. The silver impurity in the anionic complex form originated from the reaction of tetrabutylammonium salts with silver halide which precipitated on the surface of the silver oxide particles. Its effect on potentiometric titrations seems to be minor but can be eliminated by carrying out the preparation in methanol in the presence of water and then by removing any remaining amount of complexed silver in the final base

solution with a small amount of activated charcoal. Traces of alkali metal ions in quaternary ammonium titrants, which influence potentials of the glass electrode, have been removed by an anion-exchange method (211). Cundiff and Markunas made further improvements in the preparation and utilization of TBAOH by recommending the use of freshly prepared silver oxide and a low reaction temperature (212). In this manner formation of tetrabutylammonium carbonate was precluded and the solubility of silver oxide in the chilled methanol-benzene was negligible. The possibility of amine formation was also lessened by use of high purity tetrabutylammonium iodide and the low temperature.

Among the factors, studied by Harlow, that affect stability of nonaqueous quaternary ammonium titrants, were the influence of cation structure, solvent composition, water content and the temperature (213). Kinetic studies into their decomposition were also included.

THE GLASS ELECTRODE AND INVESTIGATIONS IN RELATIVE ACIDITY AND BASICITY IN NONAQUEOUS SOLVENTS

That electromotive force methods can, in principle, be applied to nonaqueous solutions for the measurements of acidity and basicity is quite apparent from the earlier discussion. The growth of their application, however, to acid-base titrations, pH standards in nonaqueous systems, acidity constants, *etc.* has been hampered because of certain practical

difficulties (87,90,95c,214).

Drifting and/or fluctuations in potential readings could be an indication that the electrodes, which are capable of functioning reversibly in aqueous solution, may be failing to do so in nonaqueous solvents. A useful summary of observations that indicate when an electrode is not behaving reversibly has been given by Kortum and Bockris (215). Popov has outlined a variety of causes for the problem of drift in electrode potentials and the slow establishment of equilibrium conditions (90). Among the reasons mentioned was the possibility that a solvolytic reaction could be slowly taking place thereby changing the activity of the ion governing the electrode reaction. The reaction of impurities with either the solute or the solvent was a further reasonable explanation. He pointed out also that the potential drift, which could be observed for varying periods of time and then ceasing, could be attributed to a slow establishment of equilibrium at the electrode surfaces.

> "The time necessary for the establishment of equilibrium usually varys in an unpredictable manner with such factors as nature and purity of solvent, nature and concentration of the 'active' ions and manner of preparation of the electrodes."

Conformation to the Nernst equation, such that the electromotive force is related to the activity of acid in solution, may not be maintained. Carefully standardized conditions for measurements are required in overcoming uncertain and often quite considerable liquid-junction

potentials which are created between the nonaqueous medium and the aqueous salt bridge around the reference electrode. Elaborate salt-bridge systems have been developed to obtain reproducible titrations of weak acids using the glass indicating electrode (210). As the water content in nonaqueous systems is diminished, the stability of the electrode system and its ability to reproduce its potential can be greatly impaired. Choice of electrodes for the reproducibility of measurements is a matter of utmost importance. There is still much conjecture over requirements for pretreatment of glass electrodes that are to be used in nonaqueous solutions. Some workers recommend that the electrode be soaked in the appropriate medium for a day or more (216,217,218). On the other hand Linnett reported from his own experience in using glass electrodes in nonaqueous titrations that the electrode should be soaked for a considerable time in an aqueous solution in order to acquire the correct degree of sensitivity and suitably low resistance to the glass membrane. It seems that the peculiar character of the swollen surface layer of the membrane becomes unfavourably affected if the electrode is used in nonaqueous media over a considerable period of time (87). In certain instances whether or not prior conditioning of glass electrodes is undertaken in the solvent in which acid-base measurements are being conducted, seems to have little effect (161).

Compared to aqueous solutions, the sensitivity of potential

measurements may be inferior in nonaqueous systems because of the high resistance between reference and indicator electrodes. This inconvenience has been circumvented in some cases by the addition of salts which are soluble in the nonaqueous medium (198,219,220). Finally, when it is necessary to find the standard potential, E^{o}, in a particular nonaqueous system, a low dielectric constant may be the cause of extensive association of salts and acids such that its determination is made difficult. One can avoid the necessity of knowing E^{o}, however, by examining relative acidity constants.

Electrode systems in nonaqueous solvents have been reviewed most thoroughly by Stock and Purdy (221), Hills (222) and Fischer et al. (223). Popov has also treated this topic briefly in his discussion (90) as well as Cruse (224). The glass electrode, in particular, has been used extensively for the study of acid-base equilibria in a variety of solvents. For aqueous solution a number of theories have been proposed to describe the mechanism by which the electrode potential develops in response to hydrogen ion activity. Certain critical experiments have clarified only recently the probable mode of potential formation (225, 226). The glass electrode has been the subject of intense examination as can be gleaned from the numerous reviews (89c,227) and books (228,229,230) that have been written.

By far the majority of these sources are taken up with a discussion of glass electrode response to hydrogen ion and/or other cations in aqueous solution but brief sections are given over to the interpretation of results and use of glass membranes in nonaqueous systems (227,89c,229a). An excellent review on the behaviour of the glass electrode in organic media has been presented by Cruse (214). Included are critical comments on such factors as dielectric constant and solvation forces, water content, gel layer and activation or formation period for the glass membrane, aging, resistance and temperature dependance.

Glass Electrode Response

Significant contributions to the development of the electromotive force method in determining hydrogen ion concentration and leading to the early growth of the glass electrode were made by Nernst (231), LeBlanc (232), Tower (233), Cremer (234), Salm (235) and Haber and Klemensiewicz (236). Szabadvary has given a useful historical survey of the development of the pH concept including these and other sources (237). A more valuable survey with reference to the use of the glass electrode has been outlined by Dole (229b). The pH function of the glass electrode was first uncovered by the biologist, Cremer, when he observed that a glass bulb, functioning as an electrode, changed its potential when immersed in solutions having different hydrogen ion content (234). Three

years later the first careful study of the electric potential developed on glass surfaces was made by Haber and Klemensiewicz (236). They constructed a glass electrode and demonstrated, by titration, that the response was in fact that of a hydrogen electrode according to the Nernst equation,

$$V = \text{constant} + \frac{RT}{F} \ln C_{H(+)} \quad , \qquad [53]$$

where V was the measured potential and $C_{H(+)}$ symbolized the hydrogen ion concentration. Extensive use of these electrodes came with the introduction of advanced instrumentation and suitable kinds of glass membranes for pH measurements (238).

A paper by Evans and Davenport outlined a potentiometric method in which the glass electrode was used for the determination of acidity of insulating oil in butanol-1 (239). The cell,

$$\text{Pt}, \; QH_2.Q \;\Big|\; \begin{matrix}0.003\text{M} \\ \text{picric acid} \\ \text{BuOH}\end{matrix} \;\Big|\; \text{glass} \;\Big]\; \begin{matrix}\text{oil sample} \\ \text{in} \\ \text{BuOH}\end{matrix} \;\Big\|\; \begin{matrix}\text{sat.KCl} \\ \text{in} \\ \text{BuOH}\end{matrix} \;\Big|\; \text{AgCl} \;\Big|\; \text{Ag}, \qquad [54]$$

was set up in which $QH_2.Q$ represents quinhydrone and BuOH depicts the alcoholic solvent. Upon addition of the early portion of the potassium hydroxide titrant, the change in potential was extremely erratic and it was only when sufficient water of neutralization had formed that uniform potential changes were observed and points of inflection in agreement with theory obtained. When potassium hydroxide was substituted by sodium butylate, no weak acid inflection point resulted and potential readings fluctuated haphazardly. Since

in this case no water could form on neutralization, the importance of the presence of a small quantity of water was clearly evident. Gemant later reported that glass electrodes could function satisfactorily, that is, reversibly to hydrogen ions, in organic solvents of dielectric constant as low as 2.3 (240). Solutions of p-toluenesulfonic acid and picric acid in xylene and dioxane were examined potentiometrically for hydrogen-ion concentration. The important work of Lykken has already been mentioned in an earlier section of this historical survey (page 73,(194)). Their paper, which included an extensive examination of numerous solvents, placed nonaqueous titrimetry with a glass and calomel electrode combination on a firm foundation. Their solvent system of benzene-isopropyl alcohol, containing approximately one percent water, not only had a successful application to petroleum lubricants but to many other materials. Recently Popovych utilized a solvent system, in which toluene replaced the benzene as used by Lykken and co-workers, in order to satisfy the need for obtaining a better insight into the apparent pH in nonaqueous solutions (241). Straight-line relationships were derived which correlated the apparent pH with acid or base concentration in the ASTM medium. The nature of the ionic dissociation was described by slopes of these lines. The magnitude of the ionic dissociation constant, the changes in the liquid-junction potentials and the primary medium effect could be discussed in terms of the intercepts. Veri-

fication of the above relationship was made for solutions of perchloric, hydrochloric, sulfuric, nitric, benzoic and acetic acids.

As more basic solvents were introduced into nonaqueous potentiometric titrimetry, difficulties were encountered by workers in obtaining a suitable response from glass electrodes especially when titrants containing sodium were used. For instance, Moss et al. reported that the electrode was unstable in ethylenediamine (with sodium aminoethoxide as titrant dissolved in the same solvent) whether filled with the usual aqueous solution or with a buffer in ethylenediamine (195). A sharp change in potential at the end point of the titration of weak acids was registered but this drifted back immediately in the direction of the original potential. Harlow, Noble and Wyld found that an anodically polarized platinum electrode was a more sensitive probe than the glass electrode in ethylenediamine when potassium hydroxide in isopropyl alcohol was used as titrant (200). Furthermore, when sodium aminoethoxide was the titrant, the glass electrode became practically useless as an acidity indicator (confirming the observation of Moss et al.) although as a reference electrode it was useful. Schaap et al. (105) commented on this problem by noting that

> "...undoubtedly the large and constant 'sodium ion error' swamps out the effects of changes in concentration of the strongly solvated (and not unusually mobile) hydrogen ions in this basic solvent."

Similar results were obtained by Fritz and Lisicki in finding

that the glass probe served as a reference in combination with an indicating antimony electrode in n-butylamine when a solution of sodium methylate in benzene-methanol was used as titrant (198). Mathews and Welch, in fact, found that the glass electrode also remained insensitive with potassium methylate in benzene-methanol as titrant and n-butylamine as solvent (242). However, Deal and Wyld found the glass-calomel electrodes to function satisfactorily for titrations of weak acids in N,N-dimethylformamide and ethylenediamine when potassium hydroxide in isopropyl alcohol was utilized as titrant (199). Suspecting that the glass membrane should be more comparable to the platinum electrode when alkali ions were absent, Wyld and co-workers began a study of quaternary ammonium titrants (199,201). In their latter paper (201) they prepared a nearly anhydrous form of tetra-n-butylammonium hydroxide titrant in isopropyl alcohol which resulted in much larger end-point inflections of weak acids in ethylenediamine and pyridine (with a glass-calomel electrode system) over that obtained with potassium hydroxide in isopropyl alcohol as titrant. The authors were not prepared, however, to wholly explain their findings on the basis of the effect of the potassium ion on the response of the glass membrane but also to differences in ion-pair association phenomena by using the different titrants. Very little information is available on the effect of 'alkali error' of the glass electrode in nonaqueous solution which is in marked contrast to the con-

siderable literature accrued on the subject in aqueous solutions. Harlow has made some contribution to this particular problem by discussing the effect of potassium ion on the shape of titration curves of weak acids in pyridine (243). Peculiar inverted inflections were observed in titration curves when potassium ion was introduced into the titration system. These were explained as a consequence of two simultaneous titrations taking place. The main one involved the expected reaction between the weak acid and the basic titrant. Here the glass electrode simply responded to the changes in hydrogen ion activity and at the end point a normal inflection was obtained. In the second case, more difficult to visualize, the glass electrode acted as the sample and a titration was assumed to occur at the tip of the probe with traces of potassium ion which contaminated the titrant.

The application of the glass electrode in liquid ammonia has been unsuccessful (244). Heyn and Bergin attributed the failure in response to a lack of equilibrium of the ammonium ion between the glass and the solution in the cell system.

$$\underset{\text{liquid } NH_3}{Pb\,\left|\,Pb(NO_3)_2 \;\; NH_4NO_3 \text{ varying concentrations}\,\right|\,\text{glass membrane}\,\left|\,NH_4NO_3\ 0.1M \;\; Pb(NO_3)_2\ 0.1M\,\right|\,Pb}\qquad\underset{\text{liquid } NH_3}{}\qquad [55]$$

The work of Tomicek and Krepelka in 1953 established conclusively that the glass probe would act as an indicator

in pyridine (245). Titrations were carried out on perchloric, formic and benzoic acids in anhydrous pyridine and the titrant used was piperidine, ammonia or diethanolamine dissolved in pyridine. In other potentiometric investigations of non-aqueous solvents Tutundzic and Putanov measured potentials of hydrogen and glass electrodes in an acetic acid-pyridine system (246). In their hands the glass electrode gave readings which were not reproducible. They also studied the acetic acid-quinoline system, however, the abstract failed to make clear whether the glass-saturated calomel electrode system was particularly suitable although the authors assumed that their potentiometric investigations, and in particular the shape of the potential-molar composition curves, could be used to examine association or compounds formed in such binary systems (247). In a later paper potentials characteristic of hydrogen and glass electrodes were observed in binary systems of acetic acid-picoline,-butidine,-collidine and - aniline (248). It was reported that the glass electrode potentials fluctuated less than those of the hydrogen electrode and that there was a faster attainment of final equilibrium values by adopting the former. The glass indicator probe has also been applied in the liquid system of diethylamine and the lower fatty acids (249).

Kozlenko has made a major contribution to our understanding of the glass membrane behaviour as a hydrogen electrode in nonaqueous media of basic character (250). For solutions

of hydrochloric acid in quinoline the following cell,

$$\text{Ag}\,|\,\text{AgCl}\,|\,\text{HCl(m) in quinoline}\,|\,(\text{glass})\,|\,\text{HCl (0.1 N in } H_2O)\,|\,\text{AgCl}\,|\,\text{Ag}, \qquad [56]$$

in which the concentration ranged from 0.1 - 0.00025 molal (m), enabled the investigator to determine the standard potential and the molal activity coefficients ($\log \gamma^*$). The slope of the curve of calculated values of $\log \gamma^*$ against $\sqrt{m}$ coincided at the limit with the theoretical slope of the limiting Debye-Huckel law. Pretreatment of the glass electrode included soaking it in water and then rinsing it with a quantity of the solution under investigation before each measurement. Measurements were also made on a cell with transport for solutions of hydrochloric acid in pyridine.

$$\text{Hg}\,|\,Hg_2Cl_2\,|\,\text{KCl (sat. in } H_2O)\,|\,\text{HCl(m) in pyridine}\,|\,(\text{glass})\,|\,\text{HCl (0.1N in } H_2O)\,|\,\text{AgCl}\,|\,\text{Ag} \qquad [57]$$

The glass electrode was connected to an aqueous calomel electrode through a system of bridges and an intermediate vessel containing a saturated solution of ammonium nitrate in pyridine. A value of the dissociation constant of hydrochloric acid in pyridine from an earlier source (119) was used to calculate the activities of hydrogen ions in the test solutions which were then plotted in the form of $-\log a_{H(+)}$ against E, the potential. The linear relationship obtained and the agreement between its slope ($\sim$58-59 mv) and the theoretical value provided the

evidence that the response of the glass electrode in a pyridine solution of an acid was that of the hydrogen electrode. Kozlenko and Miskidzh'yan (251) followed up this study with one of binary systems of acetic acid with aniline, pyridine, ethylaniline and quinoline. Their electromotive force measurements encompassed the entire composition of each component varying from zero to one hundred percent. A potassium chloride-agar-agar bridge connected the glass electrode to an aqueous saturated calomel probe. The authors noted that the potential of the glass membrane was established after a few minutes and reproducibility of the measurements was good. In each of the four cases the electromotive force -composition isotherms were of the same type. The very close similarity between the curves obtained with hydrogen and glass electrodes provided an experimental demonstration that the glass electrode could be successfully used for these measurements. Plots of $\Delta E/\Delta C$ against composition displayed rather sharp minima lying between 20 and 50 mole percent of the amine. These results were discussed in terms of an electrochemical process in which compound formation was followed by dissociation.

$$(CH_3COOH)_2 + C_6H_5NH_2 \rightleftharpoons \underset{\uparrow}{[C_6H_5NH_3^{(+)}]} \; \underset{\downarrow}{[CH_3COOH \cdot CH_3COO^{(-)}]}$$

$$[C_6H_5NH_3]^{(+)} + [CH_3COOH \cdot CH_3COO]^{(-)} \qquad [58]$$

There was an absence in the electromotive force - composition curves of any break at the equivalence point such as is

observed in the addition of bases to a strong acid because of sharp decreases in proton activity. The investigators reasoned that the dimeric acid molecule formed a compound or ion pair, for example, with aniline, which then dissociated into the anilinium ion and an acid-anion complex ion. This resulted in slow changes in proton activity and was reflected in the gradual rise in the curves. Somewhat steeper curves prevailed in binary systems of allyl mustard oil-piperidine and -diethylamine -- a consequence of the stronger bases being used (252).

The glass electrode has been found to respond satisfactorily in a number of other solvents. The deuterium ion response of the glass electrode in dueterium oxide has been investigated (253) and ionization constants of a variety of weak acids in the solvent have been determined (254). The electrode behaves as a proton electrode in hydrogen peroxide (255). A calibration of the glass electrode has been made in absolute methanol and ethanol (256). More recently, Ritchie and co-workers verified the reversibility of the glass electrode in pure methyl alcohol in their thermodynamic study of the ionization of picolinium ions (257) and bicyclo [2.2.2] octane-1-carboxylic acids (258). Acid-base equilibria in tertiary butyl alcohol was examined by carrying out potentiometric measurements with the glass electrode (220,259). The dissociation constants of weak acids varied with concentration of the acid unless a fairly high (10^{-2}M) concentration

of tetrabutylammonium perchlorate was added to keep the ionic strength constant. It was apparent that the activity coefficients of the ionic species were markedly dependent upon the ionic strength. Electromotive-force measurements in dimethyl sulfoxide (DMSO) using the system,

$$\text{glass electrode} \;\big|\; \text{HX in DMSO} \;\big\|\; \begin{matrix}\text{NaCl (sat.)}\\ \text{AgCl (sat.)}\\ \text{in DMSO}\end{matrix} \;\big|\; \text{Ag}, \qquad [59]$$

enabled Kolthoff and Reddy to substantiate results of dissociation constants of several acids (HX) with those derived from an indicator method (260). Reliable data have been furnished by the electrode in the more acidic solvents, acetic (261, 262,263,264) and formic acids (265). Cheng *et al.* made a careful examination of the 'acid error' encountered when the electrode had been exposed to a dry hydrochloric acid solution in glacial acetic acid and interpreted the results as an incorporation of the chloride ion into the surface layer of the glass membrane (264). Ionization constants of phenols have been determined in N,N-dimethylformamide by using a glass electrode filled with dimethylformamide and a calomel electrode in which the junction was made up of a saturated solution of potassium chloride in this solvent (167). A more extensive comparative study of electrode systems in dimethylformamide was made by Teze and Schaal (266). They found that the glass probe was useful for titration of a number of acids but its 'alkaline error' did not permit a

worthwhile quantitative study. An indication of complete dissociation of picric acid at concentrations of 10^{-2}M in dimethylformamide has been reported through a calibration of the glass electrode in dilute solutions of the acid (218). Acetonitrile has received much attention by workers in examining the quantitative behaviour of the glass membrane in this medium (161,179,217,267,268). The latter authors, Kolthoff and Chantooni (179,268), calibrated the electrode in acetonitrile and derived an equation for the calculation of hydrogen-ion activity in the neutralization of a weak acid with tetraalkylammonium hydroxide. Despite complications from the formation of the hydrogen-bonded acid-anion complex, $AHA^{(-)}$, from the acid (HA) and the anion ($A^{(-)}$), it was found, that at the fifty percent neutralization point, the simple equation, $pa_H = pK_{HA}$, held.

Half-Neutralization Potentials as a Measure of Relative Acid-Base Strength.

The basis of potentiometric methods involves the quantitative relationship which exists between the electromotive force of the electrochemical cell, as derived by the distribution of potential,

$$E_{cell} = E_{reference} + E_{indicator} + E_{junction}, \qquad [60]$$

and the concentration of a component under examination. The Nernst equation expresses this relationship for the indicator

electrode which is sensitive to the desired component. The junction potential, which is measured experimentally along with the two electrode potentials, is commonly assumed to remain more or less constant. It is expected that the calomel electrode will maintain a potential which is independent of the composition of the solution being measured. When these conditions are fulfilled the indicator electrode is then able to supply meaningful information about the concentration or nature of particular substances in solution. For instance, when a glass electrode is being used in combination with a reference electrode such as a saturated calomel electrode in aqueous solution (269),

$$\begin{array}{l} Ag\left|AgCl_{(s)},\ 0.1\ N\ HCl\ \right|\ glass\Big]\Big]\ \ solution\ (pH=X)\Big\| \\ \qquad KCl\ (sat.),\ Hg_2Cl_2\ \Big|\ Hg, \end{array} \qquad [61]$$

the electromotive force described by the Nernst equation takes the form,

$$E = C_1 + C_2 \log a_{H(+)}, \qquad [62]$$

where E is the measured potential of the cell; C_1 represents the constant potential term comprising the contributions from liquid junction potentials, external and internal (within the glass membrane) reference electrodes and any asymmetry potential across the glass membrane; C_2 is a constant dependent on the temperature while $a_{H(+)}$, as usual, symbolizes the hydrogen ion activity. In discussing relative acidities

the actual values of C_1 and C_2 are not needed, however, C_2 is sometimes used as a quantitative measure of how the particular electromotive force-concentration system conforms to the titration or Nernst equation.

For a typically weak acid (HX), the dissociation process in aqueous solution,

$$HX \rightleftharpoons H^{(+)} + X^{(-)}, \qquad [63]$$

has the expression,

$$K = \frac{a_{H(+)} \cdot a_{X(-)}}{a_{HX}}, \qquad [64]$$

for its dissociation constant, K. The expression describing the potential, [62], then becomes

$$E = C_1 + C_2 \log \frac{Ka_{HX}}{a_{X(-)}} \qquad [65]$$

or

$$E = C_1 + C_2 \log \frac{K [HX]}{[X^{(-)}]} \qquad [66]$$

if low acid concentrations are used and K is not taken to be strictly the thermodynamic ionization constant. In a potentiometric titration, in which the neutralization of the acid has proceeded to one half the original value, the potential equation would take the form

$$E_{\frac{1}{2}} = C_1 + C_2 \log K \qquad [67]$$

since $[HX] = [X^{(-)}]$. This latter expression describes the

proportionality which exists between the potential of the system at half neutralization and the dissociation constant in aqueous solution. A few quantitative studies have also shown the behaviour of the glass electrode to be similar in nonaqueous solutions. Calibration of the electrode in acetonitrile has been carried out by Desbarres(270) and Kolthoff and Chantooni (179,268). The potentiometric examination of Higuchi et al. has pointed out, however, that the practice of estimating the pK values of acids and bases from the pH at half neutralization as commonly done in water may not be valid in certain nonaqueous systems (262). For instance, the relative basicity of sodium acetate in acetic acid was influenced by the strength of acid (sodium perchlorate) used in its neutralization.

By far the greatest number of studies in relative acid-base behaviour have involved determination of the half-neutralization potentials of a series of acids or bases in a common nonaqueous solvent and their subsequent correlation with either the logarithm of the ionization constants in water or the Hammett sigma substituent constants. The linear relationships obtained are taken as an indication that, in this particular organic solvent, the potential at half neutralization is a measure of acid or base strength. Furthermore, such a correlation is evidence that the glass electrode is in fact measuring the activity of the hydrogen ion (in some mode of solvation) in the nonaqueous solvent otherwise linearity

would not be expected to hold. Some of these studies will be discussed later in this section but, first, it may be worthwhile to look briefly at some of the factors which influence and the care required in determining potentials at half neutralization.

Van der Heijde has treated these aspects very thoroughly in a series of papers (189) under the following major factors which influence the half-neutralization potential of acids and bases in various solvents.

"(i) The acidity and basicity of the solvent medium.

(ii) The 'intrinsic acidity' (or basicity) of the titrated acid or base.

(iii) The tendency of the ions involved in the titration towards formation of extraordinary stable complexes or insoluble salts.

(iv) The liquid junction potentials occurring at the electrode boundaries.

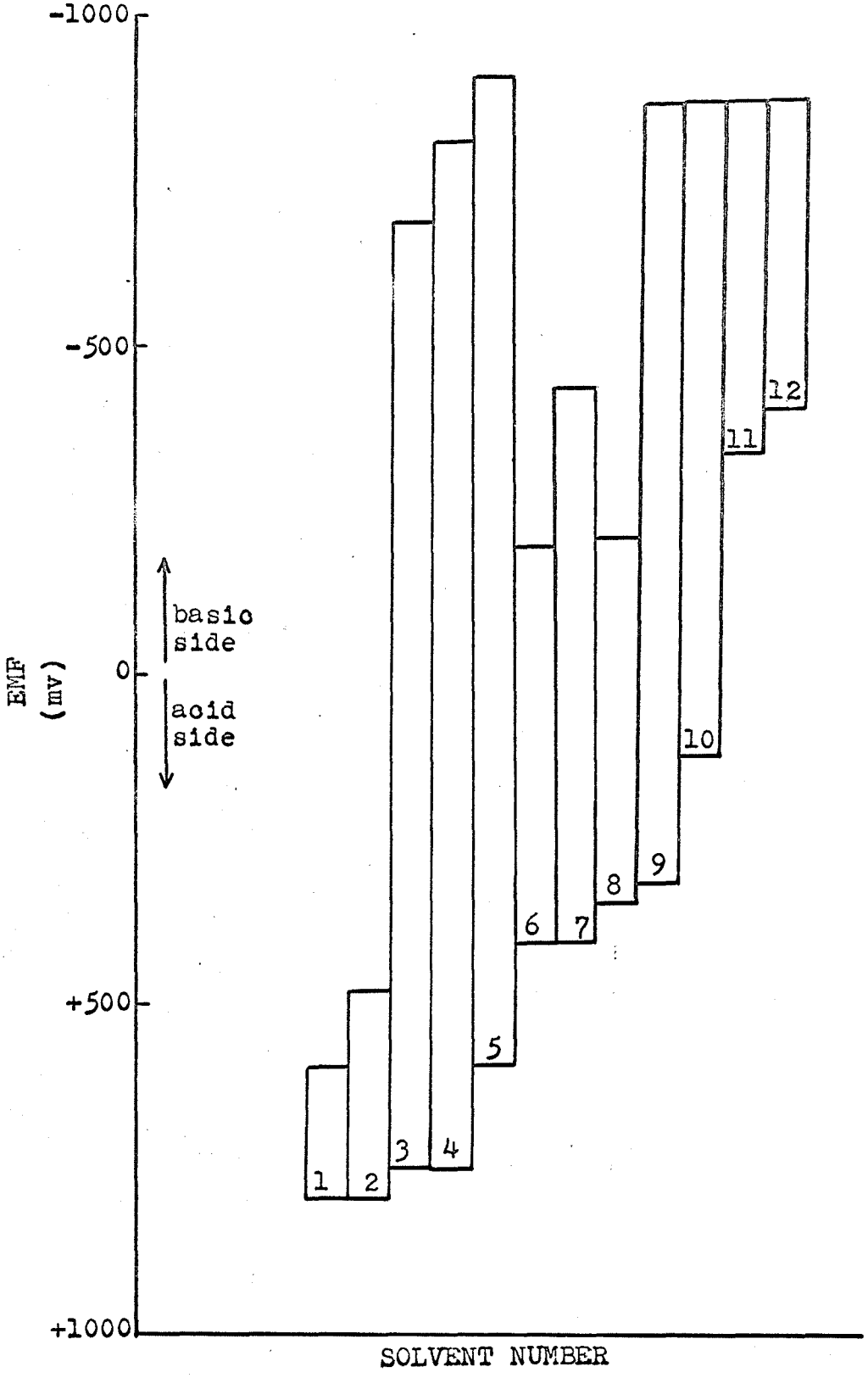
(v) The dielectric properties of the solvent medium."

The range of potential which can be measured is determined chiefly by the first factor, that is, the acidity or basicity of the solvent and can be ascertained by potentiometric titration using glass and calomel electrodes. Figure 1 shows the approximate potential ranges of twelve solvents (arranged in increasing basicity) which are considered potentially useful for titrimetry (189a). Very narrow potential ranges for the acidic solvents are noticeable. On the acidic side apparently the potential range is limited by the 'intrinsic' acid strength of perchloric acid (the strongest acid used)

FIGURE 1. The approximate potential ranges in millivolts (mv) of twelve solvents determined by glass and calomel electrode combination and arranged in order of increasing basicity. Acid or base concentrations used were approximately 0.01 N.*

1. Trifluoroacetic acid
2. Acetic acid
3. Chlorobenzene
4. Acetone
5. Acetonitrile
6. Methyl alcohol
7. Isopropyl alcohol
8. Water
9. Dimethylformamide
10. Pyridine
11. n-Butylamine
12. Ethylenediamine

* Reference (189a).


-1000
-500
0
+500
+1000
EMF (mv)
basic side
acid side
1
2
3
4
5
6
7
8
9
10
11
12
SOLVENT NUMBER

and not by the formation of the protonated solvent ions. The relatively inert solvents (3,4 and 5) possess very large potential ranges due to the fact that acids and bases are not subject to any significant levelling effect by the organic medium. In this regard methyl isobutyl ketone has been found to be an extremely versatile solvent for determining relative acidity and for resolving strong, weak and very weak acid mixtures (271). In the case of amphiprotic solvents (6,7 and 8), well reproducible limiting potentials are obtained both on the acidic and basic sides. The basicity of the tributylmethylammonium hydroxide used for the titration apparently governed the limiting potentials of basic solvents (82b). These potentials are subject to large variations with changes in the base concentration. For instance, when the concentration of the base in pyridine was approximately 0.005 N, potentials as low as -1100 millivolts (mv) could be measured but the potential of a 0.6 N solution was found to be only -200 mv. The limiting base potential for pyridine, as recorded in Figure 1 is for a 0.01 N solution of the base.

Van der Heijde and Dahmen also examined the dependency of the half-neutralization potential upon concentration (189a). Results signified the importance of using fixed concentrations of acids to be titrated when intending to determine half-neutralization potentials for comparative purposes. Factors influencing the occurrence of anomalies in potentio-

metric curves of carboxylic acids and phenols in inert and weakly basic solvents have also been discussed (189b). The anomalies described included:

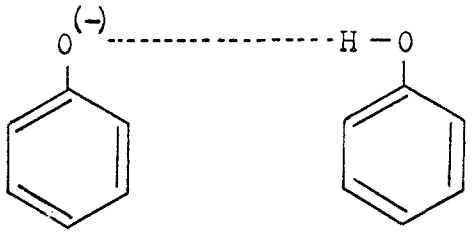
(i) additional potential rises (drops) in the region of half neutralization,

(ii) non-symmetric plateaus,

(iii) non-reproducibility of curves and

(iv) potential drops at stages of the titration corresponding to simple fractions of total neutralization (e.g. at 1/4, 1/2 or 3/4 neutralization).

It was the opinion of the author that all the abnormalities were due to insufficient solvation of the highly polar acid molecules and their ions by the inert or weakly basic solvents. In the case of factors (i) and (ii) insufficient solvation or shielding gave rise to acid-anion association and acid dimerization; adsorption of solutes onto the electrode surface was responsible for the behaviour reported under (iii) and (iv). Additional evidence for similar behaviour has been presented by Bruss and Harlow in their conductometric studies of phenols in media of low dielectric constant including pyridine (272) and their potentiometric investigation of weak acids in inert solvents such as benzene, toluene and gasoline (273). The experimental data could, in this latter instance, be accounted for by a one-to-one type of complex in which a molecule of acid was hydrogen-bonded to an anion of the acid XXXI.



XXXI

Harlow has warned of the deleterious effect of the potassium cation on the shape of titration curves (243). This is particularly important when information on relative strengths of acids is of primary interest since the mid-point potential can be shifted several hundred millivolts by traces of potassium.

One of the earliest papers to discuss the correlation between aqueous and nonaqueous acidities in utilizing the glass-calomel electrode pair combination was that of Lykken and co-workers (194). They found that the relative acid or base strengths of a series of acids and bases maintained the same order in the ASTM titration solvent consisting of benzene-isopropyl alcohol (ca. one percent water) as in water. Reasonably linear correlations were obtained for the potential at the mid-titration point of acids in the nonaqueous solvent and the pK_a in water with some slight curvature observable in the region of strong acids.

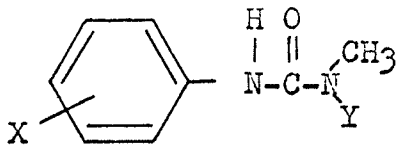
Fritz used acetonitrile as a solvent and perchloric acid in dioxane as titrant in the potentiometric titration of aliphatic amines (274). He checked to see if any relationship was present for the half-neutralization potential (HNP)

with the pK_b values of these curves in aqueous solution and found that, with few exceptions, the experimentally determined points did fall almost on a straight line. The curve showed a marked tendency to level out with amines having a pK_b less than about 6. Although there was the possibility that this could be due to a decrease in sensitivity of the indicator electrode, it was more probably a result of the levelling effect due to the acid properties of the solvent. It was interesting to note that the slope of the linear portion of the line was approximately 100 mv per pK unit as compared with a theoretical slope of 59 mv per pK unit for such a curve in water. A much more extensive examination of base strengths of amines in non-protolytic solvents was carried out by Hall (275). Potentiometric titrations of mono- and diamines were made in ethyl acetate, acetonitrile, nitrobenzene, nitromethane and 1,2-dichloroethane. Benzene, anisole, dioxane, chloroform and methylene chloride were other solvents tried with the glass-calomel electrode combination but these were unsatisfactory because of drifting millivolt readings. In order to verify the data Hall utilized the titration equation, that is, a plot of $\log \frac{X}{1-X}$ *versus* the potential reading where X is the fraction of base neutralized. Except for ethylene chloride, linear plots were attained for all other solvents. The expected theoretical slopes to each plot were not obtained. This result was reasoned to be due to a lack of constant ionic

strength which, in turn, affected the activity coefficients of the amines and the ammonium ions produced. For meta- and para-substituted anilines a quantitative linear relationship was established between the HNP and the Hammett sigma constants in water. Chatten and Harris made a further contribution to the study of relative base strengths (276). They determined the relationship between the dissociation constant, pK_b (H_2O), and HNP for a number of phenothiazines and sympathomimetric amines in glacial acetic acid, acetone, acetonitrile, isopropanol and nitromethane. Consideration was given to the influence of hydrogen bonding, steric hindrance and electrophilic groups in the solute molecules. Similar studies of bases were conducted by Streuli (277,278). Neutral and anionic bases have been shown to conform to the linear relationship between pK_a (H_2O) values and HNP in acetic anhydride (277). The slope of the neutral base line was 51 mv per pK_a (H_2O) whereas the slope of the unlevelled portion of the line corresponding to the anionic bases was 34 mv per pK_a (H_2O). Anions became stronger bases relative to the neutral substances in acetic anhydride than in water. It would seem that the lower dielectric constant of acetic anhydride (ϵ = 20.7 at 19°C.(97)) favoured the retention or, in this case, formation of an uncharged species and should, therefore, have increased the basic strength of anions in general. In his second paper (278) Streuli investigated the properties of nitromethane as a solvent for titration of

weak organic bases. The presence of intermolecular hydrogen bonding between solute species, when mono and unsubstituted amides and ureas were titrated, was evoked to explain the unusually steep pH changes in the vicinity of half neutralization. In this work use was made of the differential half-neutralization potential (ΔHNP) in correlation with pK_a (H_2O) values, a term which Streuli and Miron had introduced earlier (10). The ΔHNP value for each base was obtained by algebraically subtracting the HNP of a reference base determined on the same day from the HNP value of the compound under investigation. In this way anomalies arising from day-to-day variations in liquid-junction potentials were minimized. Reproducible results in ΔHNP were obtained within 5-6 mv while shifts in HNP of 100 millivolts over several days were not unusual.

Studies in relative strengths of acids in nonaqueous solvents by these techniques have also been prominent. A rather interesting potentiometric examination of amino acids and their N-trityl and N-benzyl derivatives in propylene glycol, chloroform, isopropyl alcohol (4:4:1 by volume with one percent water added) was undertaken by Legrand et al. (279). The values of HNP permitted the determination of the position of the trityl or benzyl substituent which was introduced into α,ω-diamino acids. Cluett studied selected substituted phenylureas (XXXII) with respect to their behaviour as acids in n-butylamine (280).



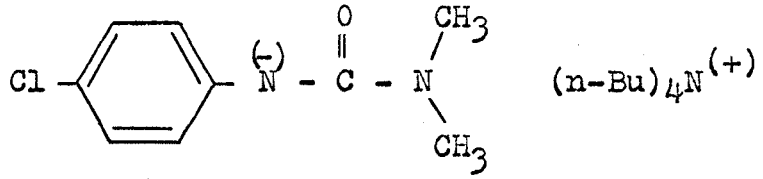
X = hydrogen or chlorine

Y = hydrogen or alkyl

XXXII

Tetra-n-butylammonium mixed hydroxide-methoxide in 9:1 benzene-methanol was used as titrant. Their electrode system consisted of a glass and saturated potassium chloride methanol-modified calomel. In aqueous solution it would be reasonable to assume that these substituted ureas would exhibit an extremely low and probably immeasurable acid strength. The author applied the potentiometric titration data in n-butylamine to the usual titration equations for acids in water. The theoretical relationship between the electrometrically determined acidity (potential) and the logarithms of the ratio of the concentration of the conjugate base of the acid and the free acid ($\log \frac{X}{1-X}$) is linear in the case of weak acids. The linear relationship for strong acids in water exists between the measured potential and the logarithm of the reciprocal of the acid concentration ($\log \frac{1}{1-X}$). The more acidic ureas (XXXII), namely, X = p-Cl, Y = CH_3; X = 3,4-diCl, Y = CH_3; and X = 3,4-diCl, Y = C_2H_4OH, conformed to the first equation. Compared to the theoretical slope of 59 millivolts for weak acids in water, the respective slopes

of the linear equation were 68,50 and 52 mv. Also tested were benzoic, hydrochloric and perchloric acids. The data for perchloric acid fitted precisely the relationship reserved for strong acids while, in the case of hydrochloric acid, curvature was observed when plots of both the log $\frac{1}{1-X}$ and log $\frac{X}{1-X}$ scales were made. This would be the behaviour expected of an appreciably but not completely ionized acid in water. A very slight curvature was apparent on the log $\frac{X}{1-X}$ scale for benzoic acid, indicating that this acid was only slightly ionized in the basic solvent. In addition, the HNP values obtained for ureas substituted with chlorine in the phenyl group were correlated with Hammett sigma values reasonably well, giving further evidence that the glass electrode was measuring the activity of the hydrogen ion in n-butylamine solutions. Accompanying the potentiometric titrations were other studies of conductance and spectrophotometric measurements. These were useful in classifying the nature of ionic species present in solution during the titration. It was concluded that the reaction between the titrant and the ureas resulted in the formation of an electrolyte (XXXIII) existing primarily as ion pairs but building up to more complex triple ions, etc. at higher concentrations.



XXXIII

Acidic behaviour of substituted phenols has also been examined by a number of workers (281,282,283). Crabb and Critchfield discussed two methods of defining the differentiating quality of nine of the more commonly used solvents for titrating mixtures of phenols (281). One technique had been described by Streuli (10) in which ΔHNP (solvent) versus pK_a (H_2O) curves were utilized. The best solvent investigated for purposes of differentiation, as determined by the magnitude of the slope of the curves, was tert-butyl alcohol. A glass indicator electrode and a calomel (saturated tetrabutylammonium perchlorate in methanol) reference electrode pair were used by Crabb and Critchfield in their experiments. It is interesting to note the changes that occurred in the slope of ΔHNP (solvent) versus pK_a (H_2O) curves. The values followed the sequence:

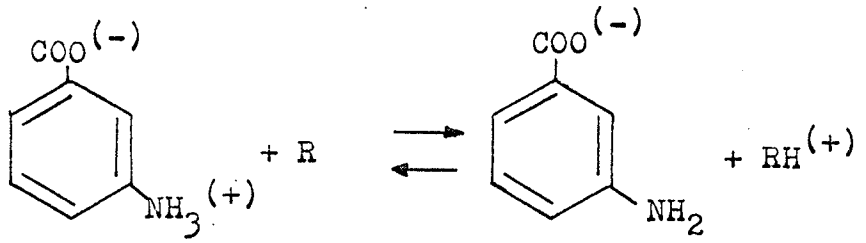
t-butyl alcohol > pyridine ~ tetrahydrofuran > 2-propanol > dimethyl sulfoxide > acetone > acetonitrile > ethylene glycol > water

The slopes for the first and last mentioned solvents were 157 and 57 respectively. A second method involved the measurement of the magnitude of the potentiometric break for the stronger acid when an equimolar mixture of two phenols having similar pK_a (H_2O) values was titrated. Relative acidities of hydroxy-aromatic compounds in pyridine were investigated by Streuli and compared to aqueous acidities (283). Unusual steepness in the titration curves in pyridine

was displayed by the very weak phenols. Recalling the conductometric work of Bruss and Harlow (272), in which unhindered phenols were shown to associate extensively by hydrogen bonding in pyridine, Streuli reasoned that the titration behaviour he observed might also be related to this phenomenon. The titration curves also illustrated the considerable enhancement of acidity of phenols relative to carboxylic acids when titrated in pyridine. For instance both o- and p-nitrophenol were apparently stronger acids in pyridine than was benzoic acid where pK_a values in water are 7.17, 7.15 and 4.19 respectively at 25°C.(126a).

Potentiometric studies on relative acidities of aromatic acids have been no less prominent. Miron and Hercules contributed significantly by correlating structural properties of acids in a variety of nonaqueous solvents (9). Linear relations of ΔHNP with pK_a or Hammett's sigma substituent values were established in pyridine, acetonitrile, 4-methyl-2-pentanone, 2-nitropropane, o-nitrotoluene, nitrobenzene, N,N-dimethylformamide, chlorobenzene and bromobenzene. Deviations in these plots by m-aminobenzoic, p-aminobenzoic, p-methylbenzoic and p-nitrobenzoic acids were explained in terms of equilibria or resonance considerations. Meta-aminobenzoic acid (MABA) showed a consistently negative deviation in plots of ΔHNP *versus* pK_a, particularly in solvents of low dielectric constant and this gave indication that the acid was behaving as a stronger acid relative to other acids being

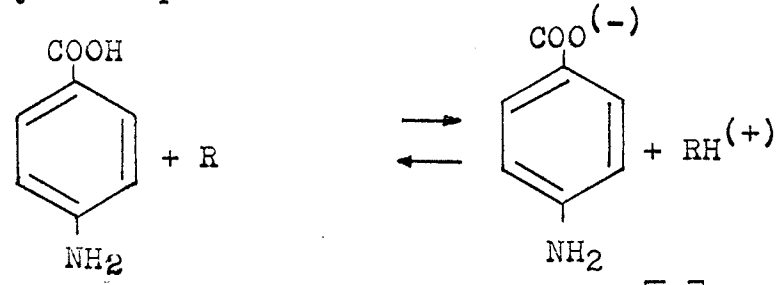
titrated in the same solvent. On the other hand the para derivative showed no significant deviation in a similar plot. From studies of apparent molal volumes in aqueous solution it had been suggested that MABA exists largely in the zwitterionic form (284). Furthermore, Miron and Hercules found that the acid was insoluble in several of the low dielectric solvents in which p-aminobenzoic acid (PABA) was soluble. Equipped with this evidence they felt that the ionization of MABA should be represented by



[68]

R ≡ solvent

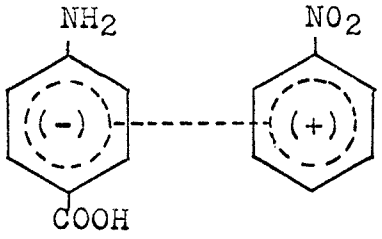
while the ionization of the para isomer could be described by the equation



[69] .

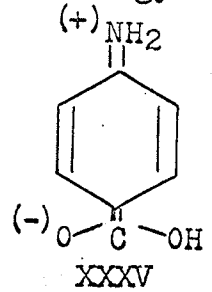
The process depicted by equation [68] involves very little additional charge separation in the unprotonated acid compared with the protonated acid but with the para isomer (or all other acids for that matter) a complete separation of charge must occur when the molecule ionizes. They argued

that MABA should tend to show stronger acidity relative to other acids as the dielectric constant of the solvent is reduced because ionization would be easier. The data further favoured this explanation since MABA displayed approximately normal behaviour in solvents of high dielectric but increased acidity in solvents of low dielectric constant. Large deviations from normal behaviour were exhibited by PABA for plots of Δ HNP *vs.* σ in the solvents 2-nitropropane, 2-nitrotoluene and nitrobenzene. A charge transfer complex (XXXIV),



XXXIV

if formed, between the amino acid and the nitro compound could cause the acid to increase in relative acidity in such solvents. The 'positively' charged ring of an aromatic nitro compound would tend to maintain the negative charge on PABA (created by electron release of the amino group) within the ring and to reduce the contribution of structures like XXXV to the ground state energy of the molecule.



XXXV

In a more thorough study of the relative acidity of acids in pyridine, Streuli and Miron included a large number of o-, m- and p-substituted benzoic acids as well as aliphatic mono- and dicarboxylic acids (10). With the exception of formic acid, all the carboxylic acids gave titration curves which were qualitatively characteristic of weak acids. It is interesting to note that the relationship of ΔHNP against σ for m- and p-substituted benzoic acids in pyridine established by Miron and Hercules (slope = -147 mv/σ)(9) compared favourably with the value (-151 mv/σ) that could be calculated from the data obtained by Streuli and Miron in their study. Similar experimental conditions were followed in each case including use of the glass and calomel electrode system, the latter being modified in that a saturated methanolic potassium chloride solution replaced the usual aqueous salt bridge. The ortho-substituted benzoic acids also showed a linear relation between ΔHNP (pyridine) and pK_a (H_2O) but the relation was not the same as that for the meta- and para-substituted isomers. In fact most of the ortho acids seemed to become relatively weaker in pyridine than in water, if the line describing the relationship of the relative acidities of meta- and para-substituted benzoic acids in pyridine and water was taken as the normal criterion, and on the basis of ΔHNP values, they approached the corresponding para isomers in acidity. The implication drawn by the investigators was that the 'ortho effect' worked less

effectively in pyridine and that changes in acidity of the substituted benzoic acids may be attributed primarily to inductive and electronic effects. Salicylic and anthranilic acids, however, constituted notable exceptions since both were stronger acids in pyridine than in water. These results were ascribed to an increase of acidity by anion stabilization through intramolecular hydrogen bonding and possible existence of a zwitterionic form for salicylic and anthranilic acids respectively. Cundiff and Markunas had made an earlier observation in their potentiometric titration of o-, m- and p-hydroxybenzoic acids in pyridine that the ortho-hydroxy acid gave only a single inflection representing the carboxyl group whereas the meta and para isomers gave two well defined inflections (202). By having the carboxyl and hydroxyl groups in a favourable orientation, internal hydrogen bonding evidently causes one of the hydrogens (COOH) to become more acidic while the other decreases in acid strength to the point where addition of further titrant is without effect. Certain dibasic phenols have also exhibited similar titration behaviour in toluene (273) and ethylenediamine (285). Even in the very basic n-butylamine the phenolic group of salicylic acid is only weakly acidic, however, two inflections are observed (antimony-indicator electrode and glass probe as reference). In this latter solvent the hydroxyl group of p-hydroxybenzoic acid became sufficiently acidic so that it

was determined together with the carboxyl group in a single neutralization point. Two neutralization points corresponding to both acidic protons of salicylic acid are also obtainable in ethylenediamine (195). In the case of anthranilic acid the interpretation given by Streuli and Miron (10) for its relative position of acidity in pyridine differed with that offered by Moss et al., (195). The latter workers had used ethylenediamine as solvent and found that amino acids, including anthranilic and p-aminobenzoic, behaved as typically unsubstituted carboxylic acids. The strongly basic amine suppressed the ionization of the amino group to the extent that the buffering effect of this group was completely eliminated.

The acidic behaviour of salicylic acid in nonaqueous solvents has continued to receive special attention by investigators. Simon included an examination of salicylic and substituted salicylic acids in his exhaustive study of determining the apparent acidity constants of numerous acids and bases in the system methyl cellosolve, (MCS-$CH_3OCH_2CH_2OH$)-water (80:20 percent by weight, ϵ = 32.0 at 25°C.(286)), using a glass and calomel electrode combination (286). At half neutralization the apparent pH of the solution was assumed to be equal to pK^*_{MCS}. Correlations of pK^*_{MCS} values with the corresponding pK_{H_2O} values for o-, m- and p-substituted benzoic acids were established in which meta and para isomers were grouped satisfactorily together in one regression line

and the ortho compounds into another. As was true in pyridine (10) the ortho isomers were relatively weaker in MCS than in water when compared to the meta- and para-substituted benzoic acids. Salicylic acid once again proved an exception by deviating from the line formed by all other ortho-substituted acids. The position of the point representing anthranilic acid did not seem to deviate significantly from the drawn line but, without the actual data available in the paper, it was difficult to say this with much certainty. The pK^*_{MCS} values for substituted salicylic acids (3-OH, 4-OH, 5-OH, 4-NH_2, 4-CH_3, 4-OCH_3, 4-C_6H_5CONH, 5-Br and 5-Cl) were also determined and related to sigma substituent constants. Recorded in Table V are reaction constants for acid-base equilibria in MCS compaired to results in aqueous solution.

TABLE V

REACTION CONSTANTS, RHO, FOR ACID-BASE EQUILIBRIA IN METHYL CELLOSOLVE (MCS) AND WATER AT 25°C.[a]

Monosubstituted Acid	rho (MCS)	rho (H_2O)
Phenol	2.56	2.113[b]; 2.23[c]
Benzoic	1.68	1.000
Salicylic	1.80	1.103[b]; 0.889[d]

[a]Taken from reference (36) unless otherwise noted.
[b]Reference (22).
[c]Reference (23).
[d]Reference (287).

Only the simple Hammett equation was used in correlating the salicylic acid data in MCS and no attempt was made to utilize an extended form of the relationship in order to investigate the relative importance of chelation in acid strength.

The effect of intramolecular hydrogen bonding on the relative acidities of substituted salicylic acids has been put on a more quantitative basis by the imaginative potentiometric study carried out by Dunn and Penner (11). The HNP of fifteen 4- and 5-substituted salicylic acids were determined in benzene solution and compared to the parent acid, salicylic, in order to arrive at $\triangle$HNP values for each acid investigated. Because of the possibility of an intramolecular hydrogen bond affecting the acidity of the carboxyl group, the influence of substituents in the 4 and 5 positions by two paths was examined by utilizing an extended form of the Hammett equation first proposed by Jaffe (22,47). A substituent could act by a 'direct' route through the carboxyl group and conceivably by an 'indirect' one through the phenolic group via the intramolecular hydrogen bond. In its most general form the Hammett equation expresses the total effect of a substituent on the ionization constant of a substituted salicylic acid with three terms.

$$\log \frac{K}{K_o} = \rho_1\sigma_1 + \rho_2\sigma_2^- + \rho_3\sigma_1 \qquad [70]$$

In the above expression K and Ko have their usual significance. The usual or 'direct' substituent effect found in benzoic acids is described by the first term ($\rho_1\sigma_1$). The second term represents the effect of the same substituent on the acidity of the phenolic group. In this case ρ_2 measures the susceptibility of the ionization constants of salicylic acid to influences by way of the chelate hydrogen bond. The term, $\rho_3\sigma_1$, is the contribution of the substituent effect to the basicity of the carboxylate ion which in term affects the hydrogen bond strength. Since processes occurring at the carboxyl group are represented by the first and third terms, equation [70] reduces to

$$\log \frac{K}{Ko} = (\rho_1+\rho_3)\sigma_1 + \rho_2\sigma_2^- \qquad [71]$$

From the evidence presented earlier in this section it is clear that ΔHNP should be a measure of electronic influences on the carboxyl group produced by the 4 and 5 substituents in salicylic acids. The relationship then becomes

$$\Delta\text{HNP} = \rho'\sigma_1 + \rho_2\sigma_2^- \quad . \qquad [72]$$

Dunn and Penner found that the measured potentials gave a significantly better correlation with the extended form of the Hammett equation [72] than with the simple Hammett expression,

$$\Delta\text{HNP} = \rho_1\sigma_1 \quad . \qquad [73]$$

In benzene the ratio, $\rho_2/\rho_1 = 0.4$, indicated that between a third to one half of the substituent effect was transmitted to the carboxyl group through the phenolic linkage. This behaviour of substituted salicylic acids in benzene-methanol was interestingly compared to the ionization constants in water previously determined by Dunn and Kung (287). In aqueous solution ρ_2 was very small and $\rho_2/\rho_1 = 0.1$, suggesting that electronic effects of substituents transmitted through the phenolic hydroxyl group were of much less importance in aqueous solution than in the non-aqueous system.

In summing up it may be definitely stated that investigations of acid-base behaviour in nonaqueous solvents have accelerated enormously within the last two decades and the accomplishments in this field have been so significant that future work holds much promise. The development of practical or analytical applications has held sway up until only recently but more and more workers are concentrating their efforts on the theoretical implications of their studies in acidity and basicity in organic media. The approaches to problems that arise are being creatively examined by numerous techniques. Included among these are potentiometric methods in which the glass electrode is utilized as an indicator probe. The reversibility of the glass membrane in numerous organic solvents has been well documented but there are enough anomalies, difficulties in the interpretation of results,

as well as the intriguing problem of theoretically explaining its behaviour and response, that investigators have far from exhausted an examination of this field. It is perhaps in the area of relative acidity and basicity correlations in organic and aqueous solutions that the most attractive work has been carried out. In particular, workers have been able to make interesting inferences from data as to the species present in nonaqueous solvents.

C. DECARBOXYLATION

INTRODUCTION

A number of areas of chemistry have profited immeasurably through the use and study of the process of decarboxylation. Degradative and synthetic procedures in organic chemistry have been aided by its implementation. Physical chemists have used decarboxylation techniques in their fundamental studies of reaction kinetics in solution. An extension of this work followed in the development of mechanistic studies of the decarboxylation process particularly by thermal and catalytic means. Success in this direction has given impetus to investigations of the mechanism of enzymic decarboxylative reactions in the biochemical field.

Decarboxylations of organic acids have been studied in the solid (288), melt (289,290), gas phase (291), aqueous (3,292) and nonaqueous solution (2,5) and have been carried

out by a number of procedures. Included among these are anodic (293), metal-catalyzed (294,295) and photochemical (296,297) methods. Enzymic reactions have been observed to be the cause of numerous biochemical decarboxylations (298). The most extensive studies have been made in acid- and base-catalyzed and thermal decompositions, reviews of which have been made by Brown (299) and Kosower (298). Work in non-aqueous solvents has picked up considerably within the last 15 to 20 years. Other reviews have also appeared (300, 301, 302). Some consideration of decarboxylation is also found in standard works (51c, 52b, 303), the latter author stressing steric requirements in these decompositions.

Evidence has accumulated to show that decarboxylations may occur either by a unimolecular or by a bimolecular mechanism. Since protodecarboxylations can be considered to be essentially a replacement of the carboxyl group by hydrogen, the following formulations of electrophilic substitution have been put forward (299,304,305) analogous to the original terminology used in aliphatic nucleophilic substitution reactions.

S_E1

(a) $RCO_2H \longrightarrow HR + CO_2$ [74]

$(H^{(+)}RCO_2^{(-)})$

(b) $RCO_2^{(-)} \longrightarrow R^{(-)} + CO_2$ [75]

S_E2

(a) $RCO_2H + H^{(+)} \longrightarrow HR + CO_2 + H^{(+)}$ [76]

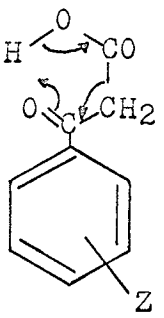
(b) $RCO_2^{(-)} + H^{(+)} \longrightarrow HR + CO_2$ [77]

Electrophilic substitution by a unimolecular process designated as S_E1, can conceivably occur by the decarboxylation of the free acid molecule (or zwitterion) or anion. The symbol S_E2 is used to describe the electrophilic replacement by a bimolecular mechanism. The process depicted by S_E1(a) could be envisaged to involve heterolytic fission in which the R group departed without its electron pair (forming a carbonium ion) and the hydrogen split off as a hydride ion. There are apparently no cases in which hydrogen gas is evolved as one of the reaction products, thereby pointing out that hydride ions are not involved in decarboxylations in protic solvents. Experimentally what is found is that in cases where either the anion or zwitterion decarboxylate unimolecularly, the process involves the R group as a carbanion intermediate.

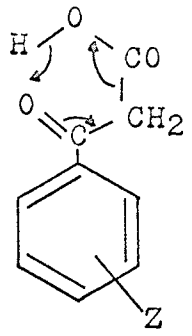
$$R\text{-}C(=O)\text{-}O^{(-)} \longrightarrow R^{(-)} + CO_2 \xrightarrow[H^+]{\text{solvent}} R - H \qquad [78]$$

Occurrences of intramolecular hydrogen bonding of the free acid prior to decomposition are sometimes difficult to distinguish from purely zwitterionic forms.

A rather interesting study was made by Swain in which substituent effects were used in order to differentiate between proton (XXXVI) and hydride (XXXVII) transfers in the decarboxylation of substituted benzoylacetic acids in benzene at 50°C. (306).



XXXVI



XXXVII

In an earlier paper (307) Swain pointed out the theoretical reasons for expecting the magnitude of the substituent effects on the hydrogen isotope effect, k_H/k_D, to be large for proton transfers, increasing markedly on introduction of electron-attracting substituents, but to be much less sensitive to substituents for hydride transfers. If hydride transfers were involved, the two electrons contributed by the hydride and accommodated in the molecular σ orbital of lowest energy would help to cement the three nuclei (O...H - O) together in a strong, short, highly covalent and relatively non-polarizable bond. On the other hand proton transfers have greater distances and more polarizable bonding between hydrogen-bonded atoms because anti-bonding orbitals are occupied.

The largest isotope effect, 2.8, was recorded for the m-nitro substituent (in toluene) followed by k_H/k_D values of 1.7 for p-chloro, 1.4 for the unsubstituted, 1.2 for the p-methoxy and 0.85 for the p-methyl substituted acids all in benzene solution. The apparent anomaly in the relative position of the p-methoxy compound was attributed to an interplay of inductive and resonance effects. The results are in accord with a transition state in which hydrogen is much more loosely

bonded than in the ground state for the m-nitro compound but is more tightly bound in the transition state than in the ground state for the p-methyl substituted acid. That this large variation in isotope effect reflects a variation in transition state rather than in the ground state is assured from the fact that these substituents have negligible effect on hydroxyl frequences in the ground state. Furthermore, the large variation in isotope effect with substituents is inconsistent with a cyclic hydride transfer but in accord with a cyclic proton transfer mechanism.

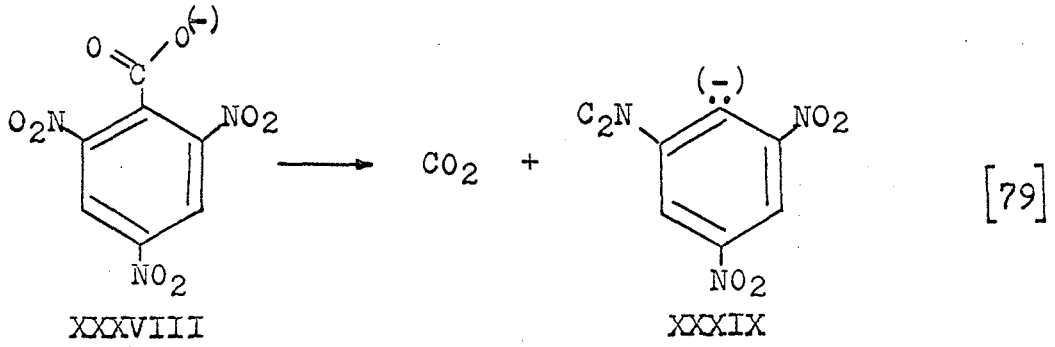
Accepting XXXVI from the evidence of substituent effects on the hydrogen isotope effect, one can then ascribe the low reactivity of the m-nitro compound to the relatively low electron density on the keto oxygen (due to the electron-deficient carbonyl carbon) which, as a base, attacks the proton. Although the authors did not attempt one, a Hammett plot of the logarithm of the first order rate constants ($\log k_H$) against sigma did, in fact, yield a straight line with negative slope ($\rho \cong -1.5$). The $\log k_H$ value for m-nitrobenzoylacetic acid was not included in the plot because it was determined in toluene.

Overwhelming evidence for the decomposition of the free acid molecule by a unimolecular mechanism has not as yet been presented. One fact is apparent in that the activation energy for the fission of the carbon-carbon bond is decreased by prior formation of the anion. A considerable amount of experi-

mental evidence has been obtained to convincingly demonstrate that the S_E1 mechanism proceeds through a form containing the carboxylate anion group or at least the carboxyl group hydrogen bonded internally to a basic moiety in the molecule.

Among the best examples of aliphatic acids that decarboxylate by an $S_E1(b)$ mechanism are trihaloacetic acids. In contrast to acetic acid, which is relatively stable to decomposition, these negatively substituted acids reduce the activation energy for the heterolytic fission of the carbon-carbon bond sufficiently to enable decarboxylation to proceed at temperatures well below 100°C. The evidence has been summarized by Brown (299).

The relative ease of decomposition of the 2,4,6-trinitrophenyl carboxylate anion (XXXVIII) was attributed to the carbanion (XXXIX) stability, as the electron-withdrawing groups could conjugate with carbon 1 assisting in the negative charge dispersal.



XXXVIII XXXIX [79]

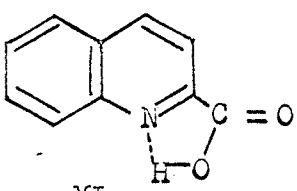
Rates of decarboxylation of 2,4,6-trinitrobenzoic acid have been studied in aqueous solution (308), in ethanol (309) and in dioxane-water mixtures (310). In the latter two systems

evidence was provided to show that the trinitrobenzoic acid decarboxylated in the carboxylate form. That the 2,4,6-trinitrophenyl anion is a relatively stable entity is supported by the observation of deuterium exchange of trinitrobenzene in alkaline ethanol solution (311) and by the fact that electron-withdrawing substituents (-F,-CF_3) in the ortho position facilitate formation of phenyl anions (312).

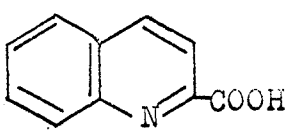
Examples of the S_E1(a) mechanism can be found by examining the case in which the acid molecule is able to exist as the zwitterion. Brown (299) has pointed out that the activation energy needed for decarboxylation of a zwitterion could be predicted to be less than that for the corresponding acid anion on electronic grounds, thereby anticipating the rate constants for the S_E1(a) process to be greater than for the S_E1(b) or purely anionic decomposition.

Nitrogen-containing acids of the α-amino type, such as picolinic, quinaldinic and isoquinaldinic acids, have been extensively studied by Brown, Hammick and co-workers (313,314, 315,316). First order kinetics were observed in the decarboxylation of quinaldinic acid in quinoline.

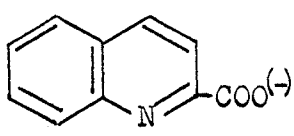
Evidence was presented to decide, qualitatively at least, between the possible species of acid (XL,XLI,XLII, XLIII) in quinoline that could lose carbon dioxide.



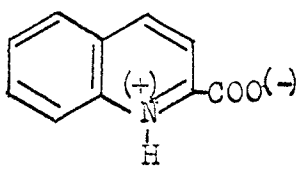
XL



XLI

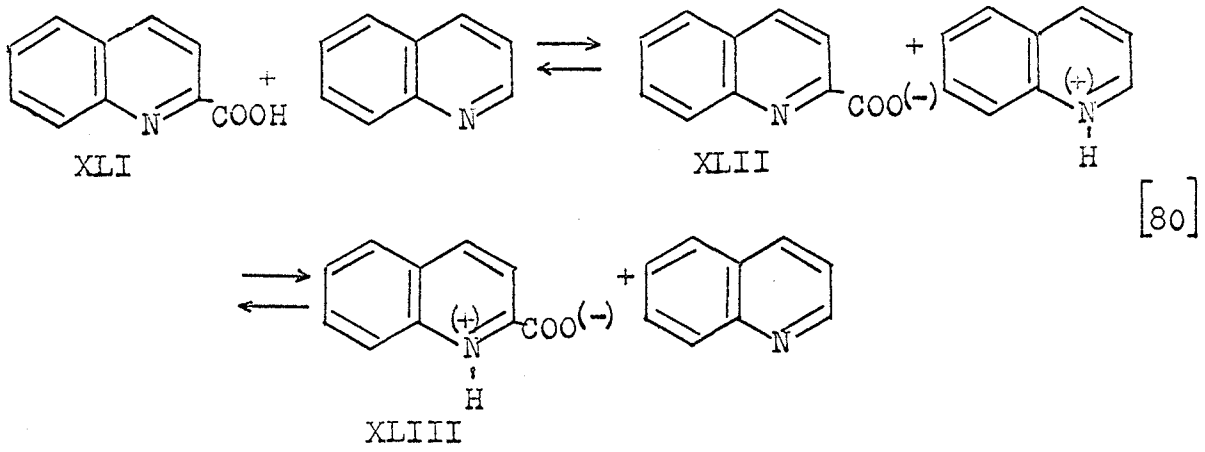


XLII



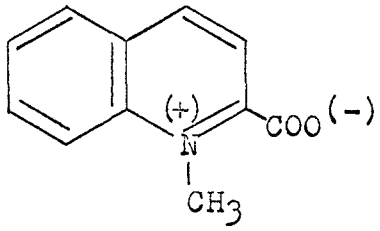
XLIII

Structure (XL) was discounted mainly from an examination of scale drawings, that gave an indication that such hydrogen bonding was unlikely to occur, rather than from any chemical evidence. The following equilibria were proposed to exist in solution.



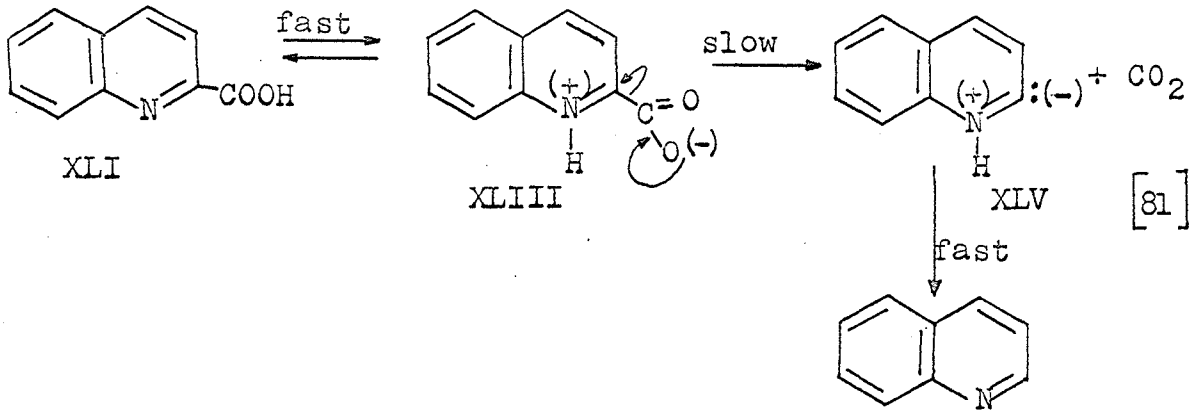
XLI XLII XLIII [80]

Addition of the acid in the form of the hydrochloride of XLI or as quinolinium chloride would be expected to increase the concentration of the free acid (XLI), or the zwitterion (XLIII) and decrease that of the quinaldinate ion (XLII). An increase in rate is produced by the addition of hydrochloric acid but is not directly proportional to it, falling off as the quinoline hydrochloride concentration increases - - a feature expected for a dissociation phenomenon (316). They also observed that the methyl betaine, 1-methylquinolinium-2-carboxylate (XLIV), which could not tautomerize to a non-zwitterionic form analogous to XLI, decomposed relatively rapidly, demonstrating that the analogous zwitterion (XLIII) and not the undissociated acid (XLI) would very likely undergo decarboxylation.



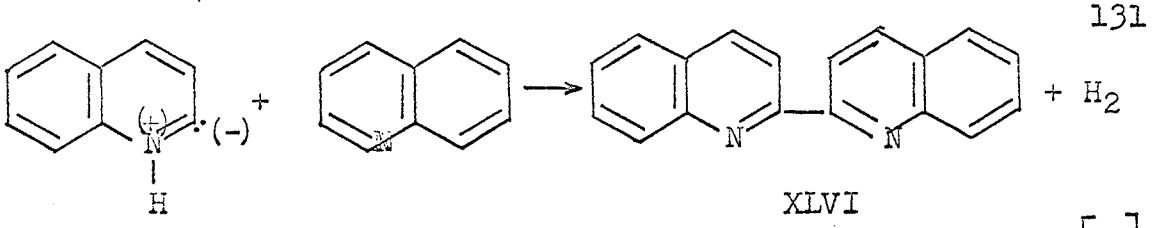
XLIV

The foregoing could most reasonably be represented by the following mechanism in which the dipolar-ion tautomer or zwitterion (XLIII) in equilibrium with the acid (XLI) was undergoing decomposition through the carbanion intermediate (XLV).



XLI XLIII XLV [81]

The existence of the ∝-quinolyl carbanion intermediate (XLV) was supported by the fact that, in carrying out the decarboxylation in such reagents as aldehydes, ketones, quinoline and aromatic nitro compounds, one could isolate from the reaction mixtures other substances, an example of which is given by ∝, ∝'-diquinolyl (XLVI).



XLVI

[82]

Decarboxylation of beta-keto or dicarboxylic acids affords an instance in which an acid may simultaneously decompose through both the anionic and zwitterionic or hydrogen-bonded forms of the free acid.

One of the most recent investigations involving this situation was outlined by Hall and Hanrahan (317) in their study of the kinetics of decarboxylation of phenylmalonic acid and its monosodium salt in water as a function of pH and in dioxane-water mixtures as a function of solvent composition. In aqueous solution decarboxylation of phenylmalonic acid may take place through one or more of the undissociated acid, the monoanion and the dianion species. The latter possibility was rejected because disodium phenylmalonate showed no appreciable decomposition in boiling water over a 24-hour period. The location of the maximum in the rate-pH curve and the variation of the rate with pH were explained by resolving the data into individual rate constants for the simultaneous decomposition of the undissociated acid and the monoanion -- the rate expression taking the form:

$$\text{rate} = k_1 \left[H_2A\right] + k_2 \left[HA^{(-)}\right] \qquad [83]$$

where k_1 is the first-order rate constant for the decarboxylation of the undissociated acid, H_2A, and k_2 is the first-order rate constant for the decomposition of the monoanion, $HA^{(-)}$. The monoanion decarboxylated 5-6 times as fast as the undissociated acid making phenylmalonic acid represent an intermediate condition between the extremes of malonic acid (318), where $k_1 \approx 10k_2$, and dibromomalonic acid (319), where $k_2 >> k_1$.

A comparison of entropies of activation of malonic and phenylmalonic acid in 100 percent water and 80 percent dioxane showed that the undissociated acid species had a more negative entropy of activation than the monoanion indicating a greater degree of ordering in the transition state than in the initial state. These data were consistent with the proposed mechanism which postulated the formation of an intramolecular hydrogen bond in the transition state somewhat similar to the structure (XL) in the transition state of decarboxylation of β-keto acids (see page 128). It would seem that an acid which has an intramolecular hydrogen bond in the initial state would correspondingly have a smaller negative entropy of activation. Intramolecular hydrogen bonding is energetically favoured in the monoanion as compared with the undissociated acid and the former should, therefore, have a less negative $\Delta S^{\ddagger}$ than the latter. The change in reaction experienced with solvent composition is often difficult to assess and does not show any systematic variation as

is the case in most mixed solvent systems (320). Rate maxima, like the one occurring in 50-80 percent dioxane in this work, have been explained as an effect of the organic solvent favouring the chelated form coupled with some assistance by water molecules in solvating partial charges in the transition state (306).

The vast accumulation of information on the decomposition of acids by a unimolecular mechanism has tended to lend support to the empirical rule, noted by Brown and Hammick originally (316), that the carboxyl group is usually in the anionic form before decarboxylation.

It is only within the last twenty years that decarboxylation by a bimolecular mechanism (S_E2) has been firmly established. In the possibilities noted earlier for bimolecular kinetics (equations [76] and [77]) the rate is, in either case, dependent on the attraction between a proton and the carbon atom alpha to the carboxyl group. Reaction generally occurs at an unsaturated carbon atom, thereby allowing the new carbon-hydrogen bond to form completely in the rate-determining step without the necessity for a simultaneous breakage of the carbon-carbon bond. We should also expect C-H bond formation to be favoured by electron-donating substituents and aromatic rings bearing such groups bonded to the β carbon of the carboxylic acid. A more common and favourable situation would be to have the α carbon itself part of the aromatic ring system. Molecular structures

of this type would be expected to disperse the positive charge of the carbonium ion intermediate and presumably the transition state leading to it.

An S_E2 mechanism for protodecarboxylation was first proposed by Schenkel and Schenkel-Rudin (305) as they showed qualitatively that 9-anthracenecarboxylic acid decomposed more rapidly in acidic solvents (chloroacetic and sulfuric) than in basic (7,8-benzoquinoline) or neutral solvents. This was in direct contrast to picolinic acid whose decarboxylation was facilitated by basic solvents (321). Anthracene-9-carboxylic acid possessed certain structural features that could accommodate a bimolecular decomposition. The α carbon, being in the 9 position, is more reactive to electrophiles because of its relatively high electron density. Furthermore, the carboxyl group in this position is sterically compressed by the peri-hydrogen atoms (322).

Some of the earliest quantitative evidence for a bimolecular mode of attack in decarboxylations was put forward by Schubert and his co-workers (323,324) in their study of mesitoic acid in strong sulfuric acid solutions. In their earlier work they proposed that the decarboxylation in 80-100 percent sulfuric acid solution occurred by a specific oxonium ion catalysis having the rate equation in the form:

$$\text{rate} = k \left[H_3O^{(+)}\right] \left[\text{acid}\right] \qquad [84]$$

Later (324) the bimolecular mechanism was modified by attributing a larger role to molecular sulfuric acid (HA) catalysis which predominates beyond 80 percent sulfuric acid. It is significant to note that the rate of reaction was not affected by the concentration of bisulfate ion ($A^{(-)}$), which showed that if a two step process were involved, the intermediate (XLVII) was converted into products much faster than its rate of reversion back to reactants as depicted in equation [85]

$$ArCO_2H + HA \underset{\text{slow}}{\rightleftharpoons} Ar^{(+)}\!\!<\!\!\begin{matrix}H\\ CO_2H\end{matrix} + A^{(-)} \xrightarrow{\text{fast}} ArH + CO_2 + HA \quad [85]$$

XLVII

Ar ≡ mesityl

The ^{13}carbon (325) and ^{14}carbon (326) isotope effects in the decarboxylation interestingly suggested that the carbon-carbon bond was broken in a step that was at least partially rate-determining.

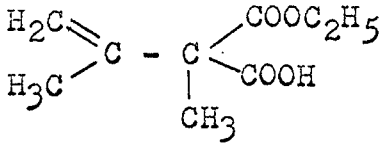
Good evidence for a bimolecular mechanism in bromodecarboxylations has been advanced by Grovenstein (327).

Since the main interest in decarboxylation experimentally has been with the aromatic acid, anthranilic, in nitrobenzene and quinoline solutions, the remaining sections of this review of decarboxylation will centre upon related studies. Special attention will be given to basic nonaqueous solvent effects, to an examination of the decomposition of aromatic hydroxy acids as well as to anthranilic acid itself.

DECARBOXYLATION IN BASIC NONAQUEOUS SOLVENTS

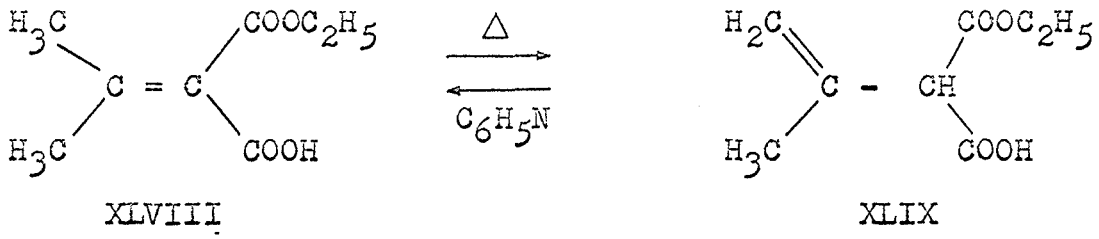
Corey (7) examined the influence of the α,β-ethylenic linkage in the decarboxylation of unsaturated malonic acids particularly to shed light on the function of pyridine as a medium for such decompositions. It is noteworthy that, despite the frequent use of aromatic bases such as pyridine in decarboxylations, little was known up to that time about the role of pyridine in the reaction or the entity undergoing decarboxylation; that is, the free acid or its conjugate base.

Decarboxylation of ethyl hydrogen isopropylidenemalonate (XLVIII) in pyridine at 111°C. produced a mixture of ethyl β,β-dimethylacrylate (LII) and ethyl β-methyl-β- butenoate (LIII) in the ratio of 1:3 respectively which remained constant under a variety of conditions which affected the rate. The entire scheme is presented on page 137. Ethyl hydrogen isopropenylmethylmalonate (LIV) decarboxylated

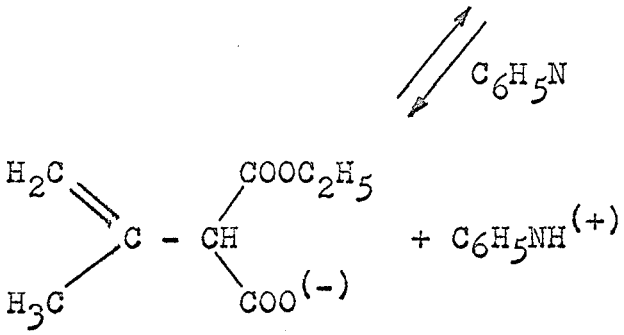


LIV

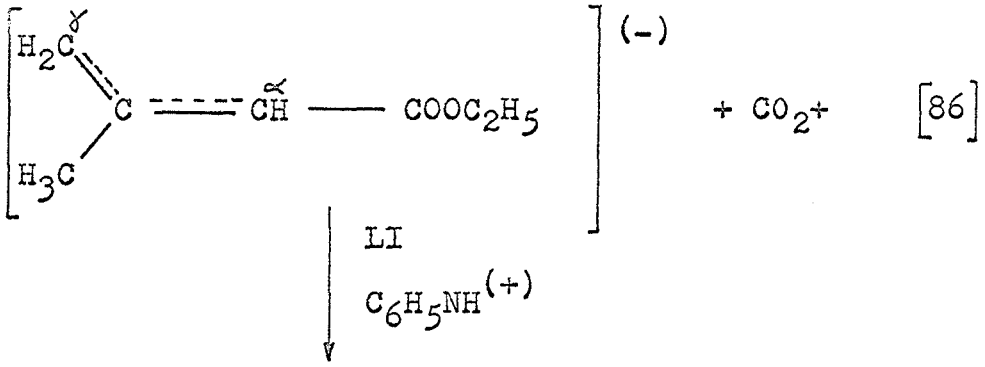
10 times faster than XLVIII under similar conditions also to yield a mixture of isomeric β,γ- and α,β-unsaturated esters (ratio 1:1) analogous to LII and LIII, whereas the compounds whose structures are represented by,



XLVIII XLIX

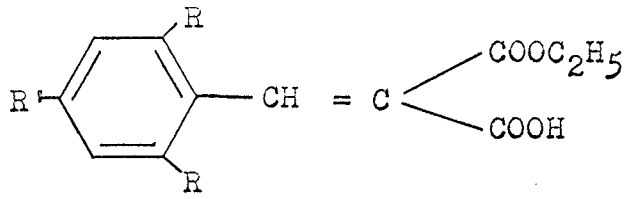


L



LI

LII LIII

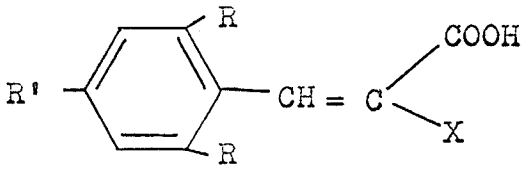


LV, R = R' = CH_3

LVI, R = Cl; R' = H

LV and LVI were resistant to decomposition. All the evidence permitted the elimination of a direct decarboxylation of α,β-unsaturated malonic acid derivatives in hot pyridine but was consistent with the decomposition of the β,γ-unsaturated acid (XLIX) which decarboxylated as the conjugate base (L). The mesomeric anion (LI) produced by the loss of CO_2 then would accept a proton irreversibly three times faster at C_α than at C_γ to give LIV or LII respectively. In a later paper a suggestion for interpretation of the isomerization step which included participation of the carboxyl group and the solvent was made (328).

Corey later extended his decarboxylative study by examining the behaviour of benzylidenemalonic acid derivatives (LVII, LVIII) in pyridine.



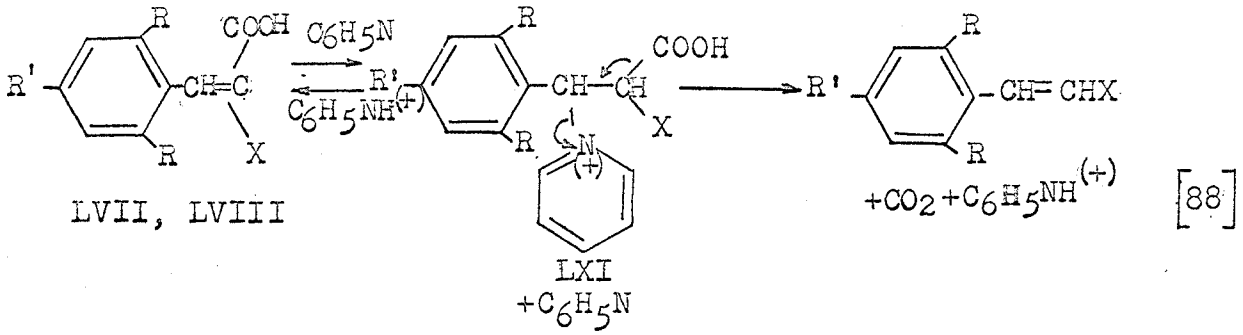
LVII, X = $COOC_2H_5$, CN, COOH; R=R'=H
LVIII, X = CN; R=H; R'=H, NO_2, CH_3, OCH_3
LIX, X = CN, $COOC_2H_5$; R=Cl, R'=H
LX, X = CN; R=R'=CH_3

under similar experimental conditions (329). First-order kinetics were observed with added pyridinium nitrate and in pyridine alone a linear relationship between $1/\sqrt{HA}$ and t, where HA refers to the unionized acid, was noted. In the case of LIX and LX the ortho substituents strongly inhibited the reaction. The kinetics of the decarboxylation of LVII were interpreted on the basis that such acids were weak in pyridine, having small dissociation and ionization constants (137). The most plausible rate expression was derived as being

$$\frac{dCO_2}{dt} = k' \left[HA\right]\left[C_6H_5NH^{(+)}\right] + k'' \left[HA\right]^2 \qquad [87]$$

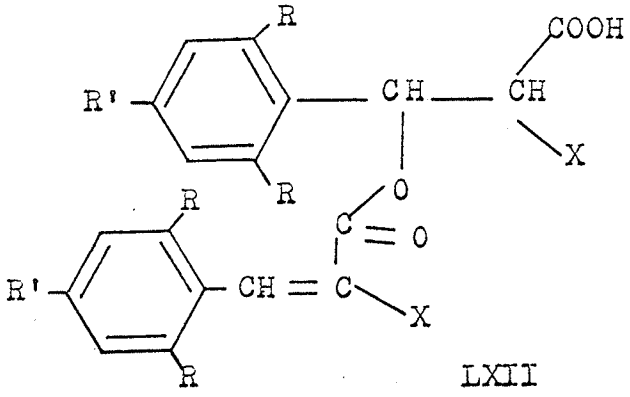
where $k'/k'' \approx 350$. The order of reactivity of p-substituted benzylidenecyanoacetic acids (LVII) in which p-NO_2 > p-H > p-CH_3 > p- OCH_3, also provided information on the nature of the decarboxylation process. A Hammett correlation of rate constants with σ was curvilinear. Deviation from the Hammett relationship was due to enhanced resonance interaction of the electron-withdrawing methyl and methoxy groups. A more satisfactory fit was made by Janzen (4) with Brown's sigma plus (σ^+) substituent constants which were not available at the time Corey undertook his investigations. The most reasonable and consistent picture of the decarboxylation process for all the data assumed a solvent molecule in the reaction of the acid and pyridinium ion. The termolecular combination was envisaged to proceed in a concerted 1,2 addition of a proton

(from $C_6H_5NH^{(+)}$ or HA) and a solvent molecule to the α, β - double bond of LVII or LVIII to give an intermediate (LXI) which then underwent 1, 2-decarboxylative elimination.



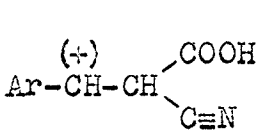
[88]

The second term of equation [87] was interpreted as being due to the acid in the form of $H^{(+)}A^{(-)}$ ion pairs or HA furnishing a proton instead of the pyridinium ion thereby leading to general acid-catalysis instead of specific pyridinium-ion catalysis. Another possibility would have a synchronous addition of HA to the α, β -double bond of a second HA molecule and the intermediate (LXII), thus formed, subsequently undergo decarboxylative elimination.

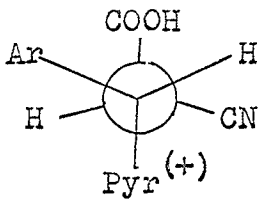


LXII

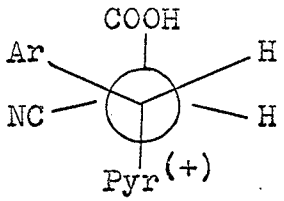
Klein and Meyer (330) have studied the steric course of the decarboxylation of benzylidenecyanoacetic and cinnamylidenemalonic acids and found it to depend on the solvent and other reaction conditions. Corey (329) earlier had recorded a product analysis in the decomposition of benzylidenecyanoacetic acid (C_6H_5 and CN cis) consisting of 65 percent trans- and 35 percent cis-cinnamonitrile and attributed this to an equilibrium of the nitriles formed under reaction conditions. From his work in quinoline Klein felt it was improbable that the primary product equilibrated when the decarboxylation was carried out in pyridine at 111°C, but that the product was kinetically controlled. It was more reasonable that the first step was not a concerted trans proton-pyridine addition to the α,β-double bond but that the carbonium ion (LXIII), solvated by pyridine molecules, first formed, then collapsed to a mixture of isomers (LXIV and LXV) where LXIV would predominate because of its greater stability.



LXIII



LXIV

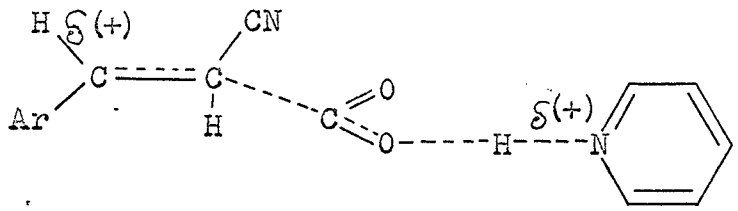


LXV

Ar ≡ aryl, $Pyr^{(+)}$ ≡ pyridinium

Another hypothesis involved the direct decarboxylation of LXIII as in LXVI in such a way that the breaking of the

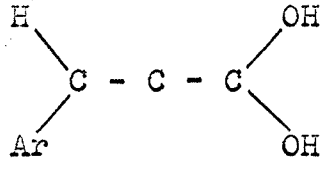
carbon-carbon bond was advanced in the transition state so that the composition of the product would be similar to the equilibrium mixture of the stereoisomers.



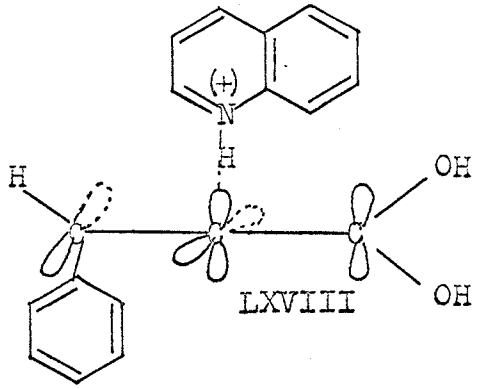
LXVI

It would seem that in both mechanisms the positive charge formed in the molecule by addition of a proton or of a pyridinium ion would favour the decarboxylation because of its electron-attracting character.

More of the less stable isomer was recovered in the decarboxylation using quinoline indicating that in this solvent a mechanism different from that in pyridine was operative or that the greater bulk of the quinoline molecule added a further steric requirement. One of a number of proposals advanced involved a prior decarboxylation of the cyanoacid or the diacid to give an allene-enol-like intermediate (LXVII) in which protonation by quinolinium ion was made more facile from the side remote from the aryl substituent as in LXVIII giving a higher yield of the cis product.



LXVII



LXVIII

Support for the view that steric hindrance plays an important role in the geometrical course of the reaction was given by similar results obtained when using the hindered pyridine derivative, 2,4,6-collidine, as solvent (330).

Yankwich and co-workers in their carbon-isotope studies on the decarboxylation of malonic acid in quinoline have offered further evidence for the involvement of basic solvents in the decomposition process suggesting at least one rapid reversible equilibrium of acid with quinoline prior to the rate-determining step (331).

The rates of decarboxylation of malonic acid at 100°C. in quinoline were higher than in quinoline solution in the presence of N-ethylpiperidine but had an essentially constant value with more than one mole of N-ethylpiperidine present per mole of diacid (8). The added amine, being a relatively strong base, apparently neutralized completely one carboxyl hydrogen of malonic acid. In dioxane—N-ethyl piperidine mixtures the reaction rates were only slightly lower than those observed in quinoline —N-ethylpiperidine solutions adding to the speculation that, in reactions in the presence of excess strong base and in media of low dielectric constant, the monoanion (LXIX) was the decarboxylating species.

$$HOOCCH_2CO_2^{(-)} \longrightarrow H_2\overset{(-)}{C}COOH + CO_2 \quad [89]$$

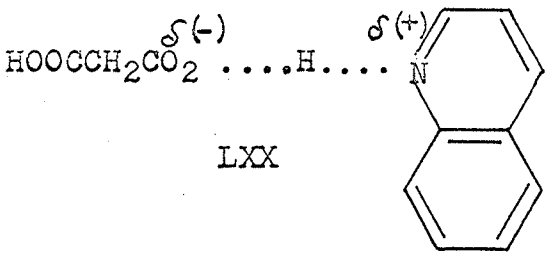
$$\downarrow$$

$$H_3CCO_2^{(-)}$$

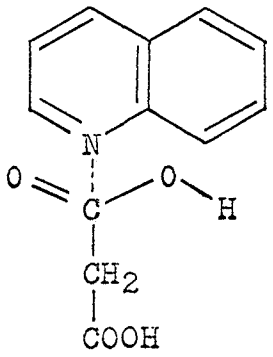
LXIX

It was noted that the enthalpy of activation for the aqueous monoanion decarboxylation was essentially the same in the non-

aqueous solvent although the rate in water was about one-hundredth of that in quinoline. The difference in the free energies of activation was manifested in a difference of the entropy of activation, the more negative $\Delta S^{\ddagger}$ representative of the aqueous monoanion indicating a greater ordering of the immediate environment around the decomposing anion or transition state than in quinoline (or dioxane). Discounting the possibility of anionic decarboxylation in pure quinoline on the earlier evidence of Corey (137) and finding the apparent rate constant for the reaction in dioxane to be a linear function of the concentration of the amine, Fraenkel et al. (8) suggested two possibilities for the quinoline-catalyzed decomposition of malonic acid. Reasons in favour of a reaction proceeding via a carboxyl-carbon solvation by quinoline (LXXI) over one assisted by hydroxyl association (LXX) were given therein.



LXX



LXXI

Activation parameters for the diacid in aqueous and quinoline decarboxylations were also compared. Clark, however, has found significantly different values for the reaction in

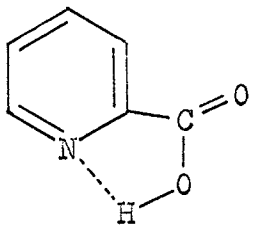
quinoline (332).

Modifications in this earlier interpretation on the nature of the solvent-containing complex were presented in later papers (333,153). Yankwich presumed that there was a direct influence of quinoline on the free carboxyl group of the anion through an interaction resulting in a hydrogen-bonded structure of the type O-H....N (333). He also noted that, if the apparent rate constants, derived in dioxane solution with increasing amounts of quinoline added, were extrapolated to 100 percent quinoline (8), a value of $6.0 \times 10^{-4} sec^{-1}$, would be observed as compared to the experimental value of the decarboxylation in pure quinoline of $4.6 \times 10^{-4} sec^{-1}$ (99.6°C.). It was inferred that general solvent and specific catalytic roles were played by quinoline and suggested that the general influence of quinoline was declerative or 'intrinsically' inhibitive to the course of the decarboxylation even though carboxyl solvation in the free acid was an apparently necessary prerequisite to the specific catalytic action of quinoline. Additional evidence of complex formation and for the site of solvent attachment was obtained in results of proton magnetic resonance experiments (153). The chemical shift anticipated for a carboxyl proton was close to that obtained in dioxane, a solvent in which solute-solvent interaction might be expected to be kept at a minimum. In quinoline, however, a relatively larger chemical shift was interpreted qualitatively as a condition attributed to a loosely shielded proton under-

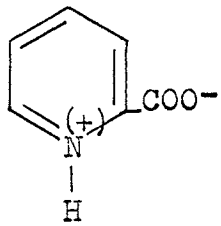
going some equilibrium process.

Considerable attention has been given to studying the mode of decomposition of pyridinecarboxylic acids in a large number of representative nonaqueous solvents. Mention has already been made of Brown and Hammick's work, with quinaldinic acid in quinoline which closely resembles picolinic acid structurally. Studies have been directed principally at examining the role that the solvent assumes in decarboxylations (290,334,335,336, 337), the effect of varying substituents in the pyridine nucleus (338), carbon-isotope effects (339) and decomposition of N-substituted pyridinecarboxylic acids (295).

Cantwell and Brown (336) could not unequivocally decide between the hydrogen-bonded structure (LXXII) or the zwitter-ionic structure (LXXIII) for picolinic acid as the species undergoing decarboxylation in acidic, neutral and basic solvents all by a first-order process.



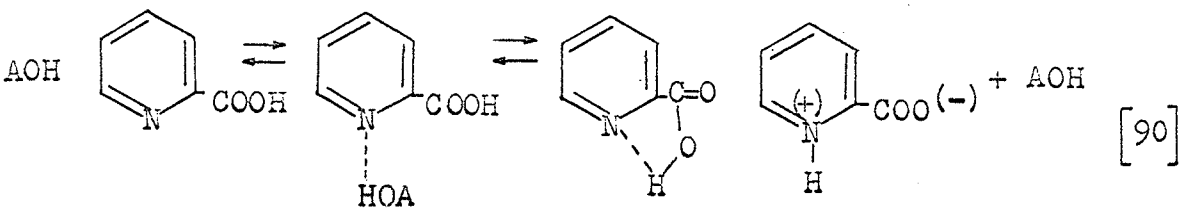
LXXII



LXXIII

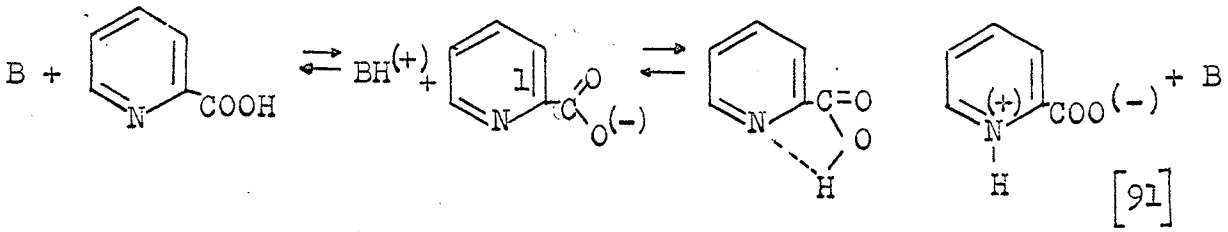
The data indicated that the rate of decarboxylation of 1-pyridinecarboxylic acid was lowered and the activation energy raised by both acids and bases. Neutral solvents (nitrobenzene,

hromobenzene, etc.) had a varied but also pronounced effect. The suppression of the rate by acids was believed to be caused by competition between the acidic hydrogen of picolinic acid and the acidic hydrogen of the solvent (phenols, AOH) for the nitrogen of the pyridine ring.



[90]

In the case of bases (anilines, quinoline, tributylamine), a probable acid-base equilibrium between the acid in question and the base (B) to form the anion could have helped to reduce the reactivity.



[91]

Clark added to the investigation by increasing the number of solvents studied (290,334,335). He noted the comparable values for the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, for

the decarboxylation of molten picolinic acid and the acid in p-cymene (the solvent used by Cantwell) and concluded that the hydrocarbon could be acting as an inert solvent, the transition complex in the solvent being identical with that in the molten flux. The results in some 30 different solvents conformed very closely to a single isokinetic-temperature line in an enthalpy-entropy plot which was parallel to a similar line obtained previously for the decarboxylation of malonic acid and its derivatives as well as oxamic acid and its derivatives in the molten state and in a variety of solvents (340). On this evidence and on information presented earlier by Fraenkel et al. (8), that the decarboxylation of malonic acid in quinoline involved the formation of an activated complex between un-ionized acid and the nucleophilic solvent, Clark favoured the hydrogen-bonded form of picolinic acid (LXXII) over the zwitterion (LXXIII). That such poor nucleophiles as phenetole and dimethoxybenzene could act in a bimolecular mechanism, as proposed by Clark, has been called into question (295).

Kinetic ^{14}carbon-isotope effects in decarboxylating picolinic acid in the fused state as well as in quinoline and phenols was studied by Zlotowski and Zielinski experimentally and compared to a theoretical model (339). Results seemed to indicate that molecular interaction between the picolinic acid molecule and quinoline was much less than that with phenols.

Clark has made an extensive study over the last ten years

on the decomposition of malonic acid and its derivatives, other aliphatic and certain aromatic acids, in an exhaustive number of nonaqueous solvents as well as in the molten state. His main thesis has been the acceptance of a mechanism or rate-controlling step which involved a bimolecular reaction and the formation of an intermediate or activated complex between acid and solvent species as originally outlined by Fraenkel (8). The co-ordination is ascribed as one existing between the rather electrophilic carbonyl carbon of the leaving carboxyl group in the decarboxylation and an unshared pair of electrons acting as a nucleophilic centre and situated on such atoms as nitrogen, oxygen or sulfur of the nonaqueous solvent or, in the case of the melt, another solute molecule. Two principal factors were thought to determine the ease of formation of the complex;

(i) the effective negative charge on the nucleophilic atom of the solvent, and

(ii) the accessibility of the nucleophilic atom.

As the effective negative charge increases, the enthalpy of activation should diminish and as the steric hindrance increases in the solvent molecule, the entropy of activation should decrease (340,341,342,343,344,345,346,347). In certain instances, in which strong bases were used with correspondingly strong acids or in solvents which favoured ionization, a mechanism where ionization was prevalent was also invoked (348,349).

During the course of these studies a rather large number of isokinetic temperatures were calculated from enthalpy-entropy relationships. Clark pointed out a rather interesting observation in that the temperature quite often corresponded to the melting point of the acid used. He suggested that the situation was not fortuitous but probably a general kinetic relationship (343,350). A further observation was made (346) in that sixteen different decarboxylation reaction series yielded seven isokinetic temperatures separated from one another by 15°C. intervals. The higher the isokinetic temperatures, in general, the stronger the mutual attractions between the electrophilic-nucleophilic pairs.

In Table VI are summarized activation parameters associated with the decarboxylation of several acids in four amines taken from reference (345). If one considers the first seven acids listed from left to right, there is a general trend that the enthalpy of activation ($\Delta H^{\ddagger}$) and the entropy of activation ($\Delta S^{\ddagger}$) decrease in the pair of solvents, aniline to o-toluidine and from quinoline to 8-methylquinoline, a feature consistent with an increased nucleophilicity and increased steric factor in the solvent. The last two acids, namely benzylmalonic and malonanilic acids, show a reversal in this trend which is not at all clear but suggestive interpretations have been given (344,345). Watson and Haake have questioned the unusually large and positive $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the decarboxylation of oxamic, oxanilic and oxalic acids, particularly in aniline and

TABLE VI

COMPARISON OF ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF SEVERAL ACIDS IN BASIC NONAQUEOUS SOLVENTS[a]

Solvent \ Acid	Malonic		Cinnamal-malonic		Oxalic[d]		Oxamic[d]		Oxanilic[d]	
	$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[b]	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Aniline	26.9	-4.5	23.8	-13.2			59.7	68.0	49.8	46.3
o-Toluidine	25.7	-7.0	21.9	-17.5			53.7	57.1	47.8	39.9
Quinoline	26.7	-2.4	23.5	-16.2	38.9	15.8[c]	47.0	37.5	38.6	16.0
8-Methylquinoline	24.4	-10.5	21.6	-21.8	37.7	13.7	36.0	12.2	35.6	10.0

[a] Reference (345).

[b] Units: $\Delta H^{\ddagger}$, kcal./mole; $\Delta S^{\ddagger}$ e.u./mole.

[c] Reference (351) gives $\Delta S^{\ddagger}$ =5.8 .

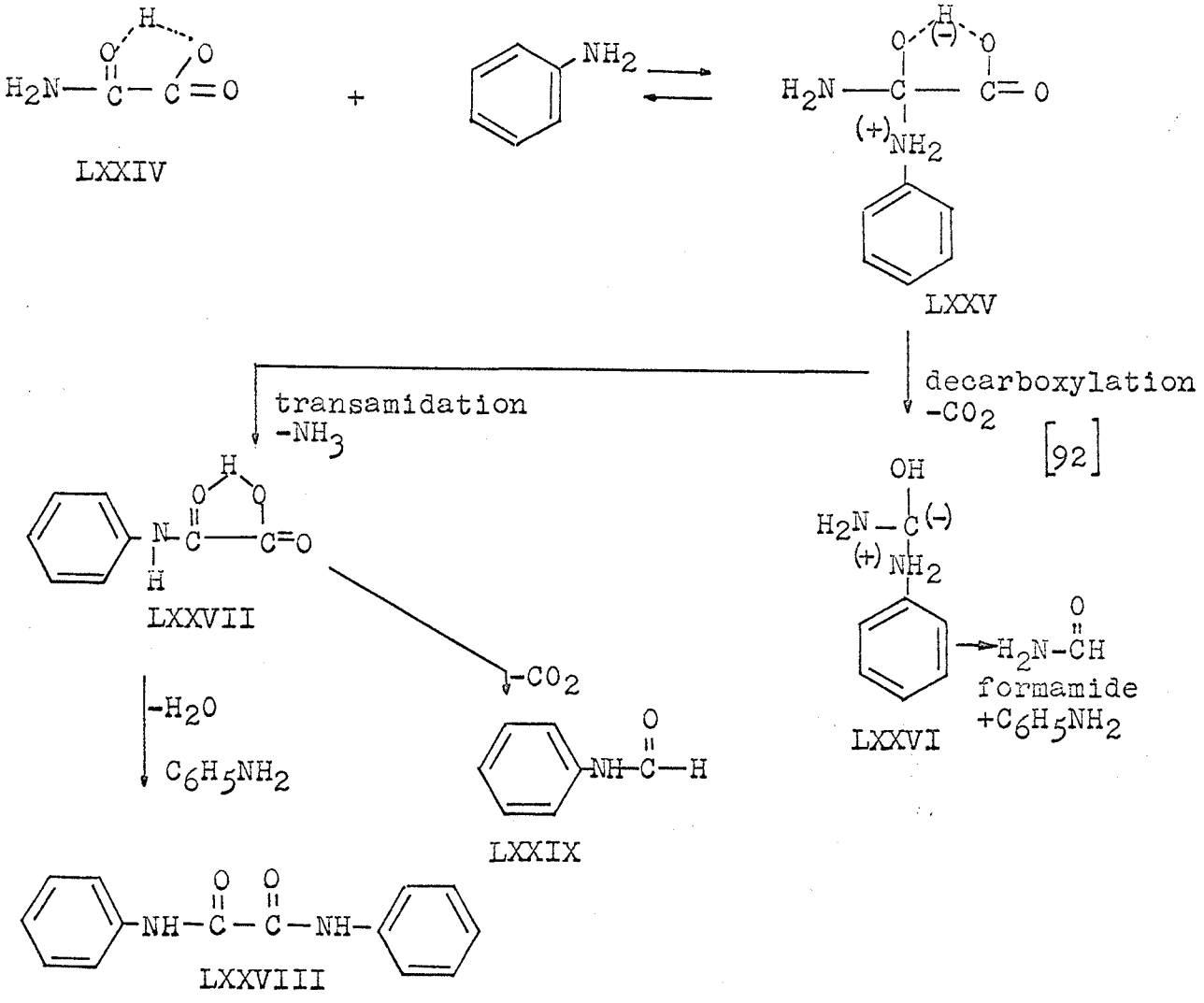
[d] See reference (351) .

Table continued :

TABLE VI CONTINUED

Solvent \ Acid	Trichloro-acetic		β-Resor-cylic		Benzyl-malonic		Malon-anilic	
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Aniline	24.5	-2.6			19.8	-21.6	27.6	-1.5
o-Toluidine	23.8	-6.8			29.9	5.0		
Quinoline	24.0	-2.4	34.5	5.95	19.9	-19.9	21.0	-17.5
8-Methylquinoline	22.3	-8.4	22.9	-21.8	26.4	-4.6	28.5	0.4

o-toluidine, and give proof that the decarboxylation of oxamic acid (LXXIV) in such solvents is complicated by a series of concurrent reactions of amidation and transamidation producing as final products oxanilide (LXXVIII) and formanilide (LXXIX)(351). Clark earlier had experienced some experimental difficulties with these acids (352,353).



The isolation of oxanilide (LXXVIII) in this experiment does mean that there is nucleophilic interaction of the solvent (aniline) with carbonyl groups and decarboxylation could proceed by the same path. Nucleophilic catalysis could be effective in oxamic acid (LXXIV) decomposition through the tetrahedral intermediate (LXXV) which increases the amount of negative charge on the carboxyl and allows the decarboxylation to proceed quickly to an ylid (LXXVI). The same intermediate on loss of ammonia in a transamidation would give oxanilic acid (LXXVII) which could undergo further reaction forming oxanilide (LXXVIII) and formanilide (LXXIX) as products.

DECARBOXYLATION OF HYDROXYAROMATIC ACIDS

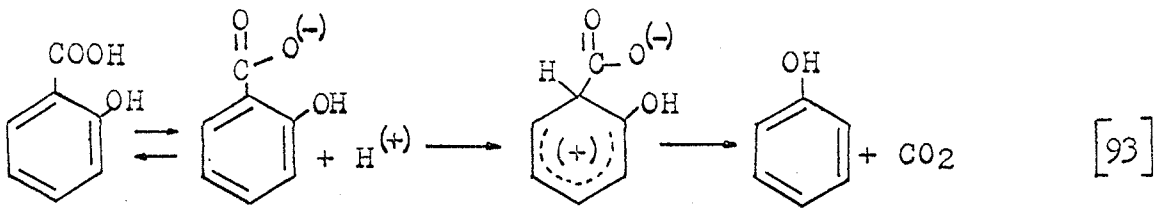
Aromatic acids with suitably substituted hydroxyl groups are relatively easily decomposed in aqueous and nonaqueous solvents and have, therefore, been a rather attractive area for decarboxylative studies.

Protic Nonaqueous Solvents

Brown, Hammick and Scholefield chose resorcinol as a nonaqueous protic solvent in order to study the nature of the bimolecular (S_E2) reaction in the decomposition of benzoic, salicylic, 4-hydroxysalicylic and 2,4,6-trihydroxybenzoic acids (354). Pseudo first-order rate constants were obtained from the hydroxy acids at 110-240°C. but benzoic acid proved

resistent to decarboxylation even at 250°C. in resorcinol. Decomposition of benzoic acid was later achieved at higher temperatures (355). The activation energy decreased with increasing hydroxyl group substitution. Successive substitutions increased the electron density on the carbon alpha to the carboxyl group, thereby, facilitating an electrophilic attack by a solvated proton to that position consistent with the S_E2 mechanism. It is interesting that the activation energies for the decarboxylation of o-chlorobenzoic and 2,4-dichlorobenzoic acids in resorcinol are slightly lower than those for the corresponding mono- and disubstituted hydroxy acids (356).

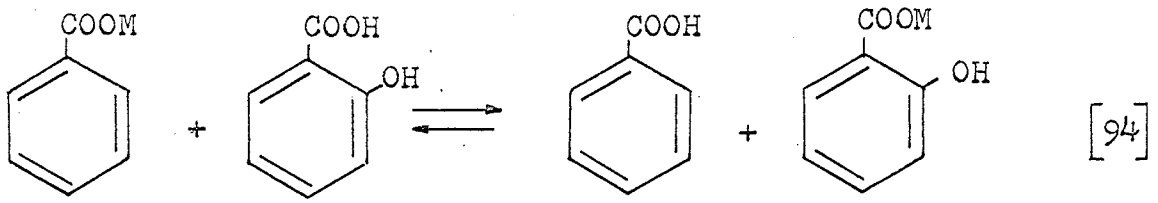
More recently, first-order decompositions of salicylic acid and a number of derivatives in benzoic acid solution at 200-230°C. have been measured by Kaeding (357). Increased rates were observed in compounds with para substituents which tended to enrich the electron density of the aromatic ring. Electron-withdrawing groups hindered the reaction. The proposed mechanism involved a competition between an oxygen atom and the carbon 1 of the ring for the proton to give either the undissociated acid or a σ-complex (LXXX) leading to products as shown in equation [93].



[93]

LXXX

It was assumed that the decrease in rate, when the benzoic acid solvent was diluted with an aprotic substance, was primarily due to an alteration of the concentration of available protons. In fact sodium salicylate in phenyl benzoate or benzoic anhydride was stable under the experimental conditions. Experiments were performed to test the proposed mechanism by altering the concentration of salicylate anion. Various metal salts of benzoic acid were added to the benzoic acid solutions containing salicylic acid. It was expected that an equilibria such as the following would be favourable with metals that are strongly chelated.

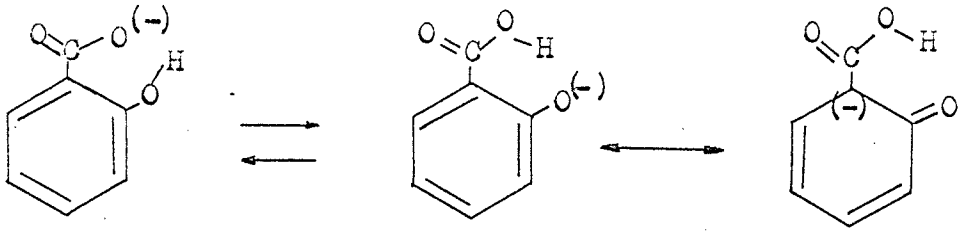


[94]

M ≡ metal

In every case, where salts were added to the solvent, the rate increased although there were considerable variations in the effect on the rate of decarboxylation. A 31-fold increase in the rate at 212°C. was observed in the presence of magnesium salt, although the energy of activation for the catalyzed reaction and that for the uncatalyzed reaction were quite similar. This would suggest that the decarboxylation occurred by the same mechanism, the difference in rate resulting from a substantial increase in salicylate ion by the

presence of the magnesium salt. Kaeding further noted that the ortho hydroxy group would influence the distribution of negative charge on the anion. Tautomeric and resonance forms such as



[95]

would suggest a more favourable charge distribution than that localized on the carboxylate group itself. The close proximity of the latter might lead to undissociated acid on interaction with a proton. Since the m- and p-hydroxybenzoic acids do not decarboxylate at a measurable rate in benzoic acid solution at 212°C., the unique steric arrangement of the o-hydroxy group is of significance.

Clark studied the decomposition of 4-hydroxysalicylic (β-resorcylic) acid in a number of aliphatic carboxylic acids and cresols (347) and compared the results with those obtained earlier for the same acid in aromatic amines and glycols (358). It was of interest to note that enthalpy of activation-entropy of activation plots for the acid in these solvents containing the four different functional groups yielded four straight, almost parallel lines and, within experimental error, the same isokinetic temperature. It is often noted that in kinetic studies a change in type of solvent results in formation of a new line parallel to the original line (359). Rate constants at the isokinetic

temperature were calculated from the knowledge of the free energy of activation and relative rates of 1:53:100:160 were established for the decarboxylation of β-resorcylic acid in aliphatic acids, phenols, aromatic amines and glycols respectively. It should be mentioned that Clark had, in an earlier paper included one glycol, 2,3-butanediol, in the same isokinetic line with the aromatic bases (358). Clark noted that the decomposition of malonic acid and its derivatives in the molten state, in acidic, neutral and basic solvents was shown to constitute a single reaction series with the same isokinetic temperature as established in the β-resorcylic acid work and proposed that this was evidence for similar mechanisms in the two sets of decompositions.

Aqueous Solvents

An extensive review of the decarboxylation of hydroxy aromatic acids, and in particular, salicylic and substituted salicylic acids in aqueous acid solutions has been given by Scheffler (3). Only a few of the more pertinent observations will be included here.

The kinetics of the acid-catalyzed decompositions of 2,4,6-trihydroxybenzoic acid in aqueous hydrochloric and perchloric acid have been examined by Brown (360) and Schubert respectively (361). Brown's results did not agree with any single mode of decarboxylation but were best interpreted on the basis of two simultaneous reactions.

$$RCO_2^{(-)} + H_3O^{(+)} \longrightarrow RH + CO_2 + H_2O \qquad [96]$$

or

$$RCOOH \longrightarrow RH + CO_2 \qquad [97]$$

and

$$RCOOH + H_3O^{(+)} \longrightarrow RH + CO_2 + H_3O^{(+)} \qquad [98]$$

Reaction [96] and [97] are indistinguishable kinetically so they could be regarded as either a bimolecular substitution of the anion with a hydronium ion ($S_E2(b)$) or a unimolecular decomposition of the free acid ($S_E1(a)$). The third reaction [98] is of the $S_E2(a)$ type. The activation energies for [96] or [97] and [98] are respectively 21,500 and 15,200 calories. Essentially the same results were obtained by Schubert (361).

Kinetic hydrogen-isotope effects on the decarboxylation of 4-hydroxysalicylic acid in water and deuterium oxide were determined by Willi (362) and give support to the bimolecular mechanisms that have rate equations

$$\text{rate} = k_H^A \left[A^{(-)}\right] \left[H^{(+)}\right] \qquad [99]$$

and

$$\text{rate} = k_D^A \left[A^{(-)}\right] \left[D^{(+)}\right] \qquad [100]$$

where $\left[A^{(-)}\right]$ is the salicylate anion concentration and $\left[H^{(+)}\right]$ and $\left[D^{(+)}\right]$ are respectively the hydronium and deuteronium ion concentrations. The value, $k_H^A/k_D^A = 1.76$, was taken to indicate that the rate-determining step was a proton attack on

the salicylate ion.

Willi (292) utilized the Hammett relationship to determine the electron requirements at the reaction centre by recording the decomposition rates of 4-methyl, 4-methoxy, 4-hydroxy and 4-aminosalicylic acids in aqueous solution. The rates were increased and the activation energies decreased as the electron-donating power of the substituent increased. The good correlation between the logarithm of the bimolecular rate constant and Brown's σ^+ substituent constants ($\rho = -4.38$ at 50°C.) supported a bimolecular mechanism with an attack of a proton on carbon 1 of the aromatic ring. Two possible mechamisms remained after interpretation of the data.

S_E2 (two step): $ArCO_2^{(-)} + H^{(+)} \xrightarrow{\text{slow}} Ar\begin{matrix} H^{(+)} \\ COO^{(-)} \end{matrix}$

$\xrightarrow{\text{fast}} Ar\text{-}H + CO_2$ [101]

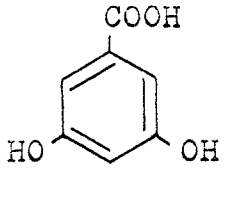
S_E2 (concerted): $ArCO_2^{(-)} + H^{(+)} \longrightarrow ArH + CO_2$ [102]

Lynn and Bourns (363) shed further light on this problem by measuring the ^{13}carbon kinetic-isotope effect in the decomposition of 4-hydroxysalicylic acid in aqueous acetate buffers. The k_{12}/k_{13} ratio increased with increasing acetate ion concentration, a situation readily accounted for by the two-step [101] process. As the acetate ion concentration is increased, there would be an increasing tendency for this

base (which is stronger relative to water), to abstract a proton from the intermediate and regenerate the reactant. This would result in the decomposition of the intermediate, with carbon-carbon bond rupture, becoming partially rate-controlling.

Basic Nonaqueous Solvents

One of the earliest studies of substituent effects on the decarboxylation of aromatic acids in nonaqueous basic solvents was made by Hemmelmayer (364). Hydroxy groups in the ortho or para position aided the decomposition. Furthermore, electron-withdrawing substituents such as bromo and nitro groups attached to the same acid further facilitated the reaction. Included with the following examples is an indication of the relative amounts (percent) of each acid decarboxylated after boiling in aniline for one hour.



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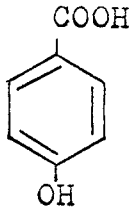

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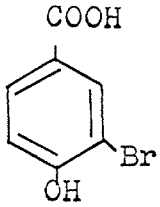

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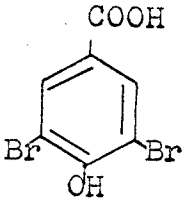

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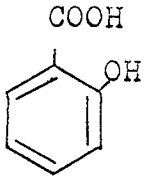


31

It would seem that strongly electron-donating hydroxyl groups were necessary to induce decarboxylation but rates

could further be enhanced through acid catalysis by phenolic products whose acid strengths would increase with electron-withdrawing groups (4).

Clark advanced information suggesting a bimolecular decarboxylation reaction for β-resorcylic acid and basic solvents such as quinoline and 8-methylquinoline (358). Both the enthalpy and entropy of activation for the reaction in 8-methylquinoline was lower indicating the importance of the more effective negative charge on the nitrogen, which it was proposed was involved in co-ordination, and of the steric effect which tended to decrease the probability of formation of the activated complex.

Janzen (4) began a decarboxylative study of 4- and 5-substituted salicylic acids in quinoline at 200°C. and found that the rates were first order with respect to the acid. A trial with salicylic acid in nitrobenzene had shown that the reaction was second order in keeping with a similar observation made with anthranilic acid in this aprotic solvent (2). In quinoline, the decarboxylation was significantly accelerated by strongly electron-releasing substituents in the para position. The rates, however, were of similar magnitude for compounds bearing these substituents. Compounds having substituents in the 5 position decomposed at about one-tenth this rate, and once again their rate constants were very similar. Significant deviations of the points in a Hammett correlation utilizing Brown's sigma-plus substituent constants

limited the amount of information that could be secured as to the nature of the reaction process. A comparatively small negative rho, however, did give an indication that electron release favoured the decarboxylation if the ∝carbon was considered as the reaction site. More importantly, the apparent inconsistencies in the data were suggestive that both electron donation and electron withdrawal were effective in aiding decarboxylation and that bond-breaking and bond-making processes other than just carbon-hydrogen bond making were involved in the rate-determining step. The main feature of the proposed mechanism in this preliminary study, however, was an internal replacement of the carboxyl group by a proton with assistance being given by a molecule of quinoline.

Rodewald (5) extended the work on the decomposition of substituted salicylic acids in quinoline to include the calculation of activation parameters, the order of the reaction with respect to quinoline in quinoline-nitrobenzene mixtures, an examination of the enthalpy-entropy relationship, the extended Hammett equation, and the basicity and steric requirements of the solvent in the decarboxylation process.

An experimental difficulty, unforeseen by Janzen (4) was uncovered by Rodewald's study. The latter worker observed that the constancy in the rates of the substituted salicylic acids containing the strongly electron-donating substituents, as observed by Janzen when using the manometric technique, was due to a measuring of the rate of evolution of gas from

the supersaturated quinoline solution rather than of rates of reaction.

A plot of the enthalpy of activation, $\Delta H^{\ddagger}$, and entropy of activation, $\Delta S^{\ddagger}$, displayed an apparent isokinetic relationship for all the acids except those bearing the 4-hydroxy, 4-ethoxy and 4-amino substituents, implying that the rates of decarboxylation could not be accommodated by a single mechanism. It was also noted, that if these three acids were neglected, an isokinetic temperature of 286°C. was obtained, well above the working temperature in the rate studies. The insensitivity of the rates of the 5-substituted acids towards varying substituents could not be simply due to the fact that the rates of reaction were measured at the isokinetic temperature but was strongly suggestive of two simultaneous processes which were oppositely influenced by substituents.

The order with respect to quinoline was determined by decarboxylating 4-methylsalicylic acid in nitrobenzene-quinoline mixtures. A first-order dependence on the quinoline concentration was calculated from data obtained in the region 0-0.03 mole /litre of quinoline. The rate of decarboxylation increased rapidly up to approximately 0.3 M quinoline and, thereafter, a retarding factor (attributed to the decreasing dielectric constant of the medium) was apparent as the rate decreased sharply and then leveled off with further increase in quinoline concentration.

In order to ascertain the effect of changing the basicity of the nitrogen atom in quinoline, salicylic acid was decomposed in 6-nitro-, 6-methoxy- and 8-hydroxyquinoline. Reaction rates were faster in the solvents containing the 6-methoxy and 8-hydroxy substituents confirming the importance of higher electron density on the nitrogen. Activation parameters were calculated for the 4-aminosalicylic acid and compared to those derived from the same acid in pyridine as noted in Table VII.

TABLE VII

ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF 4-AMINOSALICYLIC ACID*

Medium	$\triangle H^{\ddagger}$ kcal./mole	$\triangle S^{\ddagger}$ cal./mole/degree
quinoline	28.5	- 0.707
pyridine	24.9	- 9.84

*Reference (5).

Within experimental error one could at least make qualitative suggestions. The decrease in $\triangle H^{\ddagger}$ from quinoline to pyridine pointed out the involvement of the solvent prior to or in the rate-determining step. The relatively more negative $\triangle S^{\ddagger}$ recorded for pyridine indicated a more highly ordered arrangement in the transition state of the reaction compared to that in quinoline.

An application of the Hammett relation in its simplest form showed no correlation with the Hammett's sigma or Brown's sigma plus constants. That the substituent could affect the reaction occurring on the carboxyl group by two paths, namely, through carbon 1 and carbon 2, was further discounted and the conclusion accepted that processes which were oppositely influenced by substituents were involved at carbon 1. The data did fit the following extended Hammett equation:

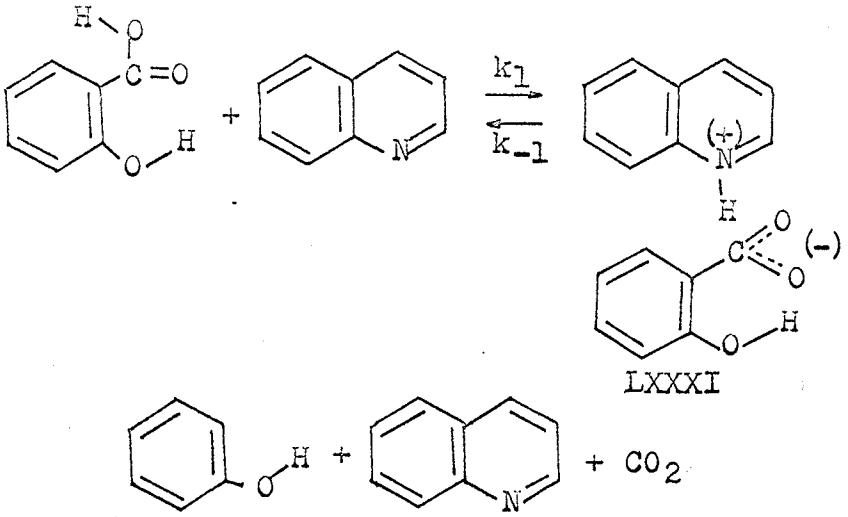
$$\log k/k_o = \rho_1\sigma^+ + \rho_1'\sigma^+ + \rho_2\sigma \qquad [103]$$

$$= \rho''\sigma^+ + \rho_2\sigma \qquad [104]$$

where ρ_1 and ρ_1' were the reaction constants referring to the carbon-hydrogen bond making and carbon-carbon breaking processes respectively in which Brown's σ^+ should apply and ρ_2 refers to the acid ionization or oxygen-hydrogen bond breaking in which Hammett's σ should apply. Values of $\rho_1'' = -4.21$ and $\rho_2 = +3.98$ were obtained. The negative rho value gave an indication that electron-releasing substituents favoured the reaction at carbon 1, an observation consistent with the assumption made that carbon-hydrogen bond making occurred at carbon 1 since a high electron density at this site would have favoured such a reaction. The positive value of ρ_2 was also in keeping with the importance of the ionization process in the reaction.

The proposed mechanism, which follows, was consistent

with all the experimental facts.



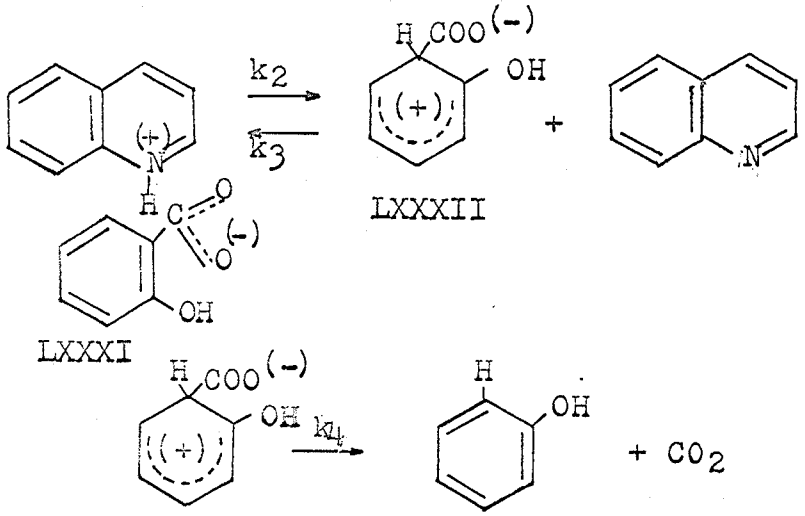
LXXXI

[105]

The mechanism as well as predicting the pseudo first-order kinetics in quinoline also accommodated the behaviour of decarboxylation in quinoline-nitrobenzene mixtures. The rate of reaction, being dependent on the concentration of ion pairs (LXXXI), would be enhanced in nitrobenzene solution in which ion-pair formation would be favoured. On increasing the quinoline concentration the equilibrium would be shifted to increase the ion-pair concentration but at the same time to decrease it as the medium's dielectric constant is decreased. The mechanism also predicts that O-H bond breaking and C-H bond making are involved prior to or in the rate-determining step. Furthermore, it would seem that an increase of electron density on the nitrogen of the solvent molecule would have an

overall favourable effect on the rate by facilitating the ionization and dissociation process even though this would necessarily presume concomitant hindering of C-H bond making. The results of the experiments in pyridine, in which a lowering of both $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$ prevailed relative to the results in quinoline, pointed out that pyridinium ion was able to interact more strongly with the anion in the transition state.

An alternate interpretation for the mechanism was put forward by Bourns (365). He maintained that it was difficult to visualize a medium effect or dielectric constant changes in the nitrobenzene-quinoline solutions causing an abrupt change such that the mass-law effect would be wiped out as suggested by Rodewald. The results could quite reasonably be explained by formation of a zwitterionic intermediate (LXXXII), which formed reversibly after a prior equilibrium to form the ion pair. Extending reaction [105] to include the extra step, one has:



[106]

The formation of the intermediate would be rate-determining ($k_4 >> k_3 [Q]$) at low concentrations of quinoline ($[Q]$) in nitrobenzene and the rate should increase linearly with quinoline concentration because of an increase in the concentration of ion pairs. At the inflection point, which was observed in the curve of rate constant against quinoline concentration, $k_3 [Q]$ becomes significant relative to k_4. At still higher $[Q]$, the two opposing mass law effects, that involving the ion-pair equilibrium and the other the zwitterionic intermediate, would essentially cancel and the medium effect then would become prominent. Work has just recently been completed in distinguishing between the proposal of Rodewald and the interpretation of Bourns (365) by use of ^{13}carbon kinetic-isotope effects (6). Both mechanisms could accommodate either an isotope effect or none at all; however, only that in which the formation of the zwitterionic intermediate is capable of existence would support the finding of a variable carbon-isotope effect. The results of the isotopic study for 4-methylsalicylic acid at 195°C. were,

$$\text{at low } [Q], \; k_{12}/k_{13} = 1.007$$

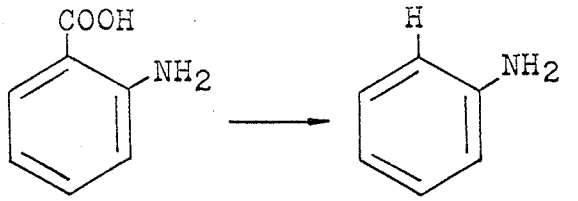
$$\text{and at high } [Q], \; k_{12}/k_{13} = 1.022,$$

obtained in 0.02 M quinoline in nitrobenzene and in pure quinoline respectively. The variable isotope effect was, therefore, a good indication that the mechanism for the decomposition involved the equilibrium formation of ion pairs, followed by the formation of a reaction intermediate (LXXXII)

which could decarboxylate to products or revert back to an ion pair.

DECARBOXYLATION OF ANTHRANILIC ACID

The decarboxylation of anthranilic acid has been produced by a number of methods with the principal products of the decomposition being aniline and carbon dioxide.



[107]

In the presence of such sensitizers as titanium (IV) oxide, aluminum (III) oxide and zinc (II) oxide, anthranilic acid has been photooxidized by sunlight to give at first the usual products carbon dioxide and aniline (296). When an aqueous solution of anthranilic acid was subjected to ultraviolet radiation for 24 hours, 5-hydroxyanthranilic acid, benzoic acid, ammonia as well as aniline and carbon dioxide were produced, whereas acidic and basic solutions containing the title compound were stable under the influence of the radiation (297). Supervoltage cathode rays have been used to decarboxylate and deaminate anthranilic acid and its para analog. Decarboxylation for both compounds occurred at approximately the same rate but this rate was lower than the rate of loss of amine function (366). Because of its importance

biologically, anthranilic acid has been the subject of decarboxylative studies by both enzymic and nonenzymic means. The results obtained in nonenzymic systems, in which the aminobenzoate isomers decarboxylated in slightly alkaline, refluxing aqueous solution using pyridoxal catalyst, were comparable with enzymic reactions. In these aqueous solutions aniline production from the ortho isomer proceeded at a rate 16 times as fast as that observed with the para isomer whereas the meta isomer was inactive (367).

The stability of the three monoaminobenzoic acids in boiling aqueous solution was investigated by McMaster and Shriner (368). The extent of reaction was determined by titrating the undecomposed amino acid with alkali. Anthranilic acid was found to decarboxylate by a first-order process twice as fast as p-aminobenzoic, the authors attributing this to the proximity of the ortho-amino group, while m-aminobenzoic acid had not decarboxylated after 3 hours under similar conditions.

Stevens and co-workers (289) extended the above work and included a carboxyl-carbon isotopic study. In their kinetic experiments they utilized a gravimetric procedure in trapping the evolved CO_2 in absorption tubes filled with Ascarite. The aqueous decarboxylations confirmed the work of McMaster (368) in that the reaction followed first-order kinetics initially and the rate was very close to the reported values of these earlier workers. However, the rate decreased

after some 15-18 percent of the acid had decomposed, a condition accounted for by the inhibition by aniline as it built up during the course of the reaction. Furthermore, when decarboxylations were carried out in aqueous sulfuric acid solutions, they were found to be catalyzed to just below the point in which the concentration of added mineral acid approximated that of the anthranilic acid; thereafter, the reaction rate decreased with increasing acid concentration. Sodium anthranilate was not decarboxylated in boiling aqueous solution in 2 hours. A mass spectrometer study of the carbon dioxide produced in the decompositions in the melt, or in aqueous and acid-catalyzed reactions showed no carboxyl ^{13} carbon-isotope effect, a fact which was evidence that the mechanism was not unimolecular.

Stevens suggested that the acid-catalyzed runs could be explained by assuming either the neutral anthranilic acid molecule or its zwitterion was the decarboxylating species. Bjerrum (369) had found that the ratio of neutral molecules to zwitterions was greater in p-aminobenzoic than in o-aminobenzoic acid solutions, which was an indication that the former should react faster if the modes of decarboxylation, as suggested by Stevens, followed either a proton attack on the oxygen of the neutral molecule or on the carbon α to the carboxyl group of the neutral molecule. Since Shriner (368) had earlier reported that p-aminobenzoic acid decomposed at a rate about one-half that for the ortho isomer

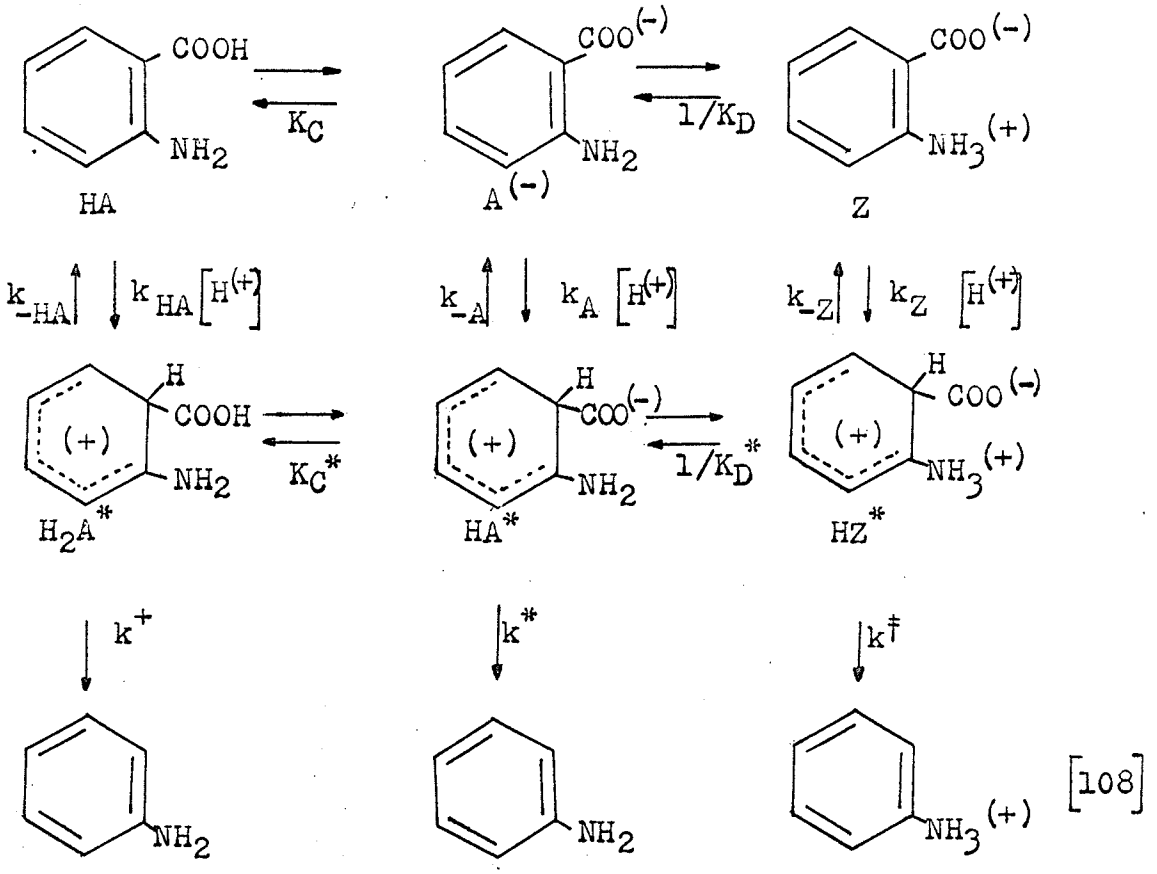
Stevens preferred a mechanism in which proton attack would occur at the ∝carbon of the zwitterion, followed by a low-activation energy carbon-carbon bond rupture. The reaction could be classified as belonging to the group of S_E 2 aromatic displacements.

Dunn, Leggate and Scheffler (3) studied the effect of changing pH upon the rate and mechanism of decarboxylation of 4-methyl- and 4-methoxyanthranilic acids. The decarboxylation was followed by noting the change in concentration of substituted anthranilic acid with time spectrophotometrically by measurements made in alkaline solution where all the acid was in anionic form. Although the effect of acidity upon the rate of decomposition of anthranilic acid in aqueous solution had been investigated earlier by Stevens and co-workers (289), no buffered or constant ionic strength solutions were used. It was on rather qualitative evidence that they concluded that the rate-determining step was protonation of the zwitterion at carbon 1 even though they found the maximum rate at a lower pH than the isoelectric point.

Kinetic studies of aromatic amino acids in aqueous solutions are complicated by the fact that the acids may be present as neutral molecules, zwitterions, cations or anions (usually referred to as Bjerrum species (see page 26)) anyone or more of which may decarboxylate themselves or produce intermediates which subsequently decompose.

Dunn *et al.* (3) found that both 4-methoxy- and 4-methylanthranilic acids decarboxylated by a first-order process. The observation of a maximum in the rate at the pH where no maximum occurred in the concentration *vs.* pH curves for Bjerrum species or other species formed from a Bjerrum species by simple protonation or deprotonation could not be accounted for by first-order decarboxylations of such species. Furthermore, no combination of Bjerrum species could account for the results obtained, so that attention was directed to considering the decarboxylation *via* an intermediate not part of the Bjerrum system. The reaction was facilitated by a high electron density on the aromatic ring as indicated by the ease of decarboxylation which increased in the order anthranilic < 4-methylanthranilic < 4-methoxyanthranilic acid. The non-Bjerrum intermediate was believed formed by protonation of the Bjerrum species at carbon 1. Once the ring was protonated, two competing reactions could occur, one of which would be loss of the ring proton and the other loss of carbon dioxide. It was further argued that one of these competing reactions must be brought about by a second proton attack. Equation [108] shows the structures of the Bjerrum species (HA, $A^{(-)}$, Z) which on ring protonation would form the non-Bjerrum intermediates (H_2A^*, HA^*, HZ^*) and which could be interconvertable with each other by gain or loss of proton from carboxyl or amino group as represented by the equilibria

K_C^* and K_D^*.



[108]

However, equation [108] could not be fitted to the kinetics. It was required that both H_2A^* and HZ^* participate but either they were not formed directly by protonation of HA and Z (k_{HA} and $k_Z = 0$) or they did not decarboxylate (k^+ and $k^{\ddagger} = 0$). A number of equations were presented to cover variations of the general mechanism which could satisfactorily account for the pH dependence of the rate of decarboxylation of 4-methoxyanthranilic and probably of other aromatic amino acids as well.

It was further suggested that the proposed mechanisms would permit predictions concerning the possibility of a carboxyl carbon-isotope effect and, therefore, aid in distinguishing the various modes of decarboxylation. Work has recently been completed in this regard (6) and results, derived from carboxyl-carbon isotopic investigations of the decarboxylation of 4-methoxysalicylic acid at 60°C. in aqueous solution of different pH and constant ionic strength (0.5), were interpreted in favour of a mechanism in which the acid (HA), the acid anion (A^-) and the zwitterion (Z) are all protonated to form the non-Bjerrum intermediates, H_2A^*, HA^* and HZ^* respectively, of which only HA^* can decarboxylate.

The thermal decarboxylation of anthranilic acid in the melt is well known. Pawlewski (370) studied the reaction over the temperature range of 150-210° C. and found that the decarboxylation was complete when the acid was heated for one hour at 205-210°C. The results agreed reasonably well with Steven's work (289), which confirmed that the reaction was first order. Clark (290) has more recently reported kinetic data on the decarboxylation of anthranilic, p-aminobenzoic and picolinic acids in the melt and compared them to a series of keto acids, namely, malonic, benzylmalonic and oxanilic acids under similar experimental conditions. Activation parameters for the amino and imino acids are noted in Table VIII. An enthalpy-entropy plot of this data together with

similar information for the keto acids yielded two straight lines, with those acids listed in Table VIII falling on one line while the keto acids followed the other. The existence of the isokinetic relationship was interpreted as support for the idea that, in the decarboxylation of picolinic and o- and p-aminobenzoic acids, the structural changes in the molecules did not change the mechanism of the reaction or the nature of the transition state. In order to explain the results Clark maintained that the rather large negative values of entropy of activation obtained for the amino acids was a consequence of possible association of these molecules to form long-chain clusters, whereas picolinic acid exhibited little or no association of its molecules or zwitterions.

TABLE VIII

ACTIVATION PARAMETERS FOR DECARBOXYLATION IN THE MELT*

Acid	$\Delta H^{\ddagger}$ kcal./mole	$\Delta S^{\ddagger}$ e.u./mole
picolinic	39.8	13.2
p-aminobenzoic	24.9	-19.9
anthranilic	21.6	-26.5

*Reference (290).

A few observations have been made to point out the apparent complexity of decarboxylations carried out in the melt, particularly with reference to anthranilic acid. The preparation of ortho deuteroaniline by the decarboxylation of partially deuterated anthranilic acid in the melt at 200-210°C. was attempted by Dunn and co-workers (1). The results showed that deuterated aniline had a little more than half its deuterium in the aromatic ring instead of one-third as predicted for a statistical distribution or less than one-third as might be expected if there were a normal isotope effect in decarboxylation. Two explanations were offered. The mechanism of decarboxylation was such that deuterium migrated in preference to protium or that deuterium entered more than one position in the ring. The latter view appeared more likely since earlier work on the decarboxylation of calcium and sodium salts of aromatic acids with calcium and sodium deuteroxide substantiated this observation (371). Hydrogen-exchange reactions before and after decarboxylation at conditions of high temperature (500°C.) were attributed to be the cause of the anomalies in the deuterium content. Prysiazniuk (2) also found an unusually high amount of deuterium in the ring of the aniline obtained on decarboxylation of partially deuterated anthranilic acid in nitrobenzene. It has been pointed out that the order of the reaction in the melt is not very informative since the composition of the reaction mixture changes during the

decarboxylation from pure anthranilic acid to pure aniline (2). The aniline, so produced, could serve as a proton donor and take over the role of a second molecule of anthranilic acid in an intermolecular reaction.

Dunn and Prysiazniuk, recognizing the difficulties in interpreting the results of decompositions in the melt, undertook a decarboxylative study of anthranilic acid by thermally decomposing the acid in the aprotic solvents nitrobenzene and 1-methylnaphthalene (2). In this way they were able to resolve whether the proton shift occurred inter- or intramolecularly, whether the neutral acid or zwitterion was involved and hence whether the proton was donated from the carboxyl or from the amino group.

A series of meta-and para-substituted anthranilic acids were decarboxylated in nitrobenzene at 210.5°C. and the reaction followed by weighing the evolved carbon dixoide in Ascarite. A few acids were also decomposed in 1-methylnaphthalene at 242°C. In both solvents the reaction was found to be second order with respect to anthranilic acid indicating that two molecules of the acid were involved in the transition state or some step preceding it and suggesting that the proton transfer was intermolecular. There were several possibilities for the rate-controlling step anyone or more of which could be actually involved. Attention was then directed to deciding among the following:

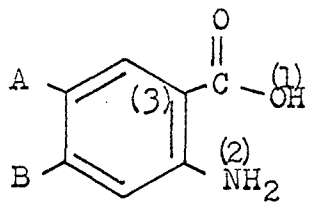
(i) hydrogen-oxygen bond making,

(ii) hydrogen-nitrogen bond breaking,

(iii) hydrogen-carbon bond making, and

(iv) carbon-carbon bond breaking.

Step (iv) was eliminated by Dunn and Prysiazniuk by noting the work of Stevens et al. (289) in which no carboxyl-carbon isotope effect was found for the decarboxylation of anthranilic acid in the melt or in aqueous solution. In order to distinguish among the remaining three possibilities, the Hammett equation was utilized in locating the site of reaction in the anthranilic acid molecule (LXXXIII),



LXXXIII

where (1) refers to the carboxyl group proton, (2) refers to the amino group and (3) indicates carbon 1 of the ring. Substituents at A or B could influence reactivity at these various sites. The Hammett equation in its extended form for the most general case, that is, where all three centres in the molecule were important, could be represented by equation [109].

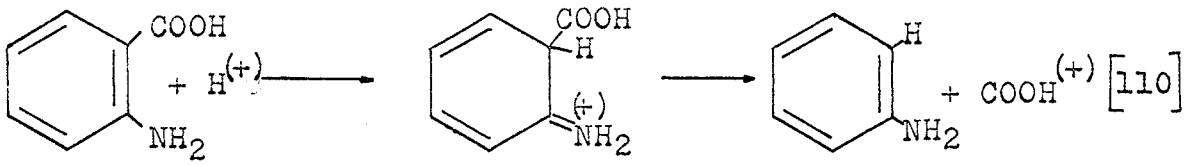
$$\log k/k_o = \rho_1 \sigma_1 + \rho_2 \sigma_2 + \rho_2 \sigma_3 \qquad [109]$$

Here, σ_1 referred to Hammett's sigma for carboxylic acid reactions, σ_2 was Hammett's sigma for amines and phenols and σ_3 was Brown's sigma plus for electrophilic substitution on the ring carbon. The correlation was also applied to the simple Hammett equation in which the relative importance of each specific site alone was considered. The various equations were examined statistically with the conclusion being that site (3), that is, carbon-hydrogen bond formation, predominated in the transition state since electron-releasing substituents aided the reaction ($\rho = -1.45$ for Brown's σ^+ plot in nitrobenzene) but some contribution from site (1) was also apparent.

A number of other observations were of significance. Although the rates of decarboxylation in the two aprotic solvents were not measured at the same temperature, it was suggested that the rates at a similar temperature could not be very different. Since nitrobenzene has a greater polarity than 1-methylnaphthalene, this was an indication that the polarity of the transition state would not differ greatly from that of the reactant. The rate of decomposition was reduced when anthranilic acid was deuterated in its functional groups. The hydrogen kinetic isotope effect, $k_H/k_D = 2.66$, indicated that the proton transfer was involved in the rate-determining step or some step preceding it. A number of N-substituted anthranilic acids were studied and increased rates were found for N-methyl- and N-phenylanthranilic while

a decrease in rate was noted for N-acetylanthranilic acid, all in agreement with the role of the ortho-amino group. Since protonation of this group would have destroyed its electron-releasing properties, decarboxylation from the neutral acid rather than the zwitterion would be preferred. Furthermore, since proton donation must necessarily come from the carboxyl group, it would seem that electron-releasing substituents should have hindered the reaction. This observation helped to corroborate the findings on the application of the Hammett relationship in that more than one site was involved in the transition state.

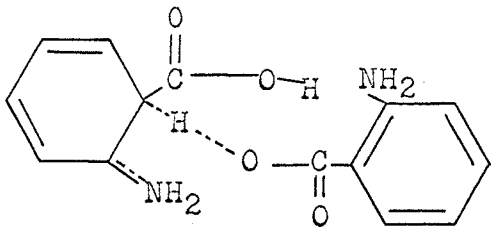
An analogy was made to the usually accepted mechanism of aromatic electrophilic substitution as shown below.



LXXXIV

The decarboxylation of anthranilic acids would seem to have differed from the usual electrophilic aromatic replacements, which predicted that the transition state resembled the intermediate (LXXXIV) in that a hydrogen-isotope effect was observed in this case and the magnitude of rho was small. These observations suggested, rather, that the transition state (LXXXV) lay closer to the reactant and not the product if the evidence

by Stevens of no carboxyl-carbon isotope effect could be accepted.



LXXXV

The small magnitude of the hydrogen-isotope effect (2-3) suggested that the O-H bond was only partially weakened but not broken in the transition state. The small negative value of ρ_1 as well as the small solvent effect on the rates mentioned previously, confirmed that the charge build up at the reaction site was small. The left-hand amino group could stabilize the transition state and the right-hand amino group close to the leaving carboxyl group might allow for a low activation-energy transfer of the proton from this group to the nitrogen. The zwitterion, so formed, could then have reverted to the neutral molecule intramolecularly. The observation that p-aminobenzoic acid decomposed at only one fifth the rate of anthranilic acid was in agreement with this interpretation.

In conclusion, it may be stated that decarboxylation studies in nonaqueous solvents within recent years have

expanded significantly both in scope and number. There are a number of mechanistic problems still left unanswered. In relatively few cases has good evidence been advanced as to the actual entity undergoing decomposition. Difficulties in interpretation are compounded because of lack of quantitative information about ionization and dissociation phenomena in these solvents, often of low dielectric constant and low ionizing power. Ion pairs, ion triplets and other ionic aggregates are not uncommon in such solutions. More work will have to be done utilizing hydrogen and carbon kinetic-isotope methods and further emphasis placed on substituent effects as well as on steric requirements in the involvement of the solvent in the reaction process.

EXPERIMENTAL

A. MATERIALS

BENZENE

Benzene (1.5 litre) was shaken with 150 ml portions of sulfuric acid until the hydrocarbon layer was colourless. The benzene was washed repeatedly with water until the latter was neutral to litmus. Most of the water was removed by drying the benzene over anhydrous calcium chloride for 2 hours; it was then stored over Drierite for 2 days. The first 100 ml was discarded on distillation at atmospheric pressure and the benzene fraction boiling over a 0.5°C. temperature range collected (79.5-80.0°C.).

NITROBENZENE

Nitrobenzene (Fisher Certified Reagent) was kept over anhydrous calcium sulfate for almost 2 months and fractionated through a Vigreux column (28 cm). The fraction from 208-209°C. at 739 mm Hg was collected and stored over calcium sulfate (Drierite). The index of refraction was 1.5527 at 20°C. (lit., n_D^{20} 1.5562 (126d)).

PYRIDINE

Pyridine (Fisher Certified Reagent) was placed over sodium hydroxide pellets for 4 days. The solvent was decanted from the caustic soda, refluxed over barium oxide (Barium and Chemicals) for 6 hours and distilled into a

receiver containing barium oxide (1/8 x 1/16" mesh). The fraction boiling at 114°C. and 733 mm Hg was collected. The index of refraction at 20°C. was 1.5100 (lit. n_D^{20} 1.5095 (126e)).

QUINOLINE

Quinoline (synthetic, Matheson Coleman and Bell or 'Baker Analyzed' reagent) was dried over Drierite for more than a week. The drying agent was then filtered and the base distilled under vacuum. A typical middle fraction such as that at 111-113°C. and 12-13.5 mm Hg was collected. This was stored over barium oxide. Approximately four days later the quinoline was freed from the drying agent by suction filtration and fresh barium oxide added to it, then stored in the dark until use. The index of refraction was 1.6255 at 20°C. (lit., n_D^{20} 1.6268 (126f)).

PREPARATION OF QUINOLINIUM NITRATE

Quinoline (13.6 ml, 0.115 mole), purified as indicated previously, and concentrated nitric acid (9.0 ml, 0.14 mole) were mixed and the solution was taken to dryness by heating it in a porcelain dish aided by a vacuum which allowed a stream of air to pass over the contents in the dish. The deep rose-coloured solid was ground up, washed with absolute ether and recrystallized from ethanol-tertiary butyl alcohol and the resulting crystals washed with absolute ether.

A second recrystallization from acetone utilizing decolourizing charcoal gave faint pink needles. The quinolinium salt was stored in a vacuum desiccator over phosphoric anhydride. Just prior to its use in the decarboxylation experiments, another recrystallization, this time from ethanol alone, was carried out. The hot solution was cooled at 0-5°C. to aid crystallization and the crystals dried in an Abderhalden drying pistol for 24 hours using ether as the boiling solvent. The melting point was 121.4-122.3°C. Beilstein makes reference to this compound but does not record a melting point (372).

PREPARATION OF QUINOLINIUM CHLORIDE

A solution of quinolinium chloride was prepared by passing hydrochloric acid gas (cylinder, Matheson) through a concentrated sulfuric acid trap and into 35-40 ml of quinoline for a few seconds. A magnetic stirrer was used to aid dissolution. Excess quinoline hydrochloride was removed by filtration. The solution, stored overnight, was refiltered to remove salt that had precipitated on standing. The amount of quinoline hydrochloride was estimated by transferring 1 ml of the prepared solution to 50 ml of pyridine and titrating potentiometrically to the end point using tetra-n-butylammonium hydroxide in methanol-benzene as titrant.

Solid quinolinium chloride was isolated in the following

manner. Dry hydrochloric acid gas was passed as above into a solution containing 8 ml of quinoline and 150 ml of absolute ether for a few minutes. The salt precipitated as a gummy mass which then hardened. The ether was decanted, the quinolinium chloride ground up and recrystallized from ethanol-benzene and dried in an Abderhalden drying apparatus for 24 hours using ethanol as the refluxing liquid. There was a slight tendency for the material to sublime and to turn a light tan colour. The melting point was not well defined but one determination was recorded as 121 (soften)-128°C.(clear liquid) (lit., 134.5°C.(373);133°C.(374)). This inability to obtain a sharp melting point was attributed to the very hygroscopic nature of the hydrochloride.

PREPARATION OF PYRIDINIUM NITRATE

Pyridine (15.3 ml, 0.190 mole), purified as indicated earlier, and concentrated nitric acid (14.0 ml, 0.216 mole) were mixed in a porcelain dish and the solvent reduced by slight heating of the solution. Evaporation was further assisted by setting up a partial vacuum over the contents which allowed a stream of air to pass over the dish. The resulting semi-solid was treated with acetone, heated, cooled and the crystals recovered by filtration. Acetone was the solvent for recrystallization. The colourless needles were collected by suction filtration, washed with anhydrous ethyl ether and placed in a vacuum desiccator over phosphoric

anhydride. The melting point of the colourless needles was 119.0-119.4°C.(lit., 116.5-118°C.(117); 117.5-118°C.(118)). Beilstein makes reference to this compound but only makes the observation that the material sublimes (375).

PREPARATION OF PYRIDINIUM PERCHLORATE

The preparation is essentially that used by Arndt and Nachtwey (376) with some modification included in the following description. It is recommended as a good procedure in the purification of pyridine (377).

Five millilitres of pyridine (6N, 0.062 mole), placed in a beaker, were cooled in an ice bath. Six normal hydrochloric acid (12.0 ml, 0.072 mole) was added slowly with stirring. This represented a slight excess of the acid as indicated by the absence of any pyridine odour from the reaction mixture. The aqueous solution of pyridinium chloride was cooled to 5-7°C. and 6N perchloric acid (20.8 ml, 0.12 mole), which had previously been cooled to ~4°C., was added slowly with stirring. The temperature during the addition was maintained at approximately 7°C. A white precipitate immediately separated and a thick mixture formed to which 10 ml of water were added to aid the stirring. The reaction mixture was allowed to remain in the ice-water bath while stirring was continued for one hour. Agitation was then discontinued but the contents were kept cool a further 0.5 hour and then filtered through

a glass-sintered crucible. The precipitate was washed with cold (0°C.) absolute ethanol, sucked dry on the vacuum and stored in a vacuum desiccator over phosphoric anhydride. The melting point of the colourless crystals was 296.4-296.8°C. (lit., 297°C.corr.(117); 288°C.(376); 280-283°C.(378)).

PREPARATION OF TETRA-N-BUTYLAMMONIUM HYDROXIDE TITRANT

Curdiff and Markunas (202) were the first to prepare anhydrous tetra-n-butylammonium hydroxide in benzene-methanol by the silver oxide process. The method used in this study follows a modification outlined by the above workers (212) in which the lowered reaction temperature lessens silver oxide solubility in methanol-benzene and reduces the possibility of incorporating an amine impurity since the tetrabutylammonium hydroxide can undergo Hofmann elimination to give tributylamine.

A solution of 40.0 g (0.125 mole) of tetra-n-butylammonium iodide (Eastman Organic Chemicals or Matheson Coleman and Bell) in 100 ml of absolute methanol (Fisher Certified Reagent) was cooled to 0°C. To the cold solution was added 21.0 g (0.0907 mole) of silver oxide (purified, Fisher Laboratory Chemical), the flask flushed with nitrogen, stoppered and the contents stirred magnetically for 2 hours. At the end of this period approximately 300 ml of dry benzene were added and the reaction mixture suction filtered through a sintered-porcelain crucible in a dry box under a nitrogen

atmosphere. Small portions of benzene were used to rinse the reaction flask. The faint yellow filtrate was transferred to a one-litre volumetric flask and stored in the refrigerator for 2 hours to observe if any silver oxide would precipitate from the solution. In virtually all instances an extra filtration was not needed. After warming to room temperature benzene was added to make the volume up to one litre. The concentration was approximately 0.1 normal and remained constant over an extended period of time.

SUBSTITUTED ANTHRANILIC AND SALICYLIC ACIDS

The anthranilic and salicylic acids used in the decarboxylation and potentiometric studies are listed in Table IX along with an indication of the source and melting point of the particular compound. All the acids were purified by one or more recrystallizations from water or aqueous ethanol (except when otherwise noted) in the presence of decolourizing charcoal. In the decarboxylation experiments the acids used were subjected to drying in an Abderhalden drying apparatus using phosphoric anhydride as desiccant and ethanol as the refluxing liquid. If the latter was not employed, an indication as to the boiling liquid used is given in the Table. Acids were then stored in a desiccator over Drierite. Most of the acids used in the potentiometric studies were the same as those used in decarboxylation. In the few instances the acid was

TABLE IX

SUBSTITUTED ANTHRANILIC ACIDS

Substituent	Source	Melting Point, °C. Observed[a]	Literature
H	BDH Laboratory Reagent Eastman Organic Chemicals Matheson Coleman and Bell	145.6-146.5 145.2-146.4	146 (126g)
4-NH_2	This investigation	126.0-126.6[b,d,e,c].	134-136 (2)
4-OCH_3	Leggate and Dunn (12) Buccini (6)	176.4-176.6[d]	180-181 (12); 180-181 (379)
5-OC_6H_5	Leggate and Dunn (12)	148.5-150.0	148-149 (12); 148 (380)
4-CH_3	Leggate and Dunn (12) Aldrich Chemical Co.	176.5-178.0 dec.	181-182 (12); 178-180 (381)
5-CH_3	Dunn and Prysiazniuk (2) Aldrich Chemical Co.	174.4-175.5 dec.	175-177 (2); 170-171 (382); 174 (383)
4-F	Leggate and Dunn (12)	195.1-195.4 dec. subl.	198-199 (12);178(383); 192.5-193 (384)
5-F	Leggate and Dunn (12)	182.4-183.4	183-184 (12); 180 (383)
4-Cl	Dunn and Prysiazniuk (2) Aldrich Chemical Co.	234.2-234.8 dec. subl.	234-235 (2); 235 (385)

TABLE IX CONTINUED

Substituent	Source	Melting Point, °C. Observed	Literature
5-Cl	Matheson Coleman and Bell	211-211.8 dec.	210 (385)
4-Br	Leggate and Dunn (12)	230-231.2 dec.subl.	225 (12); 222 (386)
5-Br	Dunn and Prysiazniuk (2) Eastman Organic Chemicals	211.3-212.9	215-217 (2); 215-216 corr.; 218-219 uncorr.(387)
5-CN	This investigation	255-256[e] dec. 247.5[f] dec.	
4-NO_2	Dunn and Prysiazniuk (2) Leggate and Dunn (12)	267.2-267.8 dec.	262-264(2); 263-265 (388); 263-264(389)
5-NO_2	Dunn and Prysiazniuk (2) Leggate and Dunn (12)	273.7 dec.	268-269 (2)

continued

TABLE IX CONTINUED

Substituent	Source	Melting Point, °C. Observed	Literature
	SUBSTITUTED SALICYLIC ACIDS		
H	May and Baker	158.3-159.2 subl. 158.8-159.6 subl.	159 (126h)
4-OCH_3	Dunn and Fei-Lin Kung (287) Penner (11)	158.9-159.6 158.5-159.1	159-160.5(287); 157 (390); 161.1-162.2 (11)
5-NO_2	Eastman Organic Chemicals	230.6-232.8	231.7-232.2 (4); 232.9-233.8(11)

[a]More than one entry in this column indicates use of different batches in some investigations.

[b]Boiling liquid in Abderhalden pistol-ethyl ether.

[c]Recrystalized from absolute methanol.

[d]Boiling liquid in Abderhalden pistol-toluene.

[e]From prepqration (i), page 196.

[f]From preparation (ii), page 205.

only air dried and stored in the desiccator. The melting points given are for the recrystallized acids determined in a modified Hershberg melting-point apparatus (391) using silicone fluid as the heating liquid and Auschutz enclosed-scale thermometers to record the temperature.

Details of the preparation of 4-amino and 5-cyano-anthranilic acids and attempted preparation of 4-cyano-anthranilic acid are given below.

PREPARATION OF 4-AMINOANTHRANILIC ACID

Five grams (0.027 mole) of 2-nitro-4-aminobenzoic acid (Bios Laboratories Inc.) and 10% palladium-on-charcoal catalyst (0.50 g) were placed in a thick-walled hydrogenation flask. Absolute methanol (150 ml) was added - CAUTION* - and the mixture hydrogenated at approximately 3 atmos. pressure in a Parr Pressure Reaction Apparatus until no further hydrogen was taken up (5 mins.). The reaction mixture was allowed to stand for 10-12 minutes, agitated once more for another 0.5 hours and then suction filtered. The palladium on charcoal was washed free of any adhering product with absolute methanol (50 ml) and this added to the original solution and the contents evaporated to dryness. A light-brown solid (3.2 g, m.p.117.5-118.5°C. dec.) was recovered and recrystallized from absolute methanol

*A small explosion was experienced when the methanol was mixed with the solid material. The situation reoccurred when the catalyst was added to the acid-methanol mixture.

using decolourizing charcoal (twice) to yield colourless crystals, m.p. 126.5-126.8°C. dec. (lit.,134-136°C.(2)).

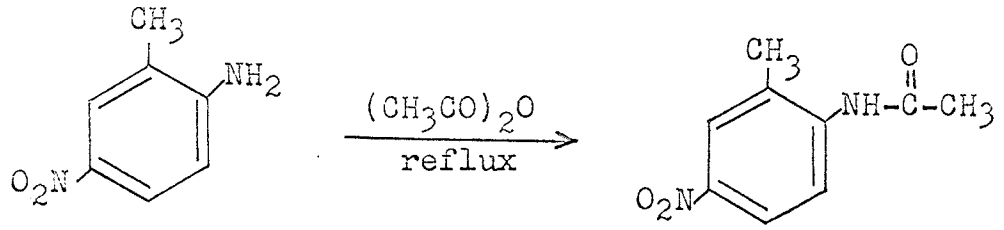
PREPARATION OF 5-CYANOANTHRANILIC ACID

(i) Figure 2 outlines the various steps used in the synthesis utilizing 2-amino-5-nitrotoluene as starting material. The title compound was incorrectly reported in Chemical Abstracts to have been made from the decomposition of 7-carboxyisatin 3-oxime. Bedford and Partridge, the workers to which the reference is made, had in fact prepared the 3-cyano derivative of anthranilic acid which melted at 280-282°C.(392).

A quantity of 2-acetamido-5-nitrotoluene had previously been prepared in this laboratory from 2-amino-5-nitrotoluene (Matheson Coleman and Bell) in a procedure given by Prysiazniuk (2). This material had a melting point of 197-202°C.(lit., 198-200°C.(2)).

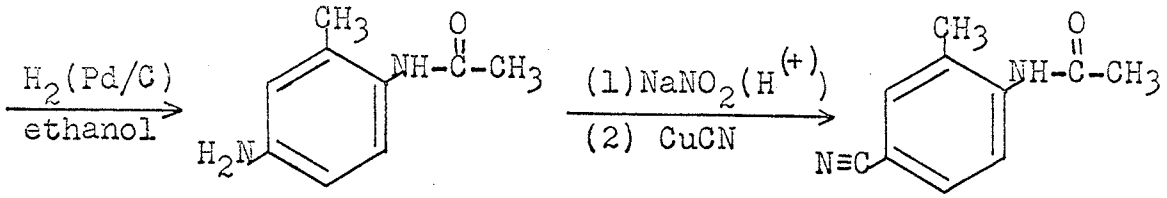
Ten grams of 2-acetamido-5-nitrotoluene (0.0515 mole) in absolute ethanol (150 ml) was hydrogenated using 10% palladium on charcoal (1.0g) as catalyst at approximately 3 atmos. pressure in a Parr Pressure Reaction Apparatus until no further hydrogen was taken up (15 minutes). The mixture was shaken for a further 40 minutes in the reaction vessel, allowed to remain at room temperature for 2.5 hours and then gravity filtered. The resulting filtrate which turned slightly pink on standing was refrigerated (-4°C.) overnight. A crop of colourless needles was collected and air dried to

FIGURE 2. Flow scheme for the preparation of 5-cyano-anthranilic acid.



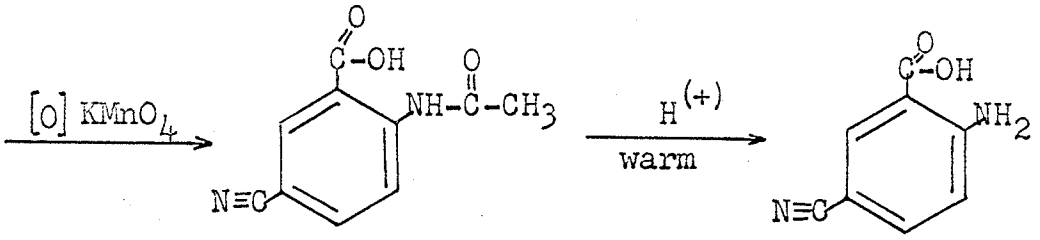
2-amino-5-nitrotoluene

2-acetamido-5-nitrotoluene
(m.p., 197-202°C.)*



2-acetamido-5-aminotoluene
(m.p. 139-143°C.)*

2-acetamido-5-cyanotoluene
(m.p. 144.5-146.5°C.)



2-acetamido-5-cyanobenzoic acid
(193.5-194.5°C.)

5-cyanoanthranilic acid
(255-256°C.)

* Not recrystallized.

yield 1.75 g of product, m.p. 139-143°C. (lit.,143°C. (393); 129-130°C. (394)). A mixed melting point with an authentic sample in the laboratory gave no depression. The supernatant was reduced in volume at the aspirator providing two further crops of crystals resulting in a total of 6.4 g of 2-acetamido-5-aminotoluene.

The method used in the preparation of 2-acetamido-5-cyanotoluene was similar to that used by Bergmann (395) in Sandmeyer reactions of monoacyl arylenediamines.

The 4-amino precursor (4.1 g, 0.025 mole) was triturated in a mortar with a few pieces of ice and 2N hydrochloric acid solution (12.5 ml). A further 18.8 ml of the acid solution was then added and diazotization carried out at 0°C. by the gradual addition of N sodium nitrite solution (25 ml, 0.025 mole) over a period of 0.5 hours. The clear solution containing the diazonium salt was added slowly with stirring to a freshly prepared cuprous cyanide solution made by dissolving potassium cyanide (8.6 g, 0.13 mole) and 95% cuprous chloride (4.0 g, 0.038 mole) in approximately 50 ml of water. The temperature during the addition (0.5 hours) was not allowed to exceed 5°C.* After the addition was completed stirring was continued at room temperature. The resulting thick-yellow mixture (considerable foaming) was treated with ethyl acetate (150 ml) and filtered. To the remaining solid was added a further volume of ethyl acetate

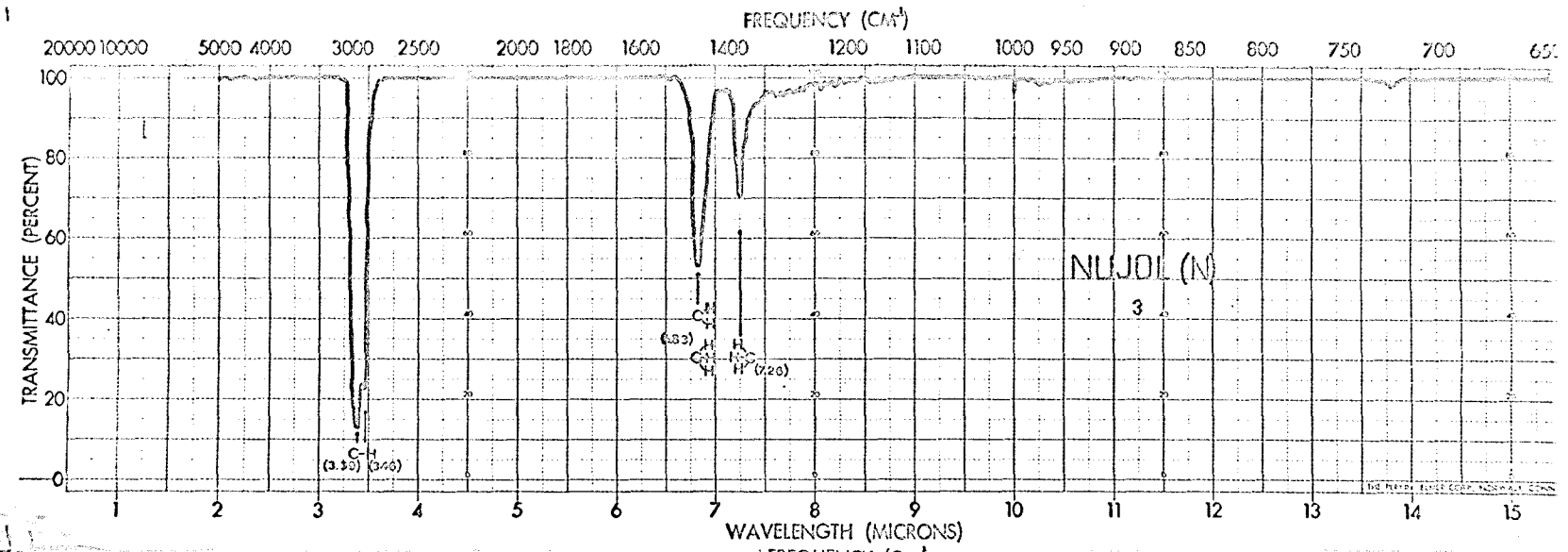
*It should be pointed out, however, that in subsequent attempts at this preparation the temperature was maintained at 10-15°C. without any noticeable adverse effects on yield or quality of the final product.

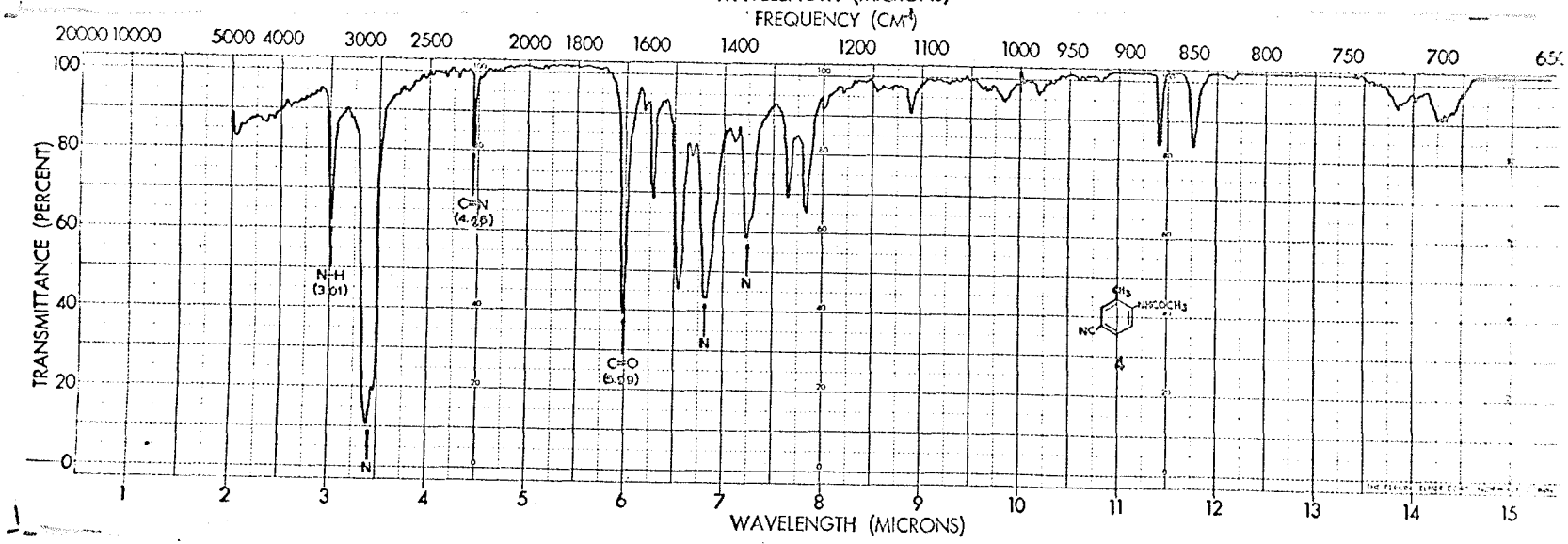
(25 ml) and the mixture warmed on a water bath for 5 minutes at 60°C. in order to assure the removal of any adhering organic product from the inorganic material. The latter was filtered off and the combined ethyl acetate extracts separated from the aqueous solution. The water solution was extracted with the ester (50 ml) once more. The whole of the ethyl acetate layer was washed with saturated sodium chloride solution (2x100 ml) until the latter was neutral to litmus and dried with anhydrous sodium sulfate overnight. The ethyl ester solution was evaporated at the aspirator yielding an orange solid (3.3 g, m.p.143-146.5°C.). A mixed melting point with the starting material gave a depression. Recrystallization from aqueous ethanol in the presence of decolourizing charcoal (twice) gave the desired 2-acetamido-5-cyanotoluene m.p.144-5-146.5°C. The characteristic nitrile band in the infrared spectrum of the compound was present at 4.46 μ as seen in Figure 4.

It is convenient to point out here that infrared spectra of this and subsequent compounds were recorded on a Perkin Elmer Model 21 (sodium chloride prism) Infrared Recording Spectrophotometer. Samples were prepared in the form of mineral-oil (Nujol) mulls between sodium chloride disks. Particular absorption bands were identified as to type and their position (in microns) noted in the original spectra. The Figures included here represent reproduced spectrograms. Since no calibration line was recorded in

FIGURE 3. Infrared spectrum of Nujol.

FIGURE 4. Infrared spectrum of 2-acetamido-5-cyanotoluene (Nujol mull).


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
C-H (3.50) (3.46)
C-H (6.83)
(7.28)
NUJOL (N)
3
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
N-H (3.01)
N
C=N (4.48)
C=O (5.99)
N
N
CH3
NC
OCH3
4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

any of the spectrums, wavelength values may not be accurate but qualitatively they are most adequate. The useful monographs of Cross (396) and Dyer (397) and the book co-authored by Colthup, Daly and Wiberly (398) assisted in identifying characteristic functional group absorptions. The Nujol spectrum is presented in Figure 3 for purposes of distinguishing the superimposed absorptions caused by C-H stretching and bending vibrations. The spectra of anthranilic and N-acetylanthranilic acid in Figures 7 and 5 respectively have been included for convenient comparison.

The methyl side chain of 2-acetamido-5-cyanotoluene was oxidized by utilizing the method of Leggate and Dunn (12).

The 2-acetamido-5-cyanotoluene (2.5 g, 0.014 mole) in acetone* (130 ml) was treated with potassium permanganate (8.2 g, 0.052 mole) and magnesium sulfate (0.96 g) and the resulting mixture stirred for 16.5 hours at room temperature. By this time a thick slush of manganese dioxide had formed. A further quantity of acetone (50 ml) was added to facilitate stirring which was continued for some 11 hours. A 20% sodium bisulfite solution (approximately 25 ml) was added to discharge the permanganate colour. The reaction mixture was filtered and the precipitated manganese dioxide washed with acetone (200 ml). When the supernatant was evaporated at the aspirator to remove most of the acetone,

---

*Acetone was initially purified for use in the permanganate oxidation by refluxing with and distillation from solid potassium permanganate.

a first crop of colourless crystals (1.1 g) separated from the solution, m.p. 146.2-147.5°C.* A mixed melting point with the starting material gave no depression. Concentrated hydrochloric acid was added to the aqueous filtrate to give a colourless flocculent precipitate which was suction filtered and washed with cold water (1.1 g, m.p. 192-193.8°C.). Mixed melting points with the starting material and with the first crop of crystals gave depressions. A recrystallization from water (little ethanol) provided colourless crystals of 2-acetamido-5-cyanobenzoic acid with a melting point of 193.5-194.5°C.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C,58.80; H,3.95; N,13.73

$C_{10}H_8N_2O_3.H_2O$: C,54.05; H,4.54; N,12.61

Found: C,54.26;H,4.64; N,12.46.

The infrared spectrum of 2-acetamido-5-cyanobenzoic acid is reproduced in Figure 6. The two partially fused absorption bands at ~6.0 μ are indicative of the two carbonyl groups in the molecule. The presence of the three reasonably distinct absorptions between 2.8-3.2 μ is more difficult to explain although the quantitative elemental analysis gives a clue to a possible interpretation. Generally, the water spectrum of a liquid sample exhibits broad absorption due

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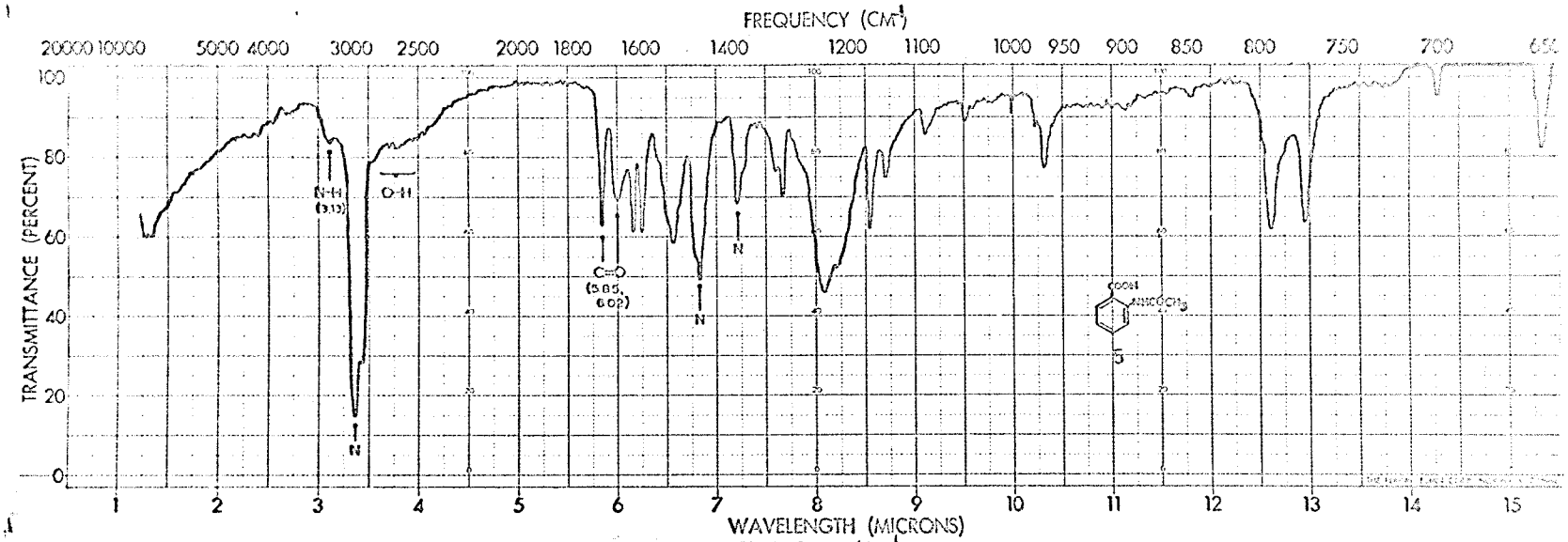
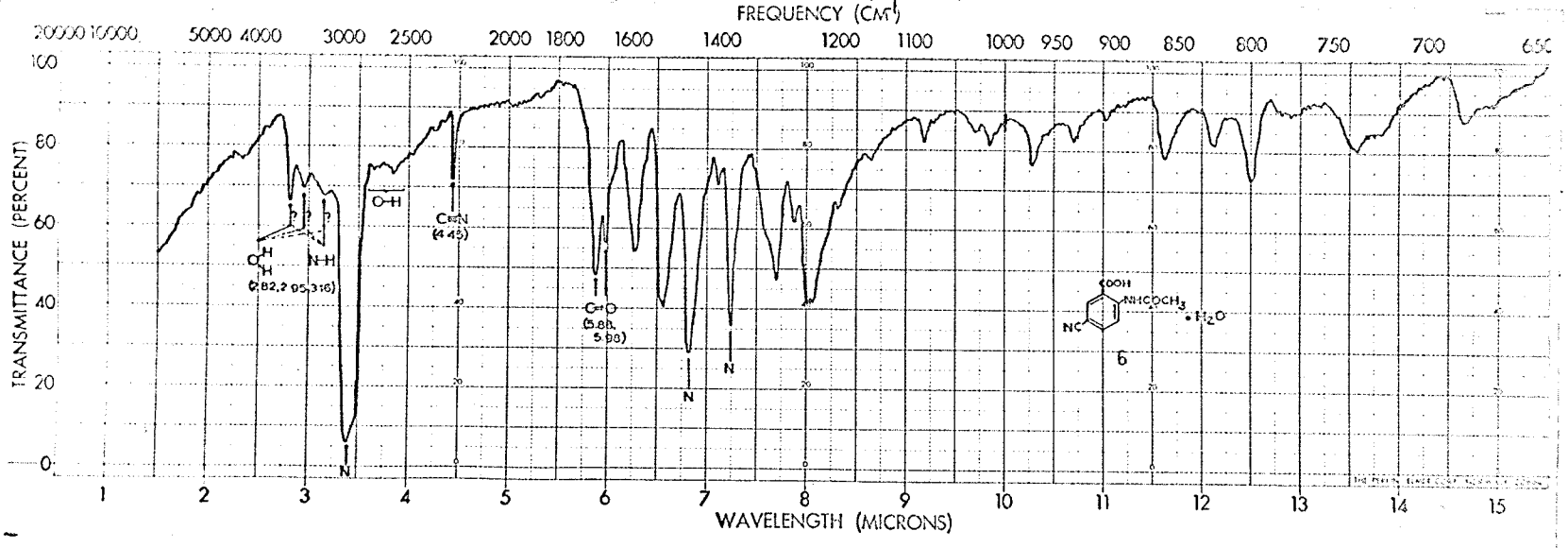
*In subsequent attempts at this preparation it was found that the separation of the unreacted material from the desired product was facilitated by extraction of the whole mixture at this stage with chloroform. The reactant passed into the haloform layer and the acid remained in the aqueous layer until recovered by the addition of strong acid.

FIGURE 5. Infrared spectrum of N-acetylanthranilic acid (Nujol mull).

FIGURE 6. Infrared spectrum of 2-acetamido-5-cyano-benzoic acid (Nujol mull).


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
N-H (3.13)
O-H
C=O (5.85, 6.02)
N
N
N
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
O-H
C≡N (4.45)
N-H
(2.82, 2.95, 3.16)
C=O (5.88, 5.98)
N
N
N
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

to O-H stretching vibrations in the region 2.7-3.2μ (398). However, if water is present in the molecule as water of crystallization then it might be expected that the vibrations associated with the hydroxyl group may become better defined depending on the kind of association present in the Nujol suspension system. The longer wavelength absorption (i.e., 3.16 μ) is tentatively ascribed to the N-H stretching vibration since all systems examined spectrally, which have an acetamido group ortho to a carboxyl function, displayed absorption in this region (i.e., >3.0 μ). This was the case with N-acetylanthranilic acid (Figure 5) and the halo acids (N-acetyl-4-chloroanthranilic and N-acetyl-4-bromoanthranilic) whose spectra are not included here. Furthermore, the N-H peak in this area is often less well defined and may appear to be absent or at least submerged in the lower wavelength shoulder of the Nujol (~3.4 μ) absorption. This seems to be the case in 2-acetamido-4-cyanobenzoic acid (Figure 11, page 211). It is recognized that associated or bonded N-H stretching vibrations commonly produce absorptions at higher wavelengths (~3.0-3.2 μ) than those attributed to free N-H stretching (~2.9 μ) (396, 397).

The amide hydrolysis of 2-acetamido-5-cyanobenzoic acid was carried out by warming 0.22 g (0.0011 mole) of the anilide with concentrated hydrochloric acid (1.0 ml) at 70-75°C. for 20 minutes. As soon as a solid began to

separate from the mixture, water (3 ml) and concentrated hydrochloric acid (1.0 ml) were added and heating continued. The pasty mass was filtered under suction and the product air dried (0.13 g, m.p. 242-246°C.dec.). A recrystallization from aqueous ethanol gave the 5-cyanoanthranilic acid, m.p. 255-256°C. dec. The infrared spectrum is given in Figure 8.

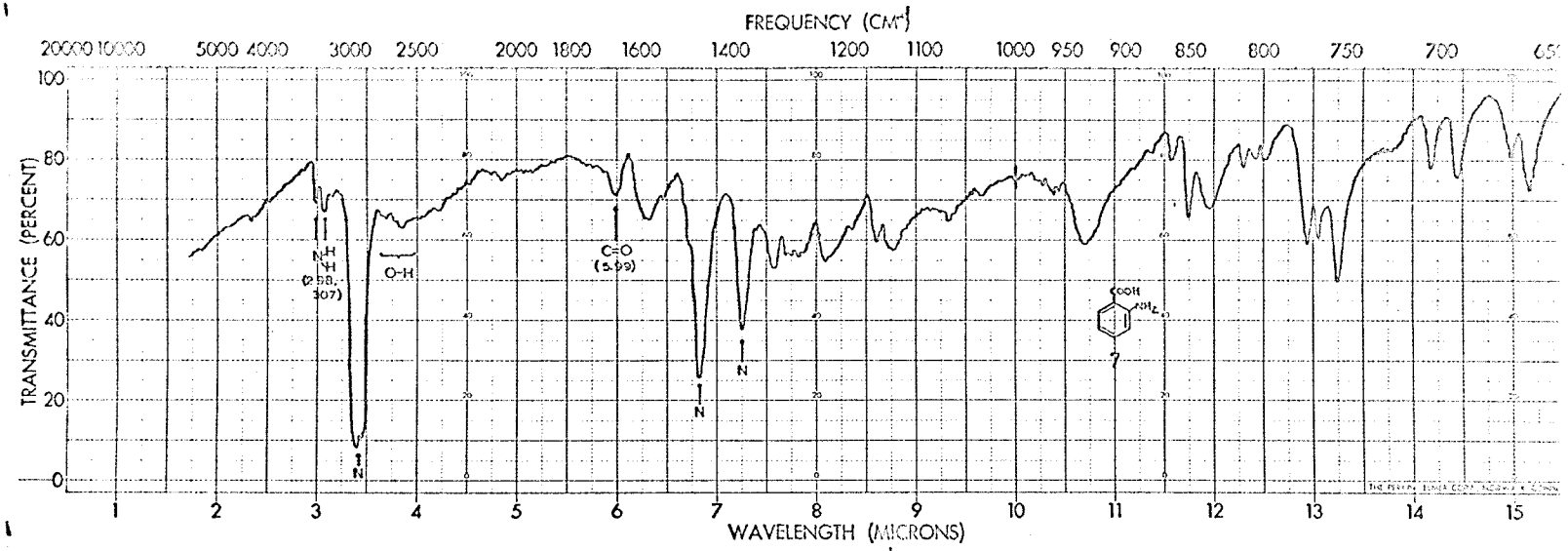
Anal. Calc'd for $C_8H_6N_2O_2$: C,59.24; H,3.73; N,17.29
Found: C,59.09; H,3.73; N,17.26

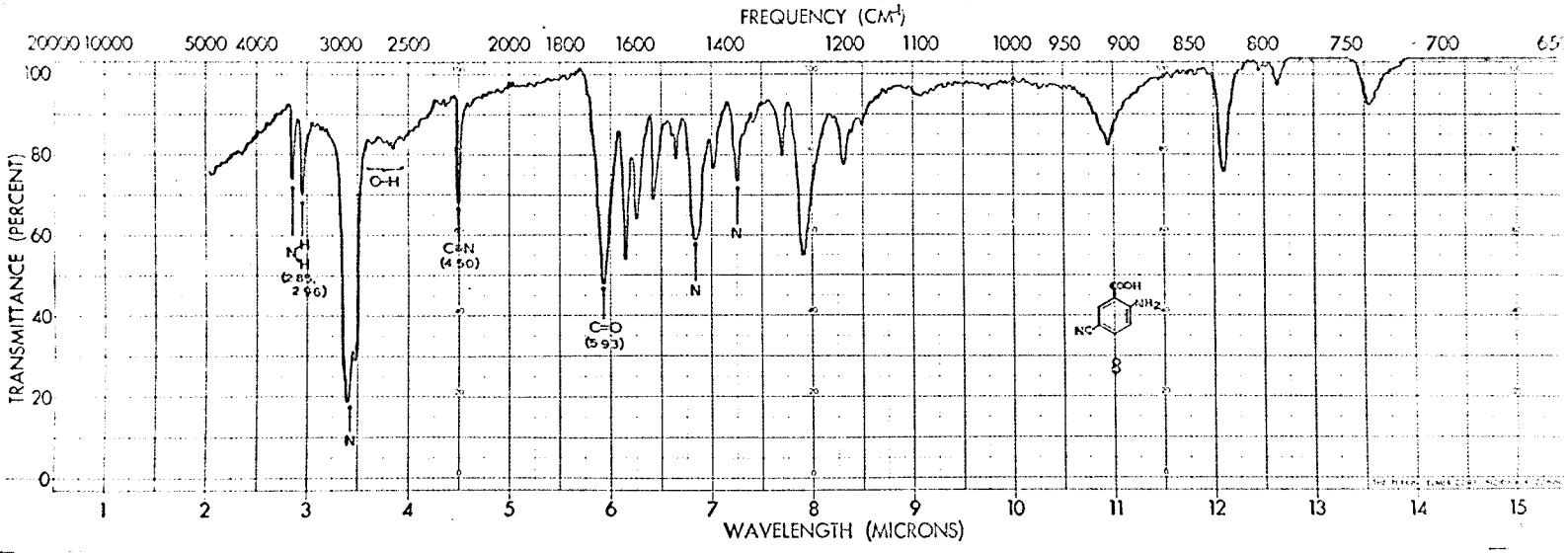
(ii) The 5-cyanoanthranilic acid was also prepared by the method of Friedman and Shecter (399) and Dunn and Kung (287). The latter workers used it to prepare 5-cyanosalicylic acid.

A mixture of 5-iodoanthranilic acid (6.0 g,0.023 mole), an Aldrich Chemical Co. preparation, and cuprous cyanide (2.4 g.,0.027 mole ; Fisher Certified Reagent) with 50 ml of dimethylformamide (Fisher Certified Reagent) was refluxed for 2.5 days. The original light green heterogeneous mixture had turned a dark brown. This was allowed to remain at room temperature for several days and then poured into a solution of ferric chloride hexahydrate (5.1 g) in concentrated hydrochloric acid (15.4 ml) and water (15.4 ml) and heated on a water bath at 80-90°C. for 45 minutes. Ether (6x100 ml) was used to extract the mixture leaving behind a thick dark-brown residual liquid. The reddish-brown

FIGURE 7. Infrared spectrum of anthranilic acid (Nujol mull).

FIGURE 8. Infrared spectrum of 5-cyanoanthranilic acid (Nujol mull).


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
N-H (2.88, 3.07)
O-H
C=O (5.99)
N
N
N
COOH
NH2
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
N-H (2.85, 2.96)
O-H
C≡N (4.50)
C=O (5.93)
N
N
N
COOH
NH2
NC
8
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

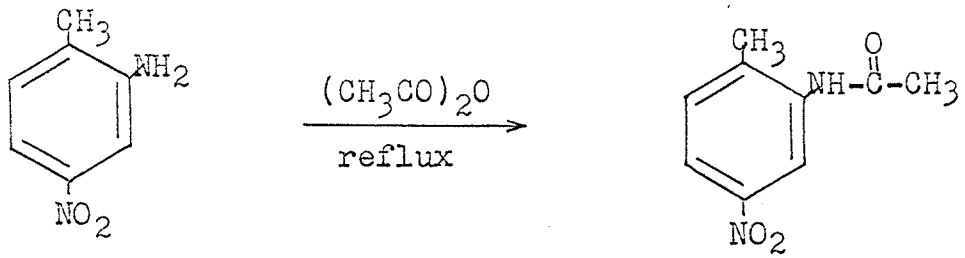
ether extracts were washed with a solution of sodium sulfite acidified with concentrated hydrochloric acid to remove the iodine colour (until only a yellow colour persists). The ether was washed with water until the wash water was neutral to litmus, dried overnight with anhydrous magnesium sulfate and evaporated leaving a yellow solid (1.2 g, m.p. 238.5°C. dec.). A recrystallization from aqueous ethanol gave colourless crystals with melting point 247.5°C. dec. A mixed melting point with the starting material produced a depression whereas the melting point of a mixture of a sample of this preparation with the 5-cyanoanthranilic acid prepared in (i) gave no depression.

Attempted Preparation of 4-Cyanoanthranilic Acid

The procedure followed in the preparation of 4-cyanoanthranilic acid was the same as that described for the 5-cyano isomer (i) and is schematically shown in the flow diagram (Figure 9). The product in the final step, that is, the deacetylation, still requires adequate confirmation. Because of the close similarities in the two preparation schemes, only those phases will be described below that have not as yet been treated or involve significant modifications. Also included will be an indication of yields from starting materials and certain physical characteristics.

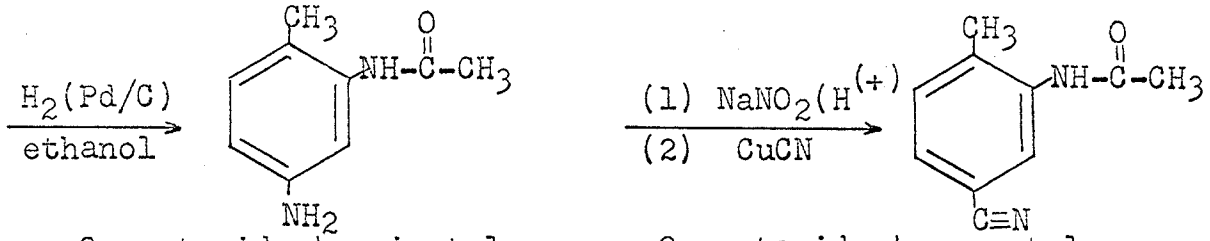
Acetylation of 2-amino-4-nitrotoluene (Matheson, Coleman and Bell) was accomplished by using the method of Dunn and

FIGURE 9. Flow scheme for the (attempted) preparation of 4-cyanoanthranilic acid.



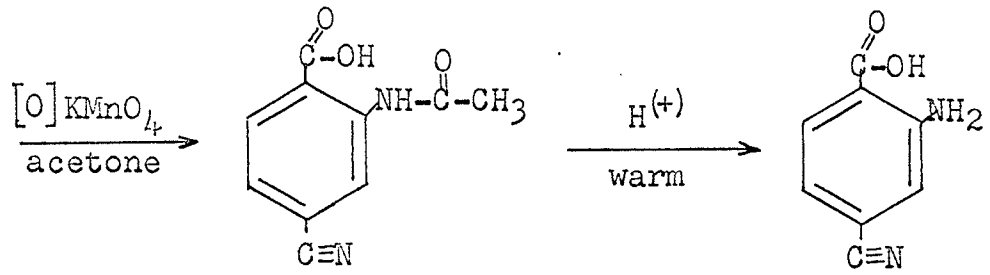
2-amino-4-nitrotoluene

2-acetamido-4-nitrotoluene
(150-154°C.) *



2-acetamido-4-aminotoluene
(142-143°C.) *

2-acetamido-4-cyanotoluene
(154.2-155.4°C.)



2-acetamido-4-cyanobenzoic acid
(232.5-233.5°C.)

4-cyanoanthranilic acid

? (240-242.5°C.)*

* Not recrystallized.

Prysiazniuk in their preparation of 2-acetamidotoluene.

Twenty-five grams (0.16 mole) of 2-amino-4-nitrotoluene (m.p. 103 - 107°C.) was refluxed for 1.5 hours with acetic anhydride (23. g, 0.22 mole) in benzene (100 ml). Water was added (3 ml) to destroy the excess anhydride and heating was continued for a further 15 minutes. The mixture was cooled and the acetyl derivative collected (28.7 g); m.p. softening at 140°C. and melting at 150 - 154°C.(lit., 149-150 (2); 151°C. (388); 150 - 151°C. (389).

Hydrogenation of 2-acetamido-4-nitrotoluene (10. g, 0.051 mole) resulted in 7.4 g of 2-acetamido-4-aminotoluene. A mixed melting point with starting material showed a depression. Included in this quantity was a first crop of colourless crystals which had a melting point/(lit., 139 - 140°C. (400)). 142-143°C.

The procedure involving diazotization and the subsequent Sandmeyer reaction for the preparation of 2-acetamido-4-cyanotoluene followed closely that developed for the 5-cyano derivative. Here, however, the ethyl acetate extract containing the reaction product was treated with decolourizing charcoal prior to recovery of the dissolved solid by evaporation of the solvent. Two crops of crystals (total 2.9 g) were obtained from 4.1 g of 2-acetamido-4-aminotoluene (0.025 mole) with the first having a melting point of 149 -152°C.

A mixed melting point with starting material gave a depression. A recrystallization from aqueous ethanol using decolourizing charcoal afforded colourless fibrous needles of 2-acetamido-4-cyanotoluene, m.p. 154.2 - 155.4°C. The characteristic nitrile band in the infrared spectrum is seen at 4.47μ in Figure 10.

Potassium permanganate oxidation of the 2-acetamido-4-cyanotoluene was carried out in aqueous solution by a method similar to that used by Dunn and Prysiazniuk (2) and in acetone by the procedure outlined previously. In one trial of the latter method a yield of 0.9 g of 2-acetamido-4-cyanobenzoic acid was obtained from 1.8 g of starting material (0.10 mole). A recrystallization from aqueous ethanol gave colourless needles with melting point 232.5 - 233.5°C.

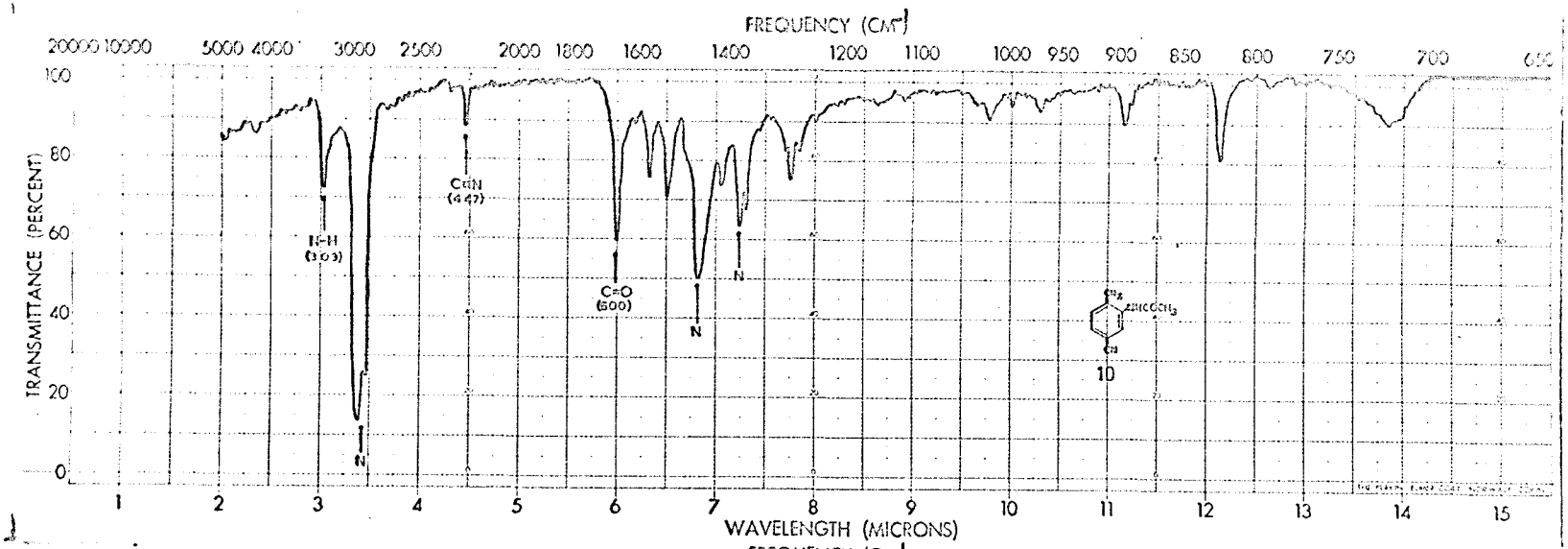
Anal. Calc'd for $C_{10}H_8N_2O_3$: C,58.80; H,3.95; N,13.73
Found: C,59.21; H,4.10; N,13.53

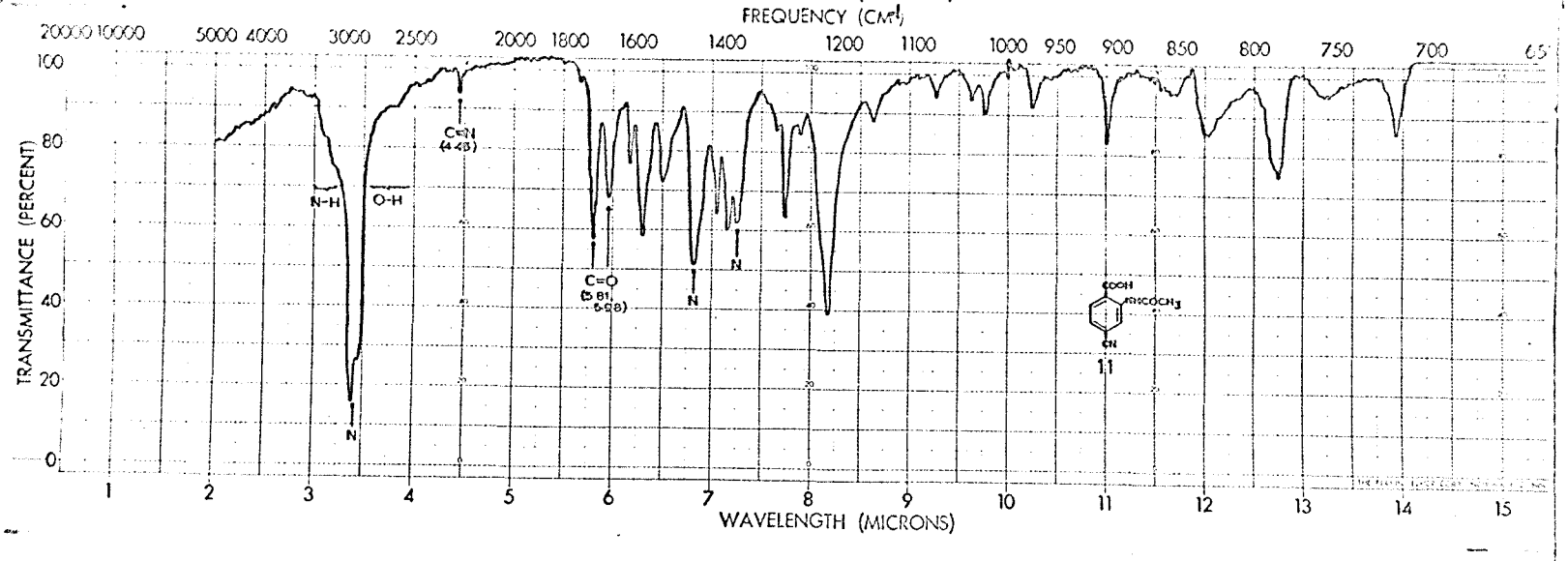
The infrared spectrum of the acid is exhibited in Figure 11. The absorption due to the N-H stretching vibrations is not clearly evident but it could well be that the acid concentration in the mineral oil suspension is not adequate, as is apparent from the small intensity of the cyano absorption at 4.46μ. Nevertheless the pair of absorptions near 6.0μ are consistent with the two carbonyl functions.

Both acidic and basic hydrolyses of the anilide

FIGURE 10. Infrared spectrum of 2-acetamido-4-cyanotoluene (Nujol mull).

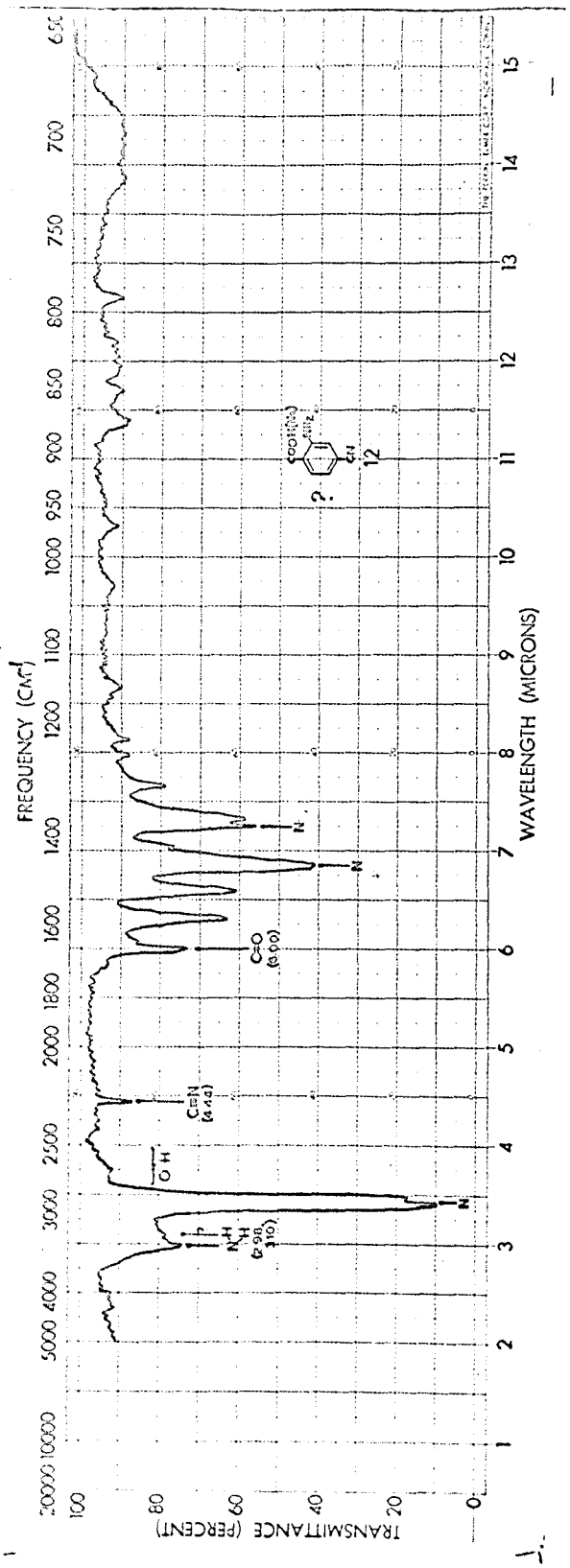
FIGURE 11. Infrared spectrum of 2-acetamido-4-cyanobenzoic acid (Nujol mull).


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
N-H (3.09)
C≡N (4.47)
C=O (6.00)
N
N
N
10


FREQUENCY (CM⁻¹)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700 65
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
N-H
O-H
C≡N (4.45)
C=O (5.81, 6.28)
N
N
N
11

were attempted. From the acidic hydrolysis, similar to that outlined earlier, 2-acetamido-4-cyanobenzoic acid (0.25 g, 0.0012 mole) afforded 0.18 g of colourless crystals with melting point 240 - 242.2°C. A mixed melting point with starting material gave 240 - 242°C. which indicated no depression and a higher temperature than the melting point established for 2-acetamido-4-cyanobenzoic acid. The acidic hydrolysis was repeated and once more a mixed melting point showed no depression. The amide (0.09 g) was also treated with 4 ml of 5% aqueous sodium hydroxide at room temperature for 5 minutes. A colourless flocculent precipitate formed which was filtered and air dried. This material appeared to begin to melt at 190°C. but the sample remained cloudy as the temperature was increased and the liquid formed. This may be an indication that some inorganic material is also present. The filtrate from the alkaline hydrolysis was acidified with concentrated hydrochloric acid and the colourless precipitate which formed was filtered. The material procured from this HCl treatment had a melting point 230 - 235°C.dec. The infrared spectrum in Figure 12 is that taken of the substance precipitated from the alkaline mixture. Only one absorption apparently remains at 6.00 μ which represents the carbonyl stretching vibrations of the carboxylate group.This is in contrast to the spectrum

FIGURE 12. Infrared spectrum of 4-cyanoanthranilic acid (?)(Nujol mull).


TRANSMITTANCE (PERCENT)
FREQUENCY (CM⁻¹)
WAVELENGTH (MICRONS)
C≡N (4.46)
C=O (5.90)
O-H
N-H (2.98, 3.10)
2.
C≡N
12

of the starting material (Figure 11). Carboxylate anion stretching absorptions are usually found to slightly longer wavelengths (396, 397). One of the probable N-H stretching absorptions typical of primary aromatic amines is not well defined but both are very similar to those of anthranilic acid (Figure 7) as to location in the spectrum. These observations may suggest that the product (at least the one for which the infrared spectrum is available) may be a mixture of the anilide and the desired 4-cyanoanthranilic acid. No further attempts were made in order to establish with certainty the nature of the products obtained in the hydrolysis experiments.

MISCELLANEOUS

A number of other materials have been utilized either in the potentiometric titrations, proton magnetic resonance or ultraviolet spectrophotometric phases of the work and are recorded below.

Benzoic acid (Fisher Certified Reagent) had a melting point of 122.0 - 123.2°C. (lit.,122.4°C.(126i)).

In the ultraviolet spectrophotometric experiments anthranilic acid and its 4-nitro, 5-nitro and 5-methyl derivatives together with salicylic acid and its 4-nitro, 5-nitro and 4-methoxy derivatives were available in the lab as a result of other work in the present investigation or from past research (11, 12, 287). In most cases they

did not correspond to the same quantities of material which were specially prepared for the decarboxylation and potentiometric titration experiments (i.e., those listed in Table IX). Sodium salicylate was a BDH chemical.

Trifluoroacetic acid and its anhydride were Eastman Organic Chemicals and have been used without further treatment.

Concentrated sulfuric acid was a C.I.L. CP reagent (95.5% min.).

Dimethyl sulfoxide was acquired from Matheson Coleman and Bell (Spectroquality Reagent), dried over calcium hydride and fractionally distilled at atmospheric pressure collecting the fraction boiling at 188°C.*

Absolute methanol was a Fisher Certified Reagent used without further purification.

In the spectrophotometric experiments the pyridine was either a Fisher Certified Reagent or the Karl Fisher Reagent from Matheson Coleman and Bell and was used without further treatment.

A methanolic solution of sodium methoxide was prepared from material obtained from Matheson Coleman and Bell.

N-ethylpiperidine, prepared originally by Byrnko (401),

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* The author is grateful to members of the nuclear magnetic resonance section of the Department for a quantity of this solvent.

was dried over barium oxide and distilled. The fraction boiling between 119 - 128°C. at 741 mm was collected. Much better physical constants were recorded for this product by Brynko. It is quite likely that a small quantity of piperidine was also present in the solvent. Mention had already been made of this possibility (401). Because of the exploratory nature of the work in this case and because the main point was to have available a strong organic nitrogenous base (pK_a (H_2O) = 10.45 at 23°C. and 11.11 at 25°C. for 1-ethylpiperidine and piperidine respectively (402)), it was felt unnecessary to purify the product further.

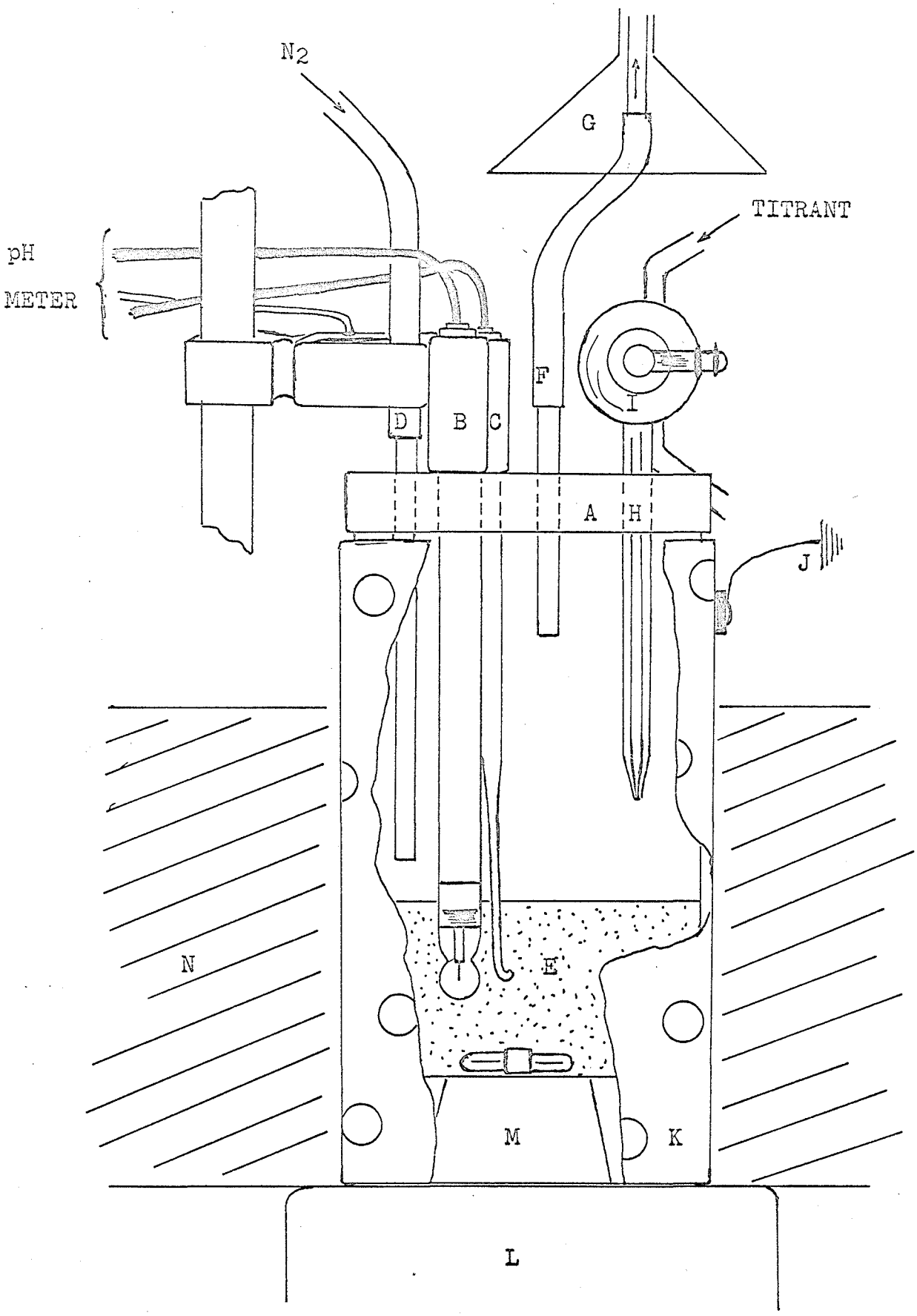
B. POTENTIOMETRIC TITRATIONS

APPARATUS

Titrations were performed using a Radiometer Type PHM 4c pH meter set to read voltage (mv) directly. The Radiometer electrodes were a G202B glass electrode and a K100 calomel reference electrode which was of the open liquid-junction type. The calomel electrode was modified by replacing the aqueous potassium chloride in the salt bridge with a saturated solution of potassium chloride in methanol (Fisher Certified Reagent).

Figure 13 shows the titration vessel assembly and Figure 14 presents a top view of the vessel cover.

FIGURE 13. Titration vessel assembly for the potentiometric titrations. Reference to the letters is made in the description of the apparatus.


N_2
G
TITRANT
pH
METER
F
I
D
B
C
A
H
J
N
E
M
K
L

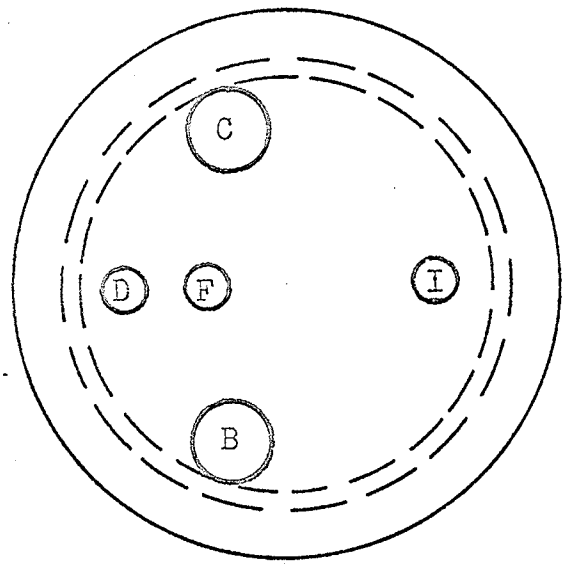


FIGURE 14. Top view of the vessel cover (A) in the titration assembly. Reference to the letters is made in the description of the apparatus.

A tall-form beaker (6 x 10 cm) served as titration vessel fitted with a masonite cover (A) into which various holes were drilled in order to accomodate the glass (B) and calomel (C) electrodes, an inlet (D) extending to approximately 0.5 - 1 inch above the surface of the solution (E) to provide a blanket of nitrogen, an outlet (F) leading to an inverted funnel (G) connected to a vacuum line under gentle suction to draw off obnoxious pyridine vapours and an opening (H) for the burette tip (I). A perforated grounded (J) steel cylinder (K) completely enclosed the vessel and thereby helped to shield the electrodes from any electrical interference. Solutions to be titrated were agitated with a magnetic

stirrer (L) during the titration. An inverted plastic cup (M) elevated the titration vessel from the bottom of the glass water bath (N). The latter was supported on top of the magnetic stirrer. The temperature of the bath water surrounding the titration vessel and recorded by an Anschutz thermometer was kept at 25.0 ±0.1°C. by means of a thermistor probe and relay system which activated an electric light bulb used to warm the water. Addition of sodium chloride to the bath water (agitated continuously with a mechanical stirrer) provided an additional shield. The pH meter, electrode holder, perforated metal shield and bath water were all grounded.

The titrant was conveniently stored in the reservoir of a 10-ml automatic-filling burette protected from atmospheric moisture and carbon dioxide by tubes of magnesium perchlorate and Ascarite. Nitrogen, which was used both to aid in filling the burette and to provide a blanket of inert atmosphere over the solution to be titrated, was first passed through tubes containing the desiccant and the Ascarite.

Prior to use, the glass electrode was rejuvenated by allowing it to soak in 0.1 N hydrochloric acid solution overnight, rinsed with water and stored ready for use in a beaker of distilled water. If titrations were discontinued for prolonged periods (1 - 2 weeks), the electrode was immersed in pyridine for a period of 0.5 -

1 hour just before commencing the titration. The aqueous solution of potassium chloride was drained from the calomel electrode and the electrode flushed with saturated potassium chloride-methanol solution several times and then stored ready for use filled with the methanolic salt solution.

PROCEDURE

A sample of the acid to be titrated (7.527×10^{-4} mole) was weighed in a tall-form beaker and dissolved in 50.0 ml of pyridine or quinoline introduced by means of a hypodermic syringe. A few acids (nitro acids in particular) were aided in dissolution by warming the mixture gently for a few seconds and stirring the solution magnetically, whereas the vast majority of acids dissolved quite readily. The glass electrode was wiped dry with a soft tissue paper and a fresh surface was provided at the open-liquid junction of the calomel electrode by allowing the methanolic potassium chloride solution to drip through the inverted opening. Solutions were titrated as soon after their preparation as possible taking care to minimize contact with the atmosphere. Titrant was added in approximately 0.1 ml increments in the region of half neutralization and by drops (0.02 - 0.03 ml) near the end point. Data was recorded by noting the volume of titrant added and the corresponding millivolt

reading on the pH meter. Some slow gradual drift in the potential was experienced during the titrations. Readings were taken approximately 10 - 15 seconds after each increment of titrant was added, allowing enough time for the neutralization reaction to proceed and the electrodes to respond to the environmental change in the solution. Titrations were carried well past the end point in all instances. At the end of the titration, the glass electrode was rinsed with ethanol and distilled water and the calomel electrode rinsed with ethanol and wiped dry once again allowing fresh methanolic salt solution to come to the open-junction surface of the electrode.

A blank titration determined on 50 ml of pyridine amounted to only 0.02 ml of titrant, the limit to which the increments of titrant could be added and, therefore, was neglected.

C. DECARBOXYLATION

APPARATUS

The rates of decarboxylation were determined by a gravimetric method in which the envolved carbon dioxide was absorbed by tubes containing Ascarite. The procedure, modified a number of times, has been used previously in this laboratory in decarboxylation studies (2, 4, 5).

The reaction vessel was modified slightly in design from that used by Janzen (4) and is shown in Figure 15 to actual size. It was built from a 34/45 male ground-glass joint and included a gas inlet and a thermocouple well. A size 19 ground-glass joint connected the vessel to the condenser.

Figure 16 presents a schematic diagram of the thermostat and manostat system used in the decarboxylations. The set up was essentially that used by Rodewald (5). The temperature of the reaction vessel was controlled by means of the manostated thermostat which consisted of a 2-litre round-bottomed flask (A) fitted with a Friedrich condenser (B), openings (C) to fit the ground-glass joints of the reaction vessel, a thermocouple well (D) and an opening to fit the thermister probe (E).* The thermostat was heated with an electric heating mantle (F) regulated by a variac (G), thereby allowing a liquid such as phenyl ether to reflux gently in the flask providing the vapour which continually bathed the reaction vessel. The exposed upper portion of the glass flask was covered with asbestos. An iron-

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* A silicone rubber plug was prepared to fit this opening in order to firmly grip the thermister probe. Two openings (C) (shown with fitted stoppers) in the round-bottomed flask for each reaction vessel. However, in attempting two decarboxylations concurrently, it proved difficult to maintain the same temperature in both vessels so that this procedure was discontinued and each run was conducted separately.

FIGURE 15. Glass reaction vessel used in decarboxylation experiments (actual size).

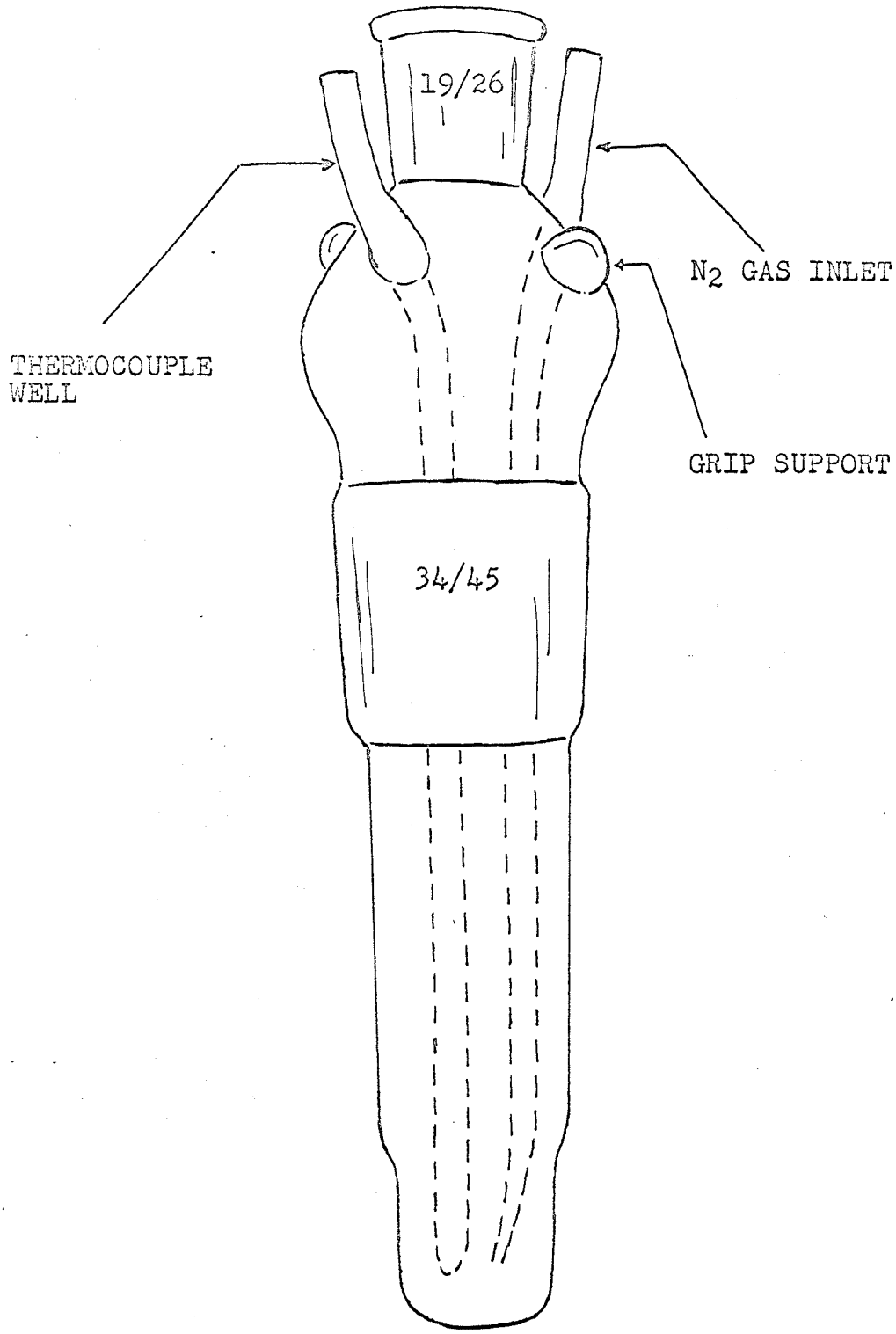
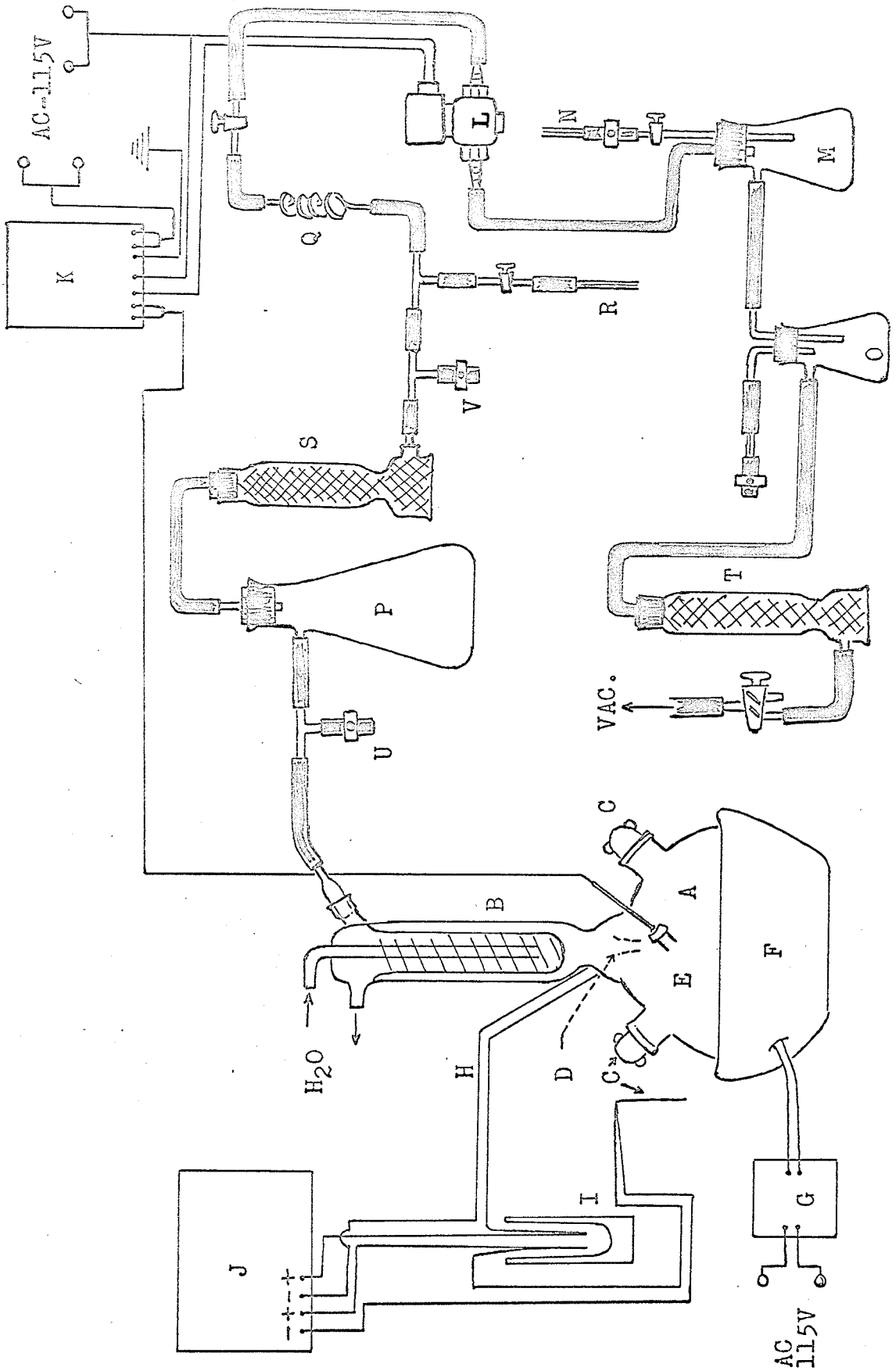

19/26
THERMOCOUPLE WELL
N_2 GAS INLET
GRIP SUPPORT
34/45

FIGURE 16. Schematic diagram of the thermostat and manostat system used in decarboxylations. Reference to the letters is made in the description of the apparatus.


AC-115V
K
L
M
N
Q
R
V
S
P
U
O
T
VAC.
C
A
B
F
E
H
D
C'
I
J
G
H_2O
AC
115V

constantan thermocouple (H) was inserted in the well (D) of the thermostat (behind the flask shown in Figure 16) and in the reaction vessel (C). This vessel has not been included in the figure here (the glass stopper in the side of the thermostat shows its location) but is shown in Figure 17 as part of the absorption train. The difference in potential created by the hot and cold junctions (ice-water in a Dewar flask (I) of the thermocouple was measured with a Tinsley portable potentiometer of the type 3184D (J). Potential difference was converted to temperature by using published tables (403).

A thermister probe and electronic relay (K) (YSI model 63) system coupled to a gas valve (L) was used to obtain a constant and reproducuble temperature in the thermostat. The manostating system was connected through the condenser (B) to the thermostat. A vacuum pump was the source of low pressure connected to a flask (M) which was provided with a capillary leak (N)(0.5 mm bore). Pressure tubing and rubber stoppers were used throughout the vacuum system. It was convenient to place another filter flask (O), fitted with a screw clamp arrangement, before M for occasions when air was allowed to enter quickly into the system. In this way the adjustment of the capillary leak (N) on flask (M) was not disturbed unnecessarily. As the thermister probe (E) activated the thermister relay, the valve (L), a Honeywell magnetic gas valve type 80Z, opened the

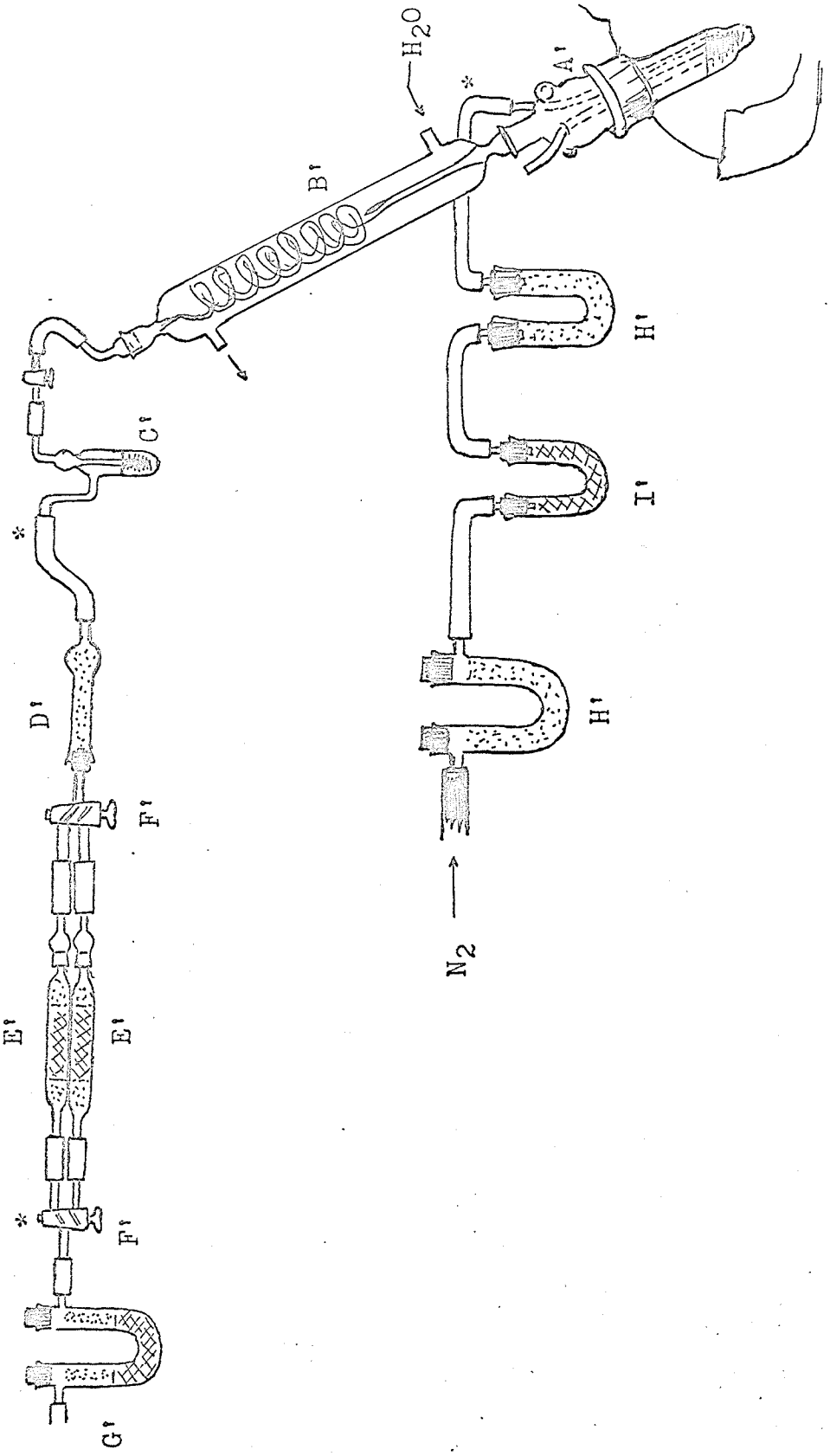
system to the low-pressure flask (M) and the pressure in the thermostat decreased. The thermister probe then deactivated the electronic relay and the gas valve closed when the temperature decreased to the desired value. The cycle repeated itself as the pressure and temperature once again increased in the thermostat. A 2-litre ballast flask (P) and capillary (Q)(1 mm bore) were inserted between the thermostat and low-pressure flask (M) to avoid surging and excess overshooting. The system functioned more satisfactorily if a capillary leak was provided (R)(1 mm bore) in order to build up pressure in the thermostat rather quickly. This allowed the opening-closing cycle of the gas valve to create a favourable equilibrium within which the temperature remained relatively constant varying only within narrow limits. The two temperatures at which most of the decarboxylation experiments were conducted, 200.2° and 230.6°C., were maintained respectively to within ± 0.3°C. and ± 0.4°C. With care in monitoring the system, these outside limits in variation could be reduced to one half the values quoted. Two drying towers were included in the system. One filled with Drierite (S) placed between the leak (R) and the thermostat kept moisture from entering the latter compartment and another filled with anhydrous calcium chloride (T) protected the vacuum pump from water vapour. The stopcocks (U, V) opened the system

to the atmosphere.

If a different temperature was required, the thermister relay control was adjusted to a new setting. In most instances, when the relay control was changed, the leaks (N, R) had to be adjusted also. When the system is being evacuated, it is recommended that these leaks be closed first to enable evacuation to proceed quickly and then reopened as the desired temperature is approached.

The nitrogen-flow system and absorption train is depicted in Figure 17. The reaction vessel (A') is shown inserted in the neck of the boiling flask. The condenser (B'), a combination of the Liebig and Graham type, and the n-butyl phthalate bubbler (C') helped to eliminate organic vapours from the rest of the train. Any water vapour that may have entered the system when the apparatus was opened, was removed by the drying tube (D') filled with Anhydrone (magnesium perchlorate). The gas stream could be directed to either absorption tube (E') by means of the two-way stopcocks (F'). These contained mostly Caroxite, an indicating Ascarite, surrounded at both ends by a small amount of magnesium perchlorate to trap any moisture which may have developed in the reaction of carbon dioxide and the Ascarite. The U tube (G') was filled with both Anhydrone and Ascarite, the latter being contained in the central portion of the

FIGURE 17. Diagram of the nitrogen-flow system and absorption train used in the decarboxylations. Reference to the letters is made in the description of the apparatus.


H_2O
A'
B'
C'
D'
E'
E'
F'
F'
G'
H'
H'
I'
N_2

tube. This protected the absorption tubes from entry of carbon dioxide and water vapour from the atmosphere. Nitrogen, that was used to sweep the evolved carbon dioxide out of the reaction vessel and along the train, was first passed through U tubes containing Anhydrone (H') and Ascarite (I'). The nitrogen flow was adjusted with a needle valve in the regulator attached to the gas cylinder. When the system was not used (i.e., reaction vessel and cylinder were absent), certain openings (*) were closed in order to lengthen the lifetime of the material in the absorption tubes. Tygon tubing was used for connections throughout except for the tubing connecting the nitrogen gas cylinder to the first U tube filled with Anhydrone (H').

PROCEDURE

After each experimental run the reaction vessel was rinsed with acetone and cleaned with chromic acid solution allowing the latter to remain in contact with the interior of the vessel at least for an overnight period. Periodically the reaction vessels were cleaned with alcoholic potassium hydroxide solution. Water, acetone or ethanol and ether were used in that order to rinse the vessel free from the cleaning solution and to assist in drying. The condenser (B') was cleaned in a similar manner although not as frequently with the chromic

acid solution. In early experiments the n-butyl phthalate bubbler was replaced after two or three determinations, however, in later runs fresh n-butyl phthalate was used with each new determination. The reaction vessels, condensers and bubblers were stored in an oven at 50 - 60°C. until used.

Acids were introduced into the reaction vessel in the form of pellets prepared by use of a hydraulic pellet press. In decarboxylation studies in nitrobenzene 0.15 - 1.0 g of the acid was used and in quinoline approximately 0.05 to 0.20 g. If a series of runs were attempted with the same acid, pellets were stored in a desiccator over Drierite, each isolated and kept in a folded piece of aluminum or tin foil.

At the start of a run an empty reaction vessel was introduced into the thermostat, the condenser attached and a temperature close to the desired one established in the system by monitoring the potentiometer (thermocouple in thermostat well) and thermister relay. Nitrogen was allowed to sweep through the whole system for approximately 10 - 15 minutes. The condenser was lifted and solvent (10 ml of nitrobenzene or 15 ml of quinoline) to be used was introduced into the reaction vessel by means of a hypodermic syringe fitted with a 5 - 6 inch needle and the absorption train reconnected. The nitrogen flow was adjusted to a convenient rate chiefly determined

by having an efficient sweep through of carbon dioxide from vessel to absorption tube particularly with those acids that decarboxylated readily. The rate of nitrogen flow was checked initially and periodically throughout the experiment by counting the bubbles appearing in the n-butyl phthalate bubbler. With the aid of the thermo-couple in the reaction-vessel well an adjustment was made to the relay control in order to obtain the desired temperature in the vessel. When the system had come to equilibrium, the absorption tubes were weighed, a pellet of the acid to be decarboxylated dropped into the top of the reaction vessel, the train reconnected and the timer started. A slight relay-control adjustment was often required at this stage. It should be noted, that at the times when the addition of solvent and pellet were made to the reaction vessel, the tube delivering the nitrogen was momentarily disconnected from the vessel to minimize loss of hot solvent but quickly replaced in order to complete the absorption train. A certain time interval was required for the pellet to dissolve and temperature equilibrium to be reestablished. In the case of acids which decarboxylated rather quickly attempts were made to keep this period to a minimum (100 - 300 secs.). With slowly decarboxylating acids the time was extended (1000 - 2000 secs.) in order to trap the first traces of carbon dioxide from the reaction vessel. The start of

zero time for the reaction was taken at the end of this initial period. Data for the experiment were recorded by weighing the absorption tubes periodically and recording the corresponding times for the collection of the carbon dioxide. The system was checked for temperature control periodically and any fine adjustments to air leaks or relay control made.

Blank determinations were carried out at the temperatures used in the decarboxylation studies. In these instances the procedure was identical excluding only the acid. The small increment increase in weight of the absorption tube was recorded corresponding to the time and these values subtracted from the weight obtained in regular experiments. For acids that decarboxylated relatively quickly the correction could virtually be neglected.

The thermocouple (used in reaction-vessel well) was calibrated by balancing the Tinsley potentiometer at various temperatures recorded by the previously calibrated Anschutz total-immersion thermometer. The hot junction for the thermocouple in this case consisted of a 4-litre beaker filled with silicone oil in which the thermometer was immersed and which was heated to temperature by an external hot plate. A mechanical stirrer helped to circulate the bath fluid. A straight line was fitted

to the data consisting of mv readings and temperatures in °C. by the method of least squares. This enabled one to calculate the temperature corresponding to any preset millivolt reading on the potentiometer.

In second-order reactions the magnitude of the specific-rate constant depends, among other things, upon the units of concentration. It was necessary to determine the concentration of the organic acid in each run at the elevated temperatures used. It should be pointed out, however, that the volume of solution contributed by the acid sample was neglected and concentrations were calculated on the basis of the solvent added. Empirical equations enabling one to calculate the density of nitrobenzene were not readily available for such high temperatures and, therefore, the density of the solvent at 200.2°C. was determined experimentally.

Use was made of a reaction vessel similar to that used by Janzen (4) and Rodewald (5) in their experiments in decarboxylation by a manometric procedure. The vessel here was utilized as a pycnometer in conjunction with the thermostat and manostat systems available from the decarboxylation experiments for purposes of determining the density of nitrobenzene at the elevated temperature. The density of this solvent at 200.2°C. was estimated to be 1.023 g/ml. From the weight of 10.0 ml of nitrobenzene a value for the volume at 200.2°C. was cal-

culated to be 11.7 ml. By interpolating between the densities of nitrobenzene at room temperature (24°C.) and 200.2°C. the corresponding volumes of the solvent at 169.7° and 149.5°C. could be estimated to be 11.4 ml and 11.2 ml respectively.

RESULTS AND OBSERVATIONS

A. POTENTIOMETRIC TITRATIONS

Experimental data for typical potentiometric titrations in pyridine and quinoline are given in Tables X and XI respectively. Curves utilizing these data in showing the variation of potential during the course of the titration in pyridine and quinoline are reproduced in Figures 18 and 19 respectively. The examples given are for anthranilic acid, considered to be the parent acid in the entire series of determinations. All the other substituted acids displayed similar behaviour in the solvent in question.

The end point in the titration was usually accompanied by a potential drop of the order of 100 millivolts and, therefore, was readily discerned. The volume of titrant at total or full neutralization (V_f) of the acid was taken to include all the titrant added up to the mid point of the increment for which the ratio $\frac{\Delta E}{\Delta V}$ had the largest value. The volume of titrant at half neutralization was determined from V_f. By interpolating between the potentials corresponding to the volumes on either side of the half-neutralization point, the half-neutralization potential (HNP) was obtained. Possible errors encountered in this interpolation were reduced by adding the titrant in small portions (0.1 ml) in the

TABLE X

POTENTIOMETRIC TITRATION OF ANTHRANILIC ACID (7.527×10^{-4} MOLE) IN PYRIDINE (50.0 ML) 25.0°C. USING 0.1 NORMAL TETRA-N-BUTYL AMMONIUM HYDROXIDE AS TITRANT AND HAVING A HALF-NEUTRALIZATION POTENTIAL (HNP) OF -429.9 MILLIVOLTS.

Volume Titrant, V (ml)	Potential, E (mv)
0	-239.0
0.63	-402.7
1.40	-411.7
2.18	-417.7
3.02	-422.7
3.68	-427.0
4.00	-429.2
4.10	-429.8
4.27	-430.8
4.57	-432.5
5.40	-439.2
6.10	-446.3
6.90	-458.3
7.58	-478.2
7.96	-505.7
8.05	-520.1
8.11	-533.8
8.15	-549.3
8.18	-563.3
8.20	-592.2
8.23	-670.6
8.25	-722.1
8.27	-743.3
8.34	-800.5
8.53	-853.7
8.87	-885.8
9.37	-903.1

FIGURE 18. Plot of the experimental data from Table X showing the variation of potential (E) in millivolts (mv) with the volume of titrant added (V) in millilitres (ml) for the titration of anthranilic acid (7.527×10^{-4} mole) in pyridine (50.0 ml) using 0.1 normal tetra-n-butylammonium hydroxide as titrant. The half-neutralization potential (HNP) is -429.9 m

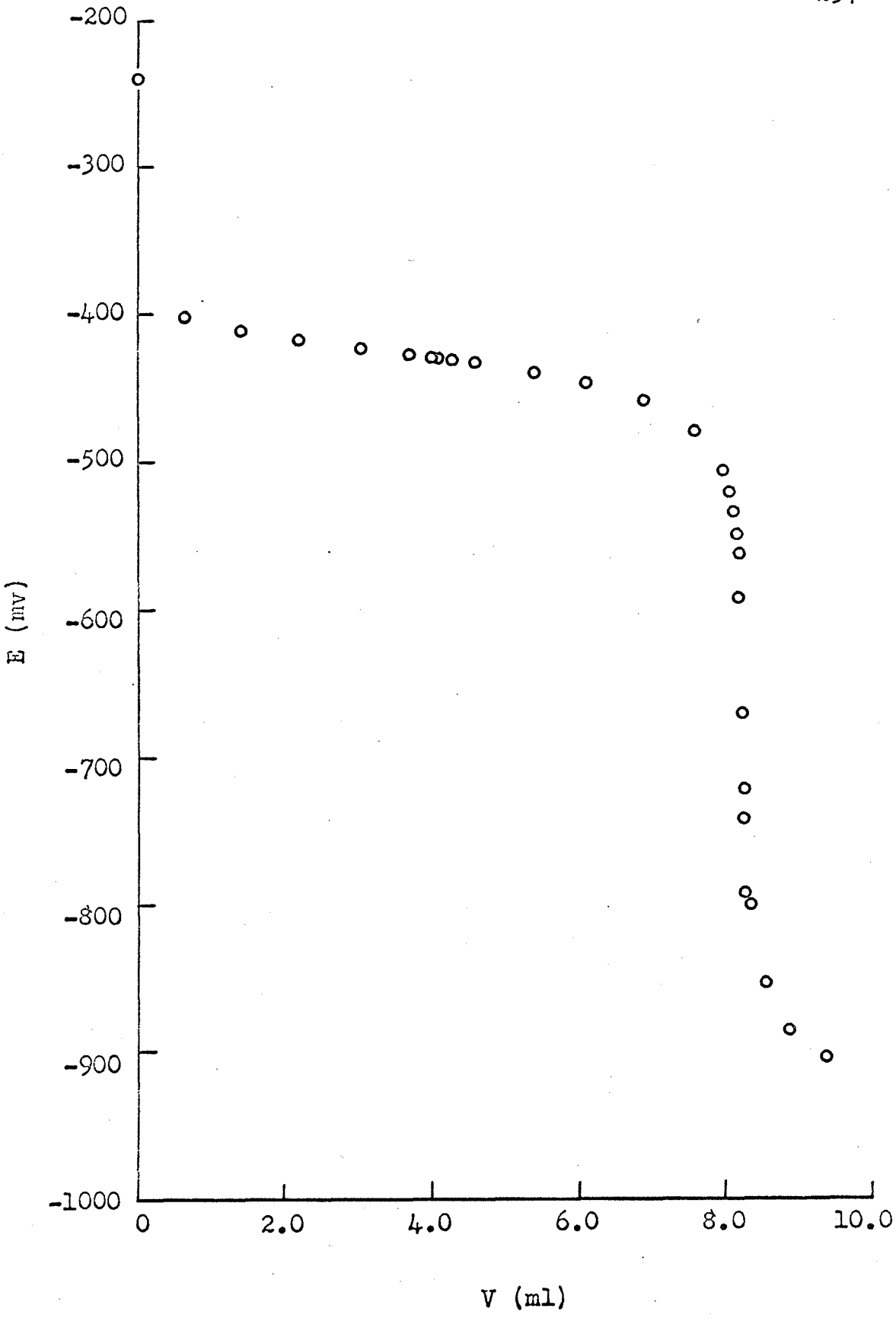

-200
-300
-400
-500
-600
-700
-800
-900
-1000
E (mv)
0
2.0
4.0
6.0
8.0
10.0
V (ml)

TABLE XI

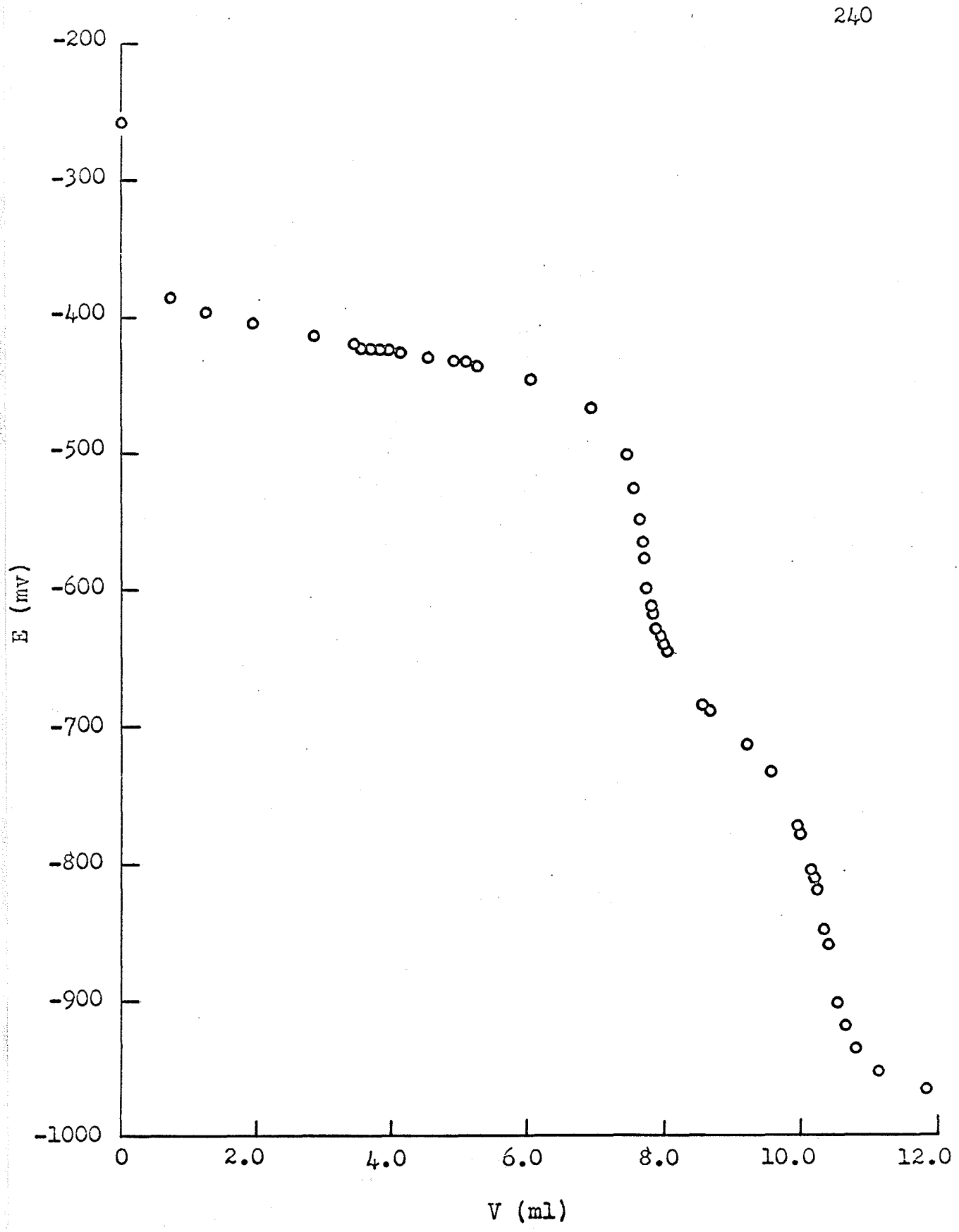
POTENTIOMETRIC TITRATION OF ANTHRANILIC ACID (7.527×10^{-4} MOLE) IN QUINOLINE (50.0 ML) AT 25.0°C. USING 0.1 NORMAL TETRA-N-BUTYL-AMMONIUM HYDROXIDE AS TITRANT AND HAVING A HALF-NEUTRALIZATION POTENTIAL (HNP) OF -423.9 MILLIVOLTS

Volume Titrant, V (ml)	Potential, E (mv)
0	-258.2
0.73	-383.6
1.25	-395.8
1.94	-405.2
2.87	-414.3
3.44	-419.8
3.56	-422.0
3.70	-422.7
3.83	-423.8
3.95	-424.4
4.12	-425.7
4.52	-429.0
4.91	-432.1
5.09	-434.2
5.27	-436.8
6.05	-446.6
6.92	-467.1
7.44	-501.6
7.57	-526.1
7.65	-548.1
7.69	-565.3
7.71	-576.8
7.76	-598.5
7.81	-612.9
7.84	-618.5
7.88	-628.2
7.91	-631.8
7.94	-634.8
7.99	-640.0
8.04	-645.7

TABLE XI Continued

Volume Titrant, V (ml)	Potential, E (mv)
8.55	-685.1
8.64	-688.9
9.20	-714.8
9.54	-734.3
9.93	-772.8
10.00	-778.1
10.15	-806.2
10.20	-811.4
10.23	-820.0
10.32	-849.2
10.40	-860.4
10.51	-904.0
10.64	-918.9
10.80	-936.4
11.15	-953.6
11.84	-966.6
12.73	-971.6
13.62	-972.2
15.84	-966.5
17.00	-962.5

FIGURE 19. Plot of the experimental data from Table XI showing the variation of potential (E) in millivolts (mv) with the volume of titrant added (V) in millilitres (ml) for the titration of anthranilic acid (7.527×10^{-4} mole) in quinoline (50.0 ml) using 0.1 normal tetra-n-butylammonium hydroxide as titrant. The half-neutralization potential (HNP) is -423.9 mv.


-200
-300
-400
-500
-600
-700
-800
-900
-1000
E (mV)
0
2.0
4.0
6.0
8.0
10.0
12.0
V (ml)

vicinity of half neutralization.

A rather interesting occurrence may be noted in Figure 19 which is not present in Figure 18. The titration curves in quinoline all showed a second inflection coming at approximately 1.3 times the complete neutralization of the acid dissolved in the solvent. This behaviour was not experienced in pyridine. A study of anomalies of associating acids in nonaqueous solvents has been made (189b, 273) but these were encountered prior to complete neutralization of the acid and usually occurring in stages of the titration corresponding to simple fractions (1/4, 1/2 or 3/4) of neutralization. Acid-anion complexes were believed to be the cause of such additional inflections. A more obvious explanation for the extra inflection would be to attribute it to the presence of a small amount of relatively weak acidic impurity in the quinoline solvent which had not been removed by the barium oxide over which quinoline was being stored. Its concentration is nevertheless very low and would amount to some ~0.06 mole percent.

Variations in experimental conditions were undertaken in order to ascertain the relative importance of certain precautions that had been taken during the course of the titrations. Although all the recorded titration data in this work were obtained with the experimental set up described previously, use of the perforated steel

cylinder encircling the titration vessel and the addition of common salt to the bath water in order to shield the electrodes from any electrical interference proved to be not a necessary feature. No significant differences in HNP values derived for titrations of anthranilic acids in pyridine with or without the two precautions being observed. Although extensive tests were not carried out, it was found that half-neutralization values changed significantly when the masonite cover over the titration vessel and the blanket of nitrogen were removed during the titration. For instance, a difference of approximately 10 millivolts was recorded in HNP for the titration of anthranilic acid in pyridine when the cover and nitrogen were not used as compared to the value obtained under normal experimental conditions.

As mentioned previously in the Experimental section, a slow gradual drift in the potential reading with time after each addition of titrant was observed in the determinations carried out in pyridine. Readings were taken a short time (10 - 15 seconds) after the increment of titrant had been added, allowing enough time for the electrodes to respond to the change. In certain instances the apparent non-equilibrium character of titrations has been attributed to a surface effect on the electrodes (189b). On the other hand with the titrations in quinoline little or no drift in potential was apparent although electrode

response seemed to be slower and approximately one minute was allowed to elapse prior to recording the potential after each addition of titrant.

The potential of the solution containing the acid before the titration commenced often was recorded as a rather unsteady fluctuating reading. This condition, however, quickly disappeared as the first volume of titrant was added thereby increasing the conductivity of the solution.

The results of the titrations of substituted anthranilic acids conducted in pyridine in this investigation are listed in Table XII. The determinations are grouped into sets, each set having acids that were titrated in a single day. Anthranilic acid, the parent acid in this study, is indicated under the 'Substituent' column as 'H' and the substituted anthranilic acids are recorded by noting the name of the substituent relative to the carboxyl group in the aromatic ring. The symbols V_f and HNP are given the same interpretation as described earlier, that is, the volume of titrant at total or full neutralization and the half-neutralization potential respectively. The distinct changes encountered occasionally in the V_f values are due to introduction of new preparations of titrant having small differences in normality. This occurs specifically at Sets 5(i) and 8(i). An

TABLE XII

RESULTS OF THE POTENTIOMETRIC TITRATIONS OF SUBSTITUTED ANTHRANILIC ACIDS IN PYRIDINE AT 25.0°C.[a]

Set	Substituent	V_f[b] (ml)	HNP[c] (mv)
1. (i)	H	8.26	-426.3
(ii)	4-NO_2	8.18	-320.7
(iii)	4-OCH_3	8.15	-462.9
2. (i)	H	8.25	-433.9
(ii)	H	8.26	-431.4
(iii)	5-Cl	8.20	-377.6
(iv)	4-CH_3	8.11	-455.4
3. (i)	H	8.16	-425.9
(ii)	4-OCH_3	8.09	-460.4
(iii)	5-Cl	8.18	-375.4
(iv)	H	8.22	-429.9
4. (i)	H	8.24	-431.6
(ii)	4-CH_3	8.05	-452.8
(iii)	4-NO_2	8.16	-314.9
(iv)	H	8.08	-438.3
5. (i)	H	7.60	-452.0
(ii)	5-Cl	7.64	-392.3
(iii)	5-Cl	7.60	-392.7
(iv)	4-OCH_3	7.72	-486.1
(v)	H	7.60	-455.6
6. (i)	5-F	7.53	-401.5
(ii)	4-F	7.66	-429.3
(iii)	5-OC_6H_5	7.51	-425.6
(iv)	H	7.60	-449.3
(v)	5-F	7.59	-395.3
(vi)	4-F	7.62	-425.3
(vii)	5-OC_6H_5	7.66	-422.5
(viii)	H	7.66	-452.1
7. (i)	H	7.44	-452.1
(ii)	5-F	7.55	-398.5
(iii)	5-CN	7.32	-351.8
(iv)	H	7.48	-453.1

continued

TABLE XII Continued

Set	Substituent	V_f[b] (ml)	HNP[c] (mv)
8. (i)	H	7.72	-442.7
(ii)	4-Br	7.74	-400.0
9. (i)	5-OC_6H_5	7.73	-423.6
(ii)	H	7.85	-453.1
10. (i)	H	7.79	-453.0
(ii)	H[d]	5.88	-459.3
(iii)	H[d]	5.88	-458.2
(iv)	H[e]	11.65	-440.4
(v)	H	7.76	-456.0
(vi)	5-CN	7.55	-359.2
(vii)	5-Br	7.88	-394.5
(viii)	4-Br	7.80	-411.3

a Acid concentration: 7.527×10^{-4} mole per 500 ml of solvent.

b Volume of titrant added at full neutralization.

c Potential at half neutralization.

d Concentration: 0.0774 g per 50.0 ml pyridine.

e Concentration: 0.1548 g per 50.0 ml pyridine.

examination of the results listed in Set 10 (i) - (v) gives an indication of the variation in HNP as the concentration of acid is changed. As a consequence of varying the acid concentration, the environmental conditions in the solution to be titrated change as more or less benzene and methanol is added during the course of the titration. Heijde and Dahmen have also noted the influence the concentration of the titrated acid has on its half-neutralization potential (189a). The results imply that it is necessary to have the determinations carried out at a fixed concentration of acid if HNP values are intended to be used for comparative purposes.

In Table XIII are recorded the mean valuesof the differential half-neutralization potentials (△HNP) of the various substituted anthranilic acids. The reference acid is taken to be anthranilic and the△HNP for each acid is obtained by subtracting algebraically the HNP of anthranilic acid from the HNP of the acid under consideration, all determined within one set as listed in Table 12. When more than one value of HNP for anthranilic is available in a set from Table XII, then the mean HNP is used in calculating the△HNP. A relative acidity scale is thus described allowing the value of△HNP for anthranilic acid to be zero. The most acidic acids have positive △HNP while acids weaker than anthranilic bear negative △HNP values. The figure under the column 'n' indicates

TABLE XIII

THE MEAN VALUE AND MAXIMUM DEVIATION (M.D.) OF THE DIFFERENTIAL HALF-NEUTRALIZATION POTENTIALS (△HNP) FOR THE SUBSTITUTED ANTHRANILIC ACIDS FROM TABLE XII

No.	Substituent	n	△HNP (mv)	± M.D. (mv)
1.	4-NO_2	2	+112.8	7.3
2.	5-CN	2	+98.2	2.6
3.	5-Br	2	+59.2	1.1
4.	5-Cl	4	+57.5	4.0
5.	5-F	3	+52.9	3.7
6.	4-Br	2	+43.1	0.4
7.	5-OC_6H_5	3	+27.6	2.5
8.	4-F	2	+23.4	2.0
9.	H	-	0.0	-
10.	4-CH_3	2	-20.3	2.5
11.	4-OCH_3	3	-33.8	2.8
12.	H[a]	2	- 4.0	0.6
13.	H[b]	1	+14.4	-

a Anthranilic acid concentration: 0.0774 g per 50.0 ml of pyridine.

b Anthranilic acid concentration: 0.1548 g per 50.0 ml of pyridine.

the number of individual ΔHNP values available for each acid from which the mean is calculated and recorded in the Table. An indication of the maximum deviation from the mean is also shown.

A number of observations may be made by considering Tables XII and XIII together. Most anthranilic acids in the potentiometric studies were the same as those used in decarboxylation experiments; that is, their purification included a drying period in an Abderhalden drying apparatus. Certain acids used in the titrations were only air dried and stored in a desiccator. For example, in the titration of 4-methoxyanthranilic acid noted in Sets 1 (iii), 3 (ii) and 5 (iv) in Table XII the first two determinations were carried out with acid treated in the latter manner whereas the acid in Set 5 (iv) was dried in the Abderhalden apparatus. A consideration of the acid's ΔHNP value and the corresponding maximum deviation in Table XIII points out that variation of this experimental detail was of no consequence.

Table XIII also lists the ΔHNP values for anthranilic acid in which the acid concentration was varied. This perhaps helps to show more clearly the importance of maintaining a fixed concentration in these comparative studies. During the course of the titrations, even though experimental conditions were kept the same, variations in the value of HNP with time was noted. The trend in this variation may

be observed by noticing how in Table XII the HNP for anthranilic acid changes from Set 1 (i) having a value of -426.3 millivolts to Set 10 (v) in this instance reaching a value of -456.0 millivolts. The gradual change in HNP may be attributed to variations in liquid junction potentials or to changes in the titre of the tetra-n-butylammonium hydroxide, but more likely it is a consequence of changes in the asymmetry potential of the glass electrode caused by differences in surface states of the membrane with age (404). However, since $\triangle$HNP values are obtained from determinations made each day, this change in HNP is of no importance to the study.

It would seem to be useful and informative to estimate the extent of experimental error that could be associated with $\triangle$HNP. In order to do this the reproducibility of HNP values for the reference acid, anthranilic, was observed in each of Sets 1 - 7 and 10 of Table XII. The mean HNP in each set was taken and the deviations from this mean recorded. All the deviations were summed and their average taken which was found to be 1.7 millivolts. One might, therefore, reasonably assume that, if the numbers of determinations for each substituted anthranilic acid had approximated that carried out for anthranilic acid itself, an experimental error of similar magnitude could be associated with the substituted anthranilic acids, an error inherent in the method itself and not a result of

changes in experimental conditions. This would make the estimate for the experimental error in ΔHNP of the order of 3.4 millivolts. If a particular acid has values of ΔHNP which differ by no more than approximately 7 millivolts, it may be concluded that the deviation is due to experimental method and not to changes in the titration conditions.

The data in Table XIV includes background information that will be required in subsequent tables as well as a few entries which will be considered in the main discussion of results later in this dissertation.

Relative acidities of organic acids, namely substituted benzoic acids, have been determined in pyridine by Streuli and Miron (10). Table XV presents a brief comparative study of ΔHNP values found in this investigation with those of the above workers. For purposes of comparison in this instance the strongest acid (salicylic) is given the most negative potential in contrast to the manner in which ΔHNP was calculated in Table XIII.

TABLE XIV

RESULTS OF THE POTENTIOMETRIC TITRATIONS OF MISCELLANEOUS ACIDS IN PYRIDINE (Py) AND QUINOLINE (Q) AT 25.0°C.[a]

Set[b]	Solvent	Acid	V_f[c,d] (ml)	HNP[e] (mv)	△HNP[f] (mv)
1. (i)	Py	BA[g]	7.62	-416.9	-
(ii)	Py	SA[h]	7.64	-191.6	-225.0
(iii)	Py	AA[i]	7.67	-422.7	+6.1
(iv)	Py	BA	7.58	-416.2	-
2. (i)	Py	BA	8.18	-416.6	-
(ii)	Py	SA	8.14	-196.1	-220.5
(iii)	Py	AA	8.17	-427.7	+11.1
3. (i)	Py	BA	8.15	-424.1	-
(ii)	Py	AA	8.26	-426.3	+2.2
4. (i)	Py	BA	8.18	-424.4	-
(ii)	Py	$HClO_4$	8.22	- 17.6	+406.8
5. (i)	Py	AA	7.44	-452.1	-
(ii)	Py	4-OCH_3SA	7.44	-250.6	+202.0
(iii)	Py	4-OCH_3SA	7.45	-252.8	+199.8
(iv)	Py	AA	7.48	-453.1	-
6. (i)	Q	AA	7.70	-423.9	-
(ii)	Q	5-NO_2SA	7.54	-101.3	+322.6
7.	Q	CF_3COOH[j]	7.64	-116.4	+307.5[k]
8. (i)	Q	4-OCH_3SA	7.65	-235.7	+190.7
(ii)	Q	4-NO_2AA	7.73	-312.9	+113.5
(iii)	Q	AA	7.82	-426.4	-

a Acid concentration: 7.527×10^{-4} mole per 50.0 ml of solvent except when otherwise noted.
b Each set possesses acids that were titrated in the same day.
c Volume of titrant added at full neutralization.
d A change in titrant is indicated in Sets 1, 2-4, 5 and 6-8.

Continued

TABLE XIV Continued

e Half-neutralization potential.
f Differential half-neutralization potential. In Sets 1-3 the strongest acid is given the most negative $\triangle$HNP (relative to benzoic acid) in contrast to the usual presentation as per Table XIII and Sets 4, 5 and 6-8 of this table. When no entry is found in this column, it is understood that the particular acid was considered as the reference (i.e., $\triangle$HNP = 0) for that Set. When more than one value of HNP for the reference is available in each set, the average is taken in order to calculate $\triangle$HNP.
g Benzoic acid.
h Salicylic acid
i Anthranilic acid.
j Acid concentration: 7.648×10^{-4} mole per 50.0 ml quinoline.
k Reference acid is taken to be anthranilic from Set 6 (i).

TABLE XV

A COMPARISON OF SELECTED △HNP VALUES FROM THIS INVESTIGATION WITH THOSE FOUND IN THE LITERATURE

Acid	△HNP[a] (mv)	±M.D.[a,b] (mv)	△HNP[c]
Benzoic[d]	0	-	0
Anthranilic	+6.5	4.7	+10
Salicylic	-222.8	2.3	-211

a This study. The mean values of △HNP for anthranilic and salicylic acids were determined from a total of three and two titrations respectively in Table XIV (Sets 1-3).
b Maximum deviation.
c Reference (10).
d Used as a basis for calculation of △HNP.

An inspection of Table XV shows that the results derived in this investigation are comparable with those from the literature.

In Table XVI are recorded the comparative values for the titrations of the strongest substituted anthranilic acid (aqueous solution) and for one of the weakest salicylic acids (aqueous solution) in pyridine and quinoline. The reference is once again anthranilic acid.

TABLE XVI

A COMPARISON OF △HNP VALUES FOUND IN PYRIDINE AND QUINOLINE SOLUTIONS

Acid	△HNP (Pyridine) (mv)	△HNP (Quinoline) (mv)
Anthranilic	0	0
4-Nitroanthranilic	+ 113[a]	+ 114[b]
4-Methoxysalicylic	+201[c]	+ 191[d]

a Table XIII, line No.1.
b Table XIV, Set 8 (ii).
c Table XIV, mean value from Set 5 (ii) and (iii).
d Table XIV, Set 8 (i).

No obvious differences are seen in the results of the potentiometric titrations in quinoline and pyridine as outlined in Table XVI. It would seem reasonable to conclude that, first, pyridine and quinoline represent solvents of comparable characteristics in these acid-base studies and, second, there is no overlapping of △HNP values between 4-nitroanthranilic and 4-methoxysalicylic acids in the two solvents. The difference in △HNP between the two acids is in fact considerable and signifies that in the basic solvents the same relative order of acid strength is apparently maintained as in aqueous solution (12, 287). In the former reference comparison must be made with the

second ionization constant, K_2.

The interpretation of results of the relative acidities will be treated in detail in the Discussion.

B. DECARBOXYLATION

QUINOLINE

Decarboxylation of anthranilic acids in quinoline was found to follow first-order kinetics. The differential equation takes the form,

$$\frac{dx}{dt} = k_1(a - x) \qquad [111]$$

which on integration and rearranging becomes

$$\log_{10}(a-x) = \left(\frac{-k_1}{2.303}\right)t + \log_{10}a \qquad [112]$$

where a is the weight in grams of carbon dioxide potentially available at the start of the reaction, calculated from the initial quantity of acid to be decarboxylated; x is the weight in grams of carbon dioxide collected at time t (sec); k_1 is the first-order specific-rate constant (sec^{-1}).

For any one experiment a is a constant and equation [112] is the equation of a straight line when $\log_{10}(a-x)$ if plotted against t. The slope of the line is given by

$$\text{slope} = \frac{-k_1}{2.303} \qquad [113]$$

from which the specific-rate constant may be determined.

Data for a typical decarboxylation is presented in Table XVII.

TABLE XVII

DATA FOR THE DETERMINATION OF THE FIRST-ORDER SPECIFIC-RATE CONSTANT BY THE GRAPHICAL METHOD IN THE DECARBOXYLATION OF 5-METHYLANTHRANILIC ACID IN QUINOLINE AT 230.6°C.*

Time (secs)	x (gm)	Blank (gm)	a-x (gm)	log(a-x)
0	0	-	0.0588	-1.231
600	0.0038	-	.0550	-1.260
1200	.0074	-	.0514	-1.289
2000	.0116	-	.0472	-1.326
3000	.0163	-	.0425	-1.372
4300	.0218	0.0001	.0370	-1.432
5000	.0245	.0001	.0343	-1.465
6100	.0285	.0001	.0303	-1.518
7500	.0328	.0001	.0260	-1.585
9500	.0381	.0001	.0207	-1.684
11500	.0426	.0002	.0162	-1.790
14000	.0472	.0002	.0116	-1.936
17000	.0513	.0003	.0075	-2.12

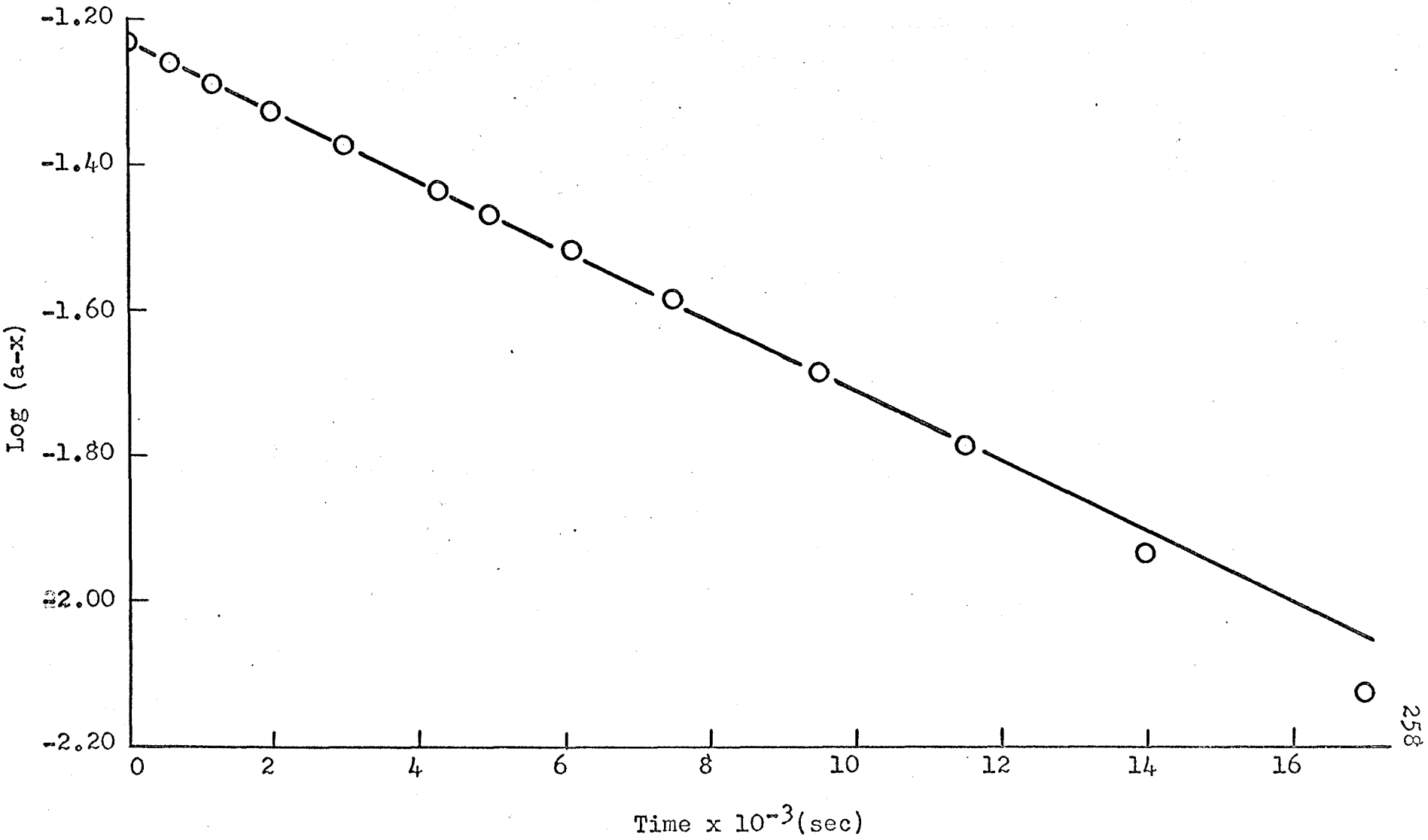
* 1.382×10^{-3} mole of acid in 15.0 ml of quinoline.

In this particular case the reaction was allowed to proceed for some 650 seconds in order to have the acid sample dissolve and the temperature equilibrium re-established in the system before zero time was taken. The small amount of carbon dioxide obtained during this period was subtracted from the amount of carbon dioxide that could

theoretically be made available from the quantity of acid used, thus arriving at a value of a = 0.0588 gm. Under the column x the weights of 'carbon dioxide' obtained periodically are uncorrected for the blank, whereas under the column a-x these weights, which record the remaining potential amount of carbon dioxide, have the blank correction incorporated in the listed values. The blank, the determination of which was described in Experimental section (page 232) amounted to 5.6×10^{-5} gm per hour under the experimental conditions employed. For acids which decarboxylate relatively quickly the value for the blank is very small, although it becomes significant for those acids which decarboxylate more slowly.

The data in Table XVII is shown in graphical form in Figure 20. Linearity in the plot is maintained up to 73 percent of the initial weight of acid decarboxylated and the best straight line was drawn to include all the points up to this stage in the decarboxylation. A value of 11.1×10^{-5} sec^{-1} was obtained for the specific rate constant. This procedure was tested by fitting a straight line in the form of equation [112] to the data by the method of least squares. In this instance a similar value of 11.1×10^{-5} sec^{-1} was obtained for K, with a standard error of $\pm 0.1 \times 10^{-5}$ sec^{-1}. (see Appendix, equations [A.14] and [A.19]). The value of a, determined

FIGURE 20. Plot of the experimental data from Table XVII showing the variation of the log (a-x) with time for the decarboxylation of 5-methylanthranilic acid (1.382×10^{-3} mole) in quinoline (15.0 ml) at 230.6°C. The first-order specific rate constant, k_1, is $11.1 \times 10^{-5} sec^{-1}$.


-1.20
-1.40
-1.60
-1.80
-2.00
-2.20
Log (a-x)
0
2
4
6
8
10
12
14
16
Time x 10^{-3}(sec)

from the normal equations (in the form $\log_{10} a$), was 0.0591 gm.

An evaluation of the specific-rate constant could also be made by the analytical method utilizing the integrated first-order rate equation in the form:

$$\log_{10} \left(\frac{a}{a-x}\right) = \frac{k_1 t}{2.303} \qquad [114]$$

Some of the relevant computation needed in arriving at values of k_1 for various times, t, is given in Table XVIII. The average value of k_1 was established as $11.0 \times 10^{-5} sec^{-1}$ with a mean deviation of $0.1 \times 10^{-5} sec^{-1}$.

Since there was close agreement in the values of the specific rate constant derived from the various methods described, the graphical procedure, in which the best straight line was drawn through the experimental points in the $\log_{10}(a-x)$ against time plot, was used to give an estimate of k throughout the whole series of determinations.

The rate constants of decarboxylation in quinoline of the set of substituted anthranilic acids are given in Table XIX together with an estimation of the maximum deviation from the average value of the rate constant which was in turn calculated from the number of separate determinations made for each acid. The standard deviation is also recorded in the table for comparison.

TABLE XVIII

DATA FOR THE DETERMINATION OF THE FIRST-ORDER SPECIFIC-RATE CONSTANT BY AN ANALYTICAL METHOD IN THE DECARBOXYLATION OF 5-METHYLANTHRANILIC ACID[a] IN QUINOLINE AT 230.6°C.

Time (sec)	$a-x$[b] (gm)	$\frac{a}{a-x}$	$\text{Log}(\frac{a}{a-x})$	$k_1 \times 10^5$ (sec^{-1})
600	0.0550	1.069	0.02895	11.1
1200	.0514	1.143	.05806	11.1
2000	.0472	1.245	.09519	11.0
3000	.0425	1.383	.1408	10.8
4300	.0370	1.589	.2011	10.8
5000	.0343	1.714	.2340	10.8
6100	.0303	1.940	.2878	10.9
7500	.0260	2.261	.3543	10.9
9500	.0207	2.840	.4533	11.0
11500	.0162	3.629	.5597	11.2
			mean:	11.0±0.1

a 1.382×10^{-3} mole of acid in 15.0 ml quinoline.
b Value of a is 0.0588 gm.

TABLE XIX

FIRST-ORDER SPECIFIC-RATE CONSTANTS IN THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN QUINOLINE AT 230.6°C.[a]

Substituent	No.	Mole x 10^3	k_1 x 10^5 (sec^{-1})	k_{1av} x 10^5 (sec^{-1})	±M.D.[b] x 10^5 (sec^{-1})	±S.D.[c] x 10^5 (sec^{-1})
4-OCH_3	1	0.5377[d]	111.1[e1]			
	2	0.4731[d]	124.1[e2]	118.	6.	
4-CH_3	3	1.022	27.18[e3]			
	4	0.8406[d]	29.34[e4]			
	5	0.9378[d]	23.95			
	6	1.108[d]	25.10			
	7	0.7930	22.17			
	8	0.6693	22.41	25.0	4.3	2.8
5-CH_3	9	0.6938	10.57			
	10	1.382	11.09			
	11	1.197	10.20	10.6	.5	.4
H	12	1.505	6.709[e5]			
	13	0.7834[f]	6.603			
	14	1.460	8.113	7.14	.97	.84
4-Cl	15	0.8409	5.603			
	16	0.7267	6.032[g1]			
	17	0.7727	5.845			
	18	0.8100	4.763	5.56	.80	.56

Continued

TABLE XIX Continued

Substituent	No.	Mole x 10^3	k_1 x 10^5 (sec^{-1})	k_{1av} x 10^5 (sec^{-1})	±M.D.[b] x 10^5 (sec^{-1})	±S.D.[c] x 10^5 (sec^{-1})
5-Cl	19	0.7990	2.856			
	20	0.9126	2.821[h]			
	21	0.6894	3.033	2.90	.13	.11
5-NO_2	22	1.175	0.8095[g2]			
	23	0.8457	0.8417[g3]			
	24	0.6667	0.7984[e6,g4]	0.816	.025	.022
5-CN	25	0.8414	0.6840	0.684	-	-

a Volume of quinoline was 15.0 ml unless where otherwise noted. Temperature was controlled to within ±0.4°C.; see description for few exceptions.

b Maximum deviation from k_{1av}.

c Standard deviation from $k_{1av} = \left[\frac{\sum(k_1 - k_{1av})^2}{n-1}\right]^{1/2}$.

d Volume of quinoline was10.0 ml; same blank correction used.

e Initial percent reaction not considered in kinetic plot: [1]28.2, [2]14.4, [3]15.6, [4]14.3, [5]14.7, [6]10.8.

f Acid sample with no prior drying treatment in Abderhalden apparatus.

g Percent reaction in which linearity persists in kinetic plot: [1]67, [2]56, [3] 31, [4]56-74.

h Experimental procedure was modified; acid pellet was added to reaction vessel first, then solvent.

With the few exceptions noted in Table XIX linearity in the first order kinetic plots persisted to at least 70 per cent of reaction with a large number of determinations exhibiting no deviation from linearity until well past 85 per cent of reaction. Three of these exceptions were runs involving 5-nitroanthranilic, an acid which is slow to decarboxylate under conditions used, and, therefore, its decarboxylation was not followed for as long a period as normally done for the other acids.

An initial period at the start of the reaction was required for the acid to dissolve in the hot solvent, for the temperature equilibrium to be re-established and for the nitrogen to sweep the early traces of evolved carbon dioxide through the absorption train. Attempts were made to keep this time interval to a minimum. It was found in a few instances that curvature in the initial portion of the kinetic plot still persisted even after having established a zero time in which the early amount of carbon dioxide absorbed was neglected. This was attributed chiefly to the inefficient sweep through of the carbon dioxide evolved. Normally, the total extent of initial reaction not considered in determining k from the kinetic plot was only a few per cent. An indication of those cases in which this initial per cent reaction was greater than 10 per cent is given in Table XIX also. It may be noted that this problem arose chiefly with those

acids that decarboxylated relatively quickly, the difficulties being enhanced by the fact that the number of experimental points determined early in the reaction was limited to the speed with which weighings of evolved carbon dioxide were made. With the exception of run number 24, the determinations, in which the initial per cent reaction to be neglected was relatively large, maintained a linearity in the kinetic plot to approximately 90 per cent of reaction.

In three determinations temperature control in the reaction vessel proved faulty for a time interval, and deviation from the equilibrium exceeded the average value as recorded in the procedure, that is, exceeded $\pm$ 0.4°C. These situations, however, occurred when the reaction had proceeded well past 50 per cent of completion and any slight discrepancy occurring in the graphical representations was taken into consideration when establishing the best straight line through the points.

All runs were corrected with the blank correction. In some instances, in which decarboxylation of an acid was followed to completion, slightly more than the theoretical amount of carbon dioxide was collected — a situation that may be attributed perhaps to a variation in nitrogen flow among the various determinations, altering slightly the value to be used in the blank determination.

In one experiment, number 22, considerable charring

had occurred during the course of the reaction, an indication given by the tarry deposit noticed when the decarboxylation was discontinued. It is possible that some oxidative process was occurring between the nitro acid and the product of the decarboxylation.

The solubility of representative anthranilic acids was examined at elevated temperatures in order to determine if the acids were completely dissolved during the decarboxylation experiments. The results indicated, that under conditions which approximated those during decarboxylation, rapid dissolution of the acids was assured.

Finally, attention was directed to a brief examination of the effect that quinolinium salts would have on the rate of decarboxylation of salicylic acid. In a first attempt quinolinium nitrate was used but was found to decompose at the elevated temperatures used in the determination. Quinolinium chloride proved satisfactory and two experimental runs were carried out, the first using a solution of the hydrochloride in quinoline prepared as described in the Experimental (page187) and in the second the concentration of quinolinium chloride was increased by the addition of a pellet of solid material. At the end of the decarboxylations the mixtures had turned to a red syrupy consistency.

The decarboxylation of salicylic acids under these

conditions followed first-order reaction kinetics (linearity in the plot to 80 per cent of reaction or better) as anticipated by the work of Janzen (4) and Rodewald (5). Table XX presents the data from the experiments conducted in this investigation and the results are compared to that found by Rodewald at the same temperature when only salicylic acid in pure quinoline was used. No significant differences in the rate constants are noted, a result which is consistent with the mechanism proposed by Rodewald (5).

TABLE XX

DECARBOXYLATION OF SALICYLIC ACID IN QUINOLINE AND QUINOLINE-QUINOLINIUM CHLORIDE SOLUTIONS AT 179.9°C.

SA[a,b] (mole/litre)	QHCl[a,c] (mole/litre)	$k_1 \times 10^5$ (sec^{-1})
0.0540	0.210	2.219[d]
0.0632	0.437	2.360[d]
-	-	1.985[e]

a Estimated from quinoline volume (15.0 ml) at room temperature.
b Salicylic acid.
c Quinolinium chloride.
d Blank correction (4.6×10^{-5} g/hr) taken into account.
e Reference (5); temperature 180°C.

NITROBENZENE

The decarboxylation of substituted anthranilic acids in nitrobenzene followed second-order reaction kinetics,

confirming the earlier work of Prysiazniuk (2). The differential rate equation is of the form

$$\frac{dx}{dt} = k_2(a-x)^2 \qquad [115]$$

which on integration and rearranging becomes

$$\frac{1}{a-x} = k_2 t + \frac{1}{a} \qquad [116]$$

where a is the concentration in moles per litre of carbon dioxide potentially available at the start of the reaction, calculated from the initial quantity of acid to be decarboxylated; x is the concentration in moles per litre of carbon dioxide collected at time t (sec); k_2 is the second-order specific-rate constant (litre/mole sec). Since a is a constant for any one experiment, equation [116] describes a straight line when $\frac{1}{a-x}$ is plotted against t. The specific rate constant is defined by the magnitude of the slope.

In Table XXI data is presented as an example of a typical decarboxylation experiment. For the same reasons as those given on page 256 describing decarboxylation in quinoline, the reaction was allowed to proceed for 1500 seconds before zero time was established. The carbon dioxide collected during this period (amounting to 1.2 per cent of the potentially available carbon dioxide) was subtracted from the theoretical amount of carbon dioxide that could arise from the total decarboxylation of the acid used. In this manner an initial concentration of

TABLE XXI

DATA FOR THE DETERMINATION OF THE SECOND-ORDER SPECIFIC-RATE CONSTANT BY THE GRAPHICAL METHOD IN THE DECARBOXYLATION OF ANTHRANILIC ACID IN NITROBENZENE AT 200.2°C.*

Time (sec)	x (gm)	Blank (gm)	x (mole /litre)	(a-x) x 10^2 (mole/litre)	$\frac{1}{a-x}$ (litre/mole)
0	0	0	0	50.49	1.980
1500	0.0068	0.0001	1.30	49.19	2.032
3000	.0136	.0001	2.62	47.87	2.088
5000	.0215	.0002	4.14	46.35	2.157
7500	.0308	.0003	5.92	44.57	2.243
10500	.0417	.0004	8.02	42.47	2.354
20500	.0725	.0007	13.94	36.55	2.735
26000	.0854	.0009	16.41	34.08	2.934
32500	.0989	.0011	18.99	31.50	3.174
74000	.1550	.0025	29.62	20.87	4.791
84000	.1630	.0028	31.11	19.38	5.159
98500	.1730	.0033	32.96	17.53	5.704
110000	.1812	.0037	34.47	16.02	6.242
117000	.1846	.0039	35.09	15.40	6.493
164000	.2002	.0055	37.81	12.68	7.886
187000	.2058	.0062	38.76	11.73	8.525

* Acid concentration: 0.5114 mole/litre in 11.7 ml nitrobenzene.

50.49×10^{-2} mole per litre was computed. In column, x (gm), in the Table are listed the weights of 'carbon dioxide' collected (from which the blank must be subtracted) corresponding to the times noted. The blank determination for the work in nitrobenzene amounted to 1.2×10^{-4} gm per hour. The last three columns in Table XXI have the blank incorporated into the listed values.

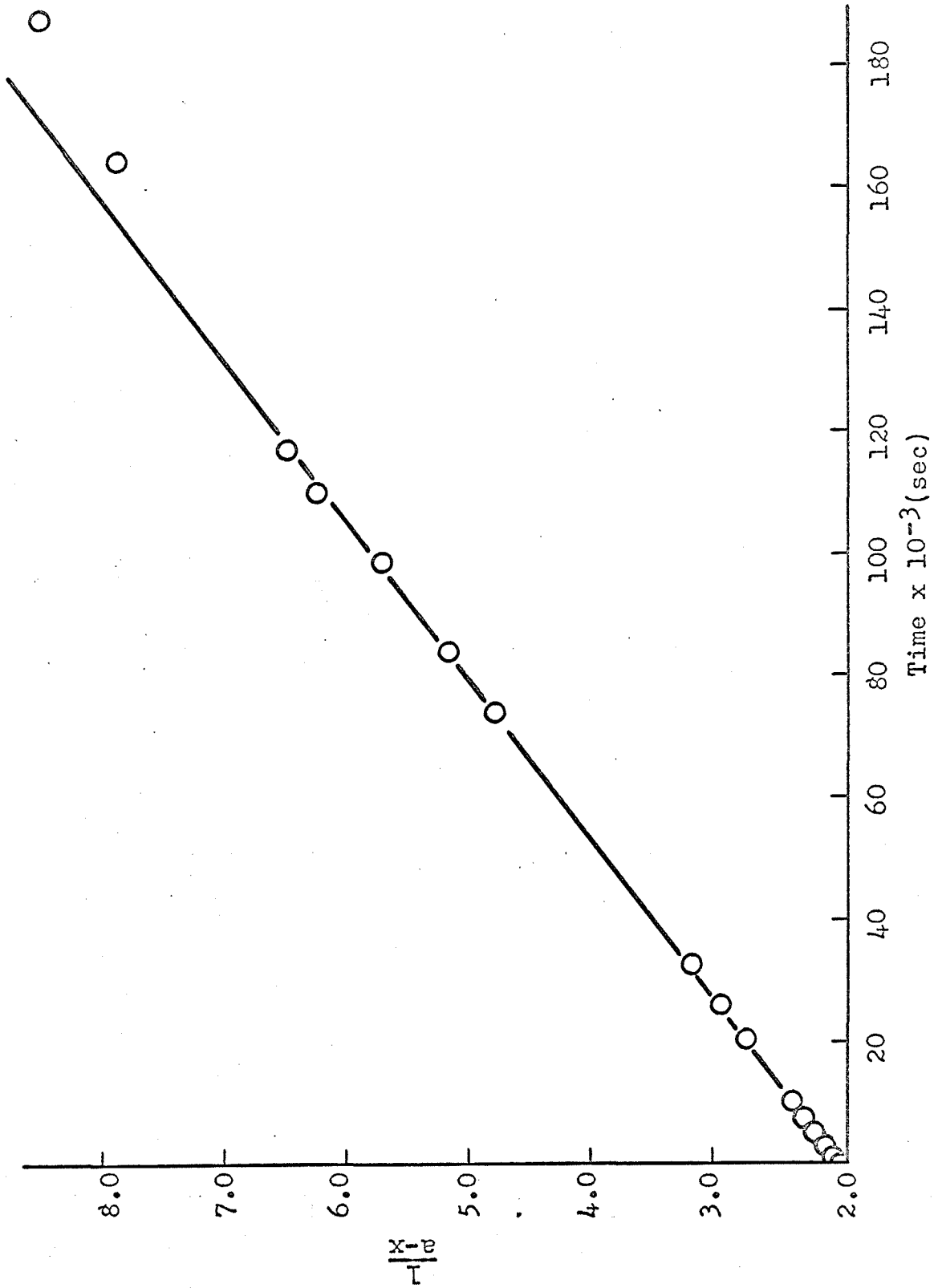
Figure 21 displays the data of Table XXI graphically. Linearity in the plot is maintained up to 70 per cent of the initial concentration of acid decarboxylated and the best straight line was drawn to include all the points up to this stage in the decarboxylation. The specific rate constant so obtained had a value of 3.87×10^{-5} (litre/mole sec). The method of least squares was used to fit a straight line in the form of equation [116] to the data and in this instance a value of 3.85×10^{-5} litre/mole sec was obtained for k_2 with a standard error of $\pm 0.02 \times 10^{-5}$ litre/mole sec (see Appendix, equations [A.14] and [A.19]). The value of a determined from the normal equations (in the form $\frac{1}{a}$) was 51.15×10^{-2} mole/litre.

The integrated second order rate expression in the form:

$$k_2 = \frac{1}{at}\left(\frac{x}{a-x}\right) \qquad [117]$$

was used to evaluate analytically the specific-rate constant.

FIGURE 21. Plot of the experimental data from Table XXI showing the variation of $\frac{1}{a-x}$ with time for the decarboxylation of anthranilic acid (0.5114 mole per litre) in nitrobenzene (11.7 ml) at 200.2°C. The second-order specific-rate constant, k, is 3.87×10^{-5} (litre/mole sec).


$\frac{1}{a-x}$
8.0
7.0
6.0
5.0
4.0
3.0
2.0
20
40
60
80
100
120
140
160
180
Time x 10^{-3}(sec)

The pertinent information is given in Table XXII including a list of the calculated k values for various times, t. The average value of k was determined to be 3.68×10^{-5} litre/mole sec. with a mean deviation of 0.11×10^{-5} litre/mole sec.

TABLE XXII

DATA FOR THE DETERMINATION OF THE SECOND-ORDER SPECIFIC-RATE CONSTANT BY AN ANALYTICAL METHOD IN THE DECARBOXYLATION OF ANTHRANILIC ACID IN NITROBENZENE AT 200.2°C.[a]

Time (sec)	$(x) \times 10^2$ (mole/litre)	$(a-x)^b \times 10^2$ (mole/litre)	$(\frac{x}{a-x}) \times 10$	$k_2 \times 10^5$ (litre/mole sec)
1500	1.30	49.19	0.2642	3.49
3000	2.62	47.87	.5473	3.61
5000	4.14	46.35	.8932	3.54
7500	5.92	44.57	1.328	3.51
10500	8.02	42.47	1.888	3.56
20500	13.94	36.55	3.813	3.68
26000	16.41	34.08	4.815	3.67
32500	18.99	31.50	6.028	3.67
74000	29.62	20.87	14.19	3.80
84000	31.11	19.38	16.05	3.78
98500	32.96	17.53	18.80	3.78
110000	34.47	16.02	21.51	3.87
117000	35.09	15.40	22.78	3.86
			mean:	3.68 ± 0.11

a Acid concentration: 0.5114 mole/litre in 11.7 ml nitrobenzene.
b Value of a is 50.49×10^{-2} mole/litre.

As was the case in the decarboxylation in quinoline, the specific-rate constants for the series of determinations

in nitrobenzene were determined graphically by drawing the best straight line through the experimental points in the $\frac{1}{a-x}$ against time plot. The exceptions to this procedure involved the runs in which 4-aminoanthranilic acid was decarboxylated. The reason is discussed below.

The rate constants for the decarboxylation of the substituted anthranilic acids in nitrobenzene are given in Table XXIII. Included is an estimation of both the maximum and standard deviations (where meaningful) from the average value of the rate constants which in turn are calculated from the separate determinations made on each acid.

The figures listed under the column 'Linearity,%' are an indication of the extent (per cent of reaction) to which linearity in the second-order kinetic plots persisted. Decarboxylation in nitrobenzene, in contrast to the work in quinoline, is relatively slow and thus only about one third of the runs were taken to or almost to completion. For most of the determinations with the 4-methoxy- and 4-aminoanthranilic acids, in which decarboxylation proceeded rather quickly, the reaction was followed to this extent. On the other hand runs such as 1, 2, 4 and 10, in which the acids were slow to decarboxylate, the linearity (as indicated) persisted up to or close to the extent to which the reaction was followed. Certain determinations proved troublesome as curvature upward or downward and some scatter

TABLE XXIII

SECOND-ORDER SPECIFIC-RATE CONSTANTS FOR THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN NITROBENZENE AT 200.2°C.[a]

Substituent	No.	Conc.[b] (mole/litre)	Linearity[c]%	$k_2 \times 10^4$ (litre/mole sec)	$k_{2av} \times 10^4$ (litre/mole sec)	$\pm$M.D.[d] $\times 10^4$ (litre/mole sec)	$\pm$S.D.[e] $\times 10^4$ (litre/mole sec)
5-Cl	1	0.1890	37	0.0921			
	2	.1310	29	.0910	0.0916	0.0006	
4-Cl	3[f]	.4914	62	.1714			
	4	.1223	35	.1729	.172	.001	
H	5[f]	.5114	70	.3868			
	6[f]	.5521	73	.3722			
	7	.3191	35	.4112			
	8	.2991	60	.4333			
	9	.2222	51	.3414	.389	.048	0.035
4-F	10	.1208	51	.4375			
	11	.1306	35	.4266	.432	.006	
5-CH_3	12[f]	.4565	53	.6307			
	13[f]	.4474	77	.6338	.632	.002	
4-CH_3	14	.1425	57	2.010			
	15	.09239	66	2.421			
	16	.09051	64	2.000	2.14	.28	.24
4-OCH_3	17[f,g1]	.3070	90	22.50			
	18[f,g2]	.2916	88	21.92			
	19[f]	.2506	92	23.36			
	20[h,f,g3]	.2482	86	23.00			
	21[f,g4]	.3157	90	20.68	22.3	1.6	1.0

Continued

TABLE XXIII Continued

Substituent	No.	Conc.[b] (mole/litre)	Linearity[c] %	$k_2 \times 10^4$ (litre/mole sec)	$k_{2av} \times 10^4$ (litre/mole sec)	$\pm$M.D.[d] $\times 10^4$ (litre/mole sec)	$\pm$S.D.[e] $\times 10^4$ (litre/mole sec)
4-NH_2	22g[5]	.6059	(68)	542.0			
	23g[6]	.04902	(65)	666.5	604.	62.	
	24g[7],i	.08270	(71)	228.7			
	25g[8],i	.05919	(69)	318.7			
	26g[9],i	.06339	(71)	242.7	263.	55.	47
	27g[10],j	.03837	(67)	134.0			
	28g[11],j	.05121	(68)	112.6	123.	11.	
	29				733.[k]		

a Volume of nitrobenzene used in each determination was estimated to be 11.7 ml at 200.2°C. Temperature was controlled to within $\pm$0.3°C.; see description for any exceptions.

b Concentration was calculated on the basis of the estimated volume of solvent at the elevated temperatures used in the decarboxylation.

c See description for definition.

d Maximum deviation.

e Standard deviation = $\left[\frac{\sum(k_2-k_{2av})^2}{n-1}\right]^{1/2}$

f Runs in which the nitrogen flow rate during the decarboxylation was significantly lower (approx. one half) than that normally used.

g Initial percent reaction not considered in the kinetic plot: [1]2.8, [2]15.4, [3]32.9, [4]17.3, [5]31.7, [6]7.9, [7]15.9, [8]11.1, [9]13.2, [10]2.1, [11]2.8.

Continued

h Acid sample with no prior drying treatment in Abderhalden apparatus but dried in vacuum desiccator over Drierite for 36 hours.

i Reaction temperature: 169.7°C.; volume of solvent estimated to be 11.4 ml at this temperature.

j Reaction temperature: 149.5°C.; volume of solvent estimated to be 11.2 ml at this temperature.

k Value at 200.2°C. derived from the Arrhenius equation (in the form utilizing two temperatures) using data from i and j.

in the points of the kinetic plots were experienced. These conditions were encountered principally in runs 3, 7, 8, 9, 11 and 14, the situation beginning to occur after the per cent of reaction shown in the table. The results with 4-aminoanthranilic acid were particularly bothersome. The acid decarboxylated so rapidly that the limit of usefulness of the experimental procedure used here was really surpassed. This was particularly the case for decarboxylations of the acid carried out at the higher temperature. For this reason runs were made at two lower temperatures to enable a check to be made of the validity for the rate constant derived at 200.2°C. by using the Arrhenius relationship. Generally, in the determinations made with 4-aminoanthranilic acid, distinct upward curvature (to lower order) and scatter in the points of the kinetic plot occurred making a reasonable estimate of the extent to which the line should be taken for purposes of determining k_2 difficult. Instead, in these runs a straight line was fitted to the points by the least squares method to the extent of 65-70 per cent of reaction, the actual value given in brackets in Table XXIII. It is not at all understood if the difficulties with the amino acid were due to fortuitous circumstances of experimental limitations or if they were encountered because of the presence of some autocatalysis.

Except for the determinations with 4-methoxy- and 4-aminoanthranilic acids the initial stage of decarboxylation

which was neglected for the reasons given on page 263 , for all other acids was two per cent of reaction or less. The runs in which the initial period exceeded this value are noted in the Table.

All trials, with the exception of the determinations of 4-aminoanthranilic acids, were adjusted with the blank correction. In the case of the amino acid there was either no need for such a correction because of the speed of the reaction or else it was neglected. This latter situation prevailed in those runs which were carried out at the two temperatures below that normally used in decarboxylating the rest of the acids. Because of the general lack of precision with this quickly decarboxylating acid and because the blank would amount to even less than 2-3 tenths of a milligram over the entire run, the latter could be disregarded without consequence. There were a number of runs in which the nitrogen flow in the experimental system was maintained at a rate much lower (approximately one half) than was normally the case. These instances are noted in Table XXIII. The same blank correction was used in these cases also even though one might have suspected that a different nitrogen flow rate would alter the value (lower) of the blank. Some tests gave an indication that differences if any would be slight.

Because of the relatively slow decarboxylations in nitrobenzene, monitoring of the temperature control on

occasion proved rather troublesome. Examination of the kinetic plots in which temperature control had proved faulty for a time interval showed in all cases except one that this was of no significance. In the one determination (run 1) the small deviation in the plot attributed to the faulty temperature control was considered in drawing the straight line through the points.

A representative number of anthranilic acids were tested for solubility at the elevated temperatures and concentrations used in these experiments and found to be soluble. It may be concluded with confidence that the acids were completely dissolved during the decarboxylation.

The interpretation of the results for the decarboxylations in the solvents quinoline and nitrobenzene will be discussed in detail in the Discussion.

Ph. D. Thesis

by

Murray Amerigo Morello

VOLUME II

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DC

STUDIES IN THE ACIDITIES AND MECHANISM OF DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC AND SALICYLIC ACIDS IN NONAQUEOUS SOLVENTS

by

Murray Amerigo Morello

A Thesis Submitted to the
Faculty of Graduate Studies and Research
of the University of Manitoba
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy

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DISCUSSION

A. ACID-BASE BEHAVIOUR OF ANTHRANILIC AND SALICYLIC ACIDS IN NITROGENOUS MEDIA.

PRELIMINARY STUDIES

Some exploratory work, utilizing proton magnetic resonance spectroscopy and ultraviolet absorption spectrophotometry, was undertaken in order to observe the nature of the acid-base reaction of anthranilic and salicylic acids in the basic solvents pyridine and quinoline and to uncover possible differences in behaviour in the two acid-solute systems. This was done in order to assess the feasibility of estimating the extent of molecular interaction of acid with the basic solvent (i.e., existence of solvent cation) and the techniques as a means for studying relative acid-base behaviour or making more quantitative measurements.

It is of interest and worthwhile to first point out some of the similarities in characteristics between the two basic nonaqueous solvents as they relate to hydrogen bonding and acid-base phenomena. Mention has already been made in the Introduction (see page 5) of the reasons for examining pyridine in these acidity studies even though quinoline was the solvent used in the decarboxylative experiments. An examination of Table XXIV helps to make the comparison clearer.

TABLE XXIV

A COMPARISON OF CERTAIN PHYSICAL AND CHEMICAL CHARACTERISTICS OF PYRIDINE AND QUINOLINE PERTINENT TO HYDROGEN BONDING OR ACID-BASE PHENOMENA WITH ACID SOLUTES

Compound	pK_a^a (H_2O)	$\Delta\nu^b$ (cm^{-1})	ΔH^c (cal/mole of soln.)	I^d (e.v.)	π-electron^h densities	ϵ^i
Pyridine	5.22	213	484	9.266[e]; 9.23[f,g]	1.586	12.3; 9.4[j]
Quinoline	4.81	217	485	8.30[f]	1.633	9.00; 7.3[k]; 5.05[l]

a Reference (402); pK is the negative logarithmof dissociation constant (aqueous) of the conjugate acid at 25°C. The reliability of the quoted constants is termed approx. (i.e., with an estimated uncertainty of $\Delta pK \leq \pm 0.04$). The method for their determination consisted of both light absorption measurements combined with electrometric measurements in each case although ionic strengths were not similar. The reference should be consulted for numerous other recorded values.

b Reference (405); $\Delta\nu$ is the shift (cm^{-1}) of the monomeric infrared OD band of methanol-d produced by the nitrogen base (1.0 M solution) compared to the same band in carbontetrachloride (0.1 M solution) used as reference.

c Reference (405); ΔH is the heat of mixing per mole of solution of equimolar quantities of the nitrogen-containing compound and chloroform.

d Reference (406) unless otherwise noted; I is the molecular ionization potential in electron volts. Consult references (407, 408) for higher values obtained from appearance potentials in mass spectrometric analysis.

e Determined by vacuum ultraviolet spectroscopy.

f Determined by photoionization.

g Reference (409).

h Reference (410); electron densities are calculated values about the N atom in the nitrogen base.

Continued

TABLE XXIV Continued

i Reference (97); ϵ is the dielectric constant measured at 25°C. unless otherwise noted.
j 116°C.
k 116°C.; value obtained by interpolation between values at 25°C. and 238°C. assuming a linear dependence in ϵ with temperature within this range.
l 238°C.

A few comments might be made regarding those values listed in which there are small differences in magnitude between the two bases. It is noted (Table XXIV, footnotes e,f) that for the molecular ionization potentials, the measurements were derived from different methods. Sometimes ionization potentials obtained by dissimilar techniques are discordant but Streitwieser has pointed out that, where available, the figures obtained from the photoionization method generally agree closely with measurements from ultraviolet spectroscopy (411). There is one further difficulty which arises, however, when discussing ionization potentials of heterocycles such as pyridine and quinoline and that is the dichotomy that the loss of electron in ionization could arise either from the aromatic π system or from the lone pair on the nitrogen. Arguments favouring the idea that the N lone pair is involved (and it should be added, the factor relevant to this discussion) come from contributions of inductive influences by substituents in the pyridine nucleus (407) and by considering the electronegativity of nitrogen per se whereas symmetry considerations with benzene (411) weaken the former evidence. An inspection of Table XXIV shows that one cannot anticipate the order of experimentally determined base strenghts from calculated π-electron densities. The differences observed in the dielectric constant between pyridine and quinoline at room temperature would not be expected to contribute

significantly to possible variations in ionization or, more particularly, dissociative phenomena in the two solvent systems. Since the decarboxylations were performed at high temperature, it should be noted that as the temperature is raised the dielectric constant is reduced and differences in the two values decrease as can be seen from the interpolated value recorded in the Table for the dielectric constant of quinoline at 116°C. compared to the constant for pyridine at the same temperature. Taking the foregoing into consideration it still can be stated rather conclusively that there are close similarities in properties of quinoline and pyridine when inferences are made to possible interaction of these molecules with protonic acids leading to hydrogen bonding or to complete acid-base reaction.

Although some interesting results were derived from the preliminary work, it did not constitute the main body of the investigation into acid-base behaviour in nitrogenous solvents which was relegated to potentiometric titrimetry. For this reason the proton magnetic resonance and ultraviolet spectrophotometric experiments are discussed in a more unified manner. A description of the pertinent literature, a brief presentation of the experimental method and the interpretation of results are included. Following this treatment the results in relative acid-base behaviour as determined from the potentiometric

titrations will be discussed.

Proton Magnetic Resonance Spectroscopy

Introduction

The study of the proton magnetic resonance spectra of systems containing carboxyl hydrogens or N-H protons are usually complicated by hydrogen bonding, intermolecular solute-solvent interaction, exchange phenomena and, in the case of the N-H system, line broadening due to quadrupolar relaxation and the possibility of triplet fine structure from spin-spin interaction with the ^{14}N nucleus ($I = 1$). Chemical shift data derived from such spectra are often not very meaningful especially for correlation of the shift of nuclei involved in these processes with molecular or structural parameters (412, 145c). It is generally recognized that the most meaningful chemical shifts are those measured at infinite dilution in an inert solvent such as carbon tetrachloride or cyclohexane where the molecule can reasonably be assumed to be in the monomeric state (145c). Nevertheless much of the data presented in the literature as well as that listed in Table XXV on page 289 can be useful in making qualitative interpretations on the nature of species in such solutions. Furthermore, good evidence has been presented to confirm the fact that hydroxyl-proton resonance signals of aliphatic alcohols, phenols and carboxylic acids

(or an exchange-averaged signal with solvent) can be well correlated with a molecular parameter such as Hammett's σ or σ^- substituent constants or pK values. Studies have been made in solvents such as pyridine (154, 157), triethylamine (157) and dimethyl sulfoxide (413). Kondo and co-workers, some of whose results are noted in Table XXV, measured infinite-dilution/chemical shifts for substituted benzoic acids in pyridine (154). Quellette recognized that a meaningful chemical shift (i.e., one from a definable species such as monomeric phenol) is not often obtainable unless extrapolation to infinite dilution is attempted since the observed signal represents a time average of all possible phenolic aggregates at the concentration under consideration. The problem of eliminating the phenolic aggregates was tackled by this author by using dimethyl sulfoxide (solutions approximately one mole per cent in phenol) a solvent serving as a good hydrogen acceptor and thereby circumvented the usual procedure of other workers (413).

Several aliphatic carboxylic acids in the pure liquid, where most of the molecules are in the dimeric state, have been found to have very similar -COOH hydrogen chemical shifts of the order of 12 ppm downfield from tetramethylsilane (414). The resonance signal for the acid protons of benzoic acid dimer in benzene has been found in the region usually associated with pure carboxylic acid shifts

(6.6 ppm to low field of benzene) but the monomer at 30°C. had a corresponding chemical shift at a higher field than ever reported previously for carboxyl protons. The behaviour of the monomer shift with temperature was suggestive of a benzoic acid-benzene interaction (415). Flett (416a) has presented in table form ranges in which one might find hydroxyl proton resonances including those of aromatic acids. The value of the carboxyl proton resonance of trifluoroacetic acid obtained by Smith and Schneider (156) is recorded in line 14(b) of Table XXV.

As far as the chemical shift of the $\diagdown\!\overset{(+)}{\!=\!}\text{N-H}$ proton is concerned, it has been pointed out how sensitive its resonance position is to moisture, solvent and anion to which it may be hydrogen bonded (417). In the spectra obtained in this study no triplet signal characteristic of a proton bonded to a nitrogen atom was observed. The presence of pyridinium ion in a solution of 5 mole per cent pyridine in trifluoroacetic acid has been confirmed by Smith and Schneider (156) in observing a triplet splitting (line 14(a)). At higher pyridine concentrations, however, the triplet structure for the $\diagdown\!\overset{(+)}{\!=\!}\text{N - H}$ proton was not observable because of faster proton exchange. It has also been noted that trifluoroacetic acid has the disadvantage of bringing about a certain amount of line broadening (145d). Krakower and Reeves (150) found only one signal, presumably of an exchange-averaged position, for quinoline in trifluoroacetic

acid (line 6) in contrast to the work of Smith and Schneider. It was suggested by Krakower and Reeves that this was a reflection of the reduced basicity of quinoline. Kotowcyz *et al.* found only broad single peaks by pyridine hydrohalides in a variety of solvents except for the hydrochloride and hydrobromide in formic acid in which triplets were observed for the $\overset{(+)}{\underset{\diagdown\!\!\diagup}{N}}-H$ resonances (417). The absence of any signal for the hydroiodide or pyridine in formic acid could not be explained.

Interpretation of Results

Proton magnetic resonance spectra of anthranilic, salicylic and trifluoroacetic acids in pyridine and quinoline solutions were measured on a Varian DA-60-I spectrometer at 28°C. A spectrum was also taken of salicylic acid in dimethyl sulfoxide.

Solutions were prepared in the appropriate concentration (0.05 - 0.10 mole fraction) by dissolving the solute in 2 ml of solvent contained in a small vial which could be easily stoppered and shaken to aid dissolution. A small amount (1 - 3 drops) of trifluoroacetic anhydride was added to those solutions containing trifluoroacetic acid to remove traces of water. No special precautions were taken, such as working under a nitrogen atmosphere, to reduce the uptake of atmospheric moisture. One or two drops of tetramethylsilane were added to the solution in the sample tube

prior to taking the resonance spectrum.

Spectra were examined for the $\overset{(+)}{\underset{\diagdown}{\overset{\diagup}{=}}}$N - H proton signal or the exchange-averaged peak of the carboxyl proton from the acid and the pyridinium or quinolinium ion proton. Chemical shifts were measured downfield relative to tetramethylsilane used as the internal standard in all cases except for the determination in dimethyl sulfoxide. In this instance the conversion to the tetramethylsilane scale was made from the dimethyl sulfoxide standard. The spectral data of the various two-component acid-base systems obtained in this preliminary examination are summarized in Table XXV. Also included are related data from the literature.

The widths of the peaks at half height for the resonance signals (determined in this study) of salicylic acid in pyridine and quinoline were of the same order of magnitude ($\sim$3 - 4 cps) as those for trifluoroacetic acid in the same solvents. The signal obtained in the salicylic acid - dimethyl sulfoxide system was broad (35-40 cps)(line 15). There were no separate peaks resolved for the $\overset{(+)}{\underset{\diagdown}{\overset{\diagup}{=}}}$N - H proton or the carboxyl hydrogen, so that in all likelihood exchange-averaged signals of such protons were being measured. Krakower and Reeves found this to be the case in their work with trifluoroacetic acid in quinoline at all concentrations (150). They observed that only at lower temperatures (-18°C.) were two distinct peaks obtained and these were considerably exchange broadened. It would seem that the data presented

TABLE XXV

^{1}H CHEMICAL SHIFTS OF THE EXCHANGE-AVERAGED PEAKS IN ACID-BASE MIXTURES AT 60 MC/SEC AT 28°C.

No.	Acid	Concentration (mole fraction)	Solvent	Chemical Shift (ppm)[a]
1.	Salicylic	0.078	Quinoline	15.0
2.	Anthranilic	.079	Quinoline	-
3.	Trifluoroacetic	.076	Quinoline	18.3
4.	Trifluoroacetic	.050	Quinoline	11.3[b]
5.	Trifluoroacetic	.90	Quinoline	12.6
6.	Trifluoroacetic	.90	Quinoline	11.7[b]
7.	Salicylic	.055	Pyridine	15.0
8.	Anthranilic	.056	Pyridine	-
9.	o-Methoxybenzoic	.00 [c]	Pyridine	15.5[d]
10.	Benzoic	.00 [c]	Pyridine	16.1[d]
11.	p-Nitrobenzoic	.00 [c]	Pyridine	18.0[d]
12.	Trifluoroacetic	.096	Pyridine	19.8
13.	Trifluoroacetic	.94	Pyridine	11.8
14(a)	Trifluoroacetic	.95[e]	Pyridine	13.9[f]
(b)				12.1[g]
15.	Salicylic	.049	Dimethyl Sulfoxide	11.6[h]

a Measured in parts per million to low field from tetramethylsilane internal reference, determined by dividing the distance of the shifts from the reference in cycles per second by the applied frequency in cycles per second (60 megacycles) and multiplying by 10^6. For example the value of the shift in line 1. was obtained as follows:

$$\delta = \frac{902 \times 10^6}{60 \times 10^6} = 15.0 \text{ parts per million.}$$

b Reference (150), estimated from the graph of chemical shift of the exchange-averaged peak in mixtures of trifluoroacetic acid-quinoline at 40 Mc/sec.

c Infinite dilution.

d Reference (154), estimated from a graph of chemical shift at infinite dilution (standard cyclohexane) *versus* Hammett's sigma substitutent constants. Chemical shifts were converted relative to tetramethylsilane (418).

e Solution of 5 mole per cent pyridine in trifluoroacetic acid with ~3 mole per cent methylene chloride added as an internal reference.

Continued

TABLE XXV Continued

f Reference (156), chemical shift refers to the centre of the pyridinium $\backslash\overset{(+)}{\underset{/\!/}{}}$N - H proton triplet signal converted from internal methylene chloride to the tetramethylsilane scale (418).

g Reference (156), chemical shift refers to the trifluoroacetic acid -COOH proton signal converted from internal methylene chloride to tetramethylsilane standard (418).

h Chemical shift was originally measured relative to internal dimethyl sulfoxide and then converted to the tetramethylsilane scale (418).

in lines 3 and 4 are discordant. Krakower and Reeves (150) found, in dilute solutions of trifluoroacetic acid in quinoline, the exchange-averaged peak position at higher field and having a value of 11.3 ppm. The value, which was obtained in this study is significantly to lower field, and is more comparable to that which Krakower and Reeves assumed for the acid proton in the ion pair, that is, 18 - 19 ppm from tetramethylsilane and occurring at 50 mole per cent acid. They reasoned that in quinoline-rich solutions the large concentration-dependent shift that was observed to high field could be associated with the rupture of hydrogen bonds in the ion pairs as the salt was diluted by quinoline. An estimate of 9.4 ppm from tetramethylsilane was made for the $\overset{(+)}{N}$ - H proton of the quinolinium ion at infinite dilution. This infinite dilution chemical shift is in contrast to that obtained by Kondo *et al.* (154) for substituted benzoic acids in pyridine (lines 9, 10 and 11). Certainly, at least in aqueous solution, trifluoroacetic acid is a much stronger acid than *o*-nitrobenzoic and it might have reasonably been expected that a chemical shift of at least comparable magnitude, if not larger, than that in line 11 would have been observed at infinite dilution for trifluoroacetic acid. On the other hand, in acid-rich solutions, the value obtained for the proton chemical shift in this study (line 5) is quite comparable to that in the literature (line 6). Furthermore, a low field shift of similar magnitude was observed

for a solution of salicylic acid (line 7) in pyridine adding some strength to the validity of the results in this work in that the observations are consistent at least for both trifluoroacetic and salicylic acids. It should be noted, however, that Toyoda *et al.* (152) in their work on the acetic acid - pyridine system observed the lowest resonance field of the OH proton for a solution of 50 mole per cent pyridine, a situation somewhat similar to that recorded by Krakower and Reeves with trifluoroacetic acid in quinoline.

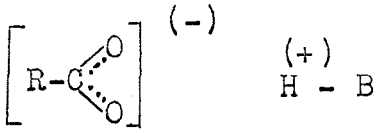
An examination of the data presented in lines 13, 14(a) and 14(b) indicate that the resonance signal from line 13 could correspond to the carboxyl proton obtained by Smith and Schneider (line 14(b)) or to an exchange-averaged signal, the position of which would be expected to be close to that for the carboxyl-proton signal in acid-rich solutions. This follows because the observed chemical shift, δ_{obs}, may be given by

$$\delta_{obs} = n_{RCOOH}\,\delta_{RCOOH} + n_{BH^{(+)}}\,\delta_{BH^{(+)}} \quad , \quad [118]$$

where n refers to the mole fraction and RCOOH and $BH^{(+)}$ represents the acid and protonated basic solvent respectively. For the case in point δ_{obs} is essentially δ_{RCOOH} since $n_{RCOOH} >> n_{BH^{(+)}}$. Comparison of chemical shifts here must be made with some reservation, however, since it is known that for accuracy in conversion of one internal reference scale to another one needs to take special precautions (145e).

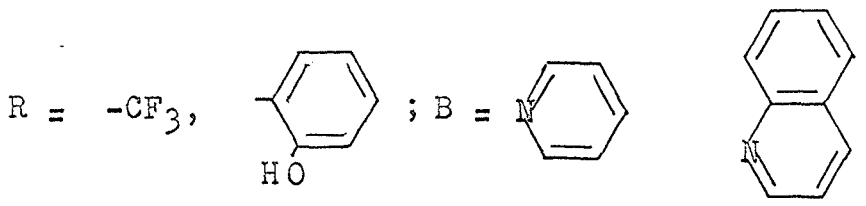
A spectrum of salicylic acid was run in dimethyl sulfoxide (line 15) for purposes of comparison. It is known that dimethyl sulfoxide serves as a good hydrogen acceptor (413). The nature of the proton signal of salicylic acid in dimethyl sulfoxide, however, cannot be discussed unequivocally. It could very well be derived from a time-averaged position of a composite of processes in solution including interaction of the carboxyl proton with the solvent. A more thorough examination would be necessary in order to uncover any contributions to this signal by intramolecular hydrogen bonding or phenolic - dimethyl sulfoxide interactions. It has been noted that a low-downfield resonance peak was observed for the carboxyl proton of the monoanions of certain dicarboxylic acids in dimethyl sulfoxide ($\sim$15 ppm to low-field relative to external H_2O). This result was attributed to strong intramolecular hydrogen bonding which was not broken by solvent interaction whereas the dicarboxylic acid spectrum displayed a signal at much higher field ($\sim$7.6 ppm to low field relative to external H_2O) (419, 420).

The general observation of extremely low-field proton shifts in base-rich solutions (line 1 , 3 , 7 and 12) points out, or at least is reasonably suggestive, that a major contribution to the over-all shift is being made by having the proton in an environment approximated by structure (LXXXVI) and which closely resembles ion-pair formation.



LXXXVI

where:



One might further argue that structure (LXXXVI) would be more favoured by trifluoroacetic acid in pyridine or quinoline in comparison to salicylic acid in the same solvents. Trifluoroacetic acid, which is presumably the stronger acid, would have a greater tendency to lose its acidic proton to the solvent and thereby deshield it more relative to the carboxyl proton of salicylic acid. If this were the case, the resonance position for the proton in the trifluoroacetic acid-base system would occur at lower field as is observed experimentally. The importance of electron density around the proton in contributing to acid proton shifts is also seen from the infinite dilution shifts of substituted benzoic acids in pyridine (line 9 , 10 , and 11). Korinek and Schneider studied hydrogen-bond or association shifts but in this case a single compound, chloroform, acted as the 'acid' in a variety of solvents or 'bases' which accepted the lone proton of chloroform. They found that the resonance signal of the proton was t o lowest field in the order triethylamine>

acetone > diethyl ether > ethyl cyanide > propyl fluoride (421). One should not discount, however, that proton chemical shifts may be interpreted not only as arising out of the electron density around the proton but also in terms of the anisotropic magnetic susceptibility of neighbouring groups. The latter may manifest itself in a number of ways, namely, through the nature of the counterion (417) and ring current effects of the pyridine molecule (422, 423). Rose has cautioned that the diamagnetic anistropy of the carboxyl bond must be considered when using the chemical shift of complexes as a criterion of hydrogen bond strength (424).

The question of the importance of the intramolecular hydrogen bond in determining the chemical shift in salicylic acid - amine systems is also not settled.

One last consideration might be given and that is to the absence of any low-field proton-resonance signal for anthranilic acid in quinoline or pyridine in the region associated with $\diagdown\!\!\diagup\overset{(+)}{N}$ - H proton peaks. This is not readily explained. The resonance spectrum was examined in the region 0 - 33 ppm from tetramethylsilane in both solvents although little or no attention was given to the area where aromatic ring protons resonated. It would seem that in basic low dielectric solvents there would be little or no tendency to have anthranilic acid present as the zwitterion although this possibility cannot be discounted. A group such as $-\overset{(+)}{N}H_3$, which would be present if anthranilic acid did exist

in zwitterionic form in basic solution, has been detected by proton magnetic resonance experiments on aliphatic amino acids. These signals, however, have been observed only in extremely acidic solution such as aqueous sulfuric (50 mole per cent) and sulfuric acid itself (425, 426) or trifluoroacetic acid (427). Bovey and Tiers prepared solutions of amino acids by dissolving 100 mg of solute in 0.50 ml of trifluoroacetic acid already 'referenced' by adding 1.0 per cent by volume of tetramethylsilane to the trifluoroacetic acid solvent (427). The solvent carboxyl-proton peak occurred at 12 to 13 ppm downfield from tetramethylsilane while the ammonio protons were observed to higher field in the region of 7.5 ppm from the internal reference. The spectrum of histidine in contrast displayed two peaks at 12.4 and 12.6 ppm, even lower than the carboxyl proton resonance of the solvent which in this instance occurred at 11.5 ppm. It was most likely that the two resonance signals were due to the two nitrogen-bound protons in the ring system. It was noted that the $\overset{(+)}{NH_3}$ proton signals were frequently so close to the resonances of aromatic ring protons, such as those in phenylalamine, that it was impossible to measure half-height widths. A similar situation could be occurring in base-rich solutions of anthranilic acids in this study. If the zwitterionic form of anthranilic acid predominated in these basic solvents, then the proximity of the negatively charged carboxylate group would likely influence the position

of any $-\overset{(+)}{N}H_3$ resonance signal by shielding the protons more and thus causing the signal to occur at relatively higher field than is usually expected for protons in this environment. Dyer has pointed out that the protons of substituted aliphatic ammonium ions absorb in the range 7.1 - 7.6 ppm downfield from tetramethylsilane while the range 8.5-9.5 ppm is usually associated with the protons of substituted aromatic ammonium ions (397). He made a further observation by noting that absorptions are broad single peaks when insufficient excess acid is present to retard chemical exchange or, when a large excess of acid is available, they appear as broad triplets.

Proton resonance line broadening due to the ^{14}N nucleus could also be responsible for not observing ammonio or $\overset{(+)}{N}-H$ hydrogen peaks. The ^{14}N nucleus may be undergoing relaxation at just the right rate in such systems to cause the protons attached to it to give the broadest possible line intermediate between the singlet and triplet patterns. Reynolds and Schaefer (155) have observed that, in solutions of substituted anilines (1-3 mole per cent) in trifluoroacetic acid, the ammonio proton signals were broad and weak such that the line widths of these signals could not be measured.

An alternative consideration to the reason why a low-field proton-resonance signal is not observed in anthranilic acid solutions may be given if one considers the relative acid strengths of the acids under consideration. The ionization

equilibria for anthranilic acid in aqueous solution is rather complex. If one makes the reasonable assumption, that, in basic nonaqueous solvents of the type encountered here, the equilibrium represented by K_1 in the aqueous system is precluded, and further, that the zwitterionic form is non existent, then the equilibrium represented between species HA and A^- (equation [13] on page 26) for which an ionization of $\sim 3 \times 10^{-5}$ has been calculated (12) might adequately describe over-all acid-base behaviour of anthranilic acid in pyridine and quinoline. This ionization constant is quite small; in fact it is lower than the aqueous ionization constant for o-methoxybenzoic acid, the weakest acid for which data were recorded by Kondo et al. (154) in their study of the infinite-dilution chemical shift of substituted benzoic acids in pyridine. It is possible that, if any molecular interaction between acid and basic solvent (acting as an electron-pair donor) does exist, it is of small magnitude causing little or no perturbation in deshielding of acidic protons and thereby producing no low-field resonance for these hydrogens. One might argue that in this case a signal due to the carboxyl proton of the molecular acid should have been observed although none was observed in this work for the acids studied in basic solvents and in that investigation undertaken by Krakower and Reeves (150). Strong signals, reasonably attributed to the aromatic ring protons of the basic solvents and acid solute, do not occur to lower field than some 8.5 ppm

from tetramethylsilane for anthranilic acid in pyridine and quinoline. Therefore, any carboxyl-proton signal would not have been expected to be obscured by ring-proton resonance positions.

It has been estimated that the limit in concentration of a single proton species that can be detected by this technique using the instrument available is 0.25 to 0.50 mole per cent but may often be much higher (428). This limit could very well be the factor underlying the differences in behaviour observed between salicylic and anthranilic acids in this preliminary work. It should be noted that the presence of pyridinium ion has been reported to explain results of proton resonance experiments for acid solute - pyridine systems in which weak acids such as acetic, phenol and even water were used. Here, however, mixtures over the entire concentration range were used and the mixture of composition about 50 mole per cent pyridine exhibited the lowest resonance field of the hydroxyl proton, conditions which were not examined in this study.

Summary

The results obtained in this preliminary study of acid-base behaviour by proton magnetic resonance and, more particularly, their interpretation will of necessity be of a tentative nature. The following main points may be made.

(i) The presence of pyridinium ion (solvated by pyridine or existing in intimate or solvent-separated ion pairs) in solutions of trifluoroacetic and salicylic acids in pyridine and quinoline solutions in the concentrations used is reasonably assured because of the presence of the very low-field chemical shift in the vicinity usually attributed to the resonating $\gtrless\overset{(+)}{N} - H$ proton. Unequivocal evidence in this regard is not forthcoming in these preliminary experiments because there was no observed triplet splitting of the proton signals characteristic of hydrogen bonded to nitrogen. In all likelihood the occurrence of rapid exchange in these systems does not permit the appearance of a triplet splitting but δ_{obs} is of a time-averaged signal which is essentially $\delta_{BH}^{(+)}$ since the condition, $n_{RCOOH} << n_{BH}^{(+)}$, exists in this case.

(ii) To a rough or first approximation the extent of chemical shift in the systems studied is a measure of strength of the acid or its proton-donor capacity. This situation might have made studies into relative acidities attractive except for the fact that no pertinent signal was exhibited for anthranilic acid. Naturally comparisons would have to be made on rigorously maintained standardized conditions but even this may not be entirely suitable since differences in counter-

ion may affect the observed chemical shift. Further reasons for maintaining reasonable care in relating acid or hydron-bond strengths to basicity of electron-donor molecules have been given (417, 429).

(iii) The absence of any low-field proton signal for anthranilic acid in pyridine or quinoline may be due to a number of reasons, not the least probable being that little or no ionization has occurred in the systems examined, at least no strong intermolecular interaction with the solvent such as RCOOH...N$\overset{=}{\diagdown}$. Broad and weak absorption signals due to relaxation effects may also contribute to its absence. It could be that anthranilic acid exists predominately in the zwitterionic form in the basic nonaqueous solvents and that the $-\overset{(+)}{N}H_3$ signal is being reduced because of exchange or broadening caused by ^{14}N quadruple relaxation or obscured by the resonance spectrum of nuclear protons of the acid and/or solvent.

(iv) Similarities between pyridine and quinoline have been further confirmed in this exploratory work.

No further attempts were made to examine any of the apparent anomalies. More detailed studies and a more careful examination of spectra would be required in order to unravel the questions still left unanswered. Information

concerning the concentration dependence of the chemical shift of the carboxyl proton would help to point out the extent to which the acid-base interaction is involved and perhaps equilibrium constants for complex formation could be calculated. A temperature study might be used to investigate the importance of line broadening by ^{14}N or the involvement of proton exchange between $\diagdown\!\overset{(+)}{N} - H$ and -COOH sites in solution. Other possibilities for further study might make use of salts of salicylic and anthranilic acids in the basic solutions to assist in determining the extent to which intramolecular hydrogen bonding persists, examining the effect of protonation of the ring nitrogen on the aromatic protons of pyridine and quinoline, investigating the effect of ring substituents in salicylic and anthranilic acid on the acidic proton chemical shift and, in the case of anthranilic acid, varying substituents on the amino nitrogen in an attempt to set up molecular structures that may favour or reduce the tendency for forming the zwitterion.

Ultraviolet Spectrophotometry

Introduction

It will be necessary first to present some of the background theoretical material proper to any discussion of the experimental results obtained in this investigation. Some comments have already been made on isolated topics in

this general area in the Review of the Literature; however, since the subject has not been treated fully as it relates to possible interpretations which may be made later, it will be dealt with here in some detail.

Acid-base equilibria have often been investigated by ultraviolet spectrophotometric techniques. In general, observations of spectra are made of the particular organic compound in neutral, acidic and basic aqueous or alcoholic solutions (12, 287, 430a, 431b). The benzene molecule, because of its conjugated system, is chromophoric in nature; that is, the system is chiefly responsible for the absorption bands occurring in the ultraviolet region of the electromagnetic spectrum.

Acidic or basic centres attached directly to the benzene ring are not capable of absorption in the visible or near ultraviolet by themselves but because they may contain groups bearing electrons capable of strong interaction with the π electrons of the ring, the absorption pattern of the chromophore may be profoundly affected (i.e., auxochromes; cf., however (432)). As a rule, the inductive characteristics of a substituent affects the position or intensity of the benzene bands very little since any electronic influence on the ground and excited states is about equal and in the same direction. For example, it has been noted that anilinium salts have spectra almost

superimposable on the benzene spectrum (see Table XXVI, lines 1 and 7)(430b). Groups such as -OH, $-NH_2$ and $-C^{=O}—OH$ (the latter substituent possessing a double bond adjacent to the ring) modify the energy levels of the entire molecule and thereby cause an intensification of the absorption band (hyperchromic effect) and movement of the band position to longer wavelengths (bathochromic shift) (416b, 430c). Doub and Vandenbelt have contributed most significantly by determining and classifying ultraviolet bands associated with mono-, di- and trisubstituted benzene derivatives in aqueous solution (433, 434, 435). A number of authors have added further comments on these results (430b, 431b, 436). The latter reference includes a discussion of correlation of band displacements with electronic effects of substituents as in the Hammett equation. In Table XXVI results of substituent effects on the benzene chromophore are revealed in the variation of band positions and intensities. Band classifications are those used by Doub and Vandenbelt (433). The criteria followed was to list the maxima as the secondary band and the first, second, etc. primary bands proceeding from long to short wavelengths. The assignments are based largely on similarity of position and band intensity. Rao has discussed the nomenclature of benzene absorption and includes a similar classification to describe the three principal bands usually accesible in the ultraviolet (431b). Forbes and co-workers over a number of years have made a major contribution in an analysis of

of ultraviolet spectra of numerous compounds including substituted benzoic acids (437, 438, 439, 440, 441).

TABLE XXVI

EFFECT OF NUCLEAR SUBSTITUENTS ON THE ULTRAVIOLET SPECTRA OF VARIOUS BENZENE DERIVATIVES IN AQUEOUS SOLUTION[a, b]

No.	Substituent	Secondary Band		First Primary Band	
		λ^{c}_{max} (mμ)	ϵ^{d}_{max}	λ^{c}_{max} (mμ)	ϵ^{d}_{max}
1.	H	254	204	203.5	7400
2.	COOH	273	970	230	11600
3.	$COO^{(-)}$	268	560	224	8700
4.	OH	270	1450	210.5	6200
5.	$O^{(-)}$	287	2600	235	9400
6.	NH_2	280	1430	230	8600
7.	$NH_3^{(+)}$	254	160	203	7500

a Data taken from reference (433).
b Solutions may contain a small concentration of methanol (i.e., ~2 per cent).
c Position of the absorption maximum in millimicrons (mμ).
d Molar extinction coefficient (litre per mole cm) corresponding to λ_{max}.

They prefer to utilize an alphabetical classification (C-secondary, B-first primary) for band positions. The compounds listed in Table XXVI have been included because of their relevance for purposes of comparison to similar compounds used in this work, in order to point out the

effectiveness of certain substituents in causing marked shifting of bands to longer wavelengths relative to benzene itself, and to examine how ionization affects band displacement and intensity. There will be no attempt at an interpretation of how band positions and absorptivities of polysubstituted benzoic acids are a result of preferential contribution from mono- or disubstituted compounds which can be thought of making up the total composite effect. These aspects are well treated in the work of Doub and Vandenbelt (433, 434, 435).

If one looks at the results for the monosubstituted derivatives of benzene in Table XXVI, it is fairly clear that the intensity of the first primary or principal band is much greater ($\epsilon_{max} > 6 \times 10^3$) than the secondary band ($\epsilon_{max} \leq 2.6 \times 10^3$), however, the variation in intensity of the latter seems to be more marked for derivatives relative to benzene. Undoubtedly, this feature, coupled with the bathochromic displacement relative to benzene of the band in a region of the ultraviolet more easily accessible by instruments (particularly in the past), has led to much quantitative work with the secondary absorption. It is also noted that displacement of benzene bands can be identified with either electron-donating or electron-withdrawing substituents. It would be expected that any influence which increases these tendencies would result in further displacement relative to the benzene band (eg., 254 mμ)

while any influence which might lessen these effects would cause a reduced band displacement by the substituent group (433). Acidic and basic ionizations are processes which can add some control on the magnitude of band shifts. In the first case loss of a proton allows for an isolated negative charge to remain on the substituent. Clearly, if this residual charge is placed on an electron-accepting group (i.e., $-COOH \longrightarrow -COO^{(-)}$), its normal characteristics are reduced whereas, a deposition of negative charge on an electron-releasing group (e.g., $-OH \longrightarrow -O^{(-)}$) would tend to enhance the existing electronic influences of that group. This is what in fact is observed (Table XXVI, cf., lines 2 and 3; 4 and 5). In basic ionization (e.g., $-NH_2 \longrightarrow NH_3^{(+)}$) introduction of a proton ties up the unshared pair of electrons of an electron-releasing substituent (by resonance) and a marked reduction in band displacement is observed. (cf., lines 6 and 7 in Table XXVI). Doub and Vandenbelt have pointed out that these general effects apply to all bands; that is, to secondary and second primary as well as to first primary absorptions. They have used the following more refined description to cover the rule predicting the ionization shifts as well as indicating the importance of ionic forms and charge separation in the photoexcited state (434).

> "Where ionization polarizes the group favourably with respect to the charge separation occurring on that group in the excited state of the unionized molecule, displacement toward longer wavelength results coincident with considerable stabilization of the excited state; where the charge resulting from ionization opposes that present on the group in the excited state of the parent molecule, the excited state loses stability leading to a hypsochromic effect."

Observations, similar to those discussed above, are generally noted also in mono- and disubstituted benzoic acids. For instance, protonation of the amino group in p-aminobenzoic acid (cf., lines 3 and 4 in Table XXXIV on page 376) leads to a movement of band position to shorter wavelengths (hypsochromic shift) with reduced intensity (hypochromic effect) such that results are similar to what one observes for the benzoic acid spectrum (Table XXVI, line 2). Two interesting examples, one of which is an apparent exception to the general rules developed above for the influence that ionization has on band displacements, are recorded in Table XXVII. The spectral behaviour of p-nitrobenzoic acid illustrates the exception (Table XXVII, lines 1 and 2). Both nitro and carboxyl groups have similar electronic characteristics but the former is a more powerful electron attractor. Generally one would expect a hypsochromic shift to be impressed on the first primary band as a consequence of ionization, however, there is actually a bathochromic shift indicating that the p-nitro group has conferred a weak electron-releasing

effect on the carboxylate centre, thereby reversing the usual ionization shifts. The effect is also apparent in m-nitrobenzoic acid (Table XXVII, lines 3 and 4).

TABLE XXVII

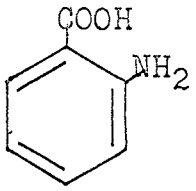
CHARACTERISTIC ULTRAVIOLET ABSORPTION BANDS OF SUBSTITUTED BENZOIC ACIDS IN AQUEOUS SOLUTION[a]

No.	Substituent	Solvent	First Primary Band	
			λ_{max} (mμ)	ϵ_{max}
1.	4-NO_2	0.1N HCl	264.5	12400
2.		N NaOH	274	10600
3.	3-NO_2[b]	0.1N HCl	261	7100
4.		N NaOH	266	7350
5.	4-OH	0.1N HCl	255	13900
6.		pH8	245	11900
7.		N NaOH	280	16300

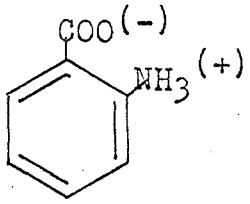
a Data is taken from reference (433) unless otherwise noted. Consult Table XXVI for explanation of terms.
b Reference (439).

The absorption bands of the various species in the ionization of p-hydroxybenzoic acid are also listed in Table XXVII (lines 5, 6 and 7). Here the normal shift to shorter wavelengths occurs accompanying the ionization of the carboxyl group but, as the pH is further increased, a strong bathochromic shift appears subsequent to the phenolic-group ionization.

For compounds containing both acidic and basic functional groups, in which acid-base equilibria occurs in conjunction with tautomeric equilibria, the interpretation of spectra is made more difficult. Such a possibility is very likely with aminobenzoic acids. It would be expected, for instance, that the tautomeric equilibrium involving the chargeless or neutral species of anthranilic acid (LXXXVII) and the zwitterion (LXXXVIII)



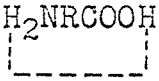
LXXXVII



LXXXVIII

would be considerably solvent dependent with the dipolar form being stabilized with respect to the former by increased solvent polarity(430d). Hunecke (442) and Klotz and Gruen(443) have undertaken an ultraviolet spectrophotometric examination of anthranilic and p-aminobenzoic acids respectively in aqueous solution in an attempt to resolve these difficulties in interpretation. The approach in both cases centered around the idea that the neutral acid and its esters would have quite similar spectral characteristics. This is to be expected since carbomethoxy and carboethoxy groups would closely parallel the electrical effects of the carboxyl group (444). The concept that

replacement of an undissociated carboxyl by a methyl-ester function produces a negligible change in the spectrum, has also been used in establishing the constitution of pyridine monocarboxylic acids in aqueous solution (445). In the work by Hunecke (442) the discussion included an appraisal of the Bjerrum species (see page 26, equation [13]) usually present in aqueous solution including those depicted by LXXXVII and LXXXVIII as well as a form which he described as the salt form LXXXIX of anthranilic acid.



LXXXIX

This presumably involved intramolecular hydrogen bonding between the carboxyl proton and the amino nitrogen. There was no conclusion reached in distinguishing this form from the dipolar ion (LXXXVIII) since it was anticipated that there would be no particular difference in absorption spectra. The results of the spectral analysis have been extracted from the spectra recorded by Hunecke and are presented in Table XXVIII

The spectra of anthranilic acid and its methyl ester were quite similar (λ_{max} =~325 mμ, ϵ_{max} =~2100). This supported the argument that anthranilic acid was chiefly in the neutral form in aqueous solution.

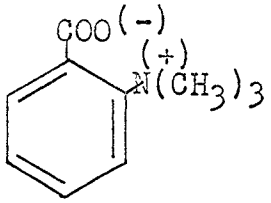
TABLE XXVIII

CHARACTERISTIC ABSORPTION BANDS OF ANTHRANILIC ACID (AA) AND ITS DERIVATIVES IN AQUEOUS SOLUTION.[a]

No.	Compound	Secondary Band[b]		First Primary Band[b]	
		λ_{max} (mμ)	ϵ_{max} x10^{-3}	λ_{max} (mμ)	ϵ_{max} x 10^{-3}
1.	AA	325	2.1		
2.	Me ester	326	2.1	244	3.8
3.	NaAA[c]	308	3.2	242	6.6
4.	AAHCl[d]	328	1.4		
5.		272	2.0		
6.	N,N-DiMeAA	273	0.8		
7.	N,N-DiMeNaAA	303[e]	1.4	261	5.2
8.	N,N,N-TriMeAA	263	1.0		

a Concentration: 1.0 x 10^{-3}M.
b Following the usual classification outlined earlier.
c Sodium anthranilate.
d In the form of the chlorohydrate of AA-HCl.$NH_2C_6H_4COOH(+H_2O)$.
e Inflection.

Acidification of the acid reduced this band (Table XXVIII, lines 4 and 5) and subsequently caused a hyperchromic effect to occur near 272 mμ. Significant absorption in the same region was apparent for N,N-dimethylanthranilic acid (line 6) as well as for the betaine (XC)(line 8),



XC

which can only exist in the dipolar form. The secondary absorption band of benzoic acid anion (Table XXVI, line 3) has its λ_{max} in this region. From the observations it was concluded that anthranilic acid existed predominantly in the neutral form, however, ionization may cause a considerable contribution to be made to its ultraviolet absorption spectrum by the anion. More recent reports have upheld the general premise worked out by Hunecke (446, 447). In particular, Uhlig and Doering have presented evidence that N-monoalkylanthranilic acids (methyl or ethyl) exist as real carboxylic acids in aqueous solution but can be characterized as having an intramolecular hydrogen bond of the type -N ⟶ H-O. The dipolar tautomer for N,N-dialkyl derivatives was also confirmed (447).

In anticipation of the usefulness of the spectrophotometric method the present work began with an exploratory examination of a number of salicylic and anthranilic acids in pyridine and modified-pyridine solutions. For purposes of comparison spectra of these acids were also taken in methanolic solutions. When nonaqueous solvents of low dielectric constant are utilized, some attempt must be made

to interpret the results in the light of possible complexities such as ion-pair or higher ionic-aggregate formation. A customary approach is to discuss acid-base equilibria in these solvents in terms of both ionization (K_i) and dissociation (K_d). Valuable insights into electrolytic equilibria have been achieved particularly in the behaviour of acids and bases in glacial acetic acid (160), phenols in pyridine (137), nitroacetanilides in liquid ammonia (134, 135), hydrogen halides in acetonitrile (127) and similar equilibria of suitably substituted alkyl halides in liquid sulfur dioxide (448). Equation [119] depicts the simple system envisaged for a weak acid (HA) in pyridine

$$n\ HA \xrightleftharpoons{K_i} (H^{(+)}\ A^{(-)})_n \xrightleftharpoons{K_d} nH^{(+)} + nA^{(-)} \qquad [119]$$

without attempting to indicate the extent of solvation although it is reasonable to assume at least that the proton exists as the pyridinium ion (solvated?) and that $n = 1$ (i.e., ion pairs are not themselves associated). The latter assumption is also reasonable at the concentration used in absorption studies. One further complicating feature, in solvents lacking suitable hydrogens for intermolecular hydrogen bonding, is that anions ($A^{(-)}$) are not adequately solvated and thus tend to associate with the molecular acid to form homoconjugate species, $AHA^{(-)}$. Further reference will be made to equation [119] and possible modifications when the results of the potentiometric titrations

are examined. For the present, spectrophotometric results may be discussed in terms of simple ionization and dissociation without invalidating any later treatment.

In spectrophotometric studies involving concurrent equilibria the common assumption is invoked that the extinction coefficients of dissociated species (in this case the anion) and the absorbing ion in the ion pair are equal. Corey, using this hypothesis, estimated the concentration of dissociated phenoxide ions, of phenoxide-pyridinium ion pairs and of unionized phenol (137). Lagowski and co-workers found that absorption bands associated with anions and/or ion pairs containing the anions of o- and p-nitroacetanilide did not change their shape or position for solutions containing varying amounts of KI or KBr (134, 135). The indication this gave was that the ionic aggregates containing the nitroacetanilide anion and the anion itself could not be distinguished spectrophotometrically. Evidence presented by Kolthoff and Bruckenstein showed that all acid forms of an indicator base (I —— p-naphtholbenzein), with an acid HX (i.e., $IH^{(+)}$, $IH^{(+)}X^{(-)}$, $X^{(-)}IH^{(+)}X^{(-)}$, etc.), had the same absorption spectra and extinction coefficients (160). Kolthoff and co-workers had earlier noted that in systems (nitrobenzene) in which pyridinium picrate (PyHPi) could undergo both molecular and ionic dissociation,

$$PyHPi \rightleftharpoons Py + HPi \qquad [120]$$

$$PyHPi \rightleftharpoons PyH^{(+)} + Pi^{(-)} \quad , \qquad [121]$$

the linear relation between the extinction coefficient and the initial picric acid concentration for solutions containing excess pyridine indicated that pyridinium picrate and picrate ions have the same molar absorptivity (449).

Not all the evidence, however, has favoured this concept and conflicting reports should be noted. Recent work by Hogen-Esch and Smid (450) has demonstrated that sodium and cesium fluorenide in tetrahydrofuran at room temperature exist as contact ion pairs giving rise to complex spectra in the ultraviolet and visible region. On the other hand the lithium salt at 20°C. or the sodium salt at -80°C. was considered to be largely in the solvent-separated ion-pair form whose ultraviolet spectra was markedly different. Steigman and Lorenz studied the reaction of the phenolic indicator bromophthalein magenta E with di-n-butylamine in benzene and found that Beer's law did not describe the system (451). They attributed the spectral complexity to the formation of ion pairs and quadrupoles in the more dilute solutions and to quadrupoles and higher aggregates in the concentrated solutions. Although the peaks of maximum absorption were about the same, the molar absorptivities were quite different for the ion pair as compared with the quadrupole and higher aggregates.

It has been pointed out that ion-pair dissociation

or association would not seem to influence absorption spectra of solutions to any significant degree provided that the attraction is purely electrostatic (452). Davis and Paabo had made an important contribution earlier in presenting a strong argument for the necessity of making a distinction between salts consisting of ion pairs and those consisting of 'hydrogen-bonded' ion pairs (453). Their study included the absorption measurements of salts of the phenolic indicator, bromophthalein magenta E (BPM-E) with the bases, tribenzylamine oxide, 1,3-diphenylguanidine and triethylamine in benzene solutions. Significant variations in the absorption band of the anion of BPM-E indicated that the nature of the cation or counterion affected the mobility of anionic electrons. Since these systems represented examples of hydrogen-bonded ion pairs, it was thought that the cation must attach itself to a specific oxygen of the anion and is not held merely by coulombic or electrostatic interaction.

Mention should also be made of a series of important papers co-authored by Izmailov and Gurevich (138, 454, 455). In examining the absorption spectra of solutions of sodium picrate (NaPi) in various alcoholic solvents, they observed distinct deviations from Beer's law (454). Spectral curve displacements and anomalous intensity changes were obtained by increasing the concentration of NaPi, by treating the alcoholic solutions of NaPi with a nonabsorbing salt con-

taining a common ion such as sodium perchlorate or by decreasing the dielectric constant of the solvent with additions of benzene to the alcoholic solutions. In this way they reasoned that the spectra of associated sodium picrate (i.e., ion pair) differed from that of dissociated NaPi. Furthermore, intersecting points observed on the spectral curves indicated the existence of an equilibrium between ions and ion pairs. In their second paper they included a spectral examination of picric acid and NaPi in pyridine (138). The absorption spectra of both compounds were very similar at all concentrations studied, a situation expected if picric acid (HPi) enters into interaction with the solvent with formation of a salt-like product which absorbs identically with NaPi. Only at the concentration 5×10^{-5} mole /litre did HPi and NaPi have exactly identical absorption spectra and this was ascribed to an ion spectrum. As concentrations increased the bands were displaced to shorter wavelengths, that is, in the direction of the spectra that the authors attributed to ion pairs of NaPi. The evidence is quite compelling but one wonders whether some consideration should not have been given, at least with respect to HPi solutions, to interpret these results in favour of suppression of ion-pair dissociation and consequent increase of ion pairs and nonionized HPi as the picric acid concentration is increased. The hypsochromic shift and reduction in band intensity are in

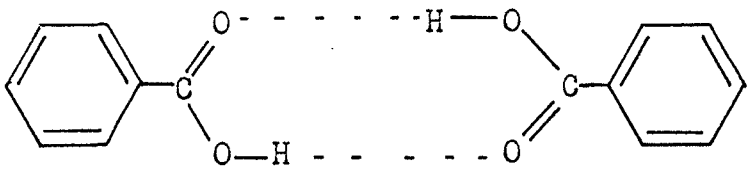
accord with common observations made when p-nitrophenolate ion reverts to its conjugate acid, p-nitrophenol, in acidic aqueous solution (433). This interpretation does not help to explain spectral differences observed in varying the concentration of NaPi unless one might assume some form of covalent bonding in contrast to simply coulombic forces between the metal cation and the phenolate oxygen. All this is rather speculative, however. One should recall that results by Izmailov and Gurevich are at some variance with those of Kolthoff and co-workers (449). Strict comparisons cannot be made since the latter authors examined NaPi solutions in nitrobenzene (dielectric constant (ϵ) = 34.8 at 25°C.(97) while the most closely comparable solvent used by Izmailov and Gurevich was acetonitrile (ϵ = 37.5 at 25°C. (97)). Beer's law was followed by NaPi solutions in nitrobenzene although concentrations up to only 10^{-4} molar were used. Perhaps it is because of the lower concentration used by Kolthoff *et al.* that anomalies uncovered by the Russian authors were not observed.

It would seem, therefore, that if equation [119] is thought to represent a reasonably accurate model of equilibrium systems in solvents under investigation, then in the future some consideration must be given to detailing the nature of the possible intermediate, $(H^{(+)}\ A^{(-)})_{solv.}$, that is, the type of associated state, its geometrical structure and the nature of the binding force acting

between its components (448). For purposes of the present discussion the working assumption will be that the force binding $H^{(+)}(PyH^{(+)})$ to $A^{(-)}$ in the complex is electrostatic in nature. Since the anion, whether it is salicylate or anthranilate, is considered to be associated with $PyH^{(+)}$ ion in the ion pair, abnormalities, as outlined by Davis (453), are not expected here. The common solvent system should enable one to make direct comparisons of behaviour of the acid solutes from these two different classes of compounds. Situations of intermediate character do exist (i.e., ones in which binding forces might better be described in valence-bond terminology indicating varying degrees of ionic character) such as incipient hydrogen-bond formation. It cannot be assumed that such interaction leading to perturbation of the chromophoric portion of the molecule will not affect the spectrum of the unionized or molecular aromatic carboxylic acid although the effect might prove less significant when compared to phenolic systems (456) since even complete ionization of the carboxyl group to the anion causes relatively smaller changes in spectral behaviour in contrast to the ionization of phenols.

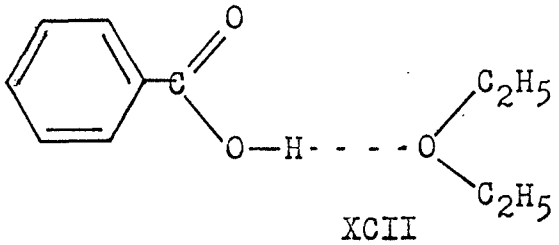
Under suitable conditions electronic absorption spectra may be used to study three types of hydrogen bonding: intramolecular hydrogen bonding, intermolecular hydrogen bonding between solute molecules and intermolecular hydrogen

bonding between solute and solvent molecules. Forbes and Templeton found a concentration dependence for the intensity of the 230 mμ and 240 mμ (in terms of ϵ_{max}) bands of benzoic and salicylic acids respectively in cyclohexane (457). Some slight changes in wavelength position were exhibited as the concentration was increased but primarily there was a pronounced increase in the observed absorption intensity. These effects were ascribed to intermolecular hydrogen bonding between solute molecules (dimerization (XCI)).



XCI

The concentration dependence decreased with the addition of ether to the cyclohexane solution indicating a competition of intermolecular hydrogen bonding between solute and solvent (XCII) takes over (458).

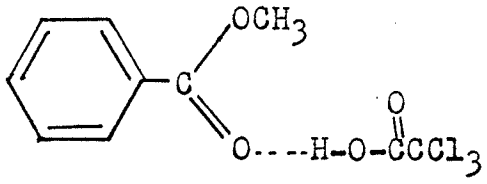


XCII

The strength of the dimeric hydrogen bond is apparently reduced by intramolecular hydrogen bonding in salicylic

acid since on addition of 5 per cent ether to a cyclohexane solution of the acid, the concentration dependence is barely recognized while the concentration dependence in benzoic acid solutions is readily discerned under similar experimental conditions.

Other extensive studies have been conducted by Ungnade and Lamb (459) and Ito et al.(460). The former workers found that changes in solvent and concentration affected the fine structure of absorption curves of benzoic acid more than their wavelength and intensities of the maxima. Results were discussed in the light of various possible sites of intermolecular association between acid and solvent molecules. Ito and his co-workers approached the problem through a temperature study for solutions of benzoic acid made from solvents containing proton donating or accepting molecules. With the aid of the closely related methyl benzoate they were able to interpret the results on the basis that the direction of spectral shift due to hydrogen-bond formation was dependent on whether benzoic acid behaved as a proton acceptor (as envisaged by XCIII),



XCIII

or as a proton donor (XCII). Hypsochromic shifts are developed if the latter condition exists whereas bathochromic displacements may be expected for systems described by structure (XCIII).

In a more recent paper in their series on the study of hydrogen bonding by ultraviolet light absorption Forbes, in collaboration with Dearden, attempted to obtain information concerning intermolecular hydrogen bonding in phenols and anilines by a number of methods (461). These were: observations of spectral changes between corresponding ortho-substituted phenols and anisoles, comparison of spectral changes between ortho-substituted phenols or anilines and the corresponding meta isomer and noting the absence of an appreciable spectral change on altering solvent conditions which may be evidence for the presence of an intramolecular hydrogen bond. The authors also included some important factors which must be considered in order to make reliable interpretations of any observed spectral changes. For instance, if the absorption band under study is determined by that part of the chromophoric system which does not contain the intramolecular hydrogen bond, then this band will be little affected by such interaction. Steric and other proximity effects, which are most likely to operate in ortho-disubstituted benzene derivatives, may be different in the reference compound and in the intramolecularly hydrogen-bonded substance. Existence of a

strong intramolecular hydrogen bond or steric hindrance preventing solute-solvent interaction may result in an absence of spectral changes with change of solvent. The first primary absorption bands relevant to salicylic acid and related compounds were the ones picked for supporting the evidence of an intramolecular hydrogen bond in salicylic acid in cyclohexane at concentrations where monomeric species were assumed to predominate. This absorption was bathochromically displaced when compared with the same band in m-hydroxybenzoic acid whereas m-methoxybenzoic acid absorbed at slightly longer wavelength compared to the ortho-methoxy isomer. Wavelength displacements between ortho- and meta-isomers of aminobenzoic acids in ethanol and ether solutions observed for both the first primary and secondary bands were related to the existence of an intramolecular hydrogen bond in anthranilic acid in these systems.

Finally mention should be made about the care that is needed in interpretating ultraviolet spectra for purposes of comparing the same compound under different environmental conditions. At times a number of factors may be involved that contribute to the resultant variation in band displacements and/or intensities so that adequate comparisons are severely limited. This superposition of individual effects which may reinforce or cancel each other and the fact that it is necessary to detect often small

changes makes their interpretation difficult. Fundamentally, the band position is affected by relative stabilization of excited and ground states through solvation. As an example, the first primary band of nitrobenzene experiences a bathochromic shift in the order water>ethanol>heptane>vapour (430b). This displacement is a result of the increased ease of excitation because of enhanced solvation by the more polar solvents causing stabilization of the excited state. One might expect these effects to be even more pronounced if transitions to extended dipolar or quinoid structures are associated with excitation. Voroshin and Vlasov found that solutions of salicylic acid in a number of 'neutral' solvents did not substantially effect the nature of the absorption spectrum but a small hypsochromic shift of the absorption maximum with transition from nonpolar to more polar solvents was apparent (462). On the other hand p-hydroxybenzoic acid behaved in just the opposite manner. Some workers have pointed to a correlation of band displacements to longer wavelengths with an increase of the dielectric constant of the solvent but there are significant exceptions to this rule (438, 463). Kumler and Strait have discredited the importance of dielectric constant changes to interpret solvent effects, at least within the p-nitroaniline system, in favour of specific hydrogen-bond formation of terminal groups in the molecule (464). Solvents which are modified

by addition of strong bases or acids may cause specific ion effects on the absorption curve (443). At times the acid or base may, apart from changing the molecular species present, be responsible for small variations observed mainly in decreases or increases of absorption intensity. Forbes and co-workers have related this effect to small changes in the force constant of the central linkages of the absorbing molecules (439).

The recognition and interpretation of the effect of hydrogen-bond formation on electronic transitions has grown steadily but difficulties can arise in distinguishing this from non hydrogen-bonding solvent interactions (148). For instance, stable hydrogen-bonded complexes have been ruled out as the cause of bathochromic shifts exhibited by phenols when the solvent was changed from isooctane to ethanol. Rather, the stabilization of polar excited states was achieved by electronic interaction between the dipole of the alcohol and the ionic forms of the excited state (465). Reference has already been made to pertinent studies on the importance of hydrogen bonding in aromatic carboxylic-acid systems. More detailed discussions of solvent effects on ultraviolet spectra are available and these have included a treatment in terms of solvent polarization, dipole - dipole, dipole - polarization and hydrogen-bonding forces (148, 431c, 466).

Interpretation of Results

The main body of the ultraviolet spectrophotometric examination was conducted by observing the change in transmittance with wavelength for the various acids under different solvent conditions in a Beckman Model DK Recording Spectrophotometer. The values of transmittance and wavelength both corresponding to points of maximum absorption were recorded from the spectral curves. Quartz cells of 1 mm path length were used throughout in combination with a hydrogen lamp source and photomultiplier detector. The bases pyridine and N-ethylpiperidine absorb strongly in the ultraviolet so that in the initial experiments use was made of absolute methanol which was completely transparent to 216 mμ under these experimental conditions. Pyridine was preferable to quinoline as the basic solvent since quinoline severely limited the ultraviolet region, which was useful for studying the anthranilic and salicylic acid absorption bands, because of its strong absorption at longer wavelengths compared to pyridine (467).

The results of the spectral examination of salicylic and anthranilic acids in methanol and pyridine are noted in Table XXIX. Included are band positions and intensities in other solvents from other sources. It is estimated that the values of λ_{max} may be read within ± 2 mμ from the values listed but usually within ± 1 mμ. The greatest error was associated with estimating λ_{max} and absorbance values when

TABLE XXIX

CHARACTERISTIC ULTRAVIOLET ABSORPTION BANDS OF SALICYLIC AND ANTHRANILIC ACIDS IN VARIOUS SOLVENTS

No.	Organic[a] Acid	Source[b]	Figure[c] No.	Solvent (Mod.)[d]	Concentration: mole/litre		Secondary Band[f]			First Primar		
					Organic Acid x 10^4	(Mod.)[e]	λ_{max}[g] (mμ)	A[h]	$\epsilon_{max} \times 10^{-3}$[i]	λ_{max} (mμ)	A	ϵ
1.	4-CH_3OSA	A		H_2O	1.4	(1.0)	299	0.832	5.9			
2.		A		H_2O	1.4		296	.790	5.6			
3.		B[j]		H_2O			294		5.5	254		
4.		B[j]		H_2O			291		5.3	250		
5.		C		H_2O	0.4		291	.200	5.0	249	0.454	
6.		A		H_2O	1.4		295	.733	5.2			
7.		C		H_2O	0.4	(2)	302	.200	5.0	~250[l]	.39	
8.		E	22	C_5H_5N	11.9	(0.040)[m]	~296[n]	.724	6.08	o		
9.		E	22	C_5H_5N	11.9		~296[n]	.724	6.08	o		
10.		E	22	C_5H_5N	11.9	(0.036)	~295[n]	.597	5.02	o		
11.	SA	A		H_2O	2.0	(1.0)	306	.694	3.5			
12.		A		H_2O	2.0		299	.717	3.6			
13.		B[j]		H_2O			302.5		3.6	237		
14.		C		H_2O	1.04		295	.358	3.43	230[l]	.701	
15.		A		H_2O	2.0		297	.709	3.5			
16.		B[j]		H_2O			296		3.5	230.5		
17.		C		H_2O	1.04	(2.)	302	.354	3.39	237[p]		
18.		E	23	CH_3OH	4.00[q]	(1.3)	302	.169	≥4.22[r]	235	.334	
19.		E	23	CH_3OH	4.00		301	.160	4.00	235	.306	
20.		E	23	CH_3OH	4.00[q]	(9 x 10^{-4}- 9 x 10^{-2})[m]	294	.162	≥4.05[r]	s		

TABLE XXIX

CHARACTERISTIC ULTRAVIOLET ABSORPTION BANDS OF SALICYLIC AND ANTHRANILIC ACIDS IN VARIOUS SOLVENTS

olvent	(Mod.)[d]	Concentration: mole/litre		Secondary Band[f]			First Primary Band[f]			Second Primary Band		
		Organic Acid x 10^4	(Mod.)[e]	λ_{max} (mμ)[g]	A[h]	ϵ_{max} x 10^{-3}[i]	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}
O	($^{pH\ 0}_{HCl}$)	1.4	(1.0)	299	0.832	5.9						
O	(pH 3)	1.4		296	.790	5.6						
O	(pH 3)			294		5.5	254		12.4	206		3.3
O	(pH 7)			291		5.3	250		12.0	k		
O	(pH 7)	0.4		291	.200	5.0	249	0.454	11.			
O	($^{pH\ 9}_{NH_3}$)	1.4		295	.733	5.2						
O	(NaOH)	0.4	(2)	302	.200	5.0	~250[l]	.39	9.8			
H_5N	($PyHNO_3$)	11.9	(0.040)[m]	~296[n]	.724	6.08	o					
H_5N		11.9		~296[n]	.724	6.08	o					
H_5N	(NEP)	11.9	(0.036)	~295[n]	.597	5.02	o					
O	($^{pH\ 0}_{HCl}$)	2.0	(1.0)	306	.694	3.5						
O	(pH 3)	2.0		299	.717	3.6						
O	(pH 3)			302.5		3.6	237		9.0	202.5		3.6
O	(pH 7)	1.04		295	.358	3.43	230[l]	.701	6.72			
O	($^{pH\ 9}_{NH_3}$)	2.0		297	.709	3.5						
O	(pH 9)			296		3.5	230.5		7.2			
O	(NaOH)	1.04	(2.)	302	.354	3.39	237[p]					
$_3$OH	(H_2SO_4)	4.00[q]	(1.3)	302	.169	≥4.22[r]	235	.334	≥8.35[r]			
$_3$OH		4.00		301	.160	4.00	235	.306	7.65			
$_3$OH	(NaOMe)	4.00[q]	(9×10^{-4} - 9×10^{-2})[m]	294	.162	≥4.05[r]	s					

TABLE XXIX Continued

No.	Organic[a] Acid	Source[b]	Figure[c] No.	Solvent (Mod.)[d]	Concentration: mole/litre Organic Acid x 10^4	(Mod.)[e]	Secondary Band[f] λ_{max} (mμ)[g]	A[h]	ϵ_{max} x 10^{-3}[i]	First Primary λ_{max} (mμ)	A	ϵ_{max}
21.	NaSA	E	23	CH_3OH	3.45		294	0.140	4.06	s		
22.	SA	F		C_2H_5OH			307		3.7	236		
23.		E	24	C_5H_5N	11.99	(6.8×10^{-4})[m]	304	.526	≥ 4.42[r]	o		
24.		E	24	C_5H_5N	11.9		304	.526	4.42	o		
25.	NaSA	E	24	C_5H_5N	11.9		~294[n]	.499	4.19	o		
26.		F		C_6H_{12}			307		4.4	237-238		
27.	5-NO_2SA	A		H_2O	0.8	(1.0)	308	.836	10.			
28.		A		H_2O	0.8		318	.749	9.4			
29.		C		H_2O	0.5	(pH 7.1)	317	.440	8.8			
30.		A		H_2O	0.8	($\frac{pH\ 9}{NH_3}$)	t			271[l]	0.280	
31.		C		H_2O	0.5	(2.)	413[u]			262[p]		
32.		E	25	CH_3OH	3.01	(0.45)	299	.342	11.4	p		
33.		E	25	CH_3OH	3.01		299	.326	10.8	p		
34.		E	25	CH_3OH	3.01	(9×10^{-4}-8×10^{-2})	313[v]	.295	9.8			
35.		E	26	C_5H_5N	6.88	(<0.09)[x]	312[y]	.697	10.1	o		
36.		E	26	C_5H_5N	6.88		313(372)[y]	.650	9.45	o		
37.		E	26	C_5H_5N	6.88	(NEP)	329[y]	.682	9.91	o		
38.	4-NO_2SA	A		H_2O	0.96	(1.0)	~356	.24	2.5	269	.96	
39.		A		H_2O	0.96		~356	.25	2.6	275	.86	
40.		A		H_2O	0.96	($\frac{pH\ 9}{NH_3}$)	~356	.25	2.6	276	.83	
41.		C		H_2O	2.0	(2.)	406	.399	2.0			
42.		E	27	CH_3OH	6.88	(1.1)	341	.194	2.82	263[z,aa]	.127	

TABLE XXIX Continued

(Mod.)[d]	Concentration: mole/litre		Secondary Band[f]			First Primary Band[f]			Second Primary Band		
	Organic Acid x 10^4	(Mod.)[e]	λ_{max} (mμ)[g]	A[h]	ϵ_{max} x 10^{-3}[i]	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}
	3.45		294	0.140	4.06	s					
			307		3.7	236		7.5			
($PyHNO_3$)	11.99	(6.8 x 10^{-4})[m]	304	.526	≥4.42[r]	o					
	11.9		304	.526	4.42	o					
	11.9		~294[n]	.499	4.19	o					
			307		4.4	237-238		8.0			
(pH 0 HCl)	0.8	(1.0)	308	.836	10.						
(pH 3)	0.8		318	.749	9.4						
(pH 7.1)	0.5		317	.440	8.8						
(pH 9 NH_3)	0.8		t			271[l]	0.280	3.5			
(NaOH)	0.5	(2.)	413[u]			262[p]					
(H_2SO_4)	3.01	(0.45)	299	.342	11.4	p			222	0.583	19.4
	3.01		299	.326	10.8	p			221	.536	17.8
(NaOMe)	3.01	(9 x 10^{-4}-8 x 10^{-2})	313[v]	.295	9.8				w		
(H_2SO_4)	6.88	(<0.09)[x]	312[y]	.697	10.1	o					
	6.88		313(372)[y]	.650	9.45	o					
(NEP)	6.88	(0.14)	329[y]	.682	9.91	o					
(pH 0 HCl)	0.96	(1.0)	~356	.24	2.5	269	.96	10.			
(pH 3)	0.96		~356	.25	2.6	275	.86	9.0			
(pH 9 NH_3)	0.96		~356	.25	2.6	276	.83	8.6			
(NaOH)	2.0	(2.)	406	.399	2.0						
(TFA)	6.88	(1.1)	341	.194	2.82	263[z,aa]	.127	9.2	242[z,aa,bb]	.127	9.2

TABLE XXIX Continued

No.	Organic[a] Acid	Source[b]	Figure[c] No.	Solvent (Mod.)[d]	Concentration: mole/litre Organic Acid x 10^4	(Mod.)[e]	Secondary Band[f] λ_{max} (mμ)[g]	A[h]	$\epsilon_{max} \times 10^{-3}$[i]	First Primary λ_{max} (mμ)	A	ϵ
43.		E	27	CH_3OH	6.88		343	0.189	2.75	263[aa]	0.618	
44.		E		CH_3OH	1.38		[cc]			266	.118	
45.		E	27	CH_3OH (NEP)	6.88	(0.55)	348	.185	2.69	[dd]		
46.		E	28	C_5H_5N (H_2SO_4)[ee]	6.55	(<0.09)[x]	349	.183	2.79	o		
47.		E	28	C_5H_5N	6.55		350	.174	2.66	o		
48.		E	28	C_5H_5N (NEP)	6.55	(0.18)	355	.170	2.60	o		
49.	5-CH_3AA	E	29	CH_3OH (H_2SO_4)	3.65[q]	(0.36)	276[ff]	.048	≥1.32[r]	228[gg]	.320	
50.		E	29	CH_3OH	3.65		340	.137	3.75	248	.237	
51.		E	29	CH_3OH (NEP)	3.65	(0.18)	319	.105	2.88	[dd]		
52.		E	30	C_5H_5N (H_2SO_4)	1.32	(<0.09)[x]	345	.676	5.12	o		
53.		E	30	C_5H_5N	1.32		345	.676	5.12	o		
54.		E	30	C_5H_5N (NEP)	1.32	(0.18)	340	.580	4.39	o		
55.	AA	D		H_2O ($HClO_4$)		(0.1)	270-275		0.85			
56.	AA[hh]	I		H_2O (HCl)	10.	(1.0)	328		1.4	272		
57.	AA	D		H_2O ($HClO_4$)		(0.01)	320-325		0.68	260-265[p]		
58.		B[j]		H_2O (pH 3.7)			327		1.9	248[ii]		
59.		D		H_2O			~320		1.9			
60.		I		H_2O	10.		325		2.1			
61.		B[j]		H_2O (pH 11)			310		2.8	240		
62.		D		H_2O (NaOH)		(0.1)	310		2.8			
63.	NaAA	I		H_2O	10.		308		3.2	242		
64.	AA	E	31	CH_3OH (H_2SO_4)	4.02[q]	(1.3)	271[ff]	.053	≥1.32[r]	225[gg]	.467	

TABLE XXIX Continued

(Mod.)[d]	Concentration: mole/litre		Secondary Band[f]			First Primary Band[f]			Second Primary Band		
	Organic Acid x 10^4	(Mod.)[e]	λ_{max} (mμ)[g]	A[h]	$\epsilon_{max} \times 10^{-3}$[i]	λ_{max} (mμ)	A	$\epsilon_{max} \times 10^{-3}$	λ_{max} (mμ)	A	$\epsilon_{max} \times 10^{-3}$
	6.88		343	0.189	2.75	263[aa]	0.618	8.98	241[aa,bb]	0.664	9.65
	1.38		cc			266	.118	8.55	242[bb]	.132	9.56
(NEP)	6.88	(0.55)	348	.185	2.69	dd			dd		
(H_2SO_4)[ee]	6.55	(<0.09)[x]	349	.183	2.79	o					
	6.55		350	.174	2.66	o					
(NEP)	6.55	(0.18)	355	.170	2.60	o					
(H_2SO_4)	3.65[q]	(0.36)	276[ff]	.048	≥1.32[r]	228[gg]	.320	≥8.77[r]			
	3.65		340	.137	3.75	248	.237	6.49	217	.947	25.9
(NEP)	3.65	(0.18)	319	.105	2.88	dd					
(H_2SO_4)	1.32	(<0.09)[x]	345	.676	5.12	o					
	1.32		345	.676	5.12	o					
(NEP)	1.32	(0.18)	340	.580	4.39	o					
($HClO_4$)		(0.1)	270-275		0.85						
(HCl)	10.	(1.0)	328		1.4	272		2.0			
($HClO_4$)		(0.01)	320-325		0.68	260-265[p]					
(pH 3.7)			327		1.9	248[ii]		3.9	216.5		18.5
			~320		1.9						
	10.		325		2.1						
(pH 11)			310		2.8	240		7.1	209		28.1
(NaOH)		(0.1)	310		2.8						
	10.		308		3.2	242		6.6			
(H_2SO_4)	4.02[q]	(1.3)	271[ff]	.053	≥1.32[r]	225[gg]	.467	≥11.6[r]			

TABLE XXIX Continued

No.	Organic[a] Acid	Source[b]	Figure[c] No.	Solvent (Mod.)[d]	Concentration: mole/litre Organic Acid x 10^4	(Mod.)[e]	Secondary Band[f] λ_{max}[g] (mμ)	A^h	ϵ_{max} x 10^{-3}[i]	First Prim λ_{max} (mμ)	A
65.	AA	D		CH_3OH			330-335		4.3		
66.		E	31	CH_3OH	4.02		333	0.188	4.68	246	0.290
67.		E	31	CH_3OH (NaOMe)	4.02[q]	($9 \times 10^{-4} - 9 \times 10^{-2}$)[m]	315	.136	⩾3.38[r]	245	.295
68.		E		CH_3OH (NEP)	4.02	(0.18)	317	.135	3.36	dd	
69.		G		C_2H_5OH			332		4.5	247	
70.		E	32	C_5H_5N (H_2SO_4)[ee]	1.46	(<0.09)[x]	338	.793	5.43	o	
71.		E	32	C_5H_5N	1.46		338	.793	5.43	o	
72.		E	32	C_5H_5N (NEP)	1.46	(0.18)	330	.668	4.58	o	
73.		H		$(C_2H_5)_2O$			333		5.2	252	
74.	5-NO_2AA	E	33	CH_3OH (H_2SO_4)	3.03[r]	(0.36)	347	.432	⩾14.2[p]	242[p]	
75.		E	33	CH_3OH	3.03		348	.417	13.8	242[p]	
76.		E	33	CH_3OH (NEP)	3.03	(0.18)	374(333)[kk]	.434	14.3	dd	
77.		E	34	C_5H_5N (H_2SO_4)	6.59	(<0.09)[x]	367	1.12	17.0	o	
78.		E	34	C_5H_5N	6.59		367	1.12	17.0	o	
79.		E	34	C_5H_5N (NEP)	6.59	(0.18)	384(337)[kk]	1.26	19.1	o	
80.	4-NO_2AA	E	35	CH_3OH (H_2SO_4)	3.03	(0.45)	397	0.063	2.08	257[p]	
81.		E	35	CH_3OH	3.03		396	.087	2.87	258[p]	
82.		E	35	CH_3OH (NEP)	3.03	(0.18)	397	.073	2.41	dd	
83.		E	36	C_5H_5N (H_2SO_4)[ee]	11.0	(<0.09)[x]	409	.323	2.94	o	
84.		E	36	C_5H_5N	11.0		409	.323	2.94	o	
85.		E	36	C_5H_5N (NEP)	11.0	(0.18)	409	.282	2.56	o	

TABLE XXIX Continued

Mod.)[d]	Concentration: mole/litre		Secondary Band[f]			First Primary Band[f]			Second Primary Band		
	Organic Acid x 10^4	(Mod.)[e]	λ_{max} (mμ)[g]	A[h]	ϵ_{max} x 10^{-3}[i]	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}	λ_{max} (mμ)	A	ϵ_{max} x 10^{-3}
			330-335		4.3						
	4.02		333	0.188	4.68	246	0.290	7.21	216	1.24	30.8
NaOMe)	4.02[q]	(9 x 10^{-4} - 9 x 10^{-2})[m]	315	.136	⩾3.38[r]	245	.295	⩾7.34[r]			
NEP)	4.02	(0.18)	317	.135	3.36	dd					
			332		4.5	247		6.5[jj]			
H_2SO_4)[ee]	1.46	(<0.09)[x]	338	.793	5.43	o					
	1.46		338	.793	5.43	o					
NEP)	1.46	(0.18)	330	.668	4.58	o					
			333		5.2	252		7.4			
H_2SO_4)	3.03[r]	(0.36)	347	.432	⩾14.2[p]	242[p]			226[p]		
	3.03		348	.417	13.8	242[p]			225[p]		
NEP)	3.03	(0.18)	374(333)[kk]	.434	14.3	dd					
H_2SO_4)	6.59	(<0.09)[x]	367	1.12	17.0	o					
	6.59		367	1.12	17.0	o					
NEP)	6.59	(0.18)	384(337)[kk]	1.26	19.1	o					
H_2SO_4)	3.03	(0.45)	397	0.063	2.08	257[p]			241	.507	16.7
	3.03		396	.087	2.87	258[p]			240	.600	19.8
NEP)	3.03	(0.18)	397	.073	2.41	dd					
H_2SO_4)[ee]	11.0	(<0.09)[x]	409	.323	2.94	o					
	11.0		409	.323	2.94	o					
NEP)	11.0	(0.18)	409	.282	2.56	o					

TABLE XXIX Continued

a Salicylic (SA) or anthranilic (AA) acid and their derivatives; NaSA and NaAA refer to sodium salicylate and anthranilate respectively. When entries are not made in this column it is understood that reference is being made to the last-noted acid.

b Data in the table is taken from the following sources:
A - Spectra recorded in the thesis of Fei-Lin Kung (287).
B - References (434, 435).
C - Recorded spectra, reference (468).
D - Recorded spectra, reference (469).
E - This investigation.
F - Reference (441).
G - Reference (438).
H - Reference (470).
I - Reference (442).

c Refers to the spectrum from this investigation.

d The solvent is indicated by molecular formula: e.g., C_6H_{12} - cyclohexane. Unless otherwise indicated the reference cell contains only the pure solvent for the spectral measurements conducted in this study. The entry in parentheses gives an indication of the pH in aqueous solution or the reagent used to modify the solvent's basic and acidic properties. These reagents included N-ethylpiperidine (NEP), methanolic sodium methoxide (NaOMe), sulfuric acid (H_2SO_4), trifluoroacetic acid (TFA), pyridinium nitrate ($PyHNO_3$). The TFA reagent was a mixture of trifluoroacetic acid and trifluoroacetic anhydride (4:1 by volume).

e Value in parentheses is the estimated concentration of added reagent noted in the previous column. The reagent was usually added to the acid solutions (contained in volumetrics) in a dropwise fashion. Approximate concentrations of the reagent were estimated by assuming that 20 drops ≅ 1 ml and using any other required physical constants. $PyHNO_3$ reagent dissolved in pyridine solution was added by pipette (one exception is noted in line 23 of Table XXIX).

f Follows the classification according to Doub and Vandenbelt (434, 435). The secondary, first primary and secondary primary bands are usually considered to be associated with respective benzene maxima at 254, 203.5 and 183.5 mμ (433, 434). Assignments made in this study are based largely on similarity of band position and intensity and comparison with other data from the literature. It has been pointed out, however, that the intensity criteria does not always strictly apply especially in the case of secondary bands.

g Position of the absorption maximum in millimicrons (mμ).

h Absorbance: $A = -\log T$.

i Molar extinction coefficient (litre/mole cm) corresponding to λ_{max}: $\epsilon = \frac{A}{bc} = \frac{-\log T}{bc}$ where A and T represent absorbance and transmittance respectively, b represents the cell length (cm) and c signifies the concentration (mole/litre).

j Spectral investigations from this source may have included aqueous solutions containing 1-2 per cent methanol.

k Below the accessible wavelength region.

l Band in fused to lower wavelength absorption.

m Reference cell contained the same concentration of reagent as the sample compartment.

n λ_{max} is difficult to estimate since this is the region where the slit width is opening rapidly and the reference energy is beginning to drop.

o Strong pyridine absorption prevents observation of shorter wavelength bands.

p Inflection, band is fused to lower wavelength absorption but band maximum has not developed.

q Concentration of the absorbing material may be slightly less than that indicated since the solution was modified by adding a few drops of the strong acid or base reagent to a quantity of the final solution containing the neutral solvent.

r Whenever the symbol $\geqslant$ is used, it is intended to signify that the value of the molar extinction coefficient may actually be slightly greater than the figure noted due to the procedure described in footnote q. Any correction, however, would be expected to be of small significance.

s Plateau at $\sim$ 225 mμ.

t Peak lies to $>$ 400 mμ and was unavailable in recorded spectrum.

u Peak off scale, maximum estimated.

v A shoulder with inflection at $\sim$ 400 mμ on the long wavelength side of this band is an indication of a submerged absorption. Subsequent tests by adding further increments of NaOMe (CH_3OH) solution to the absorbing solution (with dilution of the organic acid concentration) caused a peak to form from the shoulder with a corresponding hyperchromic effect.

w Possible λ_{max} obscured by absorbance of NaOMe.

x Concentration is indicated as $<$ 0.09 mole/litre since a precipitate (PyH_2SO_4) forms on addition of one drop of concentrated H_2SO_4. Dissolution of this precipitate is slow and incomplete. See comments in the interpretation of results.

y A shoulder on the long wavelength side of the main band indicates that the band is a possible composite of different species producing an asymmetric absorption. It's position is noted as an inflection (in parentheses) in line 36.

TABLE XXIX Continued

The shoulder is reduced in intensity in the order C_5H_5N (NEP) $>$ C_5H_5N $>$ C_5H_5N (H_2SO_4).

z Determined in solution containing 0.90 mole/litre H_2SO_4 since TFA absorbs at these wavelengths. Concentration of 4-NO_2SA was 1.38×10^{-4} mole/litre.

aa Absorption band not included in Figure 27.

bb Possible band beginning to form at even lower wavelengths near instrument cut off.

cc Not estimated.

dd Strong NEP absorption prevents measurement.

ee Spectrum was also taken by substituting $PyHNO_3$ (0.040 mole/litre) for H_2SO_4 and was identical in shape, intensity and λ_{max} all within the experimental error. In these instances the reference cell contained the same concentration of $PyHNO_3$ reagent as the sample compartment. See comments in the interpretation of results.

ff Classified as secondary when compared to benzoic acid (line 2, Table XXVI).

gg Classified as first primary when compared to benzoic acid (line 2, Table XXVI).

hh In the form of the chlorohydrate of anthranilic acid-$HCl.NH_2C_6H_4COOH(+H_2O)$.

ii Inflection.

jj Reference (440) lists $\epsilon_{max} = 6.7 \times 10^3$ litre/mole cm.

kk Value in parentheses indicates point of inflection of a shoulder of a band fused to the short wavelength side of the main absorption.

these were taken from figures of reproduced spectra in literature sources. For convenience the various solvents used for each individual acid are presented in the order of decreasing dielectric constant. Within each solvent type the order is from the most acidic to the most basic solutions. Attention will be directed primarily to results obtained with the secondary band since entries corresponding to the other absorption bands are far from complete. The Table also lists the figure from which the data noted in the particular line is taken. The Figures related to the Table are 22 to 36 inclusive.

Some general observations may be introduced first. There was some concern that pyridine solutions saturated with H_2SO_4 (PyH_2SO_4) did not supply an adequate concentration of pyridinium ions ($PyH^{(+)}$) to the systems. When H_2SO_4 was replaced by $PyHNO_3$ (0.04 mole/litre), essentially superimposable spectra were obtained indicating that pyridine solutions containing PyH_2SO_4 were just as effective. By using the estimate for the dissociation constant ($\sim 5 \times 10^{-5}$) of $PyHNO_3$ in pyridine given by Davies (117), the concentration of free $PyH^{(+)}$ was calculated to be about 1.4×10^{-3} mole/litre. With the exception of one solution (line 23, Table XXIX) this concentration was in excess of the organic acid concentration contained in the same solution.

FIGURES 22 THROUGH 36

The Ultraviolet Absorption Spectra of Salicylic and Anthranilic Acids in Methanol and Pyridine Solutions

Acid	Figure[a]	Methanol[b]			Figure[f]	Pyridine[b]		
		Acidic[c]	Neutral[d]	Basic[e]		Acidic[g]	Neutral[h]	Basic[i]
4-CH_3OSA					22	8[j]	9[j]	10
SA	23	18	19	20(21)[k]	24	23[j]	24[j]	25[l]
5-NO_2SA	25	32	33	34[m]	26	35	36	37
4-NO_2SA	27	42	43	45	28	46	47	48
5-CH_3AA	29	49	50	51	30	52[j]	53[j]	54
AA	31	64	66	67	32	70[j]	71[j]	72
5-NO_2AA	33	74	75	76	34	77[j]	78[j]	79
4-NO_2AA	35	80	81	82	36	83[j]	84[j]	85

FIGURES 22 THROUGH 36 Continued

a The number corresponding to the spectra determined in methanolic solutions.
b Lists the number corresponding to the line in Table XXIX which records the complete spectral data for that particular acid - solvent system.
c Methanolic solutions are modified by adding either H_2SO_4 or TFA reagent. Spectral curves are characterized by ———— .
d Pure methanol. Spectral curves are characterized by --------.
e Methanolic solutions are modified by adding either NaOMe or NEP reagent. Spectral curves are characterized by ····· .
f The number corresponding to the spectra determined in pyridine solution.
g Pyridine solutions are modified by adding either $PyHNO_3$ or H_2SO_4 reagent. Spectral curves are characterized by ———— .
h Pure pyridine. Spectral curves are characterized by ----- .
i Pyridine solutions are modified by adding NEP reagent. Spectral curves are characterized by ····· .
j Spectral curves are superimposed.
k Sodium salicylate is dissolved in methanol. Spectral curve is characterized by ·-·-·- .
l Sodium salicylate dissolved in pyridine. Spectral curve is characterized by ····· .
m A spectral curve is shown for the blamk solution containing only NaOMe in methanol in the same concentration as used in the solution of 34.

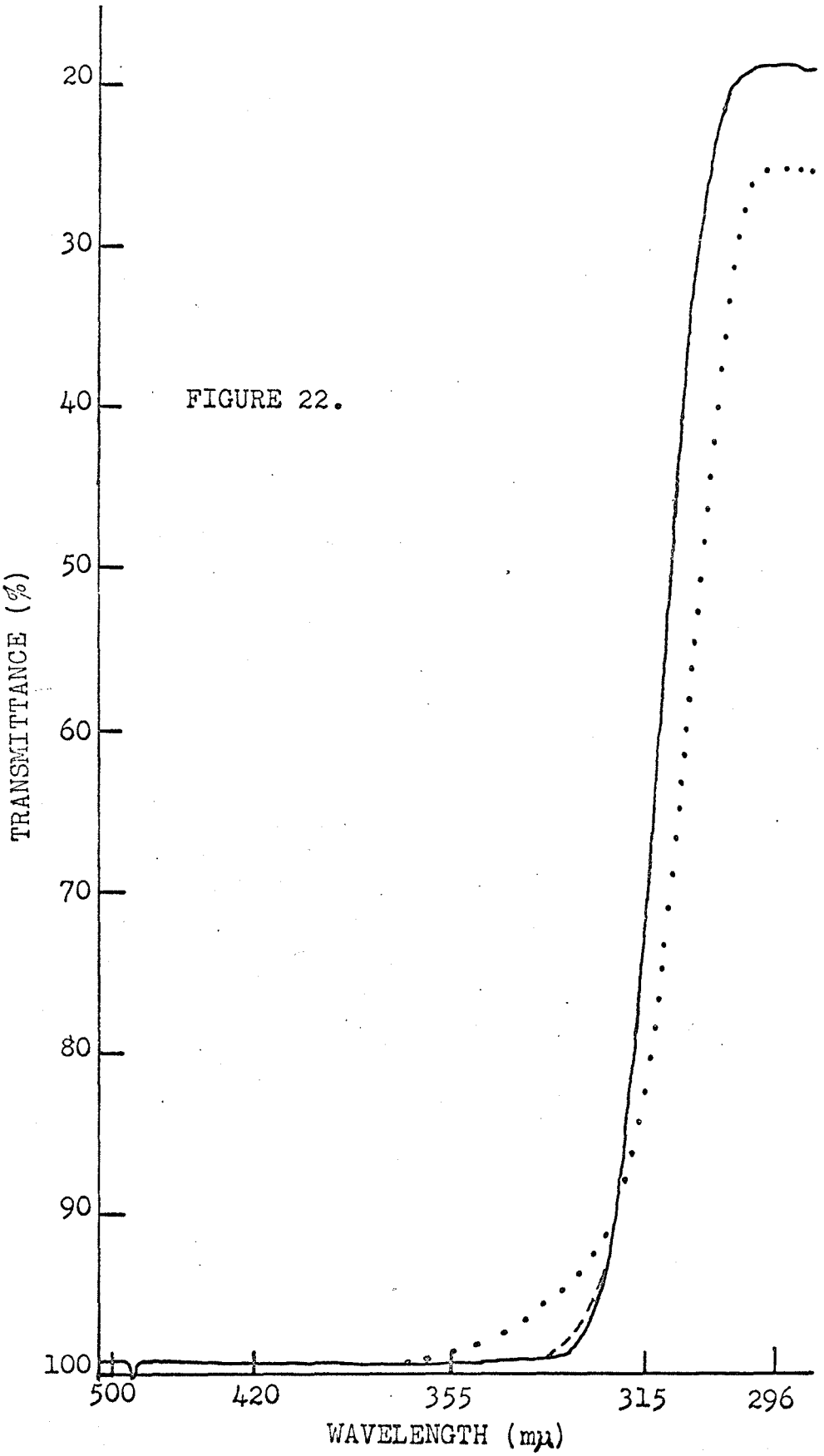

20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
500
420
355
315
296
WAVELENGTH (mμ)

FIGURE 22.

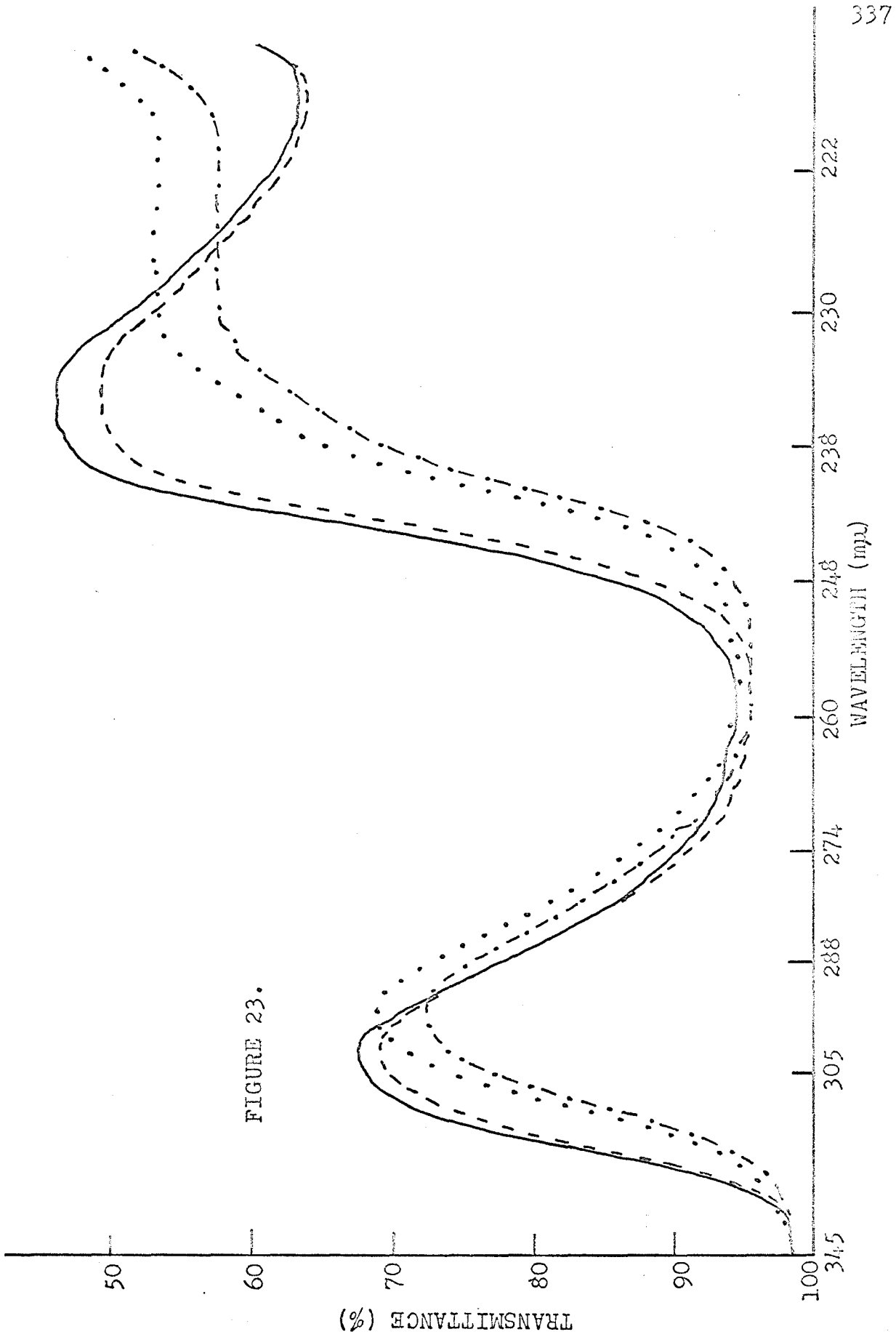

TRANSMITTANCE (%)
50
60
70
80
90
100
345
305
288
274
260
248
238
230
222
WAVELENGTH (mμ)

FIGURE 23.

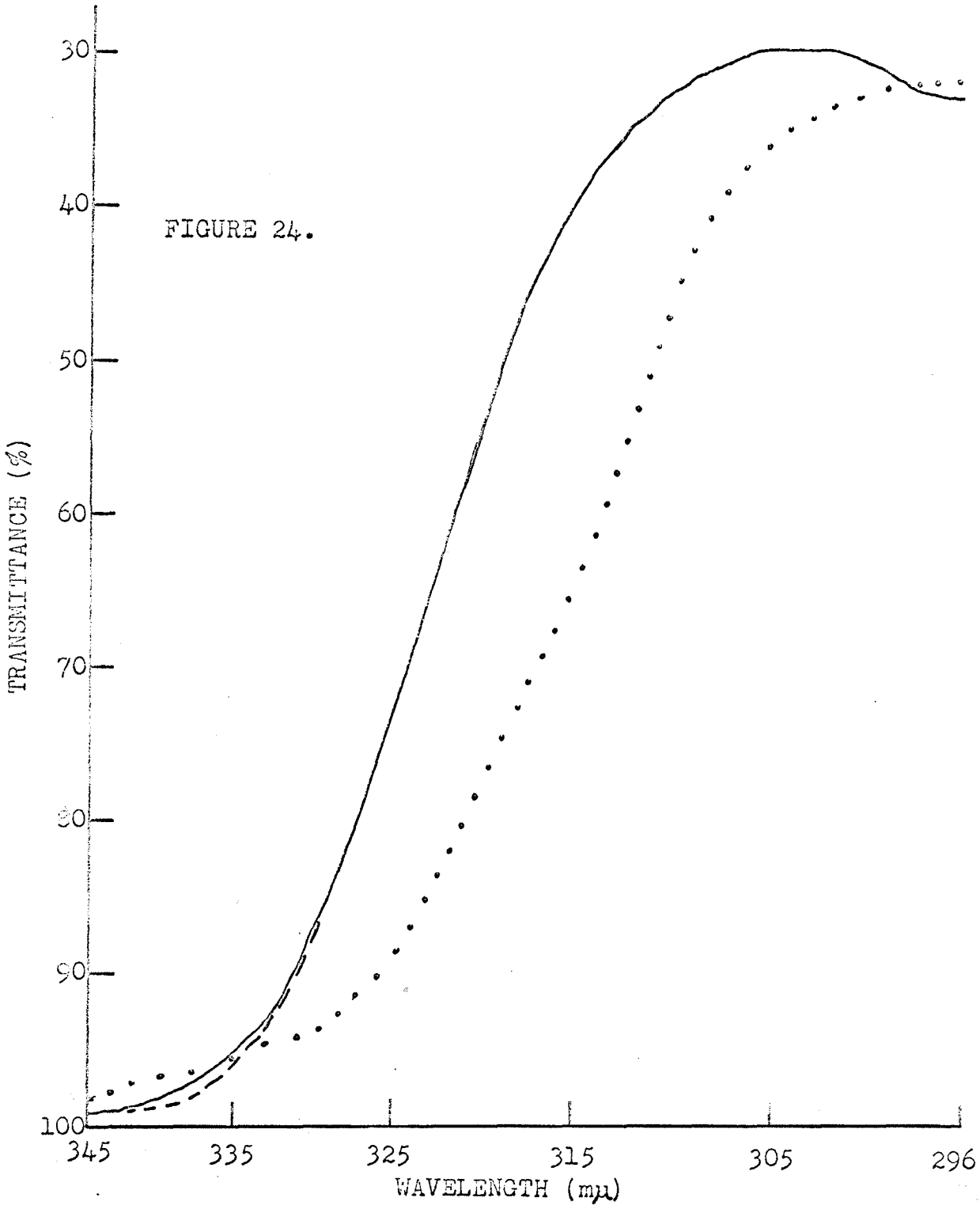

30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
345
335
325
315
305
296
WAVELENGTH (mμ)

FIGURE 24.

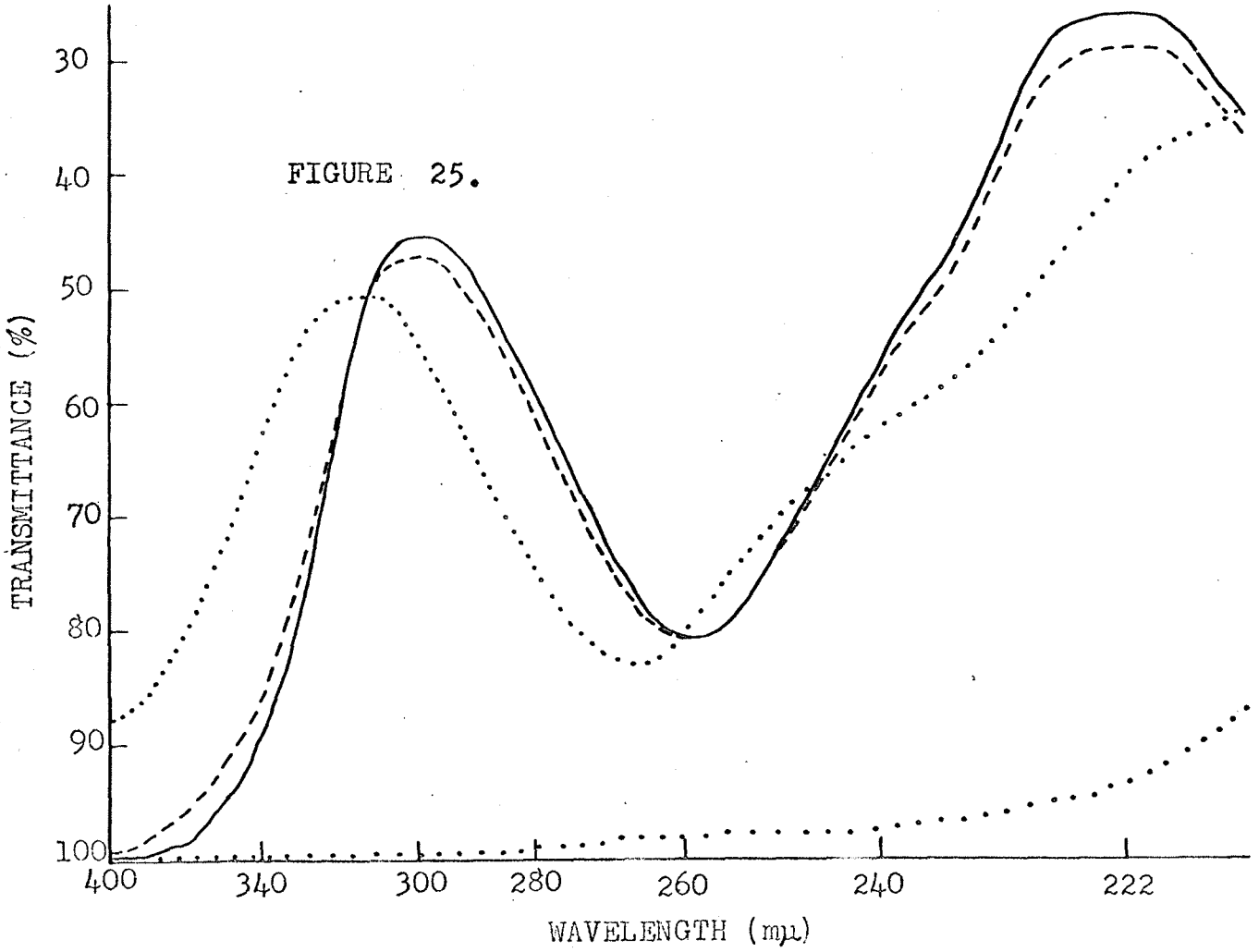

30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
400
340
300
280
260
240
222
WAVELENGTH (mμ)

FIGURE 25.

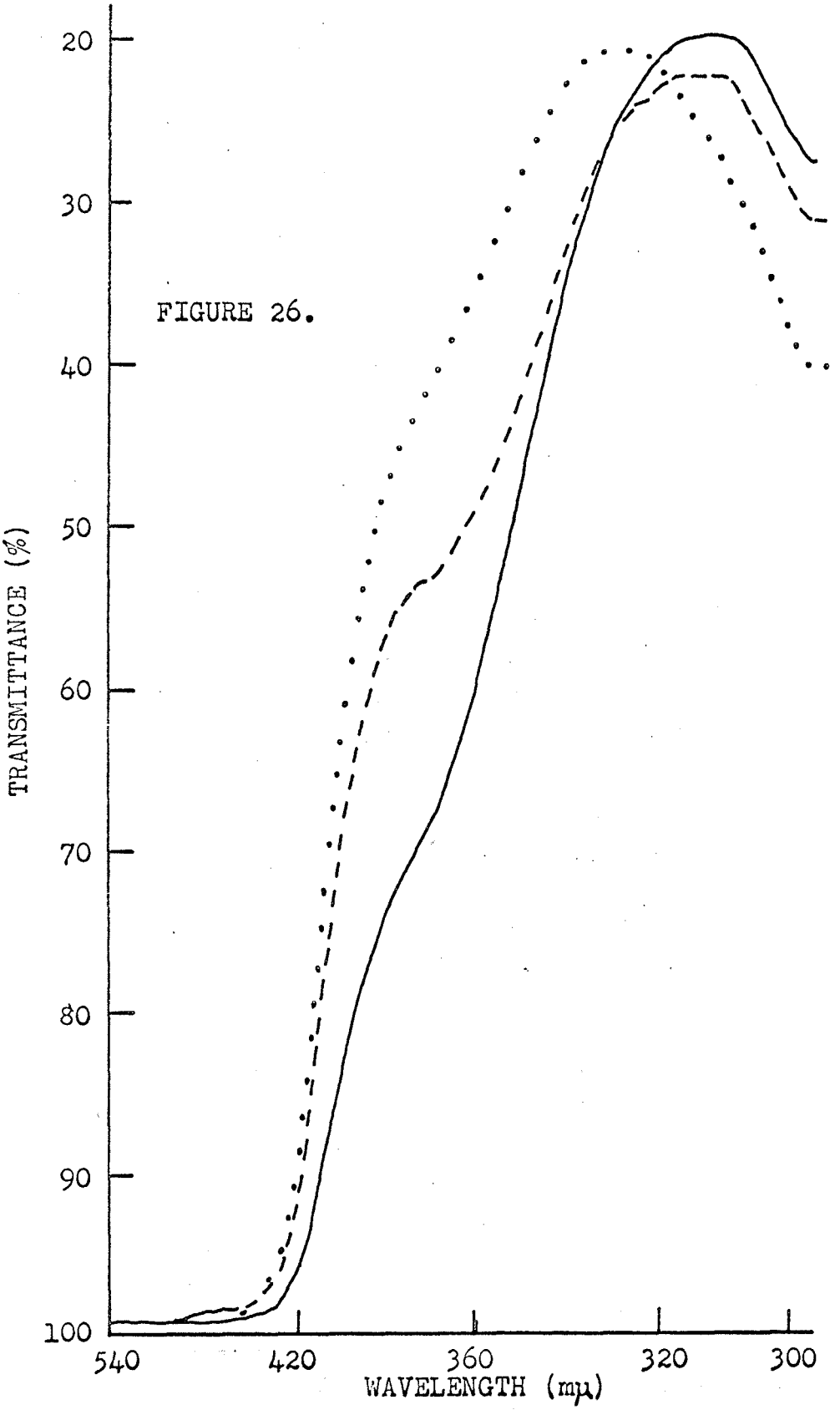

20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
540
420
360
320
300
WAVELENGTH (mμ)

FIGURE 26.

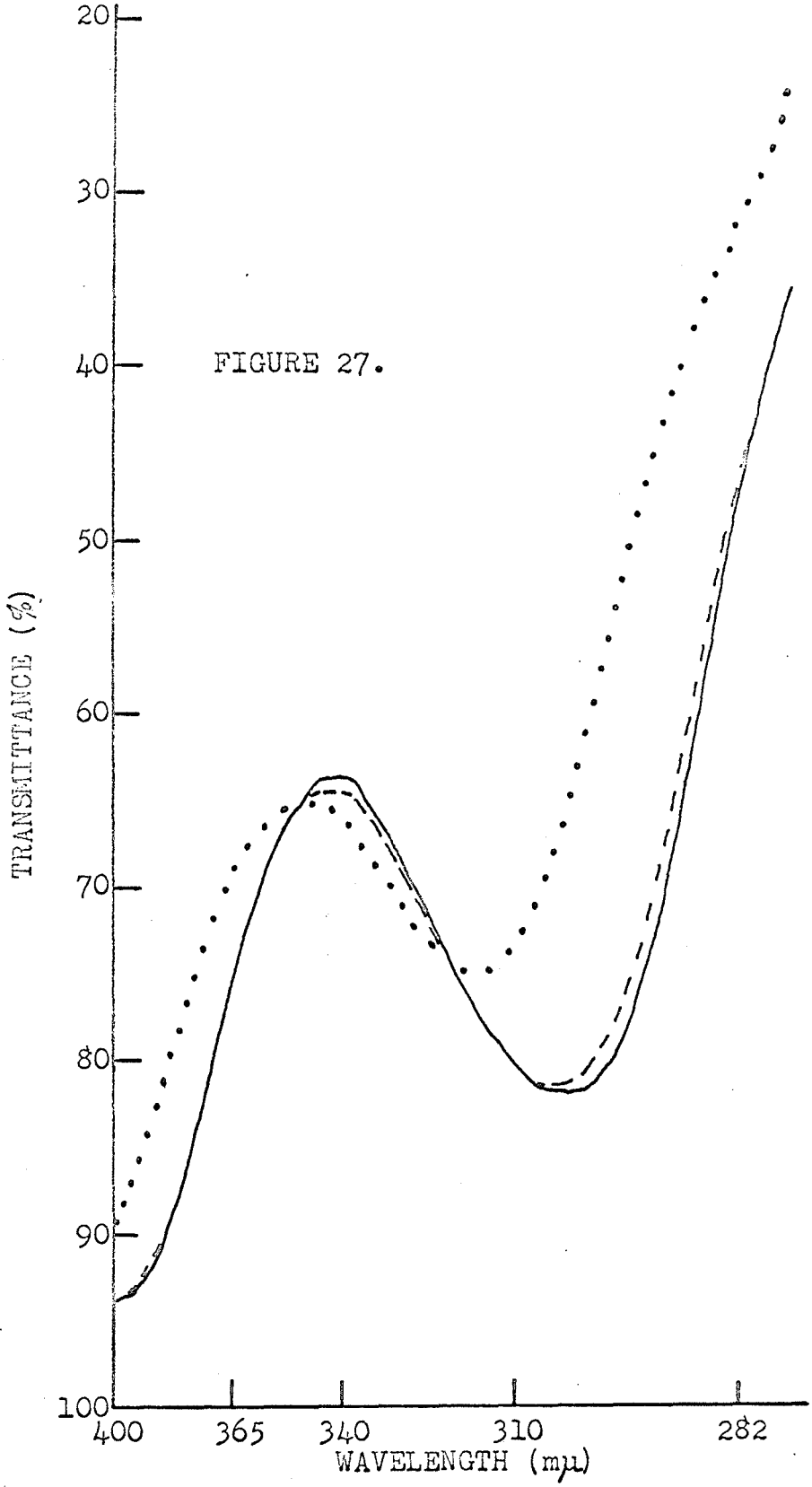
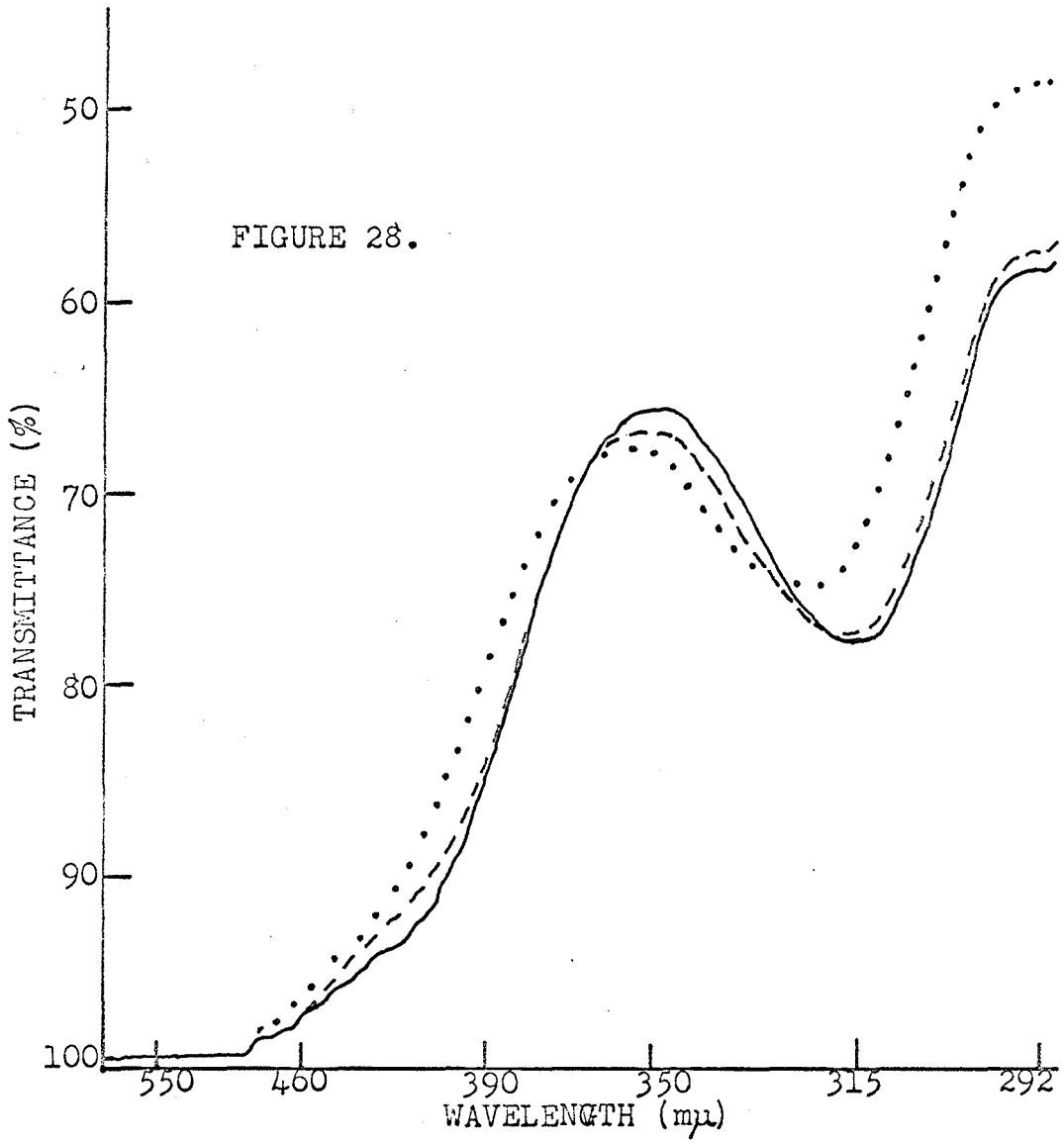

20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
400
365
340
310
282
WAVELENGTH (mμ)

FIGURE 27.

FIGURE 28.


50
60
70
80
90
100
TRANSMITTANCE (%)
550
460
390
350
315
292
WAVELENGTH (mμ)

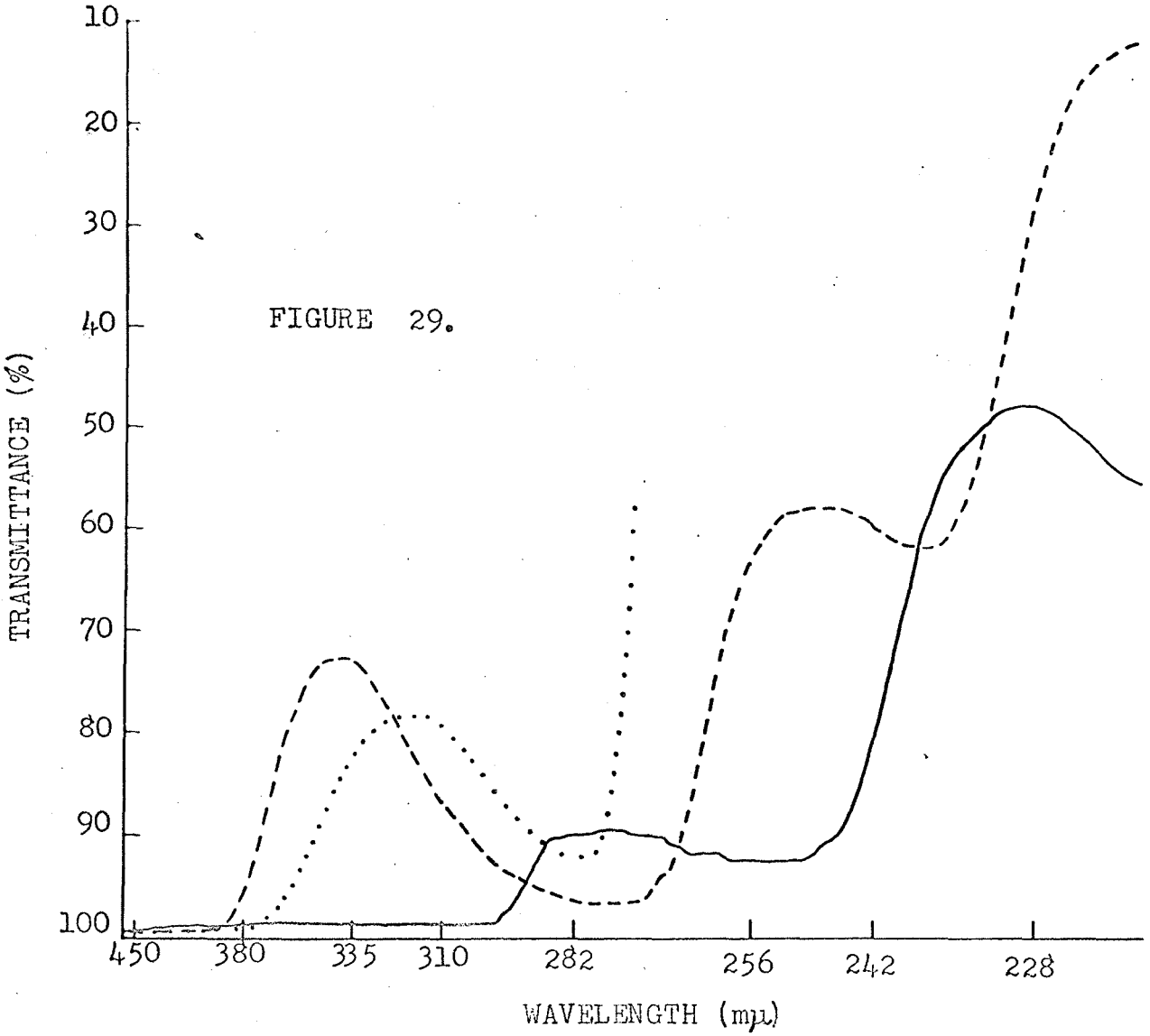

10
20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
450
380
335
310
282
256
242
228
WAVELENGTH (mμ)

FIGURE 29.

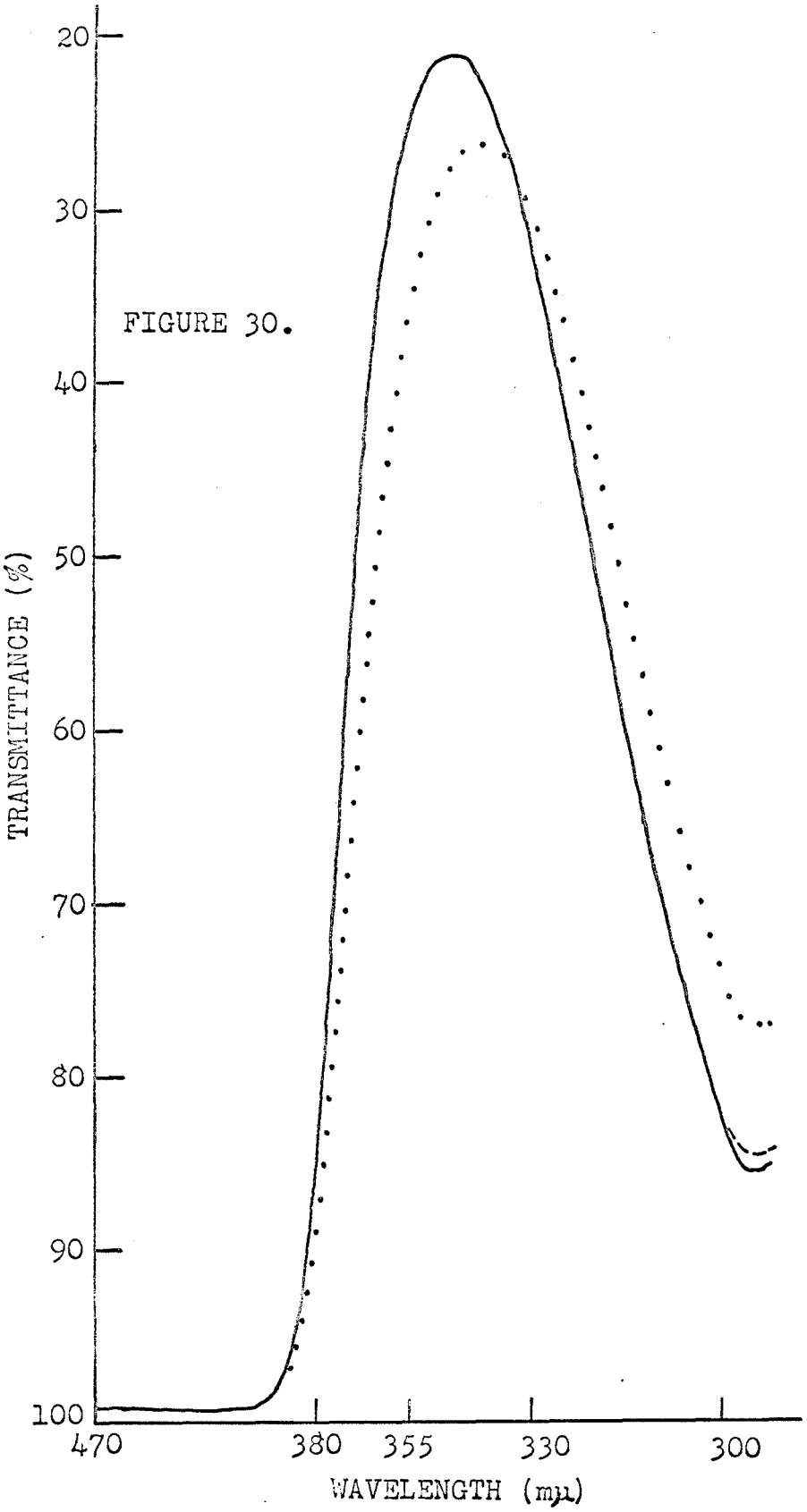

20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
470
380
355
330
300
WAVELENGTH (mμ)

FIGURE 30.

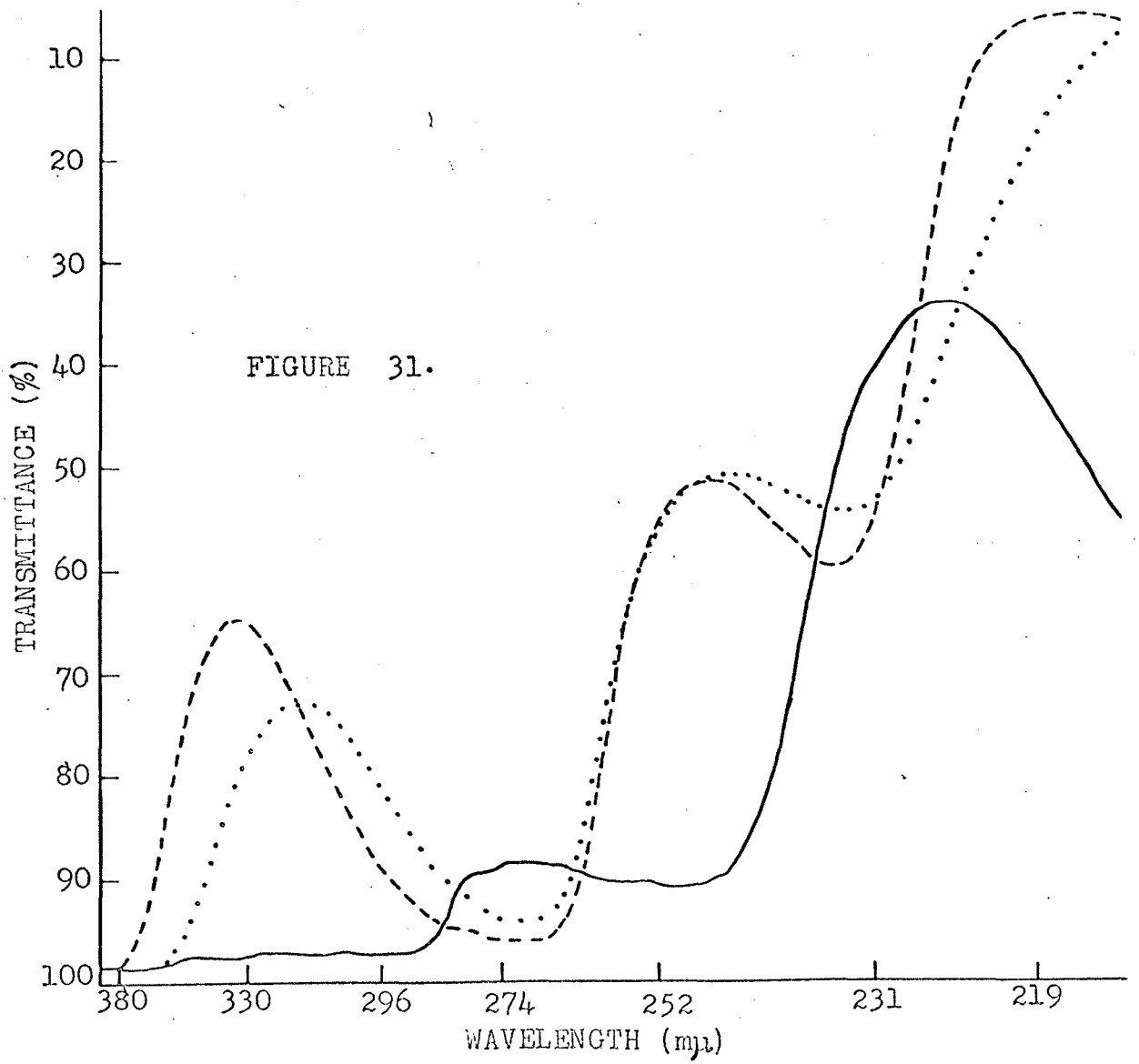

10
20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
380
330
296
274
252
231
219
WAVELENGTH (mμ)

FIGURE 31.

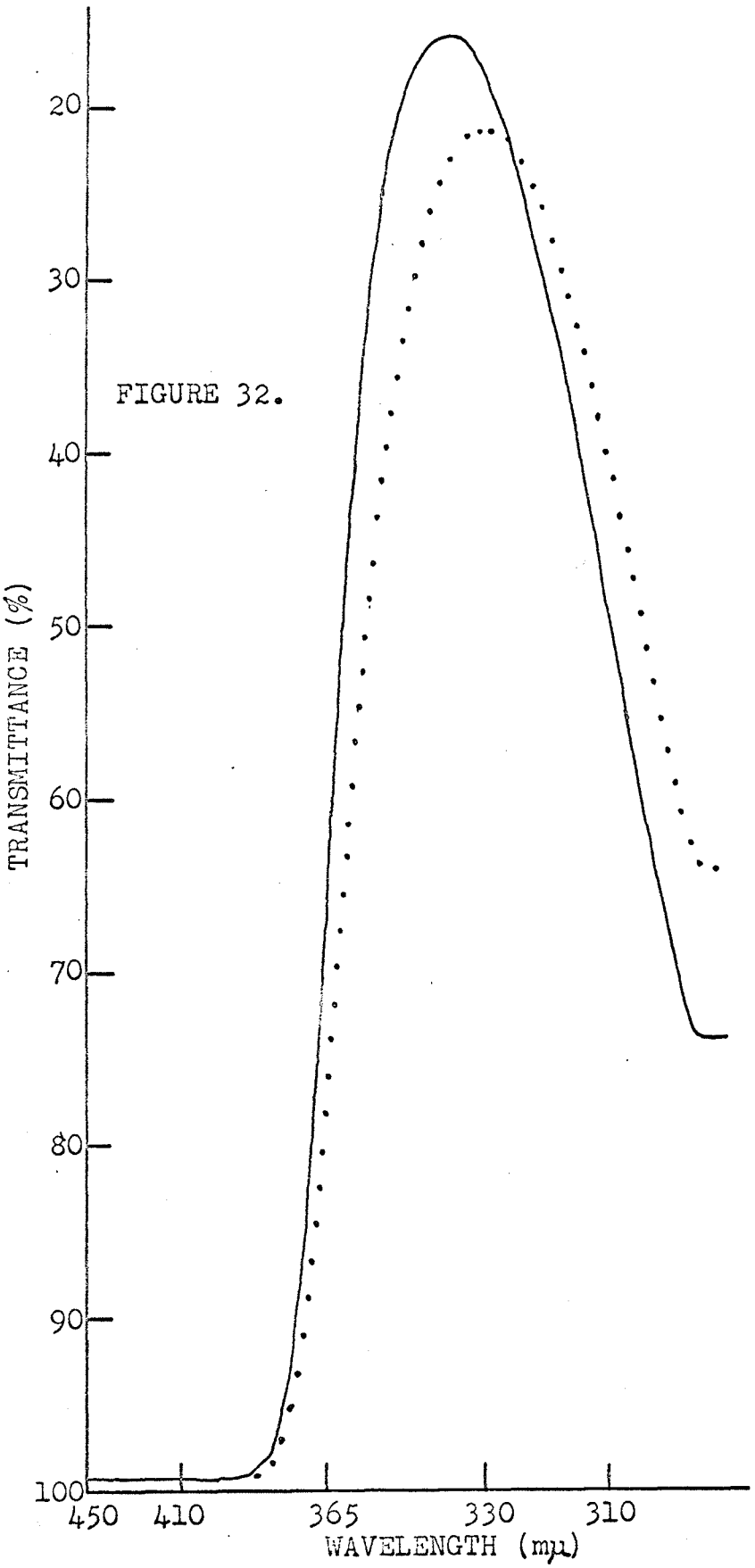

20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
450
410
365
330
310
WAVELENGTH (mμ)

FIGURE 32.

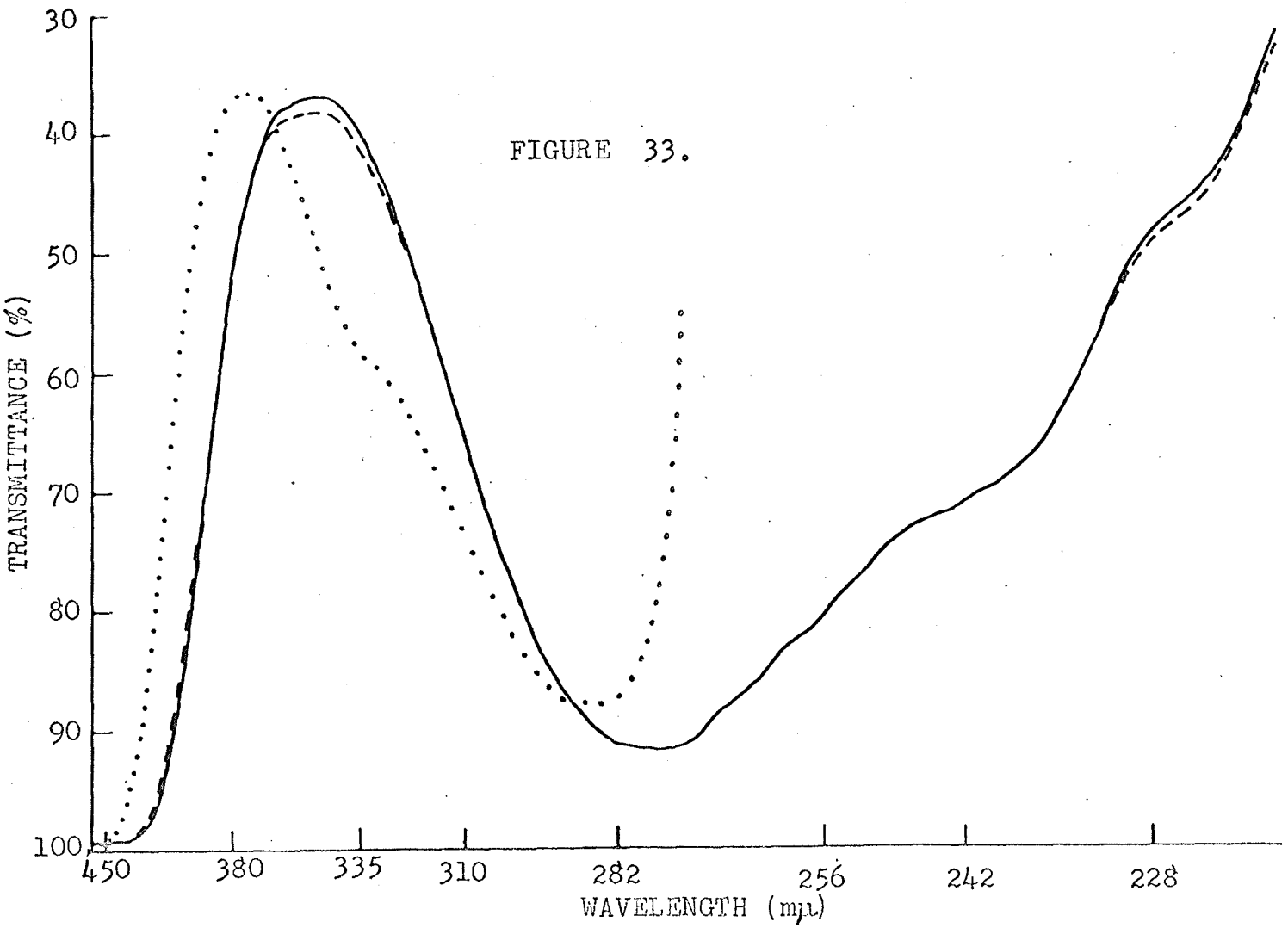

30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
450
380
335
310
282
256
242
228
WAVELENGTH (mμ)

FIGURE 33.

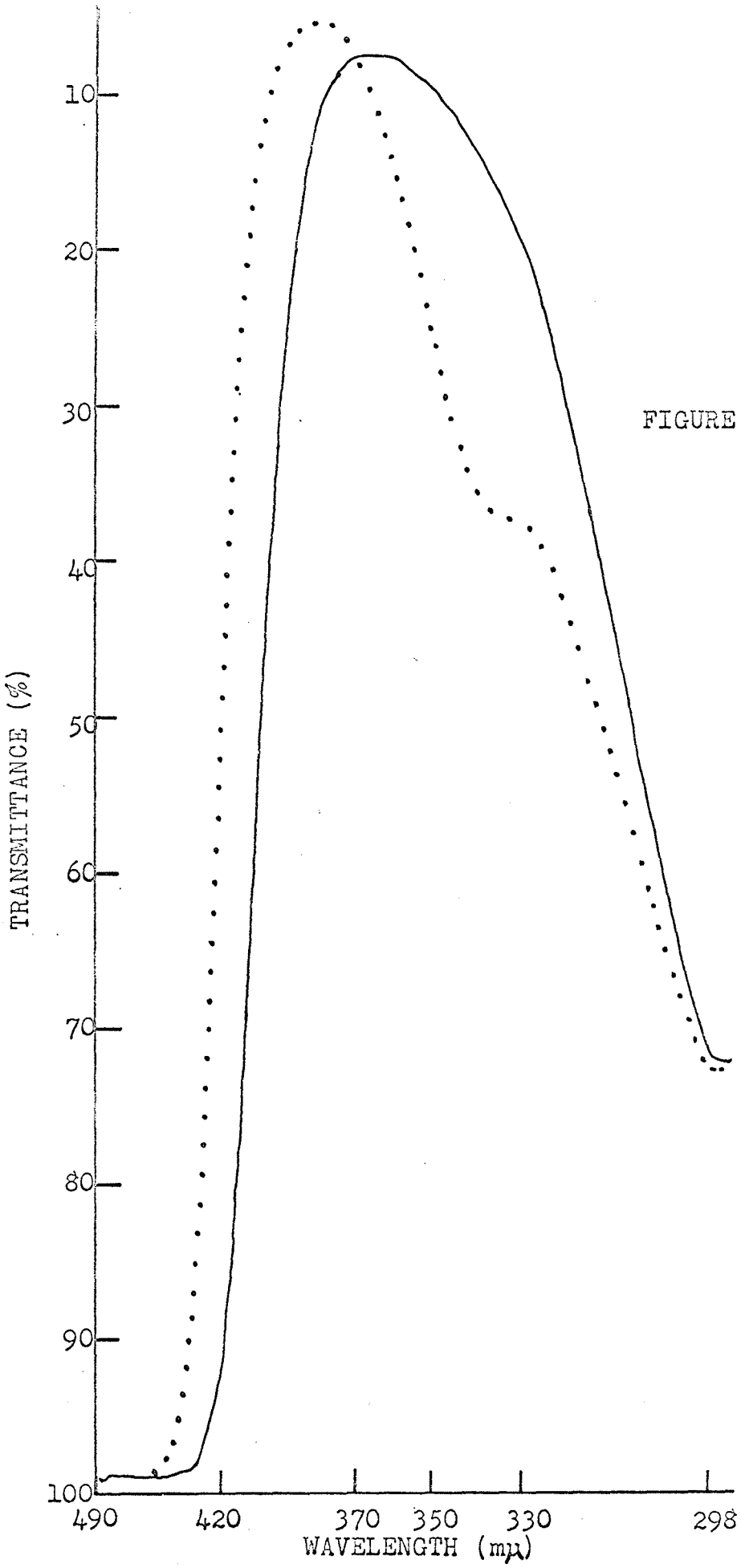
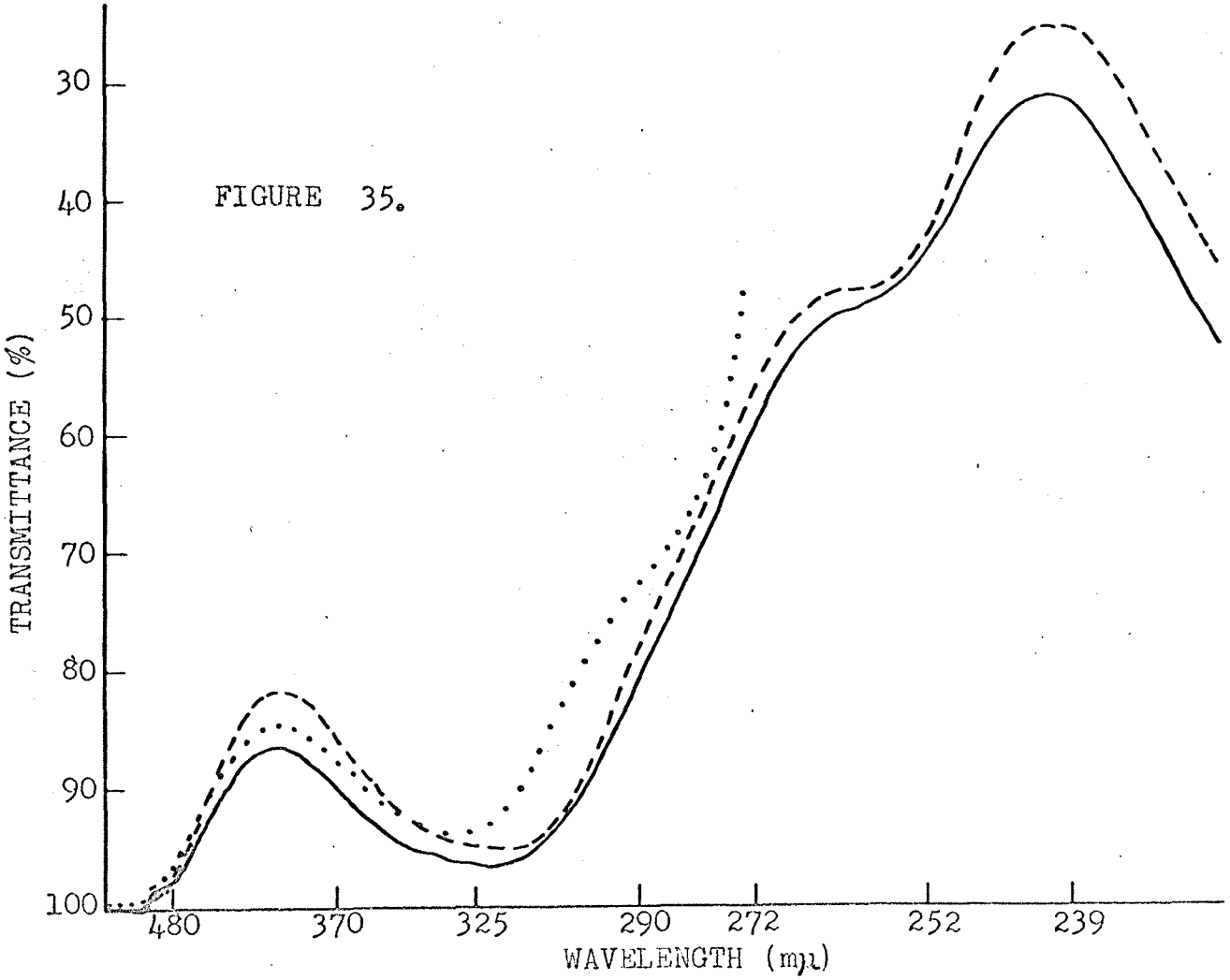

10
20
30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
490
420
370
350
330
298
WAVELENGTH (mμ)

FIGURE 34.

FIGURE 35.


30
40
50
60
70
80
90
100
TRANSMITTANCE (%)
480
370
325
290
272
252
239
WAVELENGTH (mμ)

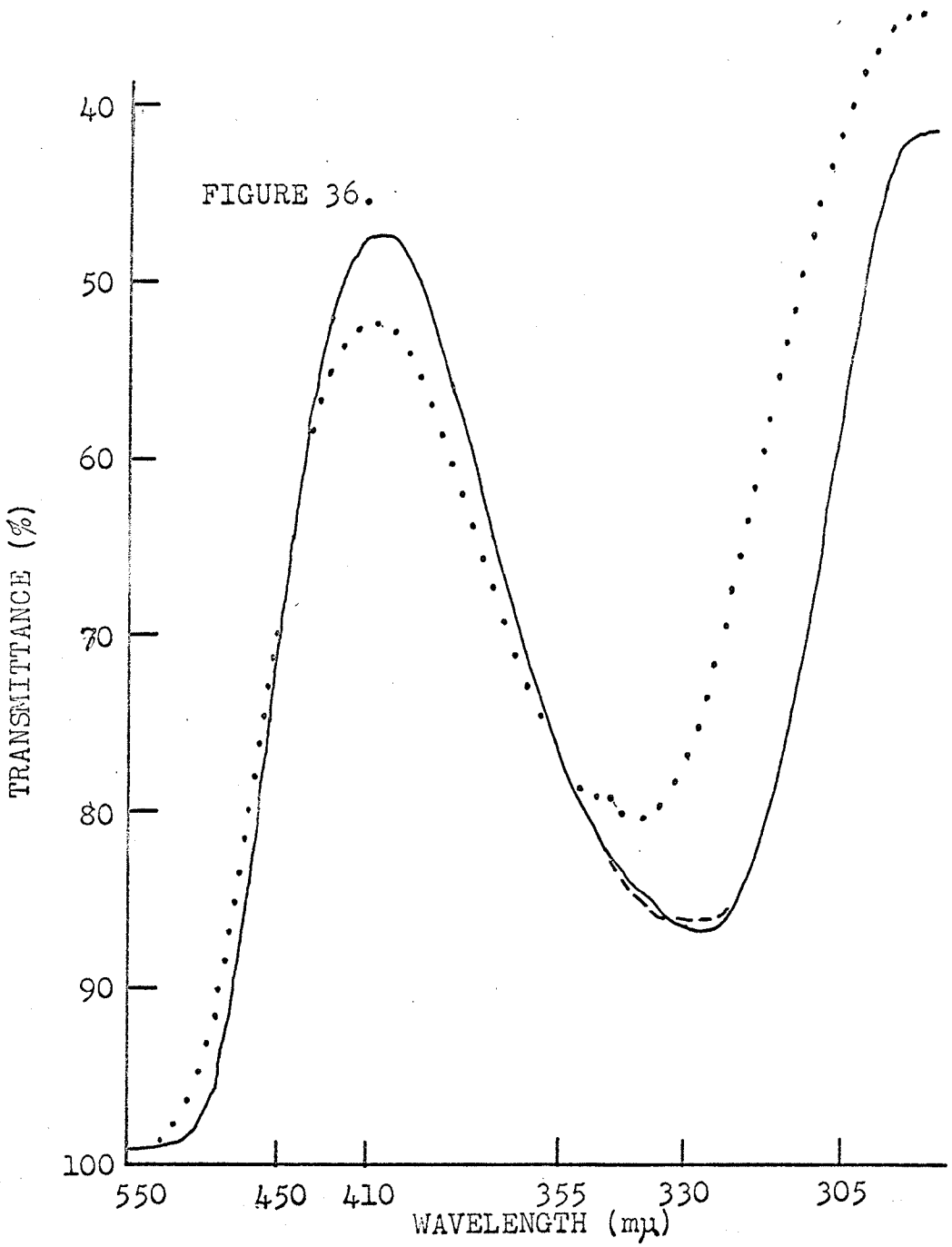

40
50
60
70
80
90
100
TRANSMITTANCE (%)
550
450
410
355
330
305
WAVELENGTH (mμ)

FIGURE 36.

It is assuring to know that addition of reagents to modify the methanol and pyridine solutions is not the cause of spectral changes occurring for reasons other than ionization phenomena. In some cases the addition of PyH_2SO_4 (or $PyHNO_3$) caused band displacements or intensity changes to occur (eg., Figures 26 and 28) when compared to spectra taken in the pure solvent whereas at other times these changes did not arise (eg., Figures 22 and 32). It would seem the observed variations were in fact real and not a consequence of some specific ion or medium effect on the systems in question. Furthermore, the similarities of spectra when using either NaOMe or NEP as the added basic reagent to methanolic solutions (lines 67 and 68) or in another instance NaOMe or NaSA (lines 20 and 21) lends added suuport to the idea that real spectral differences are not masked by changes in the medium. The comparable results in these basic systems also point out that the small dilution effects are of no significance (see Table XXIX, footnotes q and r).

The comments made earlier in the introduction to the work with ultraviolet spectrophotometry in connection with changes that are expected to occur in spectra of acidic substances when aqueous solutions are modified with addition of strong acid or base, can now be applied to nonaqueous systems. For instance, the general observation that ionization of the carboxyl group ($COOH \longrightarrow COO^{(-)}$) produces both

a hypsochromic shift and hypochromic effect in the secondary absorption band is maintained in both pyridine and methanolic solutions (Figures 22, 23, 24, 29, 30, 31 and 32). Further, for aromatic carboxylic acids which contain nitro substituents in the para or meta position, the expectation that ionization of the carboxyl group causes a displacement of the band maximum bathochromically is born out (Figures 25, 26, 27, 28, 33 and 34). The secondary band of 4-nitroanthranilic acid in methanol (Figure 35) and pyridine (Figure 36) seems to undergo virtually no displacement when conditions are varied from acidic to basic systems. In methanolic H_2SO_4 solutions protonation of the ortho-amino group in anthranilic acid (line 64) and 5-methylanthranilic acid (line 49) caused the anticipated reduction of the spectra to ones characteristic of benzoic acid. This effect was not observed for either of the above acids in pyridine and for the 4-nitro- and 5-nitroanthranilic acids in both methanol and pyridine. However, in methanol-H_2SO_4 and neutral methanol 4-nitroanthranilic acid has respective ϵ_{max} values of 2.08×10^3 (line 80) and 2.87×10^3 (line 81) indicating that the reduction in intensity might reasonably be ascribed to partial protonation of the ortho-amino group. It is apparent that the reduced basicity of the amino group in the nitro acids lessens the tendency for its ionization.

That anthranilic and 5-methylanthranilic acids in

pyridine solution did not follow the pattern established in methanol is more of a problem to explain. One possibility is to envisage anthranilic acid existing in pyridine solution wholly in the form of anthranilate-pyridinium ion pairs. Here, addition of $PyHNO_3$ would be without effect since the absorbing molecule is presumable being tied up in the ionic complex. This interpretation cannot explain the band displacement caused when pyridine (NEP) solutions are used unless a possible change of counterion (i.e., piperidinium ion for pyridinium ion) could effect the spectral characteristics of anthranilic anion. It is more reasonable to attribute this apparent anomaly to an insufficient excess of $PyH^{(+)}$ ions in pyridine solution as compared to hydrogen ions ($CH_3CH_2OH_2^{(+)}$) in methanol. The experiments were in fact conducted with much larger concentrations of H_2SO_4 in methanol compared to $PyHNO_3$ in pyridine. Alternatively stated, the basicity of the amino group in anthranilic acid is anticipated to be lower than that of pyridine itself, therefore, one would not expect it to ionize in pyridine solution although there would be variations within the series of anthranilic acids as to its basic strength. For purposes of illustration, pyridine and aniline in aqueous solution have pK_a values of 5.22 and 4.60 respectively at 25°C. (402). An indication that dianion species are being formed in the strongly basic solutions, because of the ionization of the phenolic group in

5-nitrosalicylic acid, is also apparent (lines 34; 35, 36 and 37).

Since the main attention here is to be focussed on acid-base behaviour of anthranilic and salicylic acids in pyridine solution, it is of interest to apply the model depicted by equation [119] on page 314 to assist in clarifying possible modes of such behaviour. Equation [119] is sometimes expressed in a slightly different way to point out the over-all equilibrium as well as individual ionization and dissociation equilibria. For the acid HA, the expression then becomes (including an indication of solvent participation)

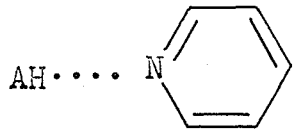
$$\begin{array}{ccc} HA + Py & \xrightleftharpoons{K_i} & PyH^{(+)}\ A^{(-)} \\ K \uparrow\downarrow & & \uparrow\downarrow K_d \\ & PyH^{(+)} + A^{(-)} & \end{array} \quad . \quad [122]$$

In the following description an outline is presented which indicates the possible changes that may be expected to occur in absorption spectra (in the light of equation [122] as such or by considering a number of its variations) when neutral pyridine solutions of these acids are modified by strong acids ($PyHNO_3$ or H_2SO_4) and bases (NEP or sodium salt of the organic acid).

I The acid solutes exist entirely as molecular monomers with no interaction with the basic solvent (i.e., K = 0).

Absorption spectra should be similar if taken in neutral or acidic ($PyHNO_3$) pyridine solutions. Basic (NEP) solutions would cause the normal hypsochromic shift and hypochromic effect except for the nitro acids where a bathochromic shift might be expected (see earlier discussion).

II The acids exist entirely as species intermolecularly hydrogen bonded to the solvent (XCIV). No ionization and no dissociation occurs (<u>i.e.</u>, $K_i = K_d = 0$).



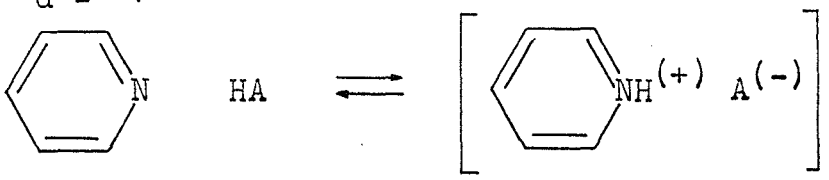
XCIV

If this were the case, a slight hyperchromic effect might be observed (depending on the hydrogen-bond strength) for the absorption band when $PyHNO_3$ is added to the solution. Preferential solvation of the stronger acid, $PyH^{(+)}$, by pyridine would disrupt the intermolecular hydrogen bond between HA and the solvent. Some band displacement might also occur the direction of which relative to the anion band position depending on whether the acids are weak or strong (<u>i.e.</u>, the latter is understood to describe the nitro acids in this discussion). For solutions containing NEP the usual hypsochromic shift and hypochromic effect or reduction in intensity would be observed. It will be remembered that nitro acids and phenolate ion may alter these latter observations. For instance bathochromic shifts might be

observed for nitro acids on addition of NEP.

III The acids are predominantly in molecular form with the only ionic species being dissociated ions and no ion pairs (i.e., $K \gg K_i$). Here the observations are similar to those described under II.

IV Another possibility is that ionization proceeds partially and the ion pair does not dissociate (i.e., $K = K_i$, $K_d = 0$).



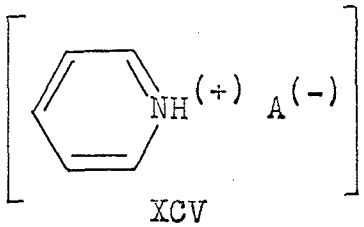
[123]

Since the expression for the ionization constant has the form

$$K_i = \frac{\left[PyH^{(+)}\ A^{(-)}\right]}{[HA]} \qquad [124]$$

in which $\left[PyH^{(+)}\right]$ does not appear, it would be expected that an acid solution containing $PyHNO_3$ would have no effect on the spectrum compared to that taken in neutral pyridine solution. Some variation may occur if it were the outcome of the change in medium which might favour or stabilize the polar ion pairs. The usual changes in basic (NEP) solutions would be anticipated.

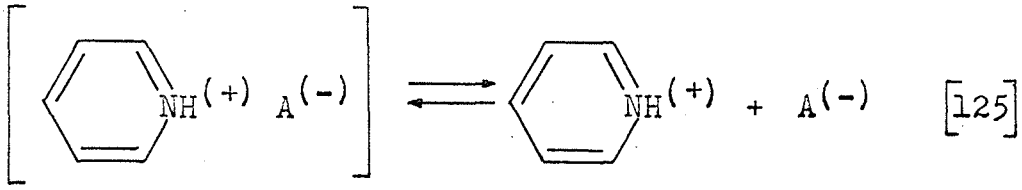
V If acids were completely ionized (XCV) but no dissociation occurred, then equilibrium conditions would be precluded.



XCV

Under these conditions it would seem that strong acidic and basic influences would have little or no effect unless their presence would perturb the system in some manner so as to re-establish an equilibrium (see VI below).

VI Situation V might more reasonably be extended to include partial dissociation. This condition is one frequently encountered in salt systems eg., pyridinium salts (118) (i.e., $K = K_d$).

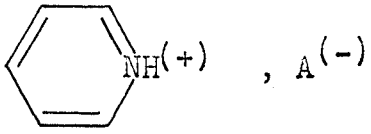


[125]

Solutions containing $PyHNO_3$ would help to suppress the dissociation and favour a return to paired pyridinium and carboxylate ions. On the other hand addition of NEP would cause the above reaction to run to completion as pyridinium ion competes for the stronger base. The exchange of piperidinium ion for $PyH^{(+)}$ as a counterion to the carboxylate group is not expected to influence the spectrum. Now, if the common assertion is invoked that spectral characteristics of the organic anion and the anion-pyridinium ion pairs are similar (i.e., extinction coefficients and absorption maximum are the same), then no differences

would be expected to appear in the absorption spectra when these environmental changes are made.

VII The extreme case for the situation envisaged in VI is to assume that cation and anion exist in a completely dissociated form (XCVI) in the concentrations used.



XCVI

The same conclusions apply here as immediately above.

VIII The most common interpretation given to acid-base behaviour in nonaqueous solutions of relatively low dielectric constant is that in which equation [122] is assumed to represent the reasonable model (i.e., $K = \frac{K_i K_d}{1+K_i} \cong K_i K_d$ (if $K_i \ll 1$). Here, addition of $PyHNO_3$ would suppres the dissociation into ions as in VI and help establish larger concentrations of both molecular acid and 'ion pair' acid. Seen from equation [122], the concentration of ion pair must necessarily increase as concentration of $PyH^{(+)}$ increases but in order for K_i to remain constant the molecular acid concentration must also increase. The over-all effect is to favour a slight shifting of the absorption band and intensifying it in favour of the molecular unionized acid. The influence of NEP-bearing solutions is the common

one when ionization of the carboxyl group occurs (hypsochromic shift and hypochromic effect) keeping in mind the exceptions the nitro acids might present.

In Table XXX the findings are summarized for the variations in spectral behaviour of salicylic and anthranilic acids in pyridine in the light of the various categories described above. This information is gathered from the relevant entries in Table XXIX and the corresponding figures. A plus (+) sign recorded in Table XXX would be an indication that the particular acid in the three solvent systems (neutral, basic and acidic) fulfills the expected behaviour of spectral variation or lack thereof. If the behaviour does not follow the prescribed pattern, a minus (-) sign is inserted in the proper place. If there is some doubt as to the reliability of the test, both signs are included.

At first inspection there seems to be enough irregularity in the number of possible categories into which the spectral behaviour may be accommodated that little is proved by this analysis. However, some comments regarding Table XXX may place the conditions in proper perspective. Category I seems to be a rather idealized one. If conditions of no solute-solvent interaction did exist, then inevitably a further complication of solute monomer-dimer equilibrium (i.e., intermolecular hydrogen bonding between

TABLE XXX

COMPARISON OF OBSERVED SPECTRAL BEHAVIOUR OF SALICYLIC AND ANTHRANILIC ACIDS IN PYRIDINE SOLUTION FROM TABLE XXIX WITH POSSIBLE CATEGORIES OF ACID-BASE BEHAVIOUR

a Category \ Acid	5-CH_3AA	AA	5-NO_2AA	4-NO_2AA	4-CH_3OSA	SA	5-NO_2SA	4-NO_2SA
I	+[b]	+	+	+	+	+-	-	-
II	-[b]	-	-	-	-	+-	+	+
III	-	-	-	-	-	+-	+	+
IV	+	+	+	+	+	+-	-	-
V	-	-	-	-	-	-	-	-
VI	-	-	-	-	-	-	-	-
VII	-	-	-	-	-	-	-	-
VIII	-	-	-	-	-	+-	+	+

a The various categories are described in the discussion.
b Symbols have been defined in the discussion.

solute molecules) would have to be considered, keeping in mind that this may be more or less pronounced at different concentrations. However, the observance of a non-concentration dependence of ϵ_{max} for solutions of salicylic acid in dioxane and that this dependence was barely recognized even in cyclohexane solutions containing only 5 per cent ether (458, 471) leads one to assume a low probability for category I.

The results for solutions of salicylic acid in pyridine are equivocal. These arise because the molarity of $PyHNO_3$ in acidic pyridine solution was about one half the molarity of the organic acid (line 23, Table XXIX) and not in excess as in a number of other cases (lines 8, 46, 70 and 83, Table XXIX; all considered on the basis of using $PyHNO_3$). The spectral curves obtained in Figure 24 for neutral and acidic pyridine solutions were superimposed but it might be suggested that a more effective $PyH^{(+)}$ may have displaced the secondary absorption band thus indicating an increase in unionized or molecular acid and favouring categories II, III or VIII. This is purely speculative but any tendency towards this behaviour would approximate the characteristic features of the spectral curves of salicylic acid in acidic and neutral methanol solutions (Figure 23). Any small dilution effects (line 23, footnote 9 of Table XXIX) would also favour this interpretation. Also, on three occasions

PyH_2SO_4 was replaced by $PyHNO_3$ (lines 46, 70 and 83) and spectral curves redetermined. The two sets in each case were virtually identical in shape, intensity and λ_{max}. If a very slight variation did occur, it was considered for the present to be well within experimental error.

In Table XXX the acids are arranged from left to right in order of the increasing acid strength (in water). It may be noted that the eight acids presently under investigation represent one of the widest variations of acid strengths available in the two families of acids. An indication of this in aqueous solution is presented in Table XXXI.

TABLE XXXI

IONIZATION CONSTANTS (K) OF SUBSTITUTED SALICYLIC[a] AND ANTHRANILIC[b] ACIDS IN AQUEOUS SOLUTION AT 25°C.

Acid	K x 10^3
4-NO_2SA	4.93
5-NO_2SA	4.82
SA	1.02
4-OCH_3SA	.494
4-NO_2AA	.197[c,d]
5-NO_2AA	.123[c]
AA	.0143[c,e] (0.027)[f]
5-CH_3AA	.00252[c]

a Taken from reference (287); thermodynamic values.
b Taken from reference (12); apparent values.
c Refers to K_2 values; i.e., ionization of a mixture of neutral acid and zwitterion to anion.
d Average of two values: 20.6 x 10^{-5} and 18.8 x 10^{-5}.
e Average of two values: 1.46 x 10^{-5} and 1.40 x 10^{-5}.
f Estimated "microscopic" ionization constant of non-dipolar acid.

Because anthranilic acids exist partially as zwitterion in aqueous solution and because the table includes both apparent and thermodynamic ionization constants, the experimentally determined K_2 is not strictly comparable with the ordinary ionization constants of the salicylic acids. As a first approximation the order of magnitude of K_2 values and the constants of nondipolar molecules are similar. Accepting this assumption one sees the extremely wide variation in acid strength which amounts to almost a 2000-fold increase between the two extreme members that make up the table. Also within the limits of the assumption 4-nitroanthranilic acid would be expected to be a slightly weaker acid than the weakest salicylic acid (i.e., 4-methoxysalicylic). In aqueous solution the zwitterionic content of the nitroanthranilic acids is very low (12) so that this comparison becomes even more reliable. In pyridine solution, where the existence of the zwitterionic form for anthranilic acid is less probable, these regularities in gradation of acid strength as witnessed in aqueous solution should be adequately maintained and in fact enhanced.

If one accepts the order of acid strengths given above, then an inspection of Table XXX, and in particular entries in categories I, II, III and VIII, points out that generally a gradual variation in spectral behaviour is observed that may parallel the acid strengths of the various acids. If the four anthranilic acids are considered as a group,

Table XXX shows that two categories need to be considered. Either the acids ionize partially in pyridine solution to ion pairs with no subsequent dissociation (category IV) or the acids do not interact with the solvent via hydrogen-bond formation (category I). It has already been emphasized that this latter category is rather idealized and should be given little consideration. However, a possibility still remains which may not be readily distinguished in the experimental approach used here. The present method may just not discern the existence of relatively weak intermolecular solute-solvent interactions with the carboxyl proton and the lone unshared pair of electrons on the solvent nitrogen.

The presence of a slightly asymmetric secondary band for 5-nitroanthranilic acid in pyridine (Figure 34) affords an opportunity to make some interesting inferences in favour of category IV at least for the strongest anthranilic acids. That the absorption peak is really a composite of perhaps two unresolved absorption bands is confirmed by the spectrum taken in basic pyridine solution. Here a fully developed shoulder appears on the short wavelength side of the absorption band. The acid does not possess a second acidic functional group which could complicate the spectrum. An interpretation consistent with the results would suggest that 5-nitroanthranilic acid in pyridine solution is partially ionized, presumably in some form of ionic aggregate since

acidic pyridine solutions do not change the spectral characteristics from those established in neutral solution. This implies little or no dissociation of ion pairs. On addition of NEP the unionized acid band is reduced and the absorption corresponding to the ionized acid (i.e., 5-nitroanthranilate anion) becomes more prominent. If this is the case, then the presence of a larger concentration of NEP or a stronger base should ultimately eliminate the shoulder.

In conclusion the anthranilic acids may be present in pyridine solution predominantly as solvates formed by relatively weak intermolecular solute-solvent hydrogen bonds (category II) or be partially ionized to ion pairs which do not dissociate (category IV).

When salicylic acids are considered three main possibilities are encountered (categories II, III and VIII). Whether or not there is a real gradation in acidic properties, as outlined in Table XXX, from 4-methoxysalicylic to 4-nitrosalicylic acid will have to remain an open question for the present. The choice of 4-methoxysalicylic acid as an example of a weak salicylic acid was in a sense unfortunate since the absorption band in question occurred very close to the wavelength region where the spectrophotometer loses its usefulness under the experimental conditions. It might be best, therefore, to place less reliability on these results now even though future work might substantiate

them further. To decide among categories II, III and VIII for the remaining salicylic acids would seem to be quite difficult. If one considers that the anthranilic acids are representative of category II but a weak form of solute-solvent hydrogen bonding must be invoked, then to make an arbitrary decision, that in passing some point the experimental method becomes sensitive enough to distinguish this from a stronger form of intermolecular hydrogen bonding, is plausible but not too convincing. In methanol solutions spectra for 4-nitrosalicylic acid (Figure 27) are very similar to those encountered in pyridine (Figure 28). If it is assumed that the tendency for ion-pair formation in methanol need not be considered because of a higher dielectric constant and better solvating characteristics of this latter solvent and also because of the concentrations used, then the interpretation favouring III for pyridine solutions would be preferred.

In pyridine solutions at a concentration of 5×10^{-5} mole/litre, picric acid is estimated to be entirely present as dissociated ions (138). The aqueous ionization constant of this very strong acid is approximately 0.2-0.6 at 25°C. (472). Corey envisaged category VIII as best describing the acidic behaviour of phenols in pyridine whereas aliphatic carboxylic acids with even lower pK_a values were estimated to be only slightly ionized, and dissociated in pyridine (137). Here pK_a values of all four salicylic acids are much lower

than 2,5-dinitrophenol and 2,6-dinitro-3,4-xylenol, two of the phenols which Corey studied. However, these comparisons with phenolic acids as to aqueous acid strengths need to be qualified. In a study of relative acidities of phenols and carboxylic acids (aromatic and aliphatic), Streuli found that aromatic hydroxy compounds showed an enhancement in acidity relative to the carboxylic acids when titrated potentiometrically in pyridine (283). For instance both p- and o-nitrophenol ($pK_a(H_2O)$ = 7.15 and 7.17 at 25°C. respectively (126a)) were apparently stronger acids in pyridine than benzoic acid ($pK_a(H_2O)$ = 4.19 (126a)). It has been suggested that this disparity arises principally from the variable behaviour of carboxylic acids. When both carboxylate oxygens can undergo hydrogen bonding with molecules of solvent (i.e., H_2O), they appear to be more strongly acidic, in this case, relative to phenols. In pyridine where anion stabilization is lessened the tendency for carboxylic acids to ionize and dissociate is reduced relative to phenolic acids (453).

Another possible method for deciding among the various categories is afforded by Beer's law. If salicylic acids were represented by category II, Beer's law should be obeyed while it would not be expected to hold if categories III and VIII were the proper models of acid-base behaviour.

The absorbance-concentration dependence study was conducted by selecting two or three different wavelengths in

the accessible region of the ultraviolet for solutions of salicylic acid and sodium salicylate in pyridine. One of these wavelengths in each case represented λ_{max} for the secondary absorption band but for sodium salicylate λ_{max} was not clearly discernible since a plateau forms in the absorbance-wavelength spectral curve in the region where the usefulness of the analysis is lost due to strong solvent absorption. The data taken from Tables XXXII and XXXIII are correspondingly depicted graphically in Figures 37 and 38 in order to test the applicability of Beer's law for solutions of sodium salicylate and salicylic acid in pyridine. The lines in the figures were drawn by visual inspection. No attempt was made to find the best fit by the least squares method. The linear function of the analytical concentration of the sodium salt with absorbance was observed at three different wavelengths (Figure 37). Although better precision in the plots would have been desirable, it seems that in these initial experiments any scatter is more or less random and no observable trend in deviation from linearity is apparent at least within the concentration range used. The dissociation constant of sodium salicylate in pyridine is not available but it is reasonable to assume that the salt exists predominantly in ion pairs with any dissociation being described by the second part of equation [119] (page 314), that is, that having the dissociation constant, K_d. For purposes of reference and comparison (although

TABLE XXXII

ABSORBANCE-CONCENTRATION DEPENDENCE FOR SOLUTIONS OF SODIUM SALICYLATE FOR DIFFERENT WAVELENGTHS IN PYRIDINE AT ROOM TEMPERATURE

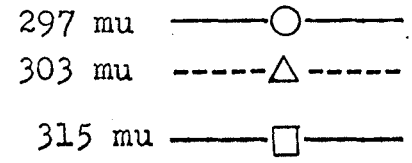
Concentration x 10^3 (mole/litre)	Absorbance		
	297 mμ	303 mμ	315 mμ
0.593	0.242	0.225	0.089
1.19	.473	.449	.176
1.78	.728	.689	.272
2.25	.881	.832	.330

TABLE XXXIII

ABSORBANCE-CONCENTRATION DEPENDENCE FOR SOLUTIONS OF SALICYLIC ACID FOR DIFFERENT WAVELENGTHS IN PYRIDINE AT ROOM TEMPERATURE

Concentration x 10^3 (mole/litre)	Absorbance	
	304 mμ	315 mμ
0.594	0.259	0.192
1.19	.510	.383
1.78	.754	.571
2.37	1.034	.762
3.56	1.623	1.185

FIGURE 37. The application of Beer's law to solutions of sodium salicylate in pyridine at room temperature. Data are taken from Table XXXII.



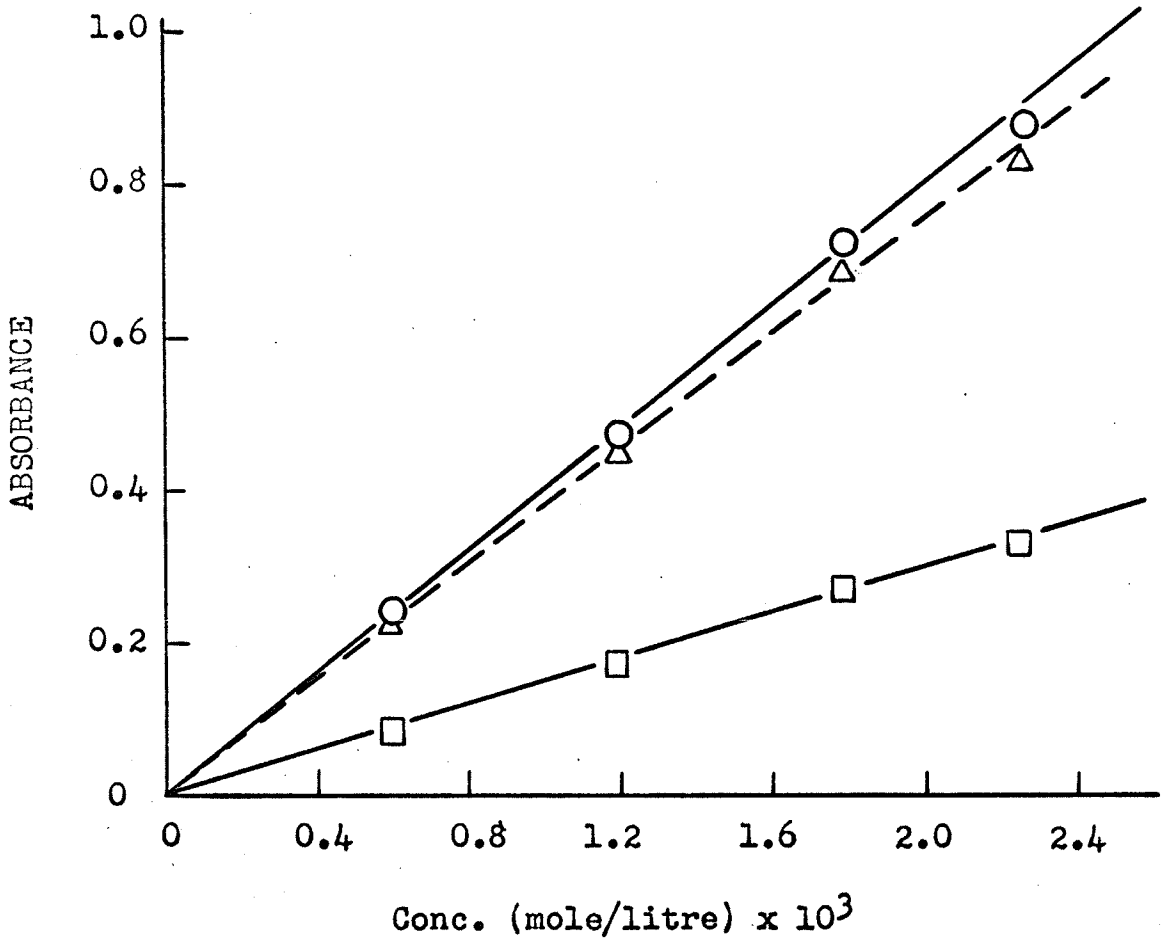
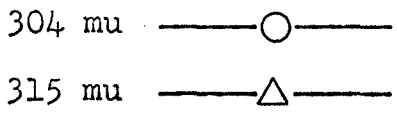
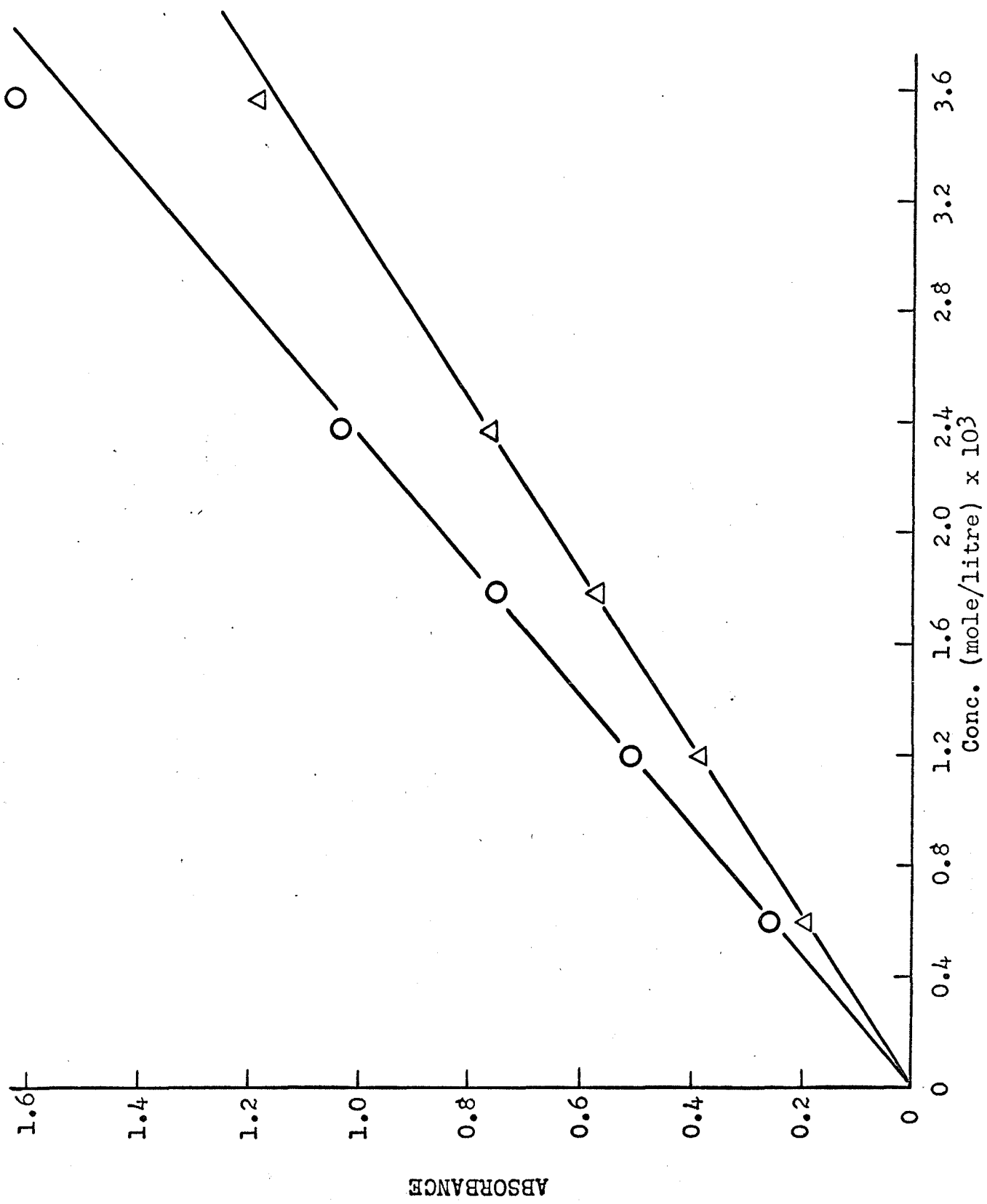

1.0
0.8
0.6
0.4
0.2
0
ABSORBANCE
0
0.4
0.8
1.2
1.6
2.0
2.4
Conc. (mole/litre) x 10³

FIGURE 38. The application of Beer's law to solutions of salicylic acid in pyridine at room temperature. Data are taken from Table XXXIII.




ABSORBANCE
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
Conc. (mole/litre) x 10³

not applicable here) the dissociation constant of sodium picrate in nitrobenzene at 20°C. has a value of 2.8×10^{-5} (473). From the literature evidence outlined earlier in the introduction to this section one would not expect this equilibrium to affect the validity of Beer's law. The apparent linearity obtained here also points out that, as the sodium salicylate concentration is increased and ionic aggregates larger than simple ion pairs possibly form, these also have the same spectral characteristics of the simple salicylate ion within experimental error.

A somewhat different picture emerges in Figure 38 in which the validity of Beer's law was tested for solutions of salicylic acid in pyridine. Plots were made at two different wavelengths, with the one at 304 mμ representing λ_{max} and the other on the long wavelength side of the band shoulder. A small perceptible positive deviation is seen to occur as the concentration of salicylic acid is increased in such a way that linearity is not strictly maintained. The possibility that the concentration dependence is a result of intermolecular hydrogen bonding between two acid-solute molecules (i.e., a monomer-dimer equilibrium), is not likely in a basic solvent like pyridine. Templeton and Forbes, for instance, found no departure from linearity in a concentration study of salicylic acid in dioxane, a much weaker base of lower dielectric constant (471). The results of spectra taken in neutral

pyridine and pyridine modified with $PyHNO_3$ were inconclusive (see earlier description on page 361) in forming a judgement of whether dissociation does proceed to some small extent in pyridine solution. If this were in fact true, then it might be reasonable to attribute the lack of linearity in the plot to a decrease in the degree of dissociation as the salicylic acid concentration is increased. Here, categories III and VIII of Table XXX could be considered as appropriate models. Since the two nitrosalicylic acids are stronger than salicylic itself, then one could argue that the acidic behaviour of these two acids could also be accommodated by either III or VIII in preference to II. Deviation from Beer's law for salicylic acid solutions is plausible evidence for discounting as the only interaction an intermolecular hydrogen bond between the acidic solute and solvent(category II).

These possibilites need not be the only ones considered, however. Although an increase of salicylic acid concentration would favour an increase in ion-pair formation, competitive reactions, in which homoconjugate species, $AHA^{(-)}$, or higher aggregates may become preferentially favoured, could also account for the observations in Figure 38. These complexes could effectively tie up molecular salicylic acid so as to prevent further ionization, and since ϵ_{max} for salicylic acid is greater than ϵ_{max}

for the salicylate ion, a small positive deviation in absorbance may appear. It is difficult to say much about any special spectral characteristics that an entity such as $AHA^{(-)}$ might possess, however. It should be pointed out, especially in using the results of Figures 37 and 38 for purposes of comparison, that the salicylic acid concentration represented by the last point in the plot of Figure 38 has a value of 3.56×10^{-3} mole/litre which is larger than the most concentrated solution of sodium salicylate (2.25×10^{-3} mole/litre) represented in Figure 37. It is not known, therefore, if any anomalies would occur in more concentrated solutions of the sodium salt. Effect of ionic strength is also not known in these solutions but is anticipated to be negligible.

In conclusion it appears that the models for acid-base behaviour of salicylic acids which best accommodate the spectral data derived from acidic, neutral and basic pyridine solutions and in a limited way from the Beer's law investigation are categories III and VIII.

It would be of much interest if inferences could be drawn regarding the relative importance of zwitterionic formation for anthranilic acid in nonaqueous solvents, especially in pyridine solutions. In order to attempt this, comparisons were made between acidic or neutral and basic solutions of anthranilic and substituted anthranilic acids as recorded in Table XXIX as well as for other amino-

benzoic acids in aqueous solutions of different pH as presented in Table XXXIV. For this purpose attention will be directed primarily to those acids which display 'normal' spectral behaviour in the ultraviolet on ionization. By this is meant that the usual hypsochromic shift, but more importantly, the reduction in ϵ_{max} or hypochromic effect, is observed when $RCOOH \longrightarrow RCOO^{(-)}$ (lines 2 and 3, Table XXVI, page 305). The nitroacids (anthranilic and salicylic) could be considered with some modification. If these acids were disregarded in this discussion, it should prove of little consequence since even in aqueous solution their zwitterionic content is very low or non-existent (lines 22 and 23, Table XXIV). An examination of Table XXIX for the remaining anthranilic and salicylic acids in the different solvents (where comparisons are available between acidic (or neutral) and basic conditions) points out that these also conform to the general view that ϵ_{max} (anion) $< \epsilon_{max}$ (acid) (cf., data in lines 1 and 6; 8 and 10; 18 and 21; 23 and 25; 50 and 51; 53 and 54; 66 and 67 (secondary band); 71 and 72). The one exception is anthranilic acid itself in aqueous solution. For example the data in lines 58 and 61 or lines 59 and 62 exhibit ϵ_{max} (anion) $> \epsilon_{max}$ (acid). This latter pattern of behaviour is also followed by all the aminobenzoic acids whose ultraviolet absorption bands are listed in Table XXXIV and have a per cent zwitterion (Z %) greater than 9.

TABLE XXXIV

CHARACTERISTIC ULTRAVIOLET ABSORPTION BANDS OF AMINOBENZOIC ACIDS IN AQUEOUS SOLUTION [a]

No.	Acid[b]	$\pm$%[c]	pH_{isoel}[d]	Solvent Conditions	Secondary Band		First Primary Band		Second Primary Band	
					λ_{max}(mμ)	$\epsilon_{max} \times 10^{-3}$	λ_{max}(mμ)	$\epsilon_{max} \times 10^{-3}$	λ_{max}(mμ)	$\epsilon_{max} \times 10^{-3}$
1.	MABA[e]		3.90[f]	pH 3.73	310	0.65	250[g]	2.4	218.5	14.0
2.				pH 11	300	1.80	241[h]	7.4	209.5	25.3
3.	PABA[i]			2N HCl	270	0.97	226.5	12.3		
4.			3.64[f]	pH 3.75	-		284	14.0	219.5	9.9
5.				0.1N NaOH	-		265	14.9		
6.	4-NH_2AA			pH 4.4	317[h]	4.3	277	11.1	228	16.4
7.				pH 11	307	4.2	266	10.0	216	25
8.	4-CH_3OAA[j]	22	3.47	1.0N HCl	-		k			
9.				0.1N HCl	320	0.42	k			
10.				pH 2.9	316	3.64	k			
11.				0.1N NaOH	302	3.97	k			
12.	l		3.32	1.0N HCl	307[g]	0.16	k			
13.	l			0.1N HCl	312	0.78	k			
14.	l			pH 2.9	316	3.84	k			
15.	l			0.1N NaOH	~298	3.78	k			
16.	5-CH_3AA	75	3.80							
17.	AA	30-50[c*]	3.51							
18.	4-Cl AA	9	2.82	pH 4	327	3.8	249	8.9	221	30
19.				pH 7	314	3.5	247	8.5	216.5	32
20.	5-Cl AA	27	3.02	pH 3	340	2.3	250	5.2	218	22
21.				pH 11	323	2.8	249	8.5	210	26
22.	5-NO_2AA	0[m]	-							
23.	4-NO_2AA	2	2.18							

TABLE XXXIV Continued

a Data in the Table are taken from references (433, 434, 435) unless where otherwise noted. See footnotes f, g and i in Table XXIX for explanation of symbols and terms.

b Data for anthranilic (AA) and substituted anthranilic acids in aqueous and /or nonaqueous solvents are recorded in Table XXIX; only additional derivatives in aqueous solution are presented here. m-aminobenzoic acid (MABA); p-aminobenzoic acid (PABA). When entries are not included in this column, it is understood that reference is being made to the last-noted acid.

c Represents the degree of zwitterion ($Z^{\pm}$) in aqueous solution relative to the nonpolar neutral-acid species. Calculated using equation [20] in reference (12) on the basis that $K_Z^o = \frac{[RH^{\pm}]}{[RH^o]} = 1$, where K_Z^o is the equilibrium constant between the zwitterionic form ($RH^{\pm}$) and neutral form (RH^o) of anthranilic acid. * The two values listed indicate the probable range for estimate of $Z^{\pm}$ content as obtained by assuming that $K_Z^o = 0.4 - 1.0$. Consequently the figures for all other entries in the column may be looked upon as indicating maximal values and may indeed be much less. See reference (12) for further details.

d $pH_{isoel} = 1/2\ (pK_1 + pK_2)$; represents the aqueous pH where the concentration of zwitterion is the highest. Values of pK are taken from reference (12) unless where otherwise noted and refer to 25°C.

e A visual comparison of the tabular data with recorded spectra in reference (469) reveals the same relative order of λ_{max} and ϵ_{max} values between solutions of different pH.

f Calculated from pK values at 25°C. given in reference (472).

g Band fused or partially fused with shorter wavelength absorption.

h Inflection.

i A visual comparison of the tabular data with recorded spectra in references (464, 469) reveals the same relative order of λ_{max} and ϵ_{max} values between solutions of different pH.

j Data taken from recorded spectra (3). ϵ_{max} values were calculated on the basis of acid concentration being 2.75×10^{-4} mole/litre.

k Data not available.

l Temperature 60°C.

m This acid was not used in reference (12) to calculate K_Z^o.

In the case of PABA comparisons should be made with the first primary band in lines 4 and 5 since no secondary band is available for this acid under the conditions indicated. The per cent zwitterion for 4-aminoanthranilic acid is not known. The presence of the extra amino group para to the carboxyl may complicate the general pattern which is established so that the intention will be to disregard the acid in this discussion.

The secondary absorption band of anthranilic acid can be decreased in intensity through the addition of strong acid which protonates the amino group and thus reduces the spectrum to essentially that of benzoic acid (line 55, Table XXIX). The development of a spectrum characteristic of benzoic acid can also happen if the acid exists to a significant extent in zwitterionic form. Furthermore the absorption band may possess $\epsilon_{max} < \epsilon_{max}$ (anion) throughout the whole range of pH values until the acid is fully converted into its conjugate base. As the pH is raised the difference between these two ϵ values is decreased, that is, the band experiences a hyperchromic effect (cf., lines 57, 58, 60 and 61, Table XXIX). It seems clear, therefore, that until some lower limit is reached in zwitterionic content for the anthranilic acids, for example, 4-chloroanthranilic (lines 18 and 19, Table XXXIV), the general rule $\epsilon_{max} < \epsilon_{max}$ (anion) is observed. Here any reduction in the secondary absorption

band caused by the presence of the relatively small amount of zwitterion is offset by the larger hypochromic effect that is usually exhibited in $COOH \longrightarrow COO^{(-)}$ equilibria. If the ϵ_{max} values of the first primary band of the three monoaminobenzoic acids are compared under similar conditions (i.e.,~pH 3.7 and strongly basic solution), the difference, ϵ_{max} (~pH 3.7) - ϵ_{max} (basic), is greatest for the m-aminobenzoic acid and is least for p-aminobenzoic acid. This order is in keeping with other estimates in the literature which emphasize the high zwitterionic content possessed by m-aminobenzoic acid in aqueous solution (284) and the rather low concentration of dipolar ion available in solutions of p-aminobenzoic acid (443). The one reservation in these comparisons is that the pH_{isoel} for these acids increases in the order AA < PABA < MABA so that at the same pH (3.7) the different acids would naturally sustain different concentrations of zwitterion, anions, etc.

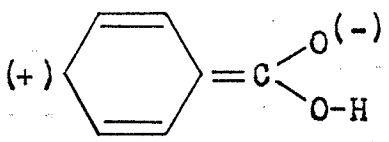
Although the general behaviour cited above can reasonably be accommodated by the interpretation given (i.e., acidsthat possess reasonably large zwitterionic contents exhibit spectral characteristics of $\epsilon_{max} < \epsilon_{max}$ (anion)), to be strictly justified one should have the necessary information for each acid in different solvents of varying characteristics. This is readily available only for anthranilic acid itself (H_2O - CH_3OH - C_5H_5N). In this case

the results uphold the premise outlined (i.e., that acids with $\epsilon_{max} > \epsilon_{max}$ (anion) possess little zwitterion). The conclusion to be drawn is that in all probability the four anthranilic acids studied in both pyridine and methanol are present almost entirely in the neutral form and possess very little, if any, zwitterion. The results were to be expected but a clear demonstration, qualitatively at least, has often been lacking. Some workers still favour an explanation based on zwitterionic content to explain enhanced acidities of anthranilic acid in nonaqueous solvents of low dielectric constant (pyridine (10)), while others invoke intramolecular hydrogen bonding (benzene (474)).

Possession of spectral data of 4-methoxyanthranilic acid in aqueous solution taken at two different temperatures, as indicated in Table XXXIV), presents an opportunity to examine if changes in spectral behaviour may be ascribed to changes in zwitterion concentration with increased temperature. Comparison of ϵ_{max} data in lines 10 and 11 and in lines 14 and 15 points out that the relative order has reversed between the two temperatures; that is, at the higher temperature ϵ_{max} (pH 2.9) $> \epsilon_{max}$ (0.1N NaOH) while the opposite is true at 25°C. These differences are rather small and should be accepted with some degree of caution. Nevertheless two other facts tend to substantiate that the zwitterion concentration is lowered by increase in the temperature. First, the isoelectric pH at 60°C. is closer to

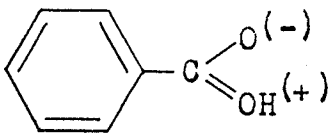
pH 2.9 (where one set of spectra were taken) than at 25°C. With this situation it would have been anticipated that a greater zwitterionic content at the higher temperature and a larger ϵ_{max} (pH 2.9) < ϵ_{max} (basic) effect would have been maintained. Further, while virtually no secondary band associated with the monoacid is seen at 1.0N HCl at 25°C. (line 8, Table XXXIV) a small band fused to a shorter wavelength absorption is still visible under the same conditions at 60°C. (line 12, Table XXXIV). It would seem, therefore, that more acid exists in the neutral form at 60°C. than at 25°C. Tentatively then, a value for the per cent zwitterion at 60°C. for 4-methoxyanthranilic acid of <22 is reasonable.

The interpretation given here to explain the anomalous behaviour of certain aminobenzoic acids when compared in aqueous solution and in methanol or pyridine is at variance with the considerations given by Kumler and Strait (464). In a comparative study between the spectral behaviour of benzoic and p-aminobenzoic acids, they considered the question of why ϵ was greater in basic aqueous solution than in neutral water solution for PABA whereas the opposite effect was observed for benzoic acid solutions. They reasoned that contributions of structures such as XCVII



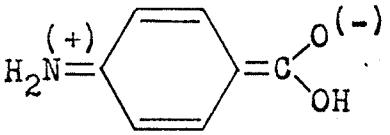
XCVII

were mainly responsible for the absorption of light in the near ultraviolet range but that this type of resonance was in competition with a carboxyl group resonance which might be indicated by structure XCVIII.



XCVIII

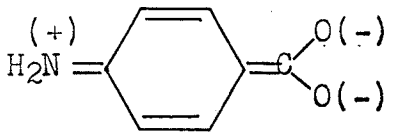
It was to be expected that this latter form would be more important in the ion than the free acid and consequently the resonance interaction between carboxylate group and the ring (XCVII) would suffer and lead to a condition where the extinction coefficient in basic solution would be less than in neutral water. For p-aminobenzoic acid the authors assumed that the same effects must be functioning but that some new factor arises which causes the reversal in behaviour to appear. Here they envisaged that in the amino acid a preferable path in the molecule would be set up which establishes a dipolar arrangement XCIX "without violating the ordinary valences of the atoms".



XCIX

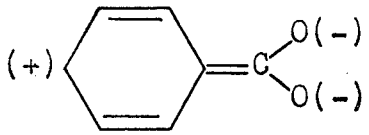
Then, for reasons detailed in their paper they argued that the presence of the additional negative dipole (as in the anion), rather than presenting an unfavourable effect,

would augment the dipolar structure of the type (C)



C

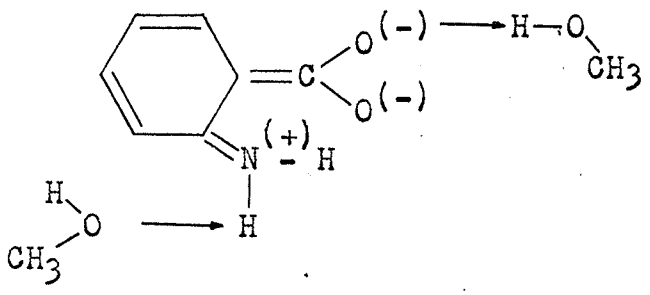
such that this form would make a greater contribution in the ion than in the free acid. In the case of the benzoic anion acid the corresponding form (CI),



CI

was considered to contribute in a small way but not enough to overcome the greater carboxyl resonance in the ion.

Now, if similar effects were considered to be the cause of the spectral behaviour of o-aminobenzoic acids in aqueous solution, then one might suggest that the reversal in nonaqueous solvents was perhaps a result of decreased stabilization of the excited state relative to the ground state of C when the aqueous solvent is replaced with methanol or pyridine. What is difficult to reconcile, however, is that methanol and water should be sufficiently different to cause such an abrupt change in spectral behaviour when both molecules can act as proton donors or proton acceptors (CII).



CII

Naturally anionic stabilization is considerably reduced in a solvent like pyridine which does not possess suitable protons for intermolecular hydrogen bonding but the spectra (secondary band) taken in neutral and basic methanol and pyridine are similar (Figures 31 and 32 respectively, pages 345, 346). It is a little difficult to visualize what modifications in ionic structures contributing to ultraviolet absorption might be made as a consequence of possible intramolecular hydrogen bonding in pyridine solution. The usual influence of such bonding, in the ground state at least, is to stabilize the anion relative to the acid. If the stabilization of the anion is enhanced in the excited state relative to the ground state, then one might have expected ϵ_{max} (anion)$>\epsilon_{max}$ (acid) in methanol or pyridine, a situation which does not prevail. Furthermore, if the interpretation given by Kumler and Strait (464) is correct, then it would be quite reasonable to have anticipated similar behaviour to occur with p-hydroxybenzoic acid which also possesses a strong electron-donating group even though the resonance inter-

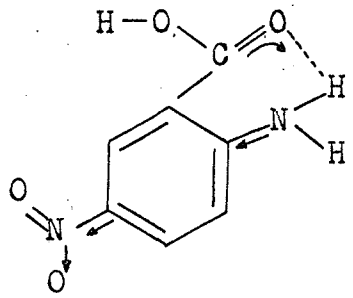
action of this group would be less than the amino group. However this is not the case, as ϵ_{max} (mono anion)$<\epsilon_{max}$ (acid) (433). Unfortunately the data for salicylic acid (lines 11 to 16, Table XXIX) from different source is inconclusive and the intensity variations are rather small.

With the experimental results available in this preliminary study, it was felt that any unequivocal evidence for the presence of intramolecular hydrogen bonding of salicylic and anthranilic acids in pyridine would not be forthcoming. Forbes and Leckie have stated that displacements and intensity changes of the secondary band can be useful criteria for confirming the existence of intramolecular hydrogen bonding but that the evidence may be somewhat ambiguous (440). Reasons given for this possibility included the fact that ortho-resonance forms as exemplified by CII may contribute to the ground and excited states and this may account for observed bathochromic displacement apart from contributions involving intramolecular hydrogen-bonded forms. Steric effects may cause interactions which are in opposition to intramolecular hydrogen bonding. The result would give rise, depending on which interaction predominates, to spectral effects causing different displacements than those expected. Explanations have been given to account for anticipated smaller steric effects in ortho-substituted anilines than, say, nitro compounds (440). It has been further noted that

steric inhibition of resonance has a more marked effect on the first primary band but different or less effect on the secondary band (438). Finally various modes of solute-solvent interaction such as intermolecular hydrogen bonding may interfere with intramolecular hydrogen bonding. Dearden and Forbes have expanded these considerations in a more recent paper and added an outline of at least three methods by which meaningful observations may be made to uncover intramolecular hydrogen bonding (461). The paper has been discussed in the introduction to this work in ultraviolet spectrophotometry (page 323).

Just one tentative observation will be made with reference to possible intramolecular hydrogen bonding of these acids in pyridine solution. By considering solutions of the various salicylic and anthranilic acids in neutral methanol and pyridine (complete data not available for 4-OCH_3SA), a comparison of the secondary band positions in Table XXIX shows that for each acid λ_{max} is displaced to longer wavelengths in neutral pyridine than in neutral methanol. To be sure the molecules have numerous sites for solute-solvent interaction and methanol also possesses the ability to donate protons in hydrogen bonding. These various modes of intermolecular hydrogen bonding may cause either bathochromic or hypsochromic shifts of the absorption bands depending on whether the organic acid behaves as a proton acceptor or a proton donor (460).

It would be expected that pyridine solvates the acid primarily through the carboxyl proton. This has the usual effect of causing a band displacement to lower wavelengths (keeping in mind the different behaviour of acids possessing nitro substituents) which is opposite to what is observed relative to methanol. It is suggested therefore that intramolecular hydrogen bonding being stronger in pyridine than in methanol is one of the contributing factors for the bathochromic displacements in pyridine as compared to methanol. The carboxyl function would then be involved in accepting a proton (from the ortho-amino or phenolic group) to its carboxyl oxygen. For purposes of illustration it could be said that an intramolecular hydrogen bond between the carboxyl oxygen and the amino hydrogen would tend to repell electrons in the N-H bond. This direction of electron flow is in keeping with the electron-release properties of the amino group. Considerable delocalization could result particularly if a nitro group para to the amino substituent were present (CIII).



CIII

The resulting bathochromic shift is also consistent with

electron withdrawal from the carboxyl oxygen allowing the carboxyl (or carboxylate) group to retain its influence of electron attraction from the benzene ring. If the presence of the intramolecular hydrogen bond assists in formation of a new or modified chromophore within which an electronic transition involving an effective charge migration occurs, and this coincides with that of the electron shifts in the ground state, then bathochromic displacements might be expected.

Summary

The amount of information derived from this spectrophotometric study has added significantly to the tentative conclusions reached in the proton magnetic resonance experiments (page 299) but some further confirmation would be desirable.

(i) In aqueous solution the eight salicylic and anthranilic acids under investigation represented a wide variation in acid strength. This general pattern of acidic behaviour was also exhibited in pyridine solutions and although there seemed to be a gradual decrease in strength from 4-nitrosalicylic acid to 5-methylanthranilic acid, the two families could be considered far enough separated (to a first approximation) that some generalization could be made in discussing their acidic behaviour separately. The conclusions reached

were that anthranilic acids are to be considered as either ionized partially in pyridine solution to ion pairs with no subsequent dissociation or that the preponderance of acid molecules existed only as solvates *via* solute-solvent hydrogen bonds. For salicylic acids the most favourable interpretations included the consideration that, in the concentration range used, the acid was dissociated partially but that the ions were free or at least sufficiently solvent separated so that ion pair formation was precluded, or that the model was best represented by category VIII, that is, with both concurrent ionization and dissociation being involved.

(ii) The lack of linearity and the presence of a positive deviation in the absorption concentration-dependence curve for solutions of salicylic acid in pyridine lent further support to the interpretation given in (i) for the salicylic acids. This was evidence for discounting the idea that simple intermolecular hydrogen bonding between the acid and solvent was the extent to which salicylic acid interacted with the solvent.

(iii) A comparison was made of spectral characteristics of a number of anthranilic acids in aqueous, methanolic and pyridine solutions in both neutral and under basic

solvent conditions. A reasonable interpretation of the observations led to the conclusion that there was very little if any zwitterion in the nonaqueous solvents. An inspection of spectral data available from the literature (3) for 4-methoxysalicylic acid in aqueous solution, allowed for a provisioned explanation to be made that zwitterion concentration was reduced as the temperature was raised.

(iv) There was no clear evidence to support the idea of significant intramolecular hydrogen bonding for salicylic and anthranilic acids in pyridine solution although the one observation put forward did favour this view.

Ultraviolet spectrophotometry has afforded additional and more unambiguous information than that obtained in the proton-resonance experiments. No further consideration will be given in attempting a quantitative determination of equilibrium constants. Rather, it is hoped that the discussion which follows related to the relative acidity studies by potentiometric titrations will help to corroborate the ideas suggested above and/or enable one to reduce the possible interpretations that were advanced regarding the extent of ionization, zwitterionic content and intramolecular hydrogen bonding for these aromatic acids in pyridine solution.

POTENTIOMETRIC TITRIMETRY

Introduction

Before attempting to present an interpretation of the data on the relative acidity of the anthranilic and salicylic acids in pyridine and quinoline, it might be useful and convenient to introduce here the most pertinent findings in the literature for acid-base behaviour related to the studies undertaken in the present study. In nonaqueous solvents certain problems become apparent that are not commonly encountered in aqueous solution. Naturally, solvation, or more particularly hydration, of molecular and ionic species of acids and bases is to be expected in aqueous solution and one should not forget the possibility of zwitterion complicating the formulation of acidity constants for those amino acids capable of existing in that state. Characteristically, however, water represents a rather special blend of relatively high dielectric constant, weak acidic and basic properties and an unusual ability to solvate ions and molecules of acids and bases, primarily through its hydrogen bonding properties. Because of these characteristics, acid-base behaviour in aqueous solution can be thought as being derived from a composite of effects each being masked or completely eliminated because of the nature of the solvent. A study of nonaqueous solvents affords one an unusual opportunity to uncover what

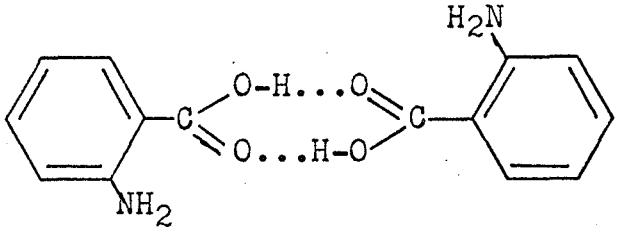
these various 'microscopic' equilibria or interactions might be. Because of the possible variations in properties mentioned above, interactions in nonaqueous solvents may involve and may experimentally be accounted for by intermolecular hydrogen bonding between solute molecules, intermolecular hydrogen bonding between solute and solvent, intramolecular hydrogen bonding by suitable oriented functional groups, ionization and dissociative processes, homoconjugation due to lack of specific solvent solvation of ionized species and intramolecular ionization to zwitterionic forms.

In the following summary special attention will be given to salicylic and anthranilic acids and their behaviour in the basic solvents quinoline and pyridine. For purposes of comparison, however, other acidic solutes and nonaqueous solvents will also be mentioned. Many of these aspects have already been treated in considerable detail in the Review of the Literature. Some have been re-interpreted in the light of evidence gleaned from studies undertaken now.

That carboxylic acids are associated in certain organic solvents through intermolecular hydrogen bonding of their solute molecules has been known for a long time (475). For example, in aprotic solvents like benzene, chloroform, carbon tetrachloride and carbon disulfide, benzoic acid commonly exists as dimers and depending on the concentration and temperature may be involved in a monomer-dimer equilibrium [126].

$$2\ C_6H_5COOH \rightleftharpoons (C_6H_5COOH)_2 \qquad [126]$$

Dimerization is less favoured as the temperature is raised (475). Salicylic acid may also form double molecules in benzene and carbon tetrachloride. Evidence has been presented to show that the dimer possesses no free hydroxyl groups, a result which is reasonably explained by having the two carboxyl groups joined as in the dimer of benzoic acid and, in addition, by formation of intramolecular hydrogen bonds of the phenolic hydrogens with adjacent oxygen atoms of the carboxyl groups (476, 477). Polymeric species of benzoic and salicylic acids in aprotic solvents cannot be discounted either (478). An infrared spectral study of substituted anthranilic acids in chloroform suggested to Kellie and co-workers the occurrence of both intra- and intermolecular hydrogen bonding (44). The latter type was envisaged to possess associated carboxyl groups in the dimer (CIV)



CIV

although this might only be one of a variety of intermolecularly bonded structures. Similar observations have been reported by Hadzi and Premru (479). In other possibilities the carboxyl group of one molecule might be linked

to the amino group of an adjacent molecule. The ebullioscopic study of Dunken and Rudakoff of a number of substituted benzoic acids in benzene pointed out that steric requirements and intramolecular hydrogen bonding reduced the tendency for dimerization (480). This is readily seen from the following table of a selected number of experimental results.

TABLE XXXV

EQUILIBRIUM CONSTANTS FOR THE DIMERIZATION OF SUBSTITUTED BENZOIC ACIDS IN BENZENE AT 353°A.[a]

Acid	K_{12}^{b} (mole/litre)$^{-1}$
pentachlorobenzoic	0.1
salicylic	12.3
o-methoxybenzoic	12.8
o-iodobenzoic	23.2
anthranilic	28.5
o-bromobenzoic	35.5
benzoic	65.6

a Ebullioscopic studies
b Equilibrium constant for the reaction:
$$2A \rightleftharpoons A_2$$
where A is the acid molecule.

The reduction in self-association of benzoic acids bearing ortho substituents was also noted in a differential vapour-pressure study which included the solvents 1,2-dichloroethane,

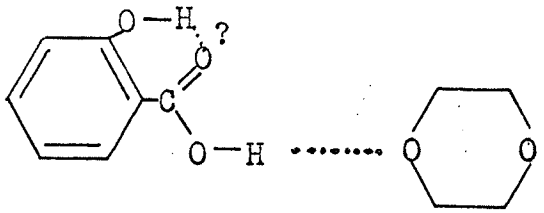
acetonitrile and nitromethane and was attributed in part to chelation (173). Furthermore self association in the case of benzoic acid was considerably reduced in the solvent order 1,2-dichloroethane>nitromethane > acetonitrile; in fact, no monomer-dimer equilibrium was detected in the latter solvent even though it has virtually the same dielectric constant as nitromethane. The results suggested that the lack of dimerization in acetonitrile was a consequence of stabilization of the monomer form by hydrogen bonding between the acid (HA) and solvent (CV).

$$CH_3CN \ldots HA$$

CV

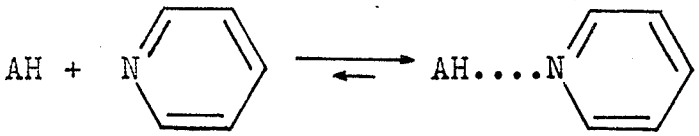
That solvent interaction with acidic solutes occurs via a dipolar mechanism or by specific intermolecular hydrogen bonding,and thereby competes with self association of acid molecules, is well established. Related to the present work Forbes and co-workers found that the concentration dependence of the first primary electronic absorption band for solutions of salicylic acid in cyclohexane was virtually eliminated when the solution also contained 5 per cent ether and did not appear in dioxane solution (458, 471) at all. The absence of a concentration dependence in these more polar solvents is good evidence that there is present predominantly only one molecular species of the acid which is stabilized by the solvent through

intermolecular hydrogen bonding (CVI).



CVI

Ether-bonded monomers have also been confirmed by Brooks et al. (481). Numerous other examples are available in the literature (459, 475, 476) but enough has been noted here and elsewhere in this dissertation to conclude that complication of ionization by dimer-monomer equilibria of anthranilic and salicylic acids in basic solvents such as quinoline and pyridine is not likely to occur. If the acid molecule (HA) existed primarily in the unionized form it should be fully solvated so that the equilibrium



[127]

lies to the right and may be neglected in formulating any over-all equilibrium constant or equilibrium quotient (concentration dependent)(95b).

The presence of suitably placed phenolic and amino groups in the respective molecules of salicylic and anthranilic acids gives rise to possible intramolecular hydrogen bonding of these substituents with the carboxyl group. In aqueous solution the anomalous enhancement of acidity of

salicylic acid over its para isomer has been attributed to a hydrogen bond stabilizing the salicylate anion more than it does the unionized acid (482, 483). A still more pronounced effect was observed in the case of 2,6-dihydroxybenzoic acid (484). Since that time this has become a commonly held view among chemists. Very recently, however, work by Dunn and Kung (287) and Dunn and Penner (11) on the acidities of substituted salicylic acids in aqueous and benzene solutions respectively has reopened this question of whether an intramolecular hydrogen bond in aqueous solution is the sole factor for enhancement of acidity or whether in aqueous solution the intramolecular hydrogen bonds are being replaced by intermolecular hydrogen bonds with the solvent. Further work is now in progress on investigating the transmission of substituent effects through chelation (485, 486). In an application of the extended Hammett relationship to the ionization constant of substituted anthranilic acids in aqueous solution, Leggate and Dunn uncovered no substituent effects which required the assumption of indirect effects on the acid strength exerted through the intramolecular hydrogen (12). However Hunter has advanced the interpretation that an intramolecular hydrogen bond is responsible for the increased acidity of N-acetylanthranilic acid when compared to benzoic acid and the meta and para isomers even though it would be expected that the imino-hydrogen atom might experience a reduction

in acidity and give rise to a relatively weak bond (N-H...O) in the anion (487).

Returning once more to the paper by Dunn and Penner (11), these workers found that the extended form of the Hammett equation of the type

$$\Delta HNP = \rho_1 \sigma_1 + \rho_2 \sigma_2^- \qquad [128]$$

correlated the relative acidity data for substituted salicylic acids in benzene better than the simple equation

$$\Delta HNP = \rho_1 \sigma_1 \qquad [129]$$

The symbols have been defined previously (page 120). The results favoured the interpretation that transmission of substituent effects via the phenolic linkage was important in determining the relative acidities of salicylic acids in benzene; in fact, about one third to one half of the effect was attributed to intramolecular hydrogen bonding. This seemed to give credence to the idea that the Hammett equation can adequately be used to uncover this indirect effect, as Jaffe originally suggested (47), and gave additional significance to the experimental observation that in aqueous solution acidity was just as well represented by a simple Hammett equation (287).

Davis and Hetzer, in their spectrophotometric examination of the relative strengths of substituted benzoic acids in benzene, favoured analogous chelated structures for both the salicylate and anthranilate anions in their complex

with the reference base, 1,3-diphenylguanidine (474). Two methods were used by Dearden and Forbes to secure information concerning intramolecular hydrogen bonding in salicylic and anthranilic acid by ultraviolet spectra (461). For the first acid in cyclohexane spectral changes were noted when its phenolic group was methylated and when comparisons were made with m-hydroxybenzoic acid. In the case of anthranilic acid its spectral characteristics were compared with the meta isomer in both ether and ethanol. The results were interprelated for both acids in favour of intramolecular hydrogen bonds in each solvent studied. Kellie et al. compared the carbonyl frequencies of substituted benzoic and anthranilic acids in carbon tetrachloride and chloroform respectively and concluded that the amino group exerted a constant influence on the carbonyl stretching frequency (44). It is not clear, however, if this is compatable with another suggestion appearing in the same paper that both intra- and intermolecular hydrogen bonding occurred in chloroform solutions of anthranilic acids. Among the acids examined only one (i.e., 5-chloroanthranilic) possessed a substituent para to the amino group. It could well be that the choice of acids studied lessened the possibility of viewing anomalous behaviour and that any variation in amino-hydrogen acidity produced by the substituents was not large enough to affect the strength of the intramolecular hydrogen bond.

Inferences regarding chelation may also be made from studies involving nonaqueous potentiometric titrations. Using the solvent-titrant-electrode system of pyridine, tetra-n-butylammonium hydroxide in benzene-methanol and a glass-methanol-modified calomel respectively, Cundiff and Markunas obtained two inflections for m- and p-hydroxybenzoic acids but only one inflection for the o-hydroxy acid (202). In another study Mathews and Welch found that the phenolic group of salicylic acid was only weakly acidic in the more basic n-butylamine whereas in the case of p-hydroxybenzoic acid the phenolic group was so strongly acidic that it titrated with the carboxyl group (242). These two observations lead one to suspect that in the basic solvents intramolecular hydrogen bonding, at least in part, is the cause of the effects leading to reduced acidity of the ortho-phenolic group. It is also interesting to inspect the potentiometric data determined by Streuli and Miron (10) graphically. The data is recorded in Table XXXVI. In Figure 39 the differential half-neutralization potentials derived in pyridine solution for the o-substituted benzoic acids are plotted against sigma-para substituent constants. The use of this constant implies that the electronic influences of the para substituent may be taken as a basis for analyzing the effects of the same substituent in the ortho position. Any significant deviations from a linear correlation could be interpreted in the light of steric,

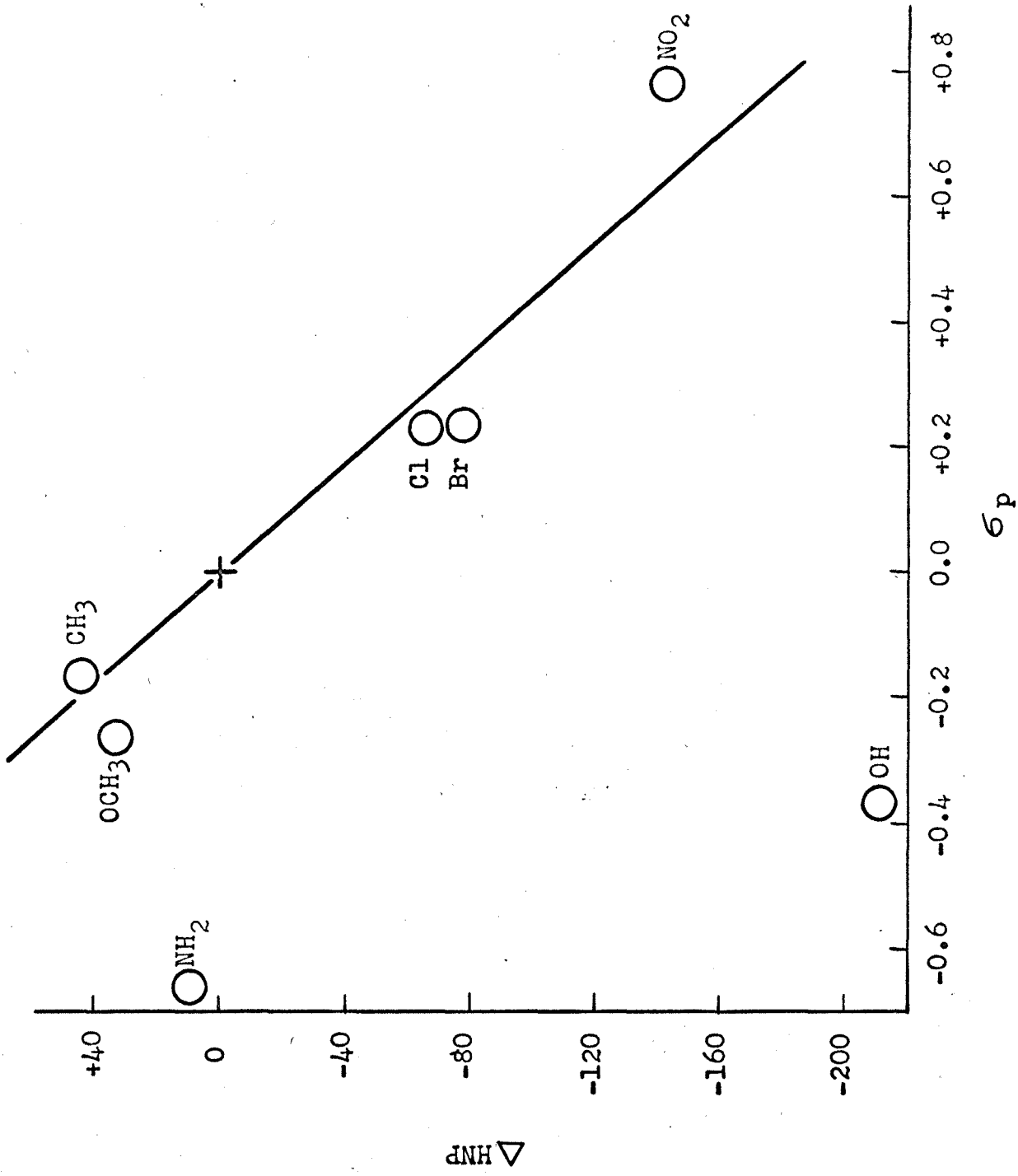
TABLE XXXVI

CORRELATION OF THE DIFFERENTIAL HALF-NEUTRALIZATION POTENTIALS (ΔHNP) OF ORTHO-SUBSTITUTED BENZOIC ACIDS IN PYRIDINE WITH HAMMETT SIGMA-PARA SUBSTITUENT CONSTANTS.[a]

Substituent	ΔHNP[b]	σ_p[c]
CH_3	44	-0.170
OCH_3	33	- .268
NH_2	10	- .66
Cl	-65	+ .227
Br	-77	+ .232
NO_2	-142	+ .778
OH	-211	- .37

a Reference (10).
b Relative to benzoic acid; the strongest acid is given the most negative ΔHNP value.
c Sigma-para substituent constants from the complication of McDaniel and Brown (444).

FIGURE 39. The correlation of the differential half-neutralization potentials (ΔHNP) of ortho-substituted benzoic acids in pyridine with sigma-para substituent constants (σ_p). Data are taken from Table XXXVI.


+40
0
-40
-80
-120
-160
-200
ΔHNP
-0.6
-0.4
-0.2
0.0
+0.2
+0.4
+0.6
+0.8
σp
NH2
OCH3
CH3
Cl
Br
NO2
OH

solvation or intramolecular hydrogen bonding effects. The straight line in Figure 39 was drawn visually to accommodate five of the acids and also the origin (i.e., $\triangle$HNP = 0 for the reference, benzoic acid). It is not the intention here to make any speculations about whether the line as described masks any minor anomalies within these five acids. Rather, if their behaviour is accepted as a normal pattern of acid strength in pyridine solution for ortho-substituted benzoic acids, then clearly both anthranilic and salicylic acids deviate significantly from the norm. They are stronger than expected on the basis that they possess ortho substituents which have normally the strongest resonance effects of electron release. It is true that anthranilic acid is seen as a slightly weaker acid than benzoic but it should have exhibited much weaker acidic properties if only polar and resonance influences were operative. Streuli and Miron in their paper had compared $\triangle$HNP with $pK_a(H_2O)$. They explained deviations from that correlation for these same two acids in terms of anionic stabilization through intramolecular hydrogen bonding for salicylic acid and the existence of the zwitterionic form for anthranilic acid. This latter interpretation is surely open to question in the light of results obtained in the ultraviolet spectral examination in this study and from what is to follow. A similar explanation for anthranilic as that given to salicylic acid is more tenable. In

passing it is interesting to note that there was no perceptible displacement of the OH resonance signal of methyl salicylate by dilution in pyridine (158). It would seem, therefore, that the intramolecular hydrogen bond was too strong to be disrupted by competition with solute-solvent intermolecular hydrogen bonding.

With particular reference to salicylic acid a more detailed discussion of the possibilities of intramolecular hydrogen bonding in aqueous and nonaqueous solvents is available (11) including an analysis and criticism of the work of Voroshin and Vlasov (462).

The existence of the zwitterionic form of anthranilic acid and its concentration relative to the uncharged form has continued to be a point of contention for systems involving both aqueous and nonaqueous solvents. Aliphatic amino acids like glycine are known to exist largely as zwitterion in aqueous solution (488) whereas aromatic amino acids are generally considered to favour the nondipolar form, particularly the ortho and para isomers (443, 489, 490). The meta isomer on the other hand has been estimated to exist predominantly in the zwitterionic form (284, 489). The most recent and undoubtedly the best estimates in respect to substituted anthranilic acids have been advanced by Leggate and Dunn (12). Calculated zwitterionic contents varied from 95 per cent in the case of 5-hydroxyanthranilic acid to virtually no zwitterion for

5-nitro acid.

When nonaqueous solvents are considered, it is generally observed that the concentration of zwitterion is considerably reduced and may be entirely eliminated depending on solvent characteristics. Infrared studies of aliphatic amino acids in solvents such as carbon tetrachloride, chloroform and n-butyl alcohol show, however, that zwitterionic species are still important depending on the range of concentration and the position of the amino group in the molecular chain. In certain instances the systems are best described by a tautomeric equilibrium between a hydrogen-bonded complex and a zwitterionic species (491). A comparison of near-ultraviolet absorption spectra of pyridine monocarboxylic acids in water and ethanol solutions indicated that these acids exist primarily in the neutral undissociated form in ethanol and in the anionic and zwitterionic forms in water (492). The three aminobenzoic acids have been examined by infrared spectroscopy in the solid state and in carbon tetrachloride solution (493). For the ortho and para isomers absorptions were observed in the region corresponding to stretching vibrations of free-and bonded-amino groups. A lack of absorption between 3500-3200 cm^{-1} led to the proposal of the dipolar ($^{(+)}NH_3C_6H_4COO^{(-)}$) structure for m-aminobenzoic acid. Although it was not made clear in the abstract it is understood that these observations refer to both the solid-state

and solution spectra. The zwitterionic structures for anthranilic acid in the solid and in chloroform solution has been discounted by Kellie and co-workers (44).

The apparently anomalous behaviour of m-aminobenzoic acid in potentiometric titrations in pyridine has been interpreted on two occasions to be the result of the zwitterionic form for this acid in the basic solvent (9, 10). In each case the acid appeared stronger than predictable from data derived for other substituted benzoic acids. It was thought that, since ionization consisted of removal of hydrogen from an $NH_3^{(+)}$ group rather than from a neutral molecule, the charge separation in the solvent of low dielectric constant was not as significant as would have been had the molecule existed in the nonpolar form. Unfortunately, however, this interpretation rested on the basis of a correlation of $\triangle$HNP values of benzoic acids with $pK_a(H_2O)$. One pair of workers also correlated the data ($\triangle$HNP) with the Hammett substituent constants (9) and a similar test was made at this time for the data taken from the other source (10). In both of these latter two correlations the point corresponding to m-aminobenzoic acid did not deviate from the straight line indicating clearly that the electronic influences of the meta-amino group were well represented by the normal inductive and mesomeric effects as indicated by the sigma constant. It also pointed out why it is unsatisfactory to use aqueous ionization constants in

assessing the effect of an amino group on the dissociation of the carboxyl proton because of the complicating zwitterionic equilibria, especially when comparisons are being made with nonaqueous systems. Davis and Hetzer have issued a similar precaution (474). It should be remembered that the value of -0.16 for the sigma constant of a meta amino group was first established by Hammett on the basis of the alkaline hydrolysis of ethyl benzoates in ~90 per cent ethanol (16). In another study in the strongly basic ethylenediamine, Moss and co-workers potentiometrically titrated both anthranilic and p-aminobenzoic acid and observed that the buffering effect of the amino group was completely eliminated and that the amino acids behaved as typically unsubstituted or normally substituted carboxylic acids (195).

Finally, the experimental evidence presented earlier in the ultraviolet spectrophotometric work demonstrated rather clearly that any possibility of complications arising from zwitterionic forms of substituted anthranilic acids in pyridine may be safely discounted.

In turning attention next to the actual ionization and dissociation equilibria occurring in basic solvents the pertinent data are conveniently summarized in Table XXXVII. The discussion of the Table will be limited to only a few more general remarks.

TABLE XXXVII

ACID-BASE BEHAVIOUR OF A VARIETY OF ACIDS IN NITROGENOUS MEDIA[a]

No.	Method[b]	Solvent	Acid (HA)	pK_a[c](H_2O)	Acid[d] Concentration	Solvent[e] Cation	K_i[f]	K_d[g]	K^h
1(a)	C(117)	Pyridine (5.19)[j](12.3)[k]	$PyHClO_4$[l]		$3.9\text{-}116 \times 10^{-5}$	I* D		7.55×10^{-4}	7.55×10^{-4}
(b)			PyHI		$15.8\text{-}91.3 \times 10^{-5}$	I* D		5.9×10^{-4}	5.9×10^{-4}
(c)			$PyHNO_3$		$3.3\text{-}105 \times 10^{-5}$	I* D		4.95×10^{-5}	4.95×10^{-5}
(d)			C_6H_5COOH	4.20	$0.95\text{-}35.8 \times 10^{-4}$	D?			1.6×10^{-10}[m]
2(a)	C(118)	Pyridine	$PyHNO_3$		$1.86\text{-}21.7 \times 10^{-5}$	I* D		5.1×10^{-5}	5.1×10^{-5}
(b)			$PipHNO_3$		$1.74\text{-}16.9 \times 10^{-5}$	I* D		1.8×10^{-5}	1.8×10^{-5}
3(a)	V-UV(137)	Pyridine	4-Nitrophenol	71.6		I			
(b)			2,5-Dinitrophenol	5.22	$0.500\text{-}1.74 \times 10^{-3}$	I D	3.3×10^{-2}	7.5×10^{-4}	7.5×10^{-4}
(c)			2,6-Dinitro-3,4-xylenol	4.92[o]	$0.189\text{-}0.942 \times 10^{-3}$	I D	3×10^{-1}	1.3×10^{-2}	3.0×10^{-3}
(d)			2,4-Dinitrophenol	4.09		~I*			
(e)			2,4,6-Trinitrophenol	0.29		I*			
(f)			EHIM[p]	3.36[q]	5.82×10^{-2}	I D	ca. 10^{-4}	$\sim 2 \times 10^{-4}$	$\sim 2 \times 10^{-8}$
	IR				0.24	—[r]			
(g)			CH_3COOH	4.76		—[r]			
(h)			ICAA[s]	3.04[q]		—[r]			
4	V-UV(138)	Pyridine	2,4,6-Trinitrophenol		5×10^{-5}	D*			
5	C and EMF(169)	Pyridine	PyHCl			I* D		7.15×10^{-7}	7.15×10^{-7}

TABLE XXXVII

ACID-BASE BEHAVIOUR OF A VARIETY OF ACIDS IN NITROGENOUS MEDIA[a]

Solvent	Acid (HA)	pK_a[c] (H_2O)	Acid[d] Concentration	Solvent[e] Cation	K_i[f]	K_d[g]	K[h]	ΔHNP[i]
Pyridine (5.19)[j](12.3)[k]	$PyHClO_4$[l]		$3.9\text{-}116 \times 10^{-5}$	I* D		7.55×10^{-4}	7.55×10^{-4}	
	PyHI		$15.8\text{-}91.3 \times 10^{-5}$	I* D		5.9×10^{-4}	5.9×10^{-4}	
	$PyHNO_3$		$3.3\text{-}105 \times 10^{-5}$	I* D		4.95×10^{-5}	4.95×10^{-5}	
	C_6H_5COOH	4.20	$0.95\text{-}35.8 \times 10^{-4}$	D?			1.6×10^{-10}[m]	0
Pyridine	$PyHNO_3$		$1.86\text{-}21.7 \times 10^{-5}$	I* D		5.1×10^{-5}	5.1×10^{-5}	
	$PipHNO_3$		$1.74\text{-}16.9 \times 10^{-5}$	I* D		1.8×10^{-5}	1.8×10^{-5}	
Pyridine	4-Nitrophenol	71.6		I				-50
	2,5-Dinitrophenol	5.22	$0.500\text{-}1.74 \times 10^{-3}$	I D	3.3×10^{-2}	7.5×10^{-4}	7.5×10^{-4}	
	2,6-Dinitro-3,4-xylenol	4.92[o]	$0.189\text{-}0.942 \times 10^{-3}$	I D	3×10^{-1}	1.3×10^{-2}	3.0×10^{-3}	
	2,4-Dinitrophenol	4.09		~I*				-359
	2,4,6-Trinitrophenol	0.29		I*				-428
	EHIM[p]	3.36[q]	5.82×10^{-2}	I D	ca. 10^{-4}	$\sim 2 \times 10^{-4}$	$\sim 2 \times 10^{-8}$	
			0.24	—[r]				
	CH_3COOH	4.76		—[r]				97
	ICAA[s]	3.04[q]		—[r]				
Pyridine	2,4,6-Trinitrophenol		5×10^{-5}	D*				
Pyridine	PyHCl			I* D		7.15×10^{-7}	7.15×10^{-7}	

TABLE XXXVII Continued

No.	Method [b]	Solvent	Acid (HA)	pK_a [c] (H_2O)	Acid [d] Concentration	Solvent [e] Cation	K_i [f]	K_d [g]	K [h]
6.(a)	C(119)	Pyridine	PyHF			I* D		3×10^{-9}	3×10^{-9}
(b)			PyHCl			I* D		4×10^{-6}	4×10^{-6}
(c)			PyHBr			I* D		10^{-4}	10^{-4}
(d)			PyHI			I* D		3×10^{-3}	3×10^{-3}
7.	IR(141)	Pyridine	C_6H_5 COOH		equimolar	—			
8.(a)	PMR [u]	Pyridine	CF_3COOH		0.096 [t]	I			
(b)			Salicylic	2.98(pK_1)	0.055 [t]	I			
(c)			Anthranilic	4.95(pK_2)	0.056 [t]	—			
9.(a)	V-UV [u]	Pyridine	5-Nitrosalicylic	2.32 [v]	6.88×10^{-4}	I D			
(b)			4-Nitrosalicylic	2.31 [v]	6.55×10^{-4}	I D			
(c)			5-Nitroanthranilic	3.91 [w]	6.59×10^{-4}	I			
10.(a)	P [x](170)		$PyHNO_3$		$0.575 - 11.5 \times 10^{-3}$	I			
(b)			CH_3COOH		$0.314 - 15.7 \times 10^{-3}$	I			
(c)			C_6H_5COOH		$0.139 - 13.9 \times 10^{-3}$	I			
(d)			CF_3COOH		$0.072 - 4.33 \times 10^{-3}$	I			
(e)			2,4-Dichlorophenol	7.85	$0.528 - 2.11 \times 10^{-3}$	I			
(f)			Phenol	9.99	$1 - 5 \times 10^{-3}$	—			
(g)			Salicylic		$0.98 - 6.86 \times 10^{-3}$	I			
(h)			H_2SO_4	ca.-3 [y]	$0.093 - 9.25 \times 10^{-3}$	I			
(i)			Phthalic	2.95(pK_1)	$0.98 - 9.83 \times 10^{-3}$	I			

TABLE XXXVII Continued

Solvent	Acid (HA)	pK_a[c] (H_2O)	Acid[d] Concentration	Solvent[e] Cation	K_i[f]	K_d[g]	K[h]	△HNP[i]
idine	PyHF			I* D		3×10^{-9}	3×10^{-9}	
	PyHCl			I* D		4×10^{-6}	4×10^{-6}	
	PyHBr			I* D		10^{-4}	10^{-4}	
	PyHI			I* D		3×10^{-3}	3×10^{-3}	
idine	C_6H_5 COOH		equimolar	—				
idine	CF_3COOH		0.096[t]	I				
	Salicylic	2.98(pK_1)	0.055[t]	I				-211
	Anthranilic	4.95(pK_2)	0.056[t]	—				10
idine	5-Nitrosalicylic	2.32[v]	6.88×10^{-4}	I D				
	4-Nitrosalicylic	2.31[v]	6.55×10^{-4}	I D				
	5-Nitroanthranilic	3.91[w]	6.59×10^{-4}	I				
	$PyHNO_3$		$0.575 - 11.5 \times 10^{-3}$	I				
	CH_3COOH		$0.314 - 15.7 \times 10^{-3}$	I				
	C_6H_5COOH		$0.139 - 13.9 \times 10^{-3}$	I				
	CF_3COOH		$0.072 - 4.33 \times 10^{-3}$	I				
	2,4-Dichlorophenol	7.85	$0.528 - 2.11 \times 10^{-3}$	I				78
	Phenol	9.99	$1 - 5 \times 10^{-3}$	—				340
	Salicylic		$0.98 - 6.86 \times 10^{-3}$	I				
	H_2SO_4	ca.-3[y]	$0.093 - 9.25 \times 10^{-3}$	I				
	Phthalic	2.95(pK_1)	$0.98 - 9.83 \times 10^{-3}$	I				-231

TABLE XXXVII Continued

No.	Method [b]	Solvent	Acid (HA)	pK_a [c] (H_2O)	Acid [d] Concentration	Solvent [e] Cation	K_i [f]	K_d [g]	K^h
11.	PMR(150)	Quinoline (5.06)(9.00)	CF_3COOH	0.23	0.04 - 0.12 [t]	I* D		6.5×10^{-2} [z]	
12.(a)	PMR [u]	Quinoline	CF_3COOH		0.076 [t]	I			
(b)			Salicylic		0.078 [t]	I			
(c)			Anthranilic		0.079 [t]	—			
13.	C(120)	Ethylenediamine(EDA) (9.98; pK_1)(14.2;20°C.)	EDAHCl		$0.384\text{-}8.25 \times 10^{-3}$	I* D		1.16×10^{-4}	1.16×10^{-4}
14.(a)	V-UV(135)	Ammonia (-55.6°C.) (9.25)(22.4; -33.4°C.)	2-Nitroacetanilide		$2.96\text{-}17.2 \times 10^{-5}$	I D	2.2×10^{-2}	2.2×10^{-4}	4.7×10^{-6}
(b)			4-Nitroacetanilide		$3.05\text{-}17.3 \times 10^{-5}$	I D	9.3×10^{-2}	0.89×10^{-4}	7.6×10^{-6}
(c)			2-Nitrophenol			I* D			
15.(a)	CR(171)	Ethanolamine (9.50)	2-Nitrophenol	7.21		I* D			
(b)			3-Nitrophenol	8.39		I* D			
(c)			4-Nitrophenol			I* D			
16.(a)	PT(280)	N-Butylamine (10.7)(5.3; 21°C.)	Benzoic		$\sim 8.3 \times 10^{-3}$	I?			
(b)			HCl		$\sim 8.3 \times 10^{-3}$	I			
(c)			$HClO_4$		$\sim 8.3 \times 10^{-3}$	I*			

TABLE XXXVII Continued

Solvent	Acid (HA)	pK_a[c] (H_2O)	Acid[d] Concentration	Solvent[e] Cation	K_i[f]	K_d[g]	K^h	$\triangle HNP^i$
ine (9.00)	CF_3COOH	0.23	0.04 - 0.12[t]	I* D		6.5×10^{-2}[z]		
ine	CF_3COOH		0.076[t]	I				
	Salicylic		0.078[t]	I				
	Anthranilic		0.079[t]	—				
nediamine(EDA) pK_1)(14.2;20°C.)	EDAHCl		0.384-8.25 x 10^{-3}	I* D		1.16×10^{-4}	1.16×10^{-4}	
a (-55.6°C.) (22.4; -33.4°C.)	2-Nitroacetanilide		2.96-17.2 x 10^{-5}	I D	2.2×10^{-2}	2.2×10^{-4}	4.7×10^{-6}	
	4-Nitroacetanilide		3.05-17.3 x 10^{-5}	I D	9.3×10^{-2}	0.89×10^{-4}	7.6×10^{-6}	
	2-Nitrophenol			I* D				
lamine	2-Nitrophenol	7.21		I* D				
	3-Nitrophenol	8.39		I* D				
	4-Nitrophenol			I* D				
lamine (5.3; 21°C.)	Benzoic		~8.3 x 10^{-3}	I?				
	HCl		~8.3 x 10^{-3}	I				
	$HClO_4$		~8.3 x 10^{-3}	I*				

TABLE XXXVII Continued

a Unless stated otherwise it is understood that the temperature at which the measurements or observations were made is at 25°C. or close to it.

b Indicates the technique or method used with the literature reference from which the information is taken in parentheses. All measurements taken from the same source and solvent have the same adjacent number but a different letter describes each acid separately.

conductivity (C)
cryoscopy (CR)
electromotive force (EMF)
infrared spectrophotometry (IR)
polarography (P)
potentiometric titrations (PT)
proton magnetic resonance (PMR)
visible and/or ultraviolet spectrophotometry (V-UV)

c At 25°C.; reference (472) unless where otherwise noted.

d Records the concentration (range) of the acidic solute in mole/litre at which the measurements or observations were taken. If different concentration units were used, this is noted.

e — indicates that, with reference to other data taken from same source and same solvent, the observation points to the absence of solvent cation;

I indicates that the presence of the solvent cation in solution is reasonable assured (i.e.,ionization) whether as a free solvent-solvated species or in an ion pair; nothing may be known about dissociation or if ionization is complete.

I* refers to the situation where the acid is considered to be essentially all ionized in that solvent but nothing may be known about any dissociation; it is assumed that pyridinium and other similar salts are at least fully ionized in solution.

D indicates that some degree of dissociation has occurred whether it is from an ionic complex (i.e., ion pair) or from the molecular acid.

D* refers to the case where the acid is fully dissociated (i.e., solvent cation exists entirely free from the anion).

f $K_i = \frac{[H^{(+)}A^{(-)}]}{[HA]}$

g $K_d = \frac{[H^{(+)}]\ [A^{(-)}]}{[H^{(+)}A^{(-)}]}$

h $K = \frac{[H^{(+)}]\ [A^{(-)}]}{[H^{(+)}A^{(-)}] + [HA]} = \frac{K_i K_d}{1+K_i}$

TABLE XXXVII Continued

i Differential half-neutralization potential from reference (10, 283) unless where otherwise noted; reference acid is benzoic and the strongest acid possesses the most negative $\triangle$HNP value.

j Values of $pK_a(H_2O)$ refer to the conjugate acid of the solvent and were determined at 25°C.; reference (402) unless where otherwise noted.

k Dielectric constant at 25°C.; reference (97) unless where otherwise noted.

l Pyridinium perchlorate.

m Of qualitative significance only.

n Piperidinium nitrate.

o In 50 per cent ethanol; reference (137).

p Ethyl hydrogen isopropylidenemalonate, $(CH_3)_2C = C(COOH)(COOC_2H_5)$; values of K and K_i are very approximate, being derived from indirect methods.

q Reference (137).

r Infrared spectrum shows no absorption at 1600 cm^{-1}, the frequency at which carboxylate ions usually absorb.

s Isopropylidenecyanoacetic acid, $(CH_3)_2C = C(CN)(COOH)$.

t Mole fraction.

u This investigation.

v Reference (287).

w Reference (12).

x Solvent contains 0.1M $LiClO_4$ as background electrolyte.

y Reference (170).

z Mole-fraction units.

(i) When results (observations of solvent cation or values of equilibrium constants) are compared from different sources using similar methods, the correspondence is fairly reasonable (lines 1(b) and 6(d)) and may be very good (lines 1(c) and 2 (a)). When results are compared from the same or different source using different techniques similarities in behaviour of the acidic solutes may not be recognized (lines 1(d), 7 and 10(c)). This may be, however, a consequence of the variations in concentrations used and the limit of detection in the various methods.

(ii) An inspection of the Table shows that aqueous $pK_a(H_2O)$ values are not entirely satisfactory in correlating or comparing acid strengths with those in nonaqueous solvents such as pyridine. Phenols generally exhibit an enhancement in acidity relative to carboxylic acids in pyridine compared to water (453) (compare lines 3(f) and 3(h) with lines 3(b), (c) and (d) or lines 8(c) and 12(c) with 3(a), (b) and 10(e)). A comparison of ΔHNP and $pK_a(H_2O)$ values (of the acids) also leads to this observation (compare lines 3(a) and 10(e) with 3(g)).

(iii) Only the strongest phenolic and carboxylic acids (aqueous) such as picric and trifluoroacetic are completely ionized in pyridine or quinoline (lines 3(e)

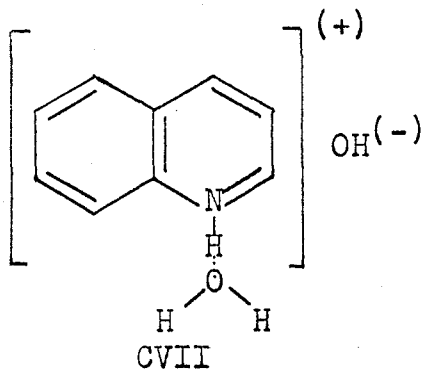
and 11 respectively) and the former is fully dissociated only at very low concentrations (line 4).

(iv) It would seem that for phenols with $pK_a(H_2O)$ greater than ~8 there is little or no ionization in pyridine (lines 10(e) and (f)) while much lower $pK_a(H_2O)$ values must be reached by carboxylic acids (aliphatic and aromatic) before ionization occurs (lines 1(d), 3(f), (g), (h) and 8(c)). In comparing these results on the basis of the potentiometric titrations the lower limit for detecting ionization would seem to be at $\triangle$HNP >100.

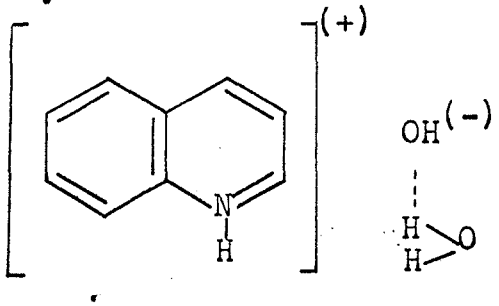
One final aspect may be considered before examining the experimental results of this investigation. The behaviour of anions in dipolar aprotic solvents, a class in which pyridine may sometimes be considered as a representative member, needs to be better understood (99). Generally, however, the class is better represented by less basic and higher dielectric constant solvents such as nitromethane, dimethyl formamide, dimethyl sulfoxide and sulpholane. Since pyridine possesses no suitably labile hydrogen atoms to form hydrogen bonds with anions, the effects of solvation experienced by these ionic species is considerably different from those in aqueous solution. Parker has pointed out that in dipolar aprotic solvents the solvation of anions occurs by ion-dipole attraction. Imposed on this is an interaction

which is greatest for large anions, due to the mutual polarizability of the anion and the solvent molecule (99). Anions ($A^{(-)}$) may, however, become stabilized by interacting with the molecular acid (HA) to form homoconjugate anions ($HA_2^{(-)}$). Their existence has been suggested in a number of solvents but interestingly enough very little seems to have been expressed in this regard by workers utilizing solvents which possess relatively moderate to strong basic strengths and relatively low dielectric constants, particularly those represented in Table XXXVII (cf., however, reference (166)).

In one paper properties of quinolinium hydrates were investigated by examining the solubility of water in quinoline, the refractive index and viscosity (494). The authors envisaged hydration to proceed in two stages, the latter consisting of a quinolinium dihydrate. Two of a number of possible forms might be represented by



CVII



CVIII

The latter form (CVIII) is essentially equivalent to having homoconjugate species, $(H_2O)OH^{(-)}$, in quinoline.

By far the greatest amount of information about these

complexes has been gleaned from studies in acetonitrile (ϵ = 37.5 at 20°C. (97))(129, 132, 179, 268, 495). Kolthoff and co-workers undertook spectrophotometric and conductometric determinations of the dissociation of various acids in acetonitrile and found that except in extremely dilute solution hydrobromic, sulfuric, nitric and hydrochloric acids (HA) dissociated according to (495)

$$2HA \rightleftharpoons H^{(+)} + AHA^{(-)} \quad . \qquad [130]$$

Perchloric acid was reported as completely dissociated in this solvent. In the case of picric acid (HPi), at concentrations smaller than 0.1M, it dissociated into $H^{(+)}$ and $Pi^{(-)}$ while at higher concentrations the data fit the dissociation

$$3HPi \rightleftharpoons H^{(+)} + Pi(HPi)_2^{(-)} \quad . \qquad [131]$$

In a later paper Kolthoff and Chantooni, using a number of techniques and substituted sulfonic acids, determined the constant for equation [130] (neglecting activity coefficients) (268)

$$K_{2(HA)} = \frac{[H^{(+)}]\,[HA_2^{(-)}]}{[HA]^2} \quad , \qquad [132]$$

and the homoconjugation constant for these same acids as well as picric acid from

$$K_{HA_2(-)} = \frac{[HA_2^{(-)}]}{[HA]\,[A^{(-)}]} \quad , \qquad [133]$$

which corresponded to the equation

$$HA + A^{(-)} \rightleftharpoons HA_2^{(-)} \quad . \qquad [134]$$

From these two expressions the simple dissociation constant could be found from the relation

$$K_{HA} = \frac{K_{2(HA)}}{K_{HA_2(-)}} \quad . \qquad [135]$$

The same authors found that the homoconjugation constant for salicylic acid was unexpectedly large in acetonitrile and was of the same order of magnitude as that for benzoic and p-hydroxybenzoic acids. They reasoned that the intramolecular hydrogen bond which stabilizes the salicylate ion was apparently much weaker than the intermolecular hydrogen bond between the carboxyl hydrogen of a second molecule of salicylic acid and the salicylate ion (179). Coetzee and Cunningham on the other hand had studied the ortho effect of a number of substituted benzoic acids in a somewhat different manner; that is, utilizing them as titrants to conductometrically titrate bases in acetonitrile. The stability of the homoconjugate complex with the free acid decreased in the order (132)

benzoic $>$ salicylic $>$ 2,6-dihydroxybenzoic.

In potentiometric and conductometric studies of weak acids (especially phenols) in inert solvents and also in pyridine, mid-point inflections were said to be caused by anion-acid association (10, 272, 273, 283). In pyridine the weaker phenols (ΔHNP $>\sim 140$) were the ones which exhibited steep titration curves but more acidic phenols showed titration curves qualitatively similar to those for carboxylic acids (283). It is further noted that, the larger the size of the anion and the better the shielding of the charge, the greater is the dissociation of the homoconjugate complex into anion and free acid (272). On the other hand stronger acids are able to form more stable hydrogen bonds and therefore more stable acid-anion complexes. In toluene Harlow and Bruss found that m-nitrophenol gave an additional inflection at the titration mid point whereas only the usual inflection was obtained for o-nitrophenol and attributed this to existence of a strong intramolecular hydrogen bond in the latter compound (273). A similar conclusion was reachedfor acetonitrile by using an electromotive-force method in comparative studies among mono-, di- and trinitro substituted phenols. The marked reduction in homoconjugation was noted as the positions ortho to the phenolic group were occupied and was ascribed mainly to stabilization of the acid form by intramolecular hydrogen bonding (129).

Van der Heijde made an extensive examination of anomalous

behaviour in potentiometric titrations of weak oxygen acids in inert and weakly basic solvents including pyridine (189b). He found that non-symmetric plateaus ('hunch') and additional potential drops at one-half and three-quarters neutralization occurred for only certain phenols while normal behaviour was shown by acids like salicylic and benzoic.

If homoconjugation were important for salicylic and anthranilic acids in pyridine and quinoline, equation [130] would most likely have to be modified to include the possibility of ionization equilibria also.

$$2HA \rightleftharpoons (H^{(+)}\ AHA^{(-)}) \rightleftharpoons H^{(+)} + AHA^{(-)} \qquad [136]$$

$$AHA^{(-)} \rightleftharpoons HA + A^{(-)} \qquad [137]$$

On the basis of the spectrophotometric and potentiometric studies conducted here, there is nothing to suggest that acid-base equilibria are in fact complicated by homoconjugative species. Furthermore, in accepting experimental evidence outlined by van der Heijde (189b) and what has been said regarding the importance of intramolecular hydrogen bonding reducing the tendency towards homoconjugation, it is assumed that the existence of species like $AHA^{(-)}$ are not anticipated at least in any significant concentration.

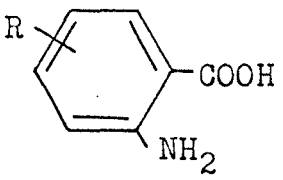
Interpretation of Results

The results of the potentiometric titrations of

anthranilic, salicylic and other acids in pyridine and quinoline have been recorded on page 235 to 255 inclusive.

The Hammett Relationship

When the aromatic ring of benzoic acid (CIX) is substituted by a fixed amino group and a variable substituent R, the close



CIX

proximity of the basic moiety to the carboxyl group may be responsible for changes in acid strength of these substituted anthranilic acids which are reflected in a different reaction constant, rho(ρ), for the Hammett equation as compared to the rho derived for the simple-substituted benzoic acids. If significant interaction between amino and carboxyl groups were to take place, one would predict that some variation in rho should also occur. These interactions may take the form of (39):

(i) electrostatic repulsion,

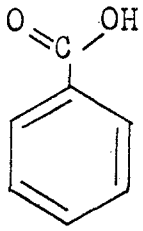
(ii) steric hindrance of resonance or steric hindrance by solvation,

(iii) tautomeric coupling (zwitterion)

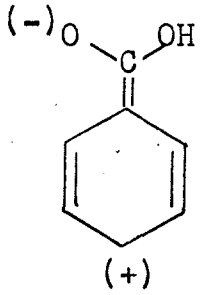
and (iv) intramolecular hydrogen bonding.

Clearly, situation (i) is difficult to imagine here but

might conceivably occur in the case of the ionization of substituted salicylate anions. Steric inhibition of resonance refers to the loss of resonance stabilization of the acid and a consequent increase in the strength of the acid (51a, 52a, 483). This may be seen by examining resonance structures of benzoic acid (CXa, CXb)

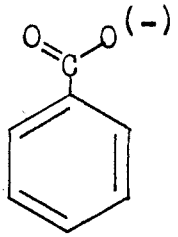


CXa

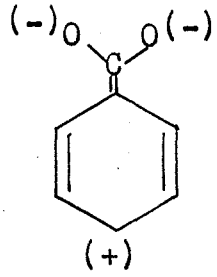


CXb

and the corresponding anion (CXIa, CXb).



CXIa



CXIb

These structures require the carboxyl or carboxylate group to be coplanar with the aromatic ring. The crowding by a bulky ortho group may be relieved by twisting of the carboxyl (carboxylate) group out of the plane of the ring with a corresponding loss of resonance stabilization (CXb and CXIb). Since the anion (CXI) already possesses a negative charge on the carboxylate group, a structure such as CXIb is

relatively unimportant and a strengthening in acidity is, therefore, anticipated. The effect has been thought to explain, at least in part, why all ortho-substituted benzoic acids are stronger than their para isomers in aqueous solution as seen in the data recorded in column four of Table XXXVIII. The influence of ortho-alkoxyl or, more particularly, alkyl substituents is that which is commonly used in discussing the effect since steric interactions here operate in the direction opposite to polar influences. The latter would be expected to have a greater acid-weakening effect than that possessed by the same substituent in the para position (11, 52a, 287, 483).

An inspection of Table XXXVIII for the results obtained in benzene and pyridine solution indicates that factors other than simple resonance destabilization of the molecular acid are operative. For instance, in benzene both o-toluic and o-methoxybenzoic acids are much weaker than their para isomers in keeping with electron-releasing properties of the substituents. Davis and Hetzer thought that the reduced tendency of the o-methoxy acid to combine with diphenylguanidine was a result of stabilization of the acid *via* a chelated structure in which the carboxyl proton is attached to the oxygen of the $-OCH_3$ group (474). In water, hydration or solvent hydrogen bonding of this latter group would likely disrupt the chelate. In pyridine solution only one acid, o-toluic, is weaker than its para analog. This is somewhat

TABLE XXXVIII

A MEASURE OF RELATIVE ACID STRENGTHS OF ORTHO- AND PARA-SUBSTITUTED BENZOIC ACIDS IN DIFFERENT SOLVENTS

Substitutent	$\frac{K_o''}{K_p''}$ [a] (benzene)	$(HNP)_o-(HNP)_p$ [b] (pyridine)	$\frac{K_o}{K_p}$ [c] (water)
OH	326.	291	40.1[d]
NO_2	4.36	32	16.9
I	2.33		
Br	2.03	47	14.1
Cl	1.83	40	11.6
F	1.44		7.49
CH_3	0.814	-41	2.92
OCH_3	0.0568	12	2.75
NH_2	3.14	95	1.96[e]
H	1.00	0	1.00

a Reference (474). K'' is the equilibrium constant determined spectrophotometrically in benzene at 25°C. for the equilibrium A(acid) + B(base) $\rightleftharpoons$ S(salt) where A is o-or p- substituted benzoic acid, B is 1,3-diphenylguanidine and S is the salt formed by the addition of A to B.

b Reference (10). HNP is the half-neutralization potential of o- or p- substituted benzoic acid determined by potentiometric titration in pyridine (assumed to be at room temperature); salicylic acid was given the value $(HNP)_o = 317$, and p-aminobenzoic acid the value $(HNP)_p = 1$.

c Reference (472). K is the aqueous ionization constant of o- or p- substituted benzoic acids.

d Derived from the first ionization constants.

e K_o was equal to 2.7×10^{-5}, a value estimated for equilibrium K_c (see page 26, equation [13] and also reference (12)). K_p was estimated by using the Hammett equation,

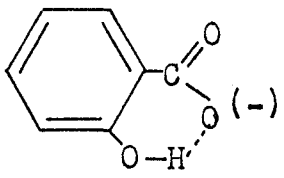
$$\log K_p = \rho\sigma + \log K_o'$$

TABLE XXXVIII Continued

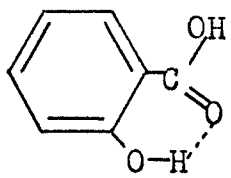
where K_o' is the ionization constant of benzoic acid (6.31×10^{-5}), σ is the Hammett substituent constant for the para - amino group (-0.66) and $\rho = 1.00$.

surprising in view of the result obtained with the methoxy acid. Workers have noted that p-methylbenzoic acid deviated significantly in a Hammett plot with sigma substituent constants by tending toward a greater relative acidity in a variety of nonaqueous solvents including pyridine (9, 10) (see Figure 40). Whether or not interactions, usually described in terms of a non-bonded resonance or hyperconjugation involving the methyl group, are greater in solvents like pyridine will have to remain an open question for now. The variability of σ_p for the methyl group in different media has been noted (22).

The ortho-hydroxy group of salicylic acid produces an acid-strengthening effect in aqueous solution which seems to be disproportionate to its size in contributing to a destabilization of the unionized acid by steric interference of the type of conjugation noted earlier. The common explanation is to assume the presence of an intramolecular hydrogen bond which stabilizes the anion (CXII) relative to the unionized acid (CXIII)(52a, 484, 496).



CXII



CXIII

An alternate suggestion is that in aqueous solution solvation

of the ortho group ($-OH, NO_2$ and $-OCH_3$) may play an important role in enhancing acid strength by increasing the effective size of the substituent (11, 287, 474). The very large increase in acid strength for salicylic acid relative to p-hydroxybenzoic acid is also apparent in benzene and pyridine, solvents in which chelation is expected to occur. Anthranilic acid also exhibits a considerable increase in acidity when compared to its para analog in these two solvents although the degree of enhancement in benzene is not as great as might have been expected. From what has been presented in the introductory discussion it seems clear that a complicating zwitterionic equilibrium would not exist in these systems. It is more reasonable to expect that a chelated anthranilic anion analogous to the generally accepted salicylate ion structure is the cause of this enhancement in acidity.

The ortho effect, which is the term often used to denote the various interactions that may occur when substituents reside on adjacent carbons of the aromatic ring, is a result of several competing and conflicting factors. Dunn and Penner have recently re-emphasized and cautioned that it may be an oversimplification to ascribe influences on the ionization of benzoic acids on any one factor (11).

It was felt that an application of the Hammett relationship to the ΔHNP data for substituted anthranilic acids in pyridine recorded in Table XIII on page 247 might be

instructive in understanding the nature of some of the factors that bring about the apparent deviations or anomalous behaviour in o-substituted benzoic acids and in particular anthranilic acid. In utilizing this treatment it is best to assume at first that the ortho-amino group acts only as a fixed noninteracting substituent whose effect (sum of inductive, field, resonance and steric effects) is constant and can be thought of as been superimposed on the variable effects on acidity caused by changing the substituent R (CIX). Under such conditions the Hammett equation would take the form

$$\triangle HNP = \rho_1 \sigma_1 + (\triangle HNP)_o \quad , \qquad [138]$$

where

$$(\triangle HNP)_o = (HNP)_{AA} - (HNP)_{BA} \quad ; \qquad [139]$$

that is, $(\triangle HNP)_o$ is the difference in the half-neutralization potential of unsubstituted anthranilic acid (AA) and benzoic acid (BA) in pyridine. The Hammett substituent constant (σ_1) is a measure of the electronic effect of the 4- and 5-substituents with reference to the carboxyl group and the reaction constant (ρ_1) indicates the susceptibility of the relative acid strengths ($\triangle HNP$) to ring substitution. An equation of this type, which is applicable to reactions or equilibria involving aromatic compounds bearing a constant ortho substituent, was first suggested by Jaffe (22, 35) and has been applied widely (22, 40, 44, 46, 49).

Before one can accept the conclusion that equation

[138] might correlate the data best, it would be desirable to test how significant the inclusion of the constant parameter, $(\triangle HNP)_o$, is to the correlation. One way to do this is to compare the goodness of fit with that obtained with the simpler Hammett equation

$$\triangle HNP = \rho_1 \sigma_1 \quad . \quad [140]$$

It is profitable that similar data is available for substituted benzoic acids in pyridine solution (10). Streuli and Miron had originally examined the correlation of $\triangle HNP$ with $pK_a(H_2O)$. It should be remembered that $\triangle HNP$ is a measure of relative acidity and, therefore, corresponds to the expression $\log K/K_o$ which is commonly used in correlations of data of ionization constants with substituent constants in aqueous solution. As usual K_o signifies the ionization constant of the unsubstituted or parent acid. From a chemical sense, therefore, it would not be expected that equation [138] would be required when benzoic acids are substituted only in the 3 or 4 position. The pertinent data relating to these latter acids is presented in Table XXXIX while that corresponding to the relative acidities of substituted anthranilic acids determined in this investigation are given in Table XL.

The statistical comparison of the two equations for the two sets of data is summarized in Table XLI. Included is a notation of the equation (to be found in the Appendix) that was used to calculate the parameter in that particular

TABLE XXXIX

APPLICATION OF THE HAMMETT RELATIONSHIP TO THE DIFFERENTIAL HALF-NEUTRALIZATION POTENTIALS (ΔHNP)[a] OF SUBSTITUTED BENZOIC ACIDS IN PYRIDINE

Substituent	ΔHNP[b] (EXPT.) (mv)	σ_1[c]
4-NO_2	-110	0.778
3-NO_2	- 97	.710
3-Br	- 63	.391
3-Cl	- 49	.373
4-Br	- 30	.232
4-Cl	- 25	.227
3-OCH_3	- 5	.115
4-CH_3	3	-.170
3-CH_3	16	-.069
3-OH	23	.121
3-NH_2	38	-.16
4-OCH_3	45	-.268
4-OH	80	-.37
4-NH_2	105	-.66

[a] Reference (10); presumably determined at room temperature.

[b] The reference acid is benzoic; the strongest acid is given the most negative ΔHNP.

[c] Hammett substituent constants based on the ionization of substituted benzoic acids (444). It is clear that σ_1 refers to the electronic influences of the substituents on the carboxyl group; the subscript is used to comply to the classification in Table XL.

TABLE XL

APPLICATION OF THE HAMMETT RELATIONSHIP TO THE DIFFERENTIAL HALF-NEUTRALIZATION POTENTIAL (ΔHNP) OF SUBSTITUTED ANTHRANILIC ACIDS IN PYRIDINE AT 25.0°C.

Substituent	ΔHNP(EXPT.)[a] (mv)	$\pm$ M.D.[a,b] (mv)	ΔHNP (CALC.)[c] $\rho_1\sigma_1 + \rho_2\sigma_2$ (mv)	σ_1[d]	σ_2[d]
4-NO_2	+112.8	7.3	+120.2	0.778	0.710
5-CN	+ 98.2	2.6	+ 96.9	.56	.983[e]
5-Br	+ 59.2	1.1	+ 57.6	.391	.232
5-Cl	+ 57.5	4.0	+ 55.1	.373	.227
5-F	+ 52.9	3.7	+ 44.7	.337	-.026[e]
4-Br	+ 43.1	0.4	+ 39.8	.232	.391
5-OC_6H_5	+ 27.6	2.5	+ 26.8	.252	-.320
4-F	+ 23.4	2.0	+ 15.7	.062	.337
4-CH_3	- 20.3	2.5	- 24.4	-.170	-.069
4-OCH_3	- 33.8	2.8	- 33.5	-.268	.115

TABLE XL Continued

[a] Taken from Table XIII, page 247; the strongest acid is given the most positive $\triangle$HNP value.

[b] Maximum deviation from the mean $\triangle$HNP (EXPT.) value.

[c] ρ_1 and ρ_2 have respective values of 134.4 and 21.99 determined using the normal equations [A.7] (Appendix).

[d] Hammett substituent constants based on the ionization of substituted benzoic acids (444) except where otherwise noted. The subscript 1 refers to the position of the substituent relative to the carboxyl group while 2 refers to its position relative to the amino group.

[e] Substituent constant based on the ionization of substituted anilines (sigma minus, σ^-) (23).

TABLE XLI

A STATISTICAL COMPARISON OF THE HAMMETT EQUATIONS USED IN CORRELATING THE RELATIVE ACIDITY[a] DATA FOR AROMATIC ACIDS IN PYRIDINE

No.	Equation	$S^{b}_{\Delta HNP.\,\sigma_1}$	$\rho_1{}^{c}$	$S_{\rho_1}{}^{d}$	$\rho_2{}^{e}$	$S_{\rho_2}{}^{f}$	$t_{\rho_2}{}^{g}$	$(\Delta HNP)_o{}^{h}$	$S_{(\Delta HNP)_o}{}^{i}$	$t_{(\Delta HNP)_o}{}^{j}$	F^{k}
								Substituted Benzoic Acids[n]			
1.	$\Delta HNP = \rho_1\sigma_1$ [140]	16.4 [A.11][a]	-145.8 [A.2]	11.0 [A.17]							
2.	$\Delta HNP = \rho_1\sigma_1 + (\Delta HNP)_o$ [138]	14.6 [A.14]	-150.6 [A.4] -147^{r}	10.0 [A.19]				8.52 [A.4] 7.82^{r}	3.99 [A.18]	2.14(N.S.)[o] [A.31]	4.56(N.S.) [A.36]
								Substituted Anthranilic Acids[s]			
3.	$\Delta HNP = \rho_1\sigma_1$ [140]	8.52 [A.11]	152.7 [A.2]	6.8 [A.17]							
4.	$\Delta HNP = \rho_1\sigma_1 + (\Delta HNP)_o$ [138]	7.75 [A.14]	143.7 [A.4]	8.2 [A.19]				5.47 [A.4] $-6.5(\pm4.7)^{v}$	3.22 [A.18]	1.70(N.S.)[t] [A.31]	2.90(N.S.) [A.36]
5.	$\Delta HNP = \rho_1\sigma_1 + \rho_2\sigma_2$ [141]	5.22^{w} [A.16]	134.4 [A.7]	6.8 [A.25]	22.0 [A.7]	5.6 [A.26]	3.91(S**)[x] [A.45]				16.1(S**)

TABLE XLI

A STATISTICAL COMPARISON OF THE HAMMETT EQUATIONS USED IN CORRELATING THE RELATIVE ACIDITY[a] DATA FOR AROMATIC ACIDS IN PYRIDINE

[1]	ρ_1[c]	$s\rho_1$[d]	ρ_2[e]	$s\rho_2$[f]	$t\rho_2$[g]	$(\Delta HNP)_o$[h]	$s_{(\Delta HNP)_o}$[i]	$t_{(\Delta HNP)_o}$[j]	F[k]	$r_{\Delta HNP, \sigma_1}$[l]	$R_{\Delta HNP. \sigma_1, \sigma_2}$[m]
						Substituted Benzoic Acids[n]					
	-145.8 [A.2]	11.0 [A.17]								0.975 [A.46]	
	-150.6 [A.4]	10.0 [A.19]				8.52 [A.4]	3.99 [A.18]	2.14(N.S.)[o]	4.56(N.S.)[p,q] [A.36]		
	-147[r]					7.82[r]					
						Substituted Anthranilic Acids[s]					
	152.7 [A.2]	6.8 [A.17]								0.987 [A.46]	
	143.7 [A.4]	8.2 [A.19]				5.47 [A.4] -6.5(±4.7)[v]	3.22 [A.18]	1.70(N.S.)[t] [A.31]	2.90(N.S.)[p,u] [A.36]		
	134.4 [A.7]	6.8 [A.25]	22.0 [A.7]	5.6 [A.26]	3.91(S**)[x] [A.45]				16.1(S**)[y]	0.578[z] [A.46]	0.994 [A.55]

TABLE XLI Continued

[a] The figures in [ ] refer to the equation found in the Appendix that was used to calculate the parameter of that particular column. The calculated value is placed immediately above the equation number.

[b] Standard error of estimate.

[c] Slope or first partial regression coefficient (reaction constant).

[d] Standard error or deviation in the slope or first partial regression coefficient.

[e] Second partial regression coefficient (reaction constant).

[f] Standard error in the second partial regression coefficient.

[g] t-statistic: tests whether the second partial regression coefficient, ρ_2, is significantly different from zero. S** means that the value for ρ_2 is (highly) significant and different from zero at the 99.5% confidence level.

[h] Intercept.

[i] Standard error in the intercept.

[j] t statistic: tests whether the intercept, $(\triangle HNP)_o$, is significantly different from zero. N.S. means that the value for the intercept is not (significant) different from zero at the 95% confidence level.

[k] Variance (F) ratio.

[l] Simple linear correlation coefficient between the two variables $\triangle HNP$ and σ_1.

TABLE XLI Continued

[m] Multiple linear correlation coefficient for the variables $\triangle HNP$, σ_1 and σ_2.

[n] From data recorded in Table XXXIX and originally determined by Streuli and Miron (10).

[o] Critical values: $t_{0.05(n-2)} = t_{0.05(12)} = 2.18$
$t_{0.10(12)} = 1.78$

[p] F ratio compares the mean square for reduction in the deviations due to the introduction of the intercept $(\triangle HNP)_o$ with the mean square for deviations from single regression (error) in which $(\triangle HNP)_o \neq 0$. N.S. indicates that the improvement is not significant at the 95% confidence level and that the data may be just as well represented by the simple Hammett equation (i.e., $(\triangle HNP)_o = 0$).

[q] See Table A.II in the Appendix.

[r] Reference (9).

[s] This investigation from data recorded in Table XL.

[t] Critical values: $t_{0.05(n-2)} = t_{0.05(8)} = 2.31$
$t_{0.10(8)} = 1.86$
$t_{0.20(8)} = 1.40$

[u] See Table A.III in the Appendix.

[v] $(\triangle HNP)_o$ experimental; equals the mean of three differences. $HNP_{AA} - HNP_{BA}$ (equation [139]). See Table XV on page 253; ± maximum deviation.

[w] $s_{\triangle HNP.\sigma_1,\sigma_2}$.

TABLE XLI Continued

[x] Critical values: $t_{0.05(n-2)} = t_{0.05(8)} = 2.31$

$t_{0.005(8)} = 3.83$

$t_{0.001(8)} = 5.04$

[y] F ratio compares the mean square for the reduction in the deviations due to the introduction of the term $\rho_2 \sigma_2$, with the mean square for the deviations from double regression (error). S** indicates that the improvement is highly significant (at the 99.5% confidence level) and that the data is best represented by the extended form of the Hammett equation. See Table A.III in the Appendix.

[z] Linear correlation coefficient between the two substituent constants σ_1 and σ_2 (r_{σ_1, σ_2}).

column. The calculated value is placed immediately above the equation number. The approach used and the details of the statistical treatment have been presented in considerable detail in the Appendix and no further comments will be made here. In comparing the standard errors of estimate for the lines constrained to pass through the origin (lines 1 and 3) with those possessing an intercept (lines 2 and 4), it is seen that for both the data of Streuli and Miron and that obtained in this study an improvement is apparent when the latter parameter is included. However, when the t statistic test is used in examining the significance of having an intercept, it is seen that at the 95% confidence level $(\triangle HNP)_o$ is not different from zero in both cases. It is interesting to note (footnotes o and t, Table XLI) that $(\triangle HNP)_o$ differs from zero at a confidence level which is higher for the data as applied to equation [138] of line 2 than that applied to the similar expression in line 4. This is quite possible since the value of the intercept derived from the latter equation is not even twice its standard deviation. Furthermore, the number of observations in compounds utilized by Streuli and Miron were four more than used in the present study and, consequently, the degrees of freedom associated with the t statistic for the substituted anthranilic acids is much lower. This causes the critical value at the selected confidence levels to be much higher. An analysis of variance to the two sets of

data produce F ratios that confirm the results of the t statistic.

In Figures 40 and 41 the data from the corresponding Tables XXXIX and XL are depicted graphically. The drawn lines in both cases were obtained by fitting the data to equation [138]. For the substituted benzoic acids the derived reaction constant has a value $\rho_1 = -150.6 \pm 10.0$ mv/σ_1 while from the data of the anthranilic acids it is $\rho_1 = 143.7 \pm 8.2$ mv/σ_1. The signs of ρ are different in the two cases since opposite conventions were adopted. The strongest acid in the benzoic acid series was given the most negative ΔHNP whereas a similar acid in the anthranilic acid series bears the most positive ΔHNP value. The slopes are seen to be the same within experimental error which would give the indication that the ortho-amino group is in fact a noninteracting substituent. Both of the plots in Figures 40 and 41 point out clearly that ΔHNP is a reasonably good measure of the electronic influences on the carboxyl group produced by the m and p substituents. However, if one restricts attention to Figure 41, which represents the system studied in the present investigation, a few acids such as 4-fluoro-, 5-fluoro-, and 5-cyano- and possibly 4-nitroanthranilic deviate from the line. It would not be possible to give a reasonable explanation for these deviations based entirely on solvation or other effects on substituents which might differ in pyridine solution as

FIGURE 40. The simple Hammett relationship: the correlation of the differential half-neutralization potentials (ΔHNP, EXPT.) of substituted benzoic acids in pyridine with sigma (σ_1) substituent constants. The reaction constant, ρ_1, is equal to -150.6 mv/σ_1. Data are taken from Table XXXIX.

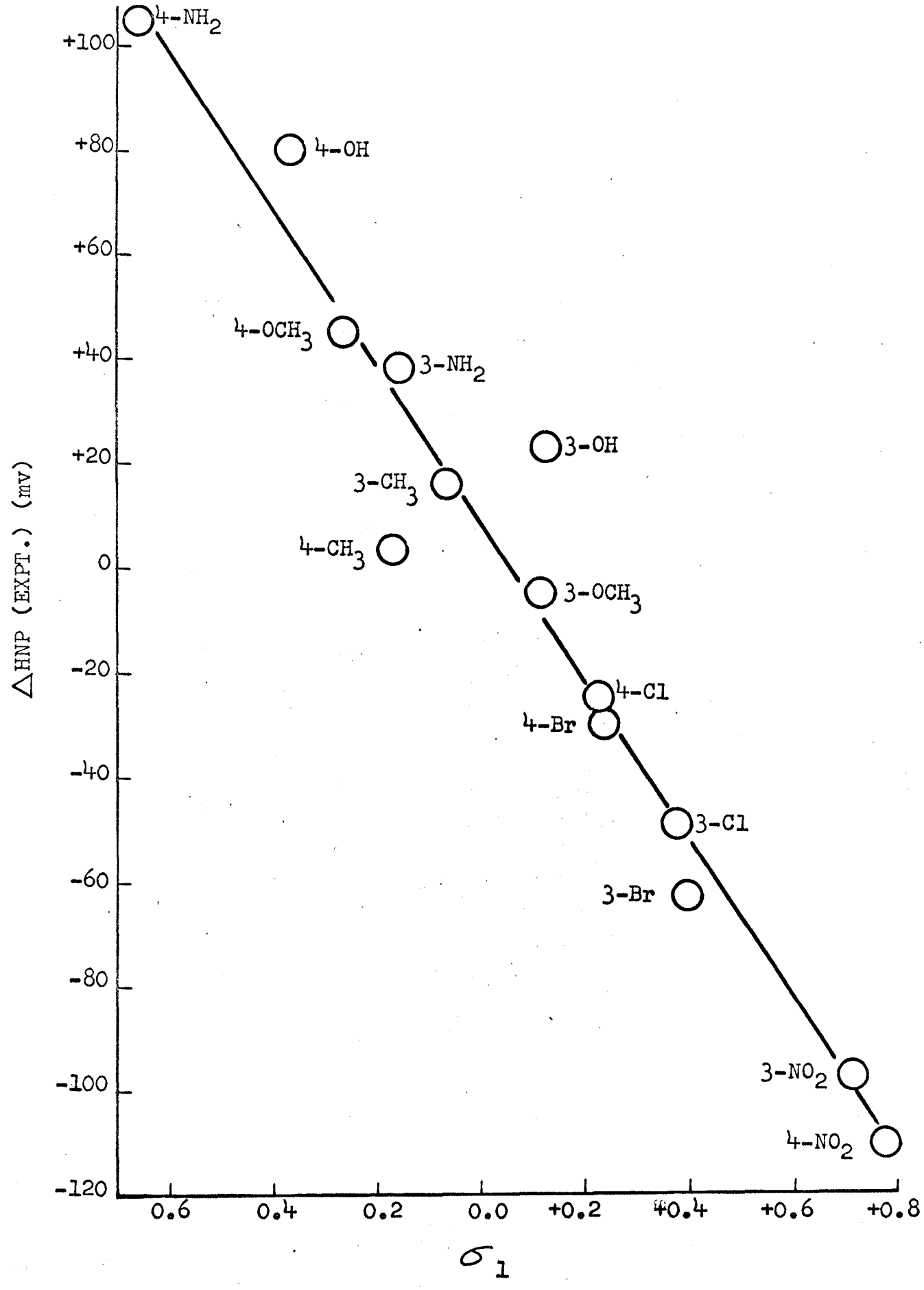
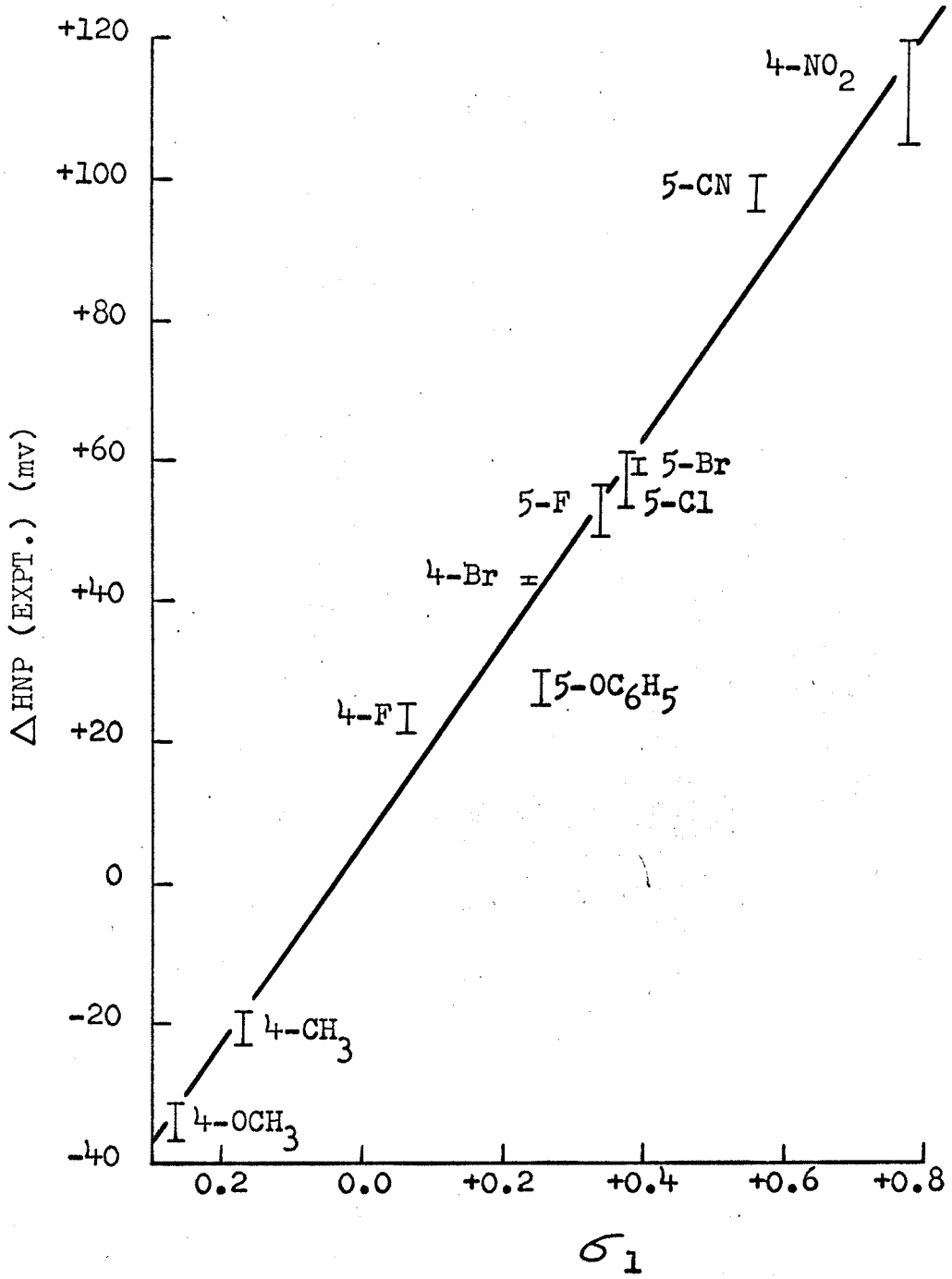

4-NH2
4-OH
4-OCH3
3-NH2
3-OH
3-CH3
4-CH3
3-OCH3
4-Cl
4-Br
3-Cl
3-Br
3-NO2
4-NO2
+100
+80
+60
+40
+20
0
-20
-40
-60
-80
-100
-120
0.6
0.4
0.2
0.0
+0.2
+0.4
+0.6
+0.8
ΔHNP (EXPT.) (mv)
σ1

FIGURE 41. The simple Hammett relationship: the correlation of the differential half-neutralization potentials ($\triangle$HNP, EXPT.) of substituted anthranilic acids in pyridine at 25.0°C. with sigma (σ_1) substituent constants. The reaction constant, ρ_1, is equal to 143.7 mv/σ_1. Data are taken from Table XL.[1]


+120
+100
+80
+60
+40
+20
0
-20
-40
Δ HNP (EXPT.) (mv)
4-NO2
5-CN
5-Br
5-Cl
5-F
4-Br
5-OC6H5
4-F
4-CH3
4-OCH3
0.2
0.0
+0.2
+0.4
+0.6
+0.8
σ1

compared in aqueous solution in which the substituent constants were originally determined.

If electronic interaction were possible between the carboxyl and amino groups, it would be expected that the substituents in the 4 or 5 position of anthranilic acid could have their electronic influences transmitted to the carboxyl group directly through the aromatic nucleus and indirectly through the amino group *via* the intramolecular hydrogen bond. Jaffe proposed that an extended form of the Hammett equation might be applicable for reactions or equilibria of compounds in which an intramolecular hydrogen bond exists (47). Such an equation here would become

$$\Delta HNP = \rho_1\sigma_1 + \rho_2\sigma_2 \quad , \qquad [141]$$

in which the direct and indirect effects are considered to be additive. The first term of equation [141] represents the normal influence of the substituent on the carboxyl group in a simple Hammett equation. The parameter, ρ_2, measures the susceptibility to ionization of the carboxyl group by electronic effects transmitted through the chelate bond. The constant, σ_2, refers to the substituent effect on the amino group and thus the requirement is that this should be a Hammett sigma-minus (σ^-) substituent constant. With the data available, only in the case of 5-cyano- and 5-fluoro-anthranilic acids are sigma-minus values significantly different from the ordinary sigma constants and this has been noted in Table XL. Jaffe has cautioned that correlations

using equation [141] may be spurious if σ_1 and σ_2 are not independent since equation [140] is only a special case of equation [141]. Thus, if σ_1 and σ_2 are linearly related

$$C\sigma_1 = \sigma_2 \quad , \qquad [142]$$

and the data can be represented by

$$\Delta HNP = \rho_1 \sigma_1 \quad , \qquad [143]$$

then a fit will also be obtained for the equation

$$\Delta HNP = \rho_1 \sigma_1 + \rho_2 \sigma_2 \qquad [144]$$

which becomes

$$\Delta HNP = (\rho_1 + C\rho_2)\sigma_1 \qquad [145]$$

$$= \rho\sigma_1 \quad . \qquad [146]$$

Jaffe further proposed that the most efficient use of equation [141] comes about when the degree of linear correlation as measured by the correlation coefficient is relatively small and never greater than 0.9. The linear correlation coefficient, r_{σ_1, σ_2}, for the ten pairs of substituent constants required for use in this work was determined and found to have the value of 0.578 which makes them most suitable in applying the correlation of the data to equation [141].

Returning once more to Table XLI the statistical treatment applied to equation [141] is recorded in line 5. The two partial regression coefficients which represent ρ_1 and ρ_2 were calculated and corresponding values of 134.4 $\pm$ 6.8 mv/σ_1 and 22.0 $\pm$ 5.6 mv/σ_2 determined. On the basis of the following four and perhaps five statistical factors,

it is clear that equation [141] does represent the data more significantly than the simple equation [140].

(i) the smaller standard error of estimate for equation [141] compared to that obtained with equation [140],

(ii) the highly significant result for the t statistic which rejects the hypothesis that $\rho_2 = 0$,

(iii) the highly significant result for the variance ratio which indicates that the reduction in the sum of the squares due to the introduction of the term $\rho_2\sigma_2$ is meaningful,

(iv) the value of ρ_2 is about four times its standard deviation

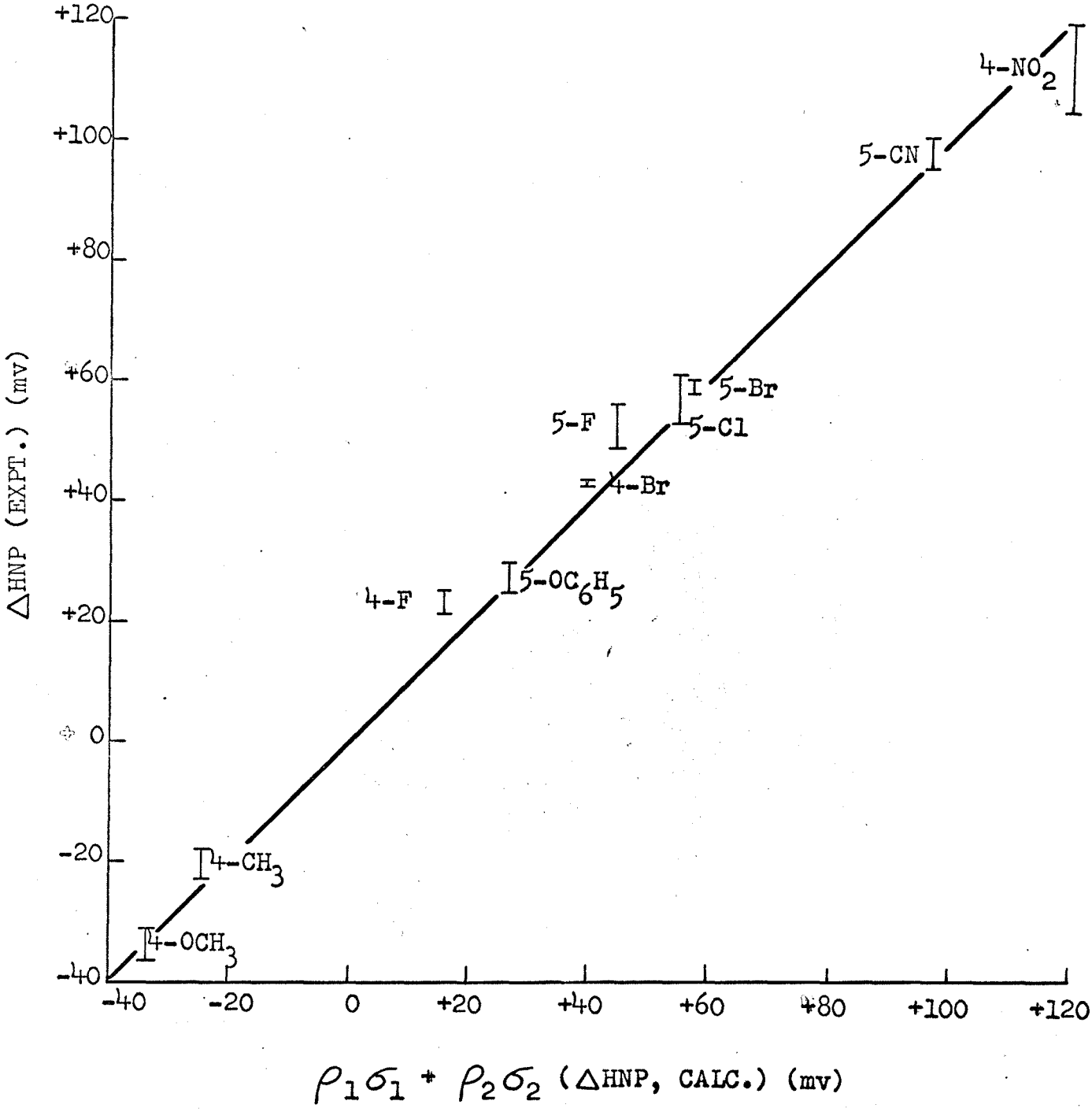
and (v) the larger multiple linear correlation coefficient (0.994) when compared to the simple linear correlation coefficient (0.987).

The importance of the last factor, however, is only tentative since the comparison really requires critical values at various confidence levels which are not readily available in the case of the multiple linear correlation coefficient for probabilities of greater than 99 percent. The results are in agreement with the prediction that the reaction centre (carboxyl group) is hydrogen bonded to the neighbouring amino group. This condition leads to an enhancement of acidity of anthranilic acids in pyridine solution (see Figure 39). By using values of ρ_1 and ρ_2 derived from the

normal equations ([A.7] in the Appendix) a new series of calculated $\triangle$HNP values were obtained and these are also recorded in Table XL. The experimental $\triangle$HNP were then plotted against these calculated $\triangle$HNP values as shown in Figure 42. The line was drawn on the basis of fitting the data to equation [141].

The values of ρ_1 and ρ_2 give a quantitative measure of the relative importance that the direct and indirect paths will have in transmitting the electronic influences of the substituent to the carboxyl group of anthranilic acid. In this investigation the value ρ_2/ρ_1 was found to be 0.16 which indicates that the effect of the substituent on the acid strength of the carboxyl proton via the intramolecular hydrogen bond is about one fifth as large as the effect directly transmitted through the carboxyl carbon. This result compares with $\rho_2/\rho_1 = 0.4$ in a similar study of relative acidities of substituted salicylic acids in benzene (11) and with a value of 0.1 for the same acids in aqueous solution (287). The greater proportion of electronic influence by the indirect path of salicylic acid (in this case via the phenolic hydrogen bond) in benzene is to be expected since salicylic acid should intrinsically possess a stronger intramolecular hydrogen bond in similar solvents (see Figure 39) and from the fact that benzene has a dielectric constant 5 to 6 times smaller than pyridine at room temperature (97).

FIGURE 42. The extended Hammett relationship: the correlation of the differential half-neutralization potentials (ΔHNP, EXPT.) of substituted anthranilic acids in pyridine at 25.0°C. with a linear combination of sigma (σ_1 and σ_2) substituent constants (i.e., ΔHNP, CALC.). The regression coefficients (reaction constants) ρ_1 and ρ_2 have the values 134.4 mv/σ_1 and 22.0 mv/σ_2 respectively. Data are taken from Table XL.


+120
+100
+80
+60
+40
+20
0
-20
-40
ΔHNP (EXPT.) (mv)
4-NO2
5-CN
5-Br
5-Cl
5-F
4-Br
5-OC6H5
4-F
4-CH3
4-OCH3
-40
-20
0
+20
+40
+60
+80
+100
+120
ρ1σ1 + ρ2σ2 (ΔHNP, CALC.) (mv)

Finally, it may be worthwhile to reinterpret the nature or significance of the first term (i.e., $\rho_1\sigma_1$) of equation [141]. It has been suggested that the total effect of a substituent on the acidity of the carboxyl hydrogen for acids capable of possessing intramolecular hydrogen bonds should involve in fact three terms (11, 287). The Hammett relationship would then take the form

$$\Delta HNP = \rho_{O\text{-}H}\sigma_1 + \rho_{O\ldots H}\sigma_1 + \rho_2\sigma_2 . \quad [147]$$

The last term, $\rho_2\sigma_2$, accounts for the variations in acidity of the amino hydrogens or in other words, describes only that portion of the influence of the hydrogen bond on the acidity that is transmitted through the amino group rather than the entire hydrogen-bond effect. The first term, $\rho_{O\text{-}H}\sigma_1$, corresponds to the common substituent effect on the carboxyl proton found in m-and p-substituted benzoic acids. The subscript symbol, O-H, is meant to indicate the hydroxyl hydrogen of the carboxyl group. A further additive term, $\rho_{O\ldots H}\sigma_1$, describes the influence of the variable substituent on the basicity of the anthranilate ion. This takes into account variations in electron density on the carboxylate group caused by a substituent which in turn affects the acidity because this electron density influences the intramolecular hydrogen-bond strength. Here the subscript, O...H, is used to signify the hydrogen donated by the amino group to the carboxyl oxygen. Since the first two terms represent processes occurring at the carboxyl group, the same

substituent constant (σ_1) applies to both. The values of $\rho_{O\text{-}H}$ and ρ_2 are understandably positive but $\rho_{O\ldots H}$ will be negative since any electronic effect which makes the carboxyl proton (or amino hydrogen) more acidic will make the carboxylate group less basic and thereby weaker the chelation. Equation [147] may be rewritten

$$\Delta HNP = (\rho_{O\text{-}H} + \rho_{O\ldots H})\sigma_1 + \rho_2\sigma_2 \qquad [148]$$

which is similar to equation [141] where

$$\rho_1 = \rho_{O\text{-}H} + \rho_{O\ldots H} \quad . \qquad [149]$$

It is clear that the value ρ_1 will be less than $\rho_{O\text{-}H}$ and that the magnitude of this latter reaction constant should be very similar to that representing the simple Hammett equation

$$\Delta HNP = \rho_1\sigma_1 \qquad [140]$$

which was found to adequately correlate the data for the relative acidities of substituted benzoic acids in pyridine (10) (Table XLI). By introducing into equation [149] the values of ρ_1 and $\rho_{O\text{-}H}$ calculated from regression equations described in lines 5 and 1 of Table XLI and shown to be respectively 134.4 and 145.8 (using the same sign convention for both) one obtains

$$\rho_{O\ldots H} = \rho_1 - \rho_{O\text{-}H} = -11.4 \quad . \qquad [150]$$

This is an indication of the amount of cancellation that occurs in $\rho_{O\text{-}H}$ which tends to diminish the importance of the substituent effect by way of the normal or direct path

in comparison with transmission through the intramolecular hydrogen bond or indirect route. It seems also, from the absolute magnitude of $\rho_{O...H}$ and ρ_2 that in the contribution to the total hydrogen-bond effect made by the substituent, the electronic pathway through the amino group is about twice as important as the anthranilate basicity.

Comparison of Acid Strengths of Anthranilic Acids in Pyridine and Aqueous Solutions

From what has been presented above and from what is known about complicating zwitterionic equilibria in aqueous solution (12), one might expect to find any correlation between the relative acidity of substituted anthranilic acids in pyridine (ΔHNP) with the ionization constants in aqueous solution (in the form pK_2) to be spurious. From the standpoint of the relative acidities in pyridine the presence of an intramolecular hydrogen bond seems firmly established. Because of the relatively small contribution made by the indirect effect on acidity, however, it would not be expected that a ΔHNP *vs.* pK_2 plot would deviate seriously from linearity if the aqueous values were derived from a system in which no zwitterion and no other strong amino-carboxyl group interaction existed in water solution. In contrast, experimental results for the relative acidities of substituted salicylic acids in benzene showed that the electronic influence of a substituent on the carboxyl-proton acid strength by way of the phenolic hydrogen-bonded path

was almost one half as large as the direct effect through the carboxyl group (11). Such being the case, a linear correlation between $\triangle$HNP values in benzene with $pK_a(H_2O)$ values which are available for the same substituted salicylic acids (287) was not anticipated. In fact, a test was conducted and the plot of $\triangle$HNP *vs.* $pK_a(H_2O)$ exhibited a curvilinear correlation indicating that a relative enhancement in acidity occurred for salicylic acids in benzene solution.

The data that is required for the correlation of acid strengths of substituted anthranilic acids in the two solvents are presented in Table XLII. The figures in the last column head '%Z' represent the degree of zwitterion in aqueous solution relative to the nonpolar neutral acid species. The equation

$$\log \frac{K_Z}{K_Z^o} = \rho_A \sigma_A - \rho_B \sigma_B \quad , \qquad [151]$$

which was deduced by Leggate and Dunn, was used in determining the value of K_Z (12). Here K_Z and K_Z^o represent the equilibrium constants between the zwitterionic form of the substituted and unsubstituted anthranilic acid (Z) and the nonpolar neutral form (HA). For example,

$$K_Z = \frac{[Z]}{[HA]} \quad . \qquad [152]$$

The equilibria involved were shown by the scheme in equation [13] on page 26 and are repeated below.

TABLE XLII

CORRELATION OF THE RELATIVE ACIDITIES OF SUBSTITUTED ANTHRANILIC ACIDS IN PYRIDINE ($\triangle$HNP) WITH THE NEGATIVE LOGARITHMS OF THE IONIZATION CONSTANTS (pK_1 AND pK_2) IN WATER[a]

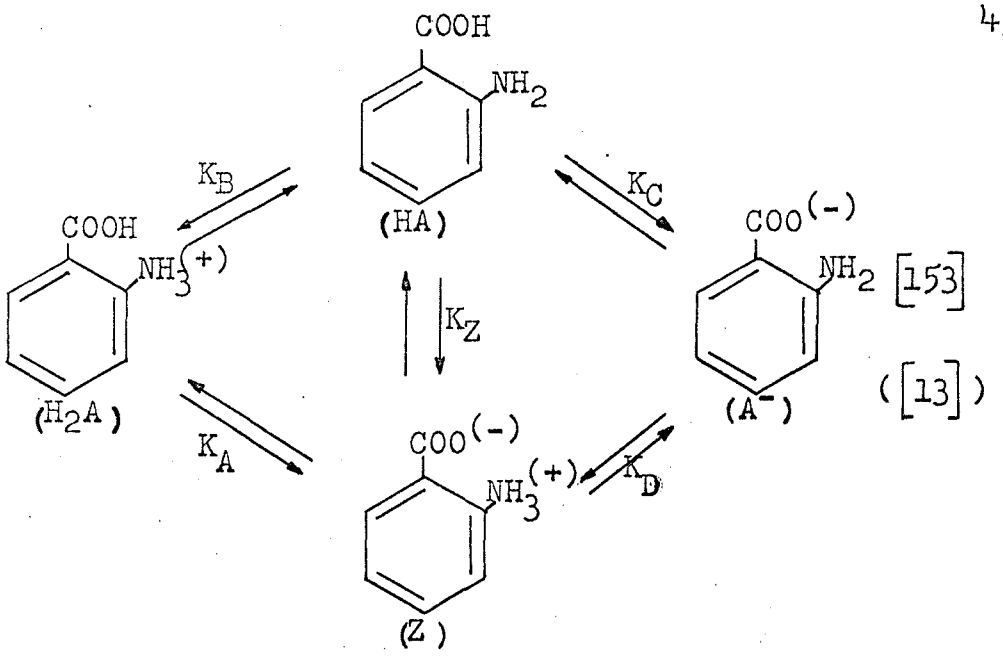
Substituent	$\triangle$HNP[b] (C_5H_5N) (mv)	pK_1[c] (H_2O)	pK_2[c] (H_2O)	Z%[d]
4-NO_2	+112.8	0.65	3.70	2
5-CN	+ 98.2			
5-Br	+ 59.2	1.60	4.41	36
5-Cl	+ 57.5	1.69	4.35	27
5-F	+ 52.9	2.03	4.82	68
4-Br	+ 43.1	1.24	4.37	8
5-OC_6H_5	+ 27.6	2.34	4.88	94
4-F	+ 23.4	1.42	4.60	9
4-CH_3	- 20.3	2.35	5.07	55
4-OCH_3	- 33.8	2.06	4.88	22

a Both sets of measurements made at 25.0°C.

b From Table XL, column $\triangle$HNP (EXPT.).

c Reference (12).

d Represents the degree of zwitterion (Z%) in aqueous solution relative to the nonpolar neutral acid species. See text for details of calculation.



[153]

([13])

The reaction constants, ρ_A and ρ_B, were defined for the reactions involving the ionization of the -COOH and $-NH_3^{(+)}$ groups respectively and had the corresponding values of 0.751 and 3.111. The Hammett constants for a given substituent, σ_A and σ_B, were considered with reference to the -COOH (or $COO^{(-)}$) and the $-NH_3^{(+)}$ (or $-NH_2$) groups respectively. They are identical to the values σ_1 and σ_2 as given in Table XL. The value of K_Z^o had been calculated by Leggate and Dunn to have a range of 0.4 - 1.0. The latter limit was used here in estimating K_Z values from equation [151]. Once these values were available an indication of percent zwitterion (Z%) was obtained from equation [152]. Since the higher value of K_Z^o was utilized in the calculations, the figures for Z% can be looked upon as indicating maximal values and the true values may indeed

be considerably smaller. The experimental ionization constants, K_1 and K_2, are related to the 'microscopic' or 'true' equilibrium constants K_A, K_B, K_C and K_D by the equations,

$$K_1 = K_A + K_B \qquad [154]$$

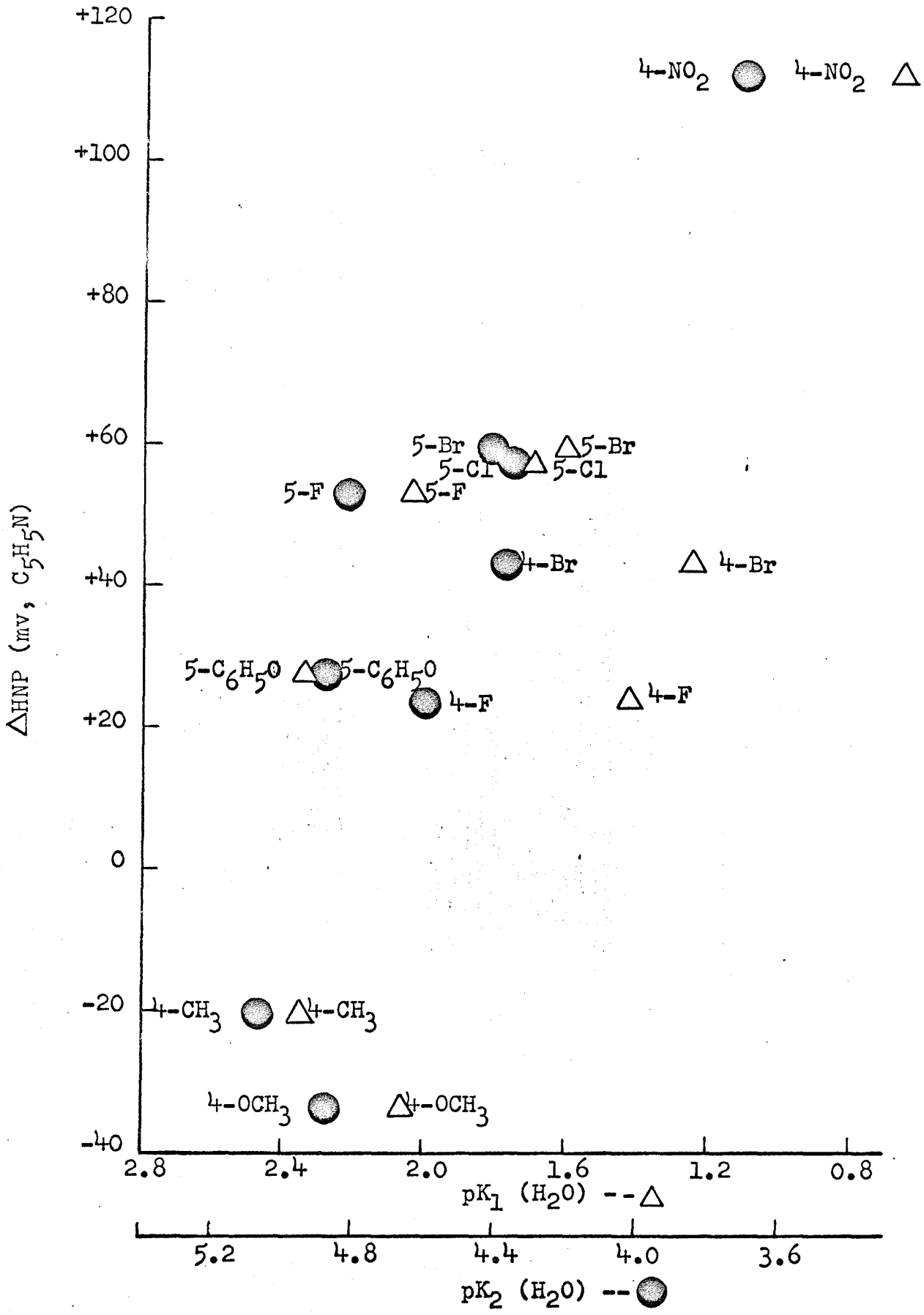
and

$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D} \qquad [155]$$

The correlation of $\triangle$HNP with both pK_1 and pK_2 is shown graphically in Figure 43. The scatter diagram associated with pK_1 values is included only for comparison. It was not expected that any correlation would be apparent with the $\triangle$HNP as derived in this study since the ionic equilibrium represented by K_1 in water has no counterpart in the basic-nonaqueous system. The second equilibrium constant, K_2, is the one most readily available experimentally that might satisfy the requirement for comparative purposes with $\triangle$HNP. What would have been more appropriate is to make the comparison with the equilibrium denoted by the constant K_C in equation [153]. Although there is considerable scatter in the plot of $\triangle$HNP *vs.* pK_2, an inspection of Table XLII shows that if three of the acids that have the largest Z% values are disregarded (*i.e.*, 4-methyl-, 5-phenoxy- and 5-fluoroanthranilic acids), then a linear correlation which is surprisingly good becomes apparent in Figure 43.

An examination of equation [155] may be used to show

FIGURE 43. A graphical correlation of the relative acidities of substituted anthranilic acids in pyridine, designated by ΔHNP (mv, C_5H_5N), with the acid strengths, pK_1 and pK_2, in water; all data was measured at 25.0°C. Data are taken from Table XLII.


+120
+100
+80
+60
+40
+20
0
-20
-40
ΔHNP (mv, C_5H_5N)
4-NO_2
4-NO_2 △
5-Br
△5-Br
5-Cl
△5-Cl
5-F
△5-F
4-Br
△ 4-Br
5-C_6H_5O
△5-C_6H_5O
4-F
△4-F
4-CH_3
△4-CH_3
4-OCH_3
△4-OCH_3
2.8
2.4
2.0
1.6
1.2
0.8
pK_1 (H_2O) --△
5.2
4.8
4.4
4.0
3.6
pK_2 (H_2O) --●

what form the Hammett equation would have to take in utilizing the true ionization constants. This expression may be rearranged to give

$$K_2 = \frac{K_C K_D}{K_C + K_D} \qquad [156]$$

where K_C and K_D represent the equilibria described in equation [153]. For the unsubstituted acid equation [156] becomes

$$K_2^o = \frac{K_C^o K_D^o}{K_C^o + K_D^o} \quad . \qquad [157]$$

By taking logarithms the ratios of the two expressions one obtains

$$\log \frac{K_2}{K_2^o} = \log \frac{K_C}{K_C^o} + \log \frac{K_D}{K_D^o} - \log \left(\frac{K_C + K_D}{K_C^o + K_D^o}\right) \quad . \qquad [158]$$

The right-hand side of equation [158] cannot be further simplified because the third term contains a sum of the two microscopic-equilibrium constants. This last equation helps to point out further that the aqueous system does not represent the conditions that are present in pyridine. It is apparent that no simple quantitative correlation exists between the acid strengths in water and the nonaqueous solvent. Because of this aqueous ionization constants (K_2) are not useful in estimating the relative order of acidities in pyridine.

Titration Equations and Ionization

In determining the half-neutralization potentials of

the various anthranilic acids in the potentiometric titrations, data were naturally recorded by indicating the potential reading as each increment of titrant was added to the solution. The availability of this information enables one to apply the data to the common titration equations in an attempt to possibly describe qualitatively the extent of ionization or dissociation of the substituted anthranilic acids in the basic solvent. The application to nonaqueous solutions of the titration equations that were originally derived for aqueous acid-base systems is still open to criticism (160, 275, 280, 497). Because of this, any observations made here will necessarily involve tentative interpretations and will really have to await more elaborate quantitative examination.

In one of the papers in the classic series co-authored by Hall, Werner and Conant, the first two workers undertook a study of potentiometric titration and dilution curves of bases dissolved in glacial acetic acid (497). They first plotted the recorded electromotive-force values against $\log \frac{X}{1-X}$ where X was the fraction of base neutralized by perchloric acid. This is the theoretical equation that would commonly be followed by relatively weak bases in aqueous solution. However, for all the bases tested in acetic acid deviations from the expected linear relationship were considerable and the lines showed a curvature which steadily increased with the strength of the base. It seemed

evident that, when titrated, the bases did not appear to act as do weak electrolytes in water but rather the curves were somewhat similar to those given by strong bases when titrated by strong acids in aqueous solution. Another plot, this time of potential *vs.* log(1-X) (*i.e.*, the unneutralized fraction), was attempted. All the bases except two exhibited curvature in the titration curves, a condition which increased as the base became weaker. The data from the titration of guanidine and diethylaniline did display linear behaviour that was ascribed to the 'strong base' type and almost theoretical slopes of 59 mv per unit change of log (1-X) were obtained. Hall and Werner recognized that a possible inference from the results would be that the diethylanilinium and guanidinium acetates were completely dissociated while those of the other bases were only partially dissociated but this view was difficult to reconcile in light of the rather low dielectric constant of acetic acid. They then turned their attention to a dilution study in which (pH) HAc of the pure bases in acetic acid were measured as the solutions were diluted and found, in contrast to the titration-equation results, that these two bases did in fact correspond quantitatively to the behaviour of a typically weak electrolyte. They advanced arguments in favour of the constancy of the liquid-junction potential when the concentration and composition of the solutions were varied. Their suggestion for explaining the anomalous behaviour exhibited by bases in titration curves was perhaps

a consequence of the large effect of interionic attraction on the activity coefficients of the ions in the low dielectric-constant solvent and to differences in the extent of solvation of the various ionic and molecular species present in solution. It was thought probable that, in the case of the stronger bases, association with the solvent was virtually complete but incomplete for the weaker bases.

Later Kolthoff and Bruckenstein clarified the apparent paradox described above in one of their own series of important papers of acid-base equilibria in glacial acetic acid (160). Equations were derived for the hydrogen ion for solutions of bases under different conditions. They showed that only if K_{BHClO_4} was equal to K_B would the plot involving the term log (1-X) be expected to yield a straight line. Here K_{BHClO_4} and K_B refer to the over-all dissociation constants of the perchlorate salt of the base and of the base itself respectively. They further suggested that no relationship existed between K_B and K_{BHClO_4} which would yield linear plots in curves using log $\frac{X}{1-X}$ and this was why Hall and Werner did not find an acid-base system which satisfied the relation. This interpretation was to be preferred over the one the latter workers ascribed to large activity-coefficient effects.

Schaap *et al.* have presented a rather detailed description of the electrochemistry in anhydrous ethylenediamine and have included a discussion of the relation of the shapes

of the neutralization curves (prior to the equivalence point) to the relative strengths of the salt formed during the titration and of the acid titrated (105). They maintained the same viewpoint advanced by Kolthoff and Bruckenstein and suggested further that the titration curves would resemble those of weak acids in water if the acid were more highly associated in solution than the salt which is a situation more commonly encountered.

Marple and Fritz conducted potentiometric studies of acid-base equilibria in tert-butyl alcohol with a constant ionic strength maintained by addition of tetrabutylammonium perchlorate to reduce activity-coefficient variations (259). Potential measurements were taken as a function of acid concentration for a number of acids including perchloric, picric, hydrochloric and hydrobromic acids. At high concentrations (10^{-3} to 10^{-4} M) curvature in the plots was apparent and was attributed mainly to incomplete dissociation of the acids. Acidities of phenol, 2- and 4-nitrophenols were also studied by plotting log (acid/salt) as a function of potential and the curves were found to have slopes of 66, 59 and 59 mv respectively. This suggested that the principal equilibria involved in the dissociation of an acid and its salt lead to similar titration characteristics to those found for a weak acid in aqueous systems but that the salts may not be highly dissociated in the alcoholic solvent. Marple and Fritz have also shown that, in tert-butyl alcoholic solution

of a weak acid (HX) and its corresponding salt (Bu_4NX), the acidity is determined by both the equilibria (220, 259)

$$HX \rightleftharpoons H^{(+)} + X^{(-)} \qquad [159]$$

and

$$Bu_4NX \rightleftharpoons Bu_4N^{(+)} + X^{(-)} \qquad [160]$$

Coetzee and Padmanabhan titrated solutions of 1, 3-diphenylguanidine (B) with perchloric acid in the acetonitrile solvent (161). They suggested that a plot of the glass electrode potential against the usual quantity $\log \left(\frac{P}{100-P}\right)$ (where P = percent of B titrated), which should describe characteristics of a typically weak base-strong acid titration, would be linear with a slope of 59 mv provided that:

"(i) the electrode responds to hydrogen-ion activity in a reversible manner,

(ii) neither the base nor its conjugate acid (salt) is involved in additional reactions,

(iii) the ratio of the activity coefficients of the base and its salt does not change significantly during the titration

and (iv) the algebraic sum of all liquid junction potentials involved does not change significantly during the titration."

Deviations from linearity in certain instances were seen to be due to hydrogen-bonded complexes of the nitrogen bases with their conjugate acid, $BHB^{(+)}$ (128, 129, 498).

It is also interesting to note the results of a recent paper describing the response of cation-sensitive glass

electrodes to alkyl-substituted ammonium ions in aqueous solution (499). It was found that with increasing ion size, there was a decrease in electrode selectivity and the theoretical Nernst function was not fully developed for ions larger than ammonium. The mono-alkyl substituted ammonium ions, however, exhibited a rather good ion function. At a temperature of 30.0°C. and pH of 8.89, the slope of the linear portion of the potential vs. logarithm of concentration plot ranged from 55.7 to 22.0 for the methylammonium to trimethylammonium cations respectively. Equilibration times for the cell potential varied from a few seconds for ammonium samples to twenty hours for the larger cations tested.

Finally, Cluett examined the titration characteristics of a number of phenylureas and benzoic, hydrochloric and perchloric acids in n-butylamine by titrating them with tetra-n-butylammonium mixed base in benzene-methanol (280). He fitted the data to the usual forms of the titration equations, that is, $\log \frac{X}{1-X}$ and $\log \frac{1}{1-X}$, where X is the fraction of acid neutralized on the basis of the amount of titrant added. For the most acidic ureas, the theoretical relationship between the potential and the logarithm of the ratio of the concentration of the conjugate base of the acid and the free acid was linear and lines having slopes of 68, 50 and 52 mv were obtained. A parallel examination using ultraviolet absorption spectra showed that even the

most acidic urea was a weak acid (i.e., not appreciably ionized in n-butylamine). The titration data for perchloric acid fitted precisely the theoretical relationship between the potential and the logarithm of the reciprocal of the acid concentration giving an indication that this acid was completely ionized. On the other hand, the data for hydrochloric acid did not show a linear relationship for either plot. Cluett reasoned that this was just the theoretical behaviour expected of appreciably but not completely ionized acids in water. Benzoic acid showed only slight curvature when the log $\frac{X}{1-X}$ scale was used and thus appeared to be very slightly ionized in n-butylamine. In order to add further confirmation to these results, the titration data of benzothiazole-2-carbamic acid methyl ester were applied to the two titration equations and the latter were found to be similar to those for the case of hydrochloric acid. An ultraviolet spectral analysis of this organic compound alone in n-butylamine and in the basic solvent with an excess of titrant added showed that only a small shift and very small differences in shapes and intensity were observed. This indicated that this acid was appreciably ionized in n-butylamine and that hydrochloric acid in all likelihood has a similar acid-base behaviour.

In applying the titration equations to the data obtained in this investigation, the intention will be to interpret the results in terms used by Cluett in his study of titration

characteristics of various acids in n-butylamine. It must be kept in mind that this does not imply that the explanations are conclusive but rather they should be regarded as tentative in view of the complexities that may be encountered in these nonaqueous solutions as has been outlined in this brief review. It might be pointed out that Cluett described the variations in conformity of the potentiometric titration data to titration equations in terms of ionization and not dissociation. In another section of his paper dealing with ionic species in solution (i.e., formation of the electrolyte between the urea anion and the titrant cation) he was well aware of the considerable association of these ions in media of low dielectric constant (ϵ = 5.3 at 21°C. (97)).

Before applying the two titration equations to the data it was necessary to transform them to a form which incorporated the various volumes associated with the titration in order to be suitable for plotting purposes. To test their validity, they in turn will be used to derive the titration equations in the form commonly described.

(i) In the case of weak acids titrated by strong bases in aqueous solution the theoretical relationship between the potential and the logarithm of the ratio of the concentration of the conjugate base of the acid and the free acid (i.e., $\log \frac{X}{1-X}$) is linear.

The over-all dissociation constant for the acid, HA, is

given by

$$K = \frac{[H^{(+)}]\ [A^{(-)}]}{[HA]} \quad , \qquad [161]$$

and thus

$$[H^{(+)}] = \frac{K[HA]}{[A^{(-)}]} \quad . \qquad [162]$$

Now

$$HA = \frac{V_f c - V_t c}{V + V_t} \qquad [163]$$

and

$$[A^{(-)}] = \frac{V_t c}{V + V_t} \quad , \qquad [164]$$

where

V_f = volume of titrant added to complete neutralization of the acid,

V_t = volume of titrant added to a particular point in the titration,

V = initial volume of solution being titrated

and c = concentration of the titrant in mole/litre.

The expression describing the potential in solution has the form

$$E = C_1 + C_2 \log [H^{(+)}] \quad . \qquad [165]$$

By introducing the equivalent term for $[H^+]$ from equation [162] and using the right-hand side of equations [163] and [164] the above expression becomes

$$E = C' - C_2 \log \frac{V_t}{V_f - V_t} \qquad [166]$$

$$E = C' - C_2 \log \frac{\frac{V_t}{V_f}}{1 - \frac{V_t}{V_f}} \qquad [167]$$

$$E = C' - C_2 \log \frac{X}{1-X} \qquad [168]$$

A plot of E against $\log \frac{V_t}{V_f - V_t}$, therefore, may be used to examine the conformity of the titration data to the titration equation in (i).

(ii) For the case of strong acids titrated by strong bases in aqueous solution the theoretical relationship between the potential and the logarithm of the reciprocal of the acid concentration (i.e., $\log \frac{1}{1-X}$) is linear.

Equation [165] then takes the form

$$E = C_1 + C_2 \log \frac{V_f c - V_t c}{V + V_t} \qquad [169]$$

$$E = C'' - C_2 \log \frac{V + V_t}{V_f - V_t} \qquad [170]$$

$$E = C'' - C_2 \log \frac{\frac{V}{V_f} - X}{1-X} \qquad [171]$$

$$E = C'' - C_2 \log \frac{V}{V_f} \left(\frac{1}{1-X}\right), \frac{V}{V_f} = \text{constant} \qquad [172]$$

Equation [172] assumes that $X \ll \frac{V}{V_f}$. A plot of E against

$\log\left(\frac{V + V_t}{V_f - V_t}\right)$ (or $\log\left(\frac{V_f - V_t}{V + V_t}\right)$ as used here) may be used to examine the conformity of the titration data to the theoretical equation in (ii).

A selected number of acids in pyridine and quinoline were chosen for the examination of the conformity to the titration equations by the potentiometric titration data. The results are depicted graphically in Figures 44 and 45. Examples of the data required in plotting the curves are given in Table XLIII for the straight line in curve(s) 7 of Figure 44 and in Table XLIV for the straight line in curve(s) 1 of Figure 45. The observations from the figures are conveniently given in Table XLV and are compared with other measurements.

The first three acids in Figure 44, considered to be the weakest, gave essentially linear plots when correlation of E was made with $\log\left(\frac{V_t}{V_f - V_t}\right)$. Only in the last one or two points in each plot is there an indication of slight curvature. Similar results were obtained for anthranilic acid in quinoline (curve 1, Figure 45). This is the behaviour which is expected of a weak acid in aqueous solution (i.e., not appreciably ionized). As the strength of the acid increases, as seen from the ΔHNP values in Table XLV, the deviation from the titration equation becomes more pronounced in both solvents. The situation is one common to an acid which is appreciabily ionized. If one

FIGURE 44. An examination of the conformity to the titration equations of the potentiometric titration data of the following acids in pyridine at 25.0°C.

(O) E *vs.* $\log V_t/(V_f - V_t)$.

(Δ) E *vs.* $\log (V_f - V_t)/(V + V_t)$.

1. 4-methoxyanthranilic
2. anthranilic
3. benzoic
4. 4-nitroanthranilic
5. 4-methoxysalicylic
6. salicylic (* potential drop after standing one minute)
7. pyridinium perchlorate

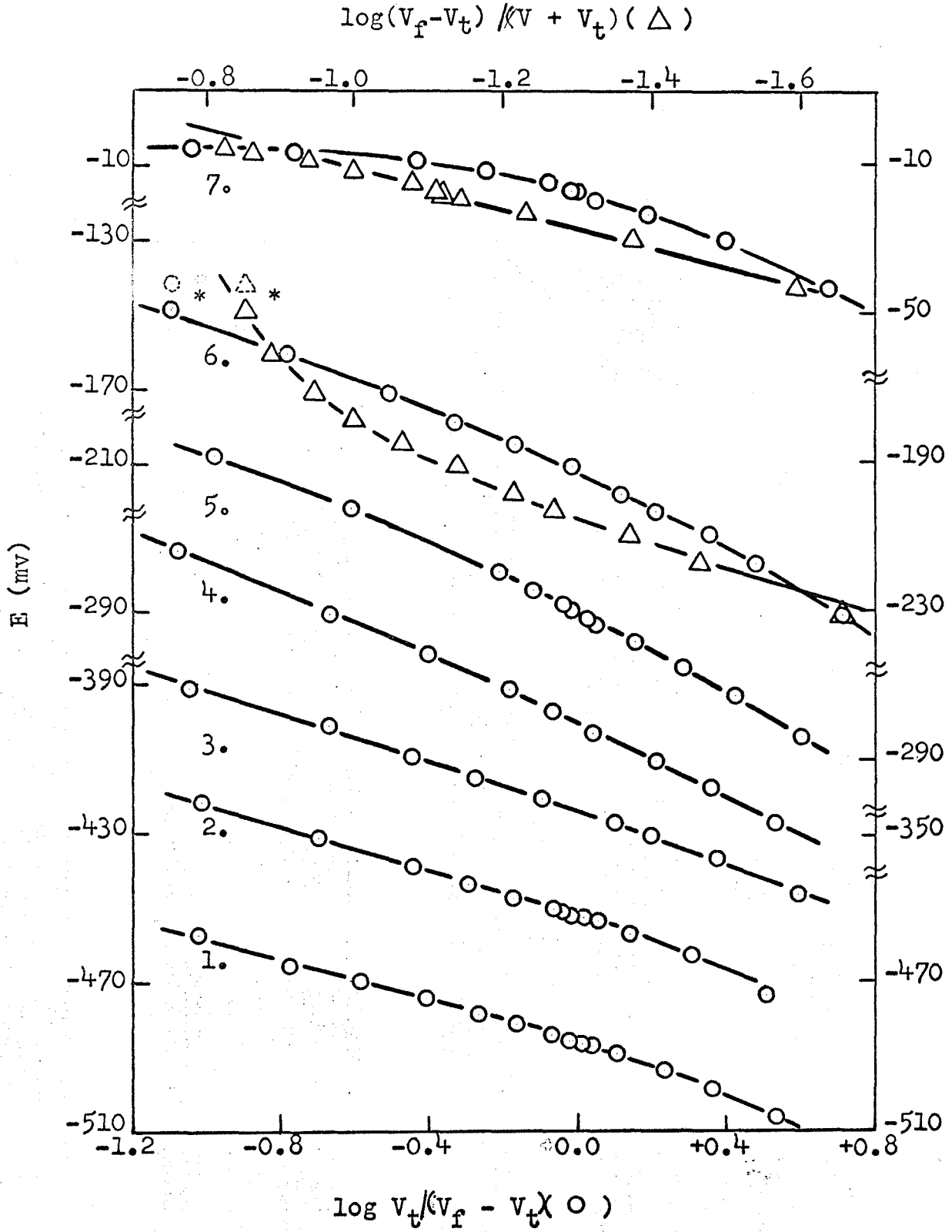

log(Vf-Vt) /(V + Vt)(△)
-0.8
-1.0
-1.2
-1.4
-1.6
-10
-130
-170
-210
-290
-390
-430
-470
-510
-10
-50
-190
-230
-290
-350
-470
-510
7.
6.
5.
4.
3.
2.
1.
E (mv)
-1.2
-0.8
-0.4
0.0
+0.4
+0.8
log Vt/(Vf - Vt)(○)

FIGURE 45. An examination of the conformity to the titration equations of the potentiometric titration data of the following acids in quinoline at 25.0°C.

(O) E <u>vs.</u> log $V_t/(V_f - V_t)$.

(△) E <u>vs.</u> log $(V_f - V_t)/(V + V_t)$.

1. anthranilic
2. 4-nitroanthranilic
3. 4-methoxysalicylic
4. trifluoracetic
5. 5-nitrosalicylic

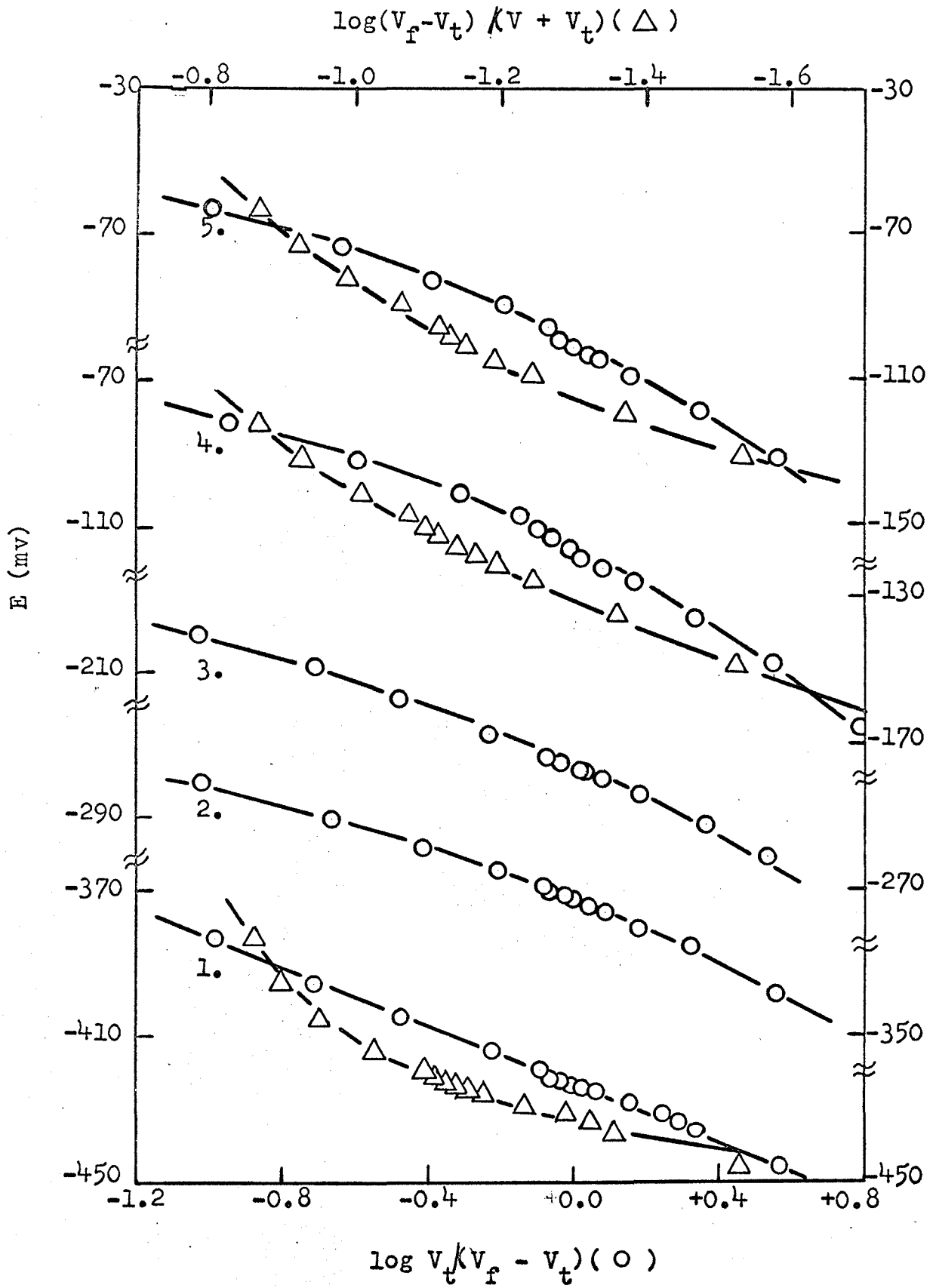

log(V_f-V_t) /(V + V_t)(△)
-0.8
-1.0
-1.2
-1.4
-1.6
-30
-70
-110
-150
-130
-170
-210
-290
-270
-370
-350
-410
-450
E (mv)
5.
4.
3.
2.
1.
-1.2
-0.8
-0.4
+0.0
+0.4
+0.8
log V_t/(V_f - V_t)(O)

TABLE XLIII

APPLICATION OF THE DATA FOR THE POTENTIOMETRIC TITRATION OF PYRIDINIUM PERCHLORATE IN PYRIDINE TO THE TITRATION EQUATION[a]

E[b] (mv)	V_t[c] (ml)	$V_f - V_t$[d] (ml)	$V + V_t$[e] (ml)	$\log \frac{V_f - V_t}{V + V_t}$
-5.4	0.68	7.54	50.68	-0.827
-6.4	1.20	7.02	51.20	- .863
-8.5	2.22	6.00	52.22	- .939
-11.4	2.97	5.25	52.97	-1.004
-14.7	3.75	4.47	53.75	-1.080
-17.1	4.03	4.19	54.03	-1.111
-17.7	4.12	4.10	54.12	-1.120
-19.2	4.33	3.89	54.33	-1.145
-23.1	5.00	3.22	55.00	-1.233
-30.2	5.87	2.35	55.87	-1.376
-43.6	6.78	1.44	56.78	-1.595

[a] 7.527×10^{-4} mole of pyridinium perchlorate in 50.0 ml pyridine was titrated with 0.1N tetra-n-butylammonium hydroxide in benzene-methanol at 25.0°C; the graphical representation is given by the straight line in curve(s) 7 of Figure 44.

[b] Potential in millivolts.

[c] Volume of titrant added to a particular point in the titration.

[d] Volume of titration added to complete neutralization of the acid; V_f = 8.22 ml.

[e] Initial volume of solution being titrated; V = 50.0 ml.

TABLE XLIV

APPLICATION OF THE DATA FOR THE POTENTIOMETRIC TITRATION OF ANTHRANILIC ACID IN QUINOLINE TO THE TITRATION EQUATION[a]

E[b] (mv)	V_t[c] (ml)	$V_f - V_t$[d] (ml)	$\log \frac{V_t}{V_f - V_t}$
-383.6	0.73	6.97	-0.980
-395.8	1.25	6.45	- .713
-405.2	1.94	5.76	- .473
-414.3	2.87	4.83	- .226
-419.8	3.44	4.26	- .093
-422.0	3.56	4.14	- .066
-422.7	3.70	4.00	- .034
-423.8	3.83	3.87	- .004
-424.4	3.95	3.75	+ .022
-425.7	4.12	3.58	+ .061
-429.0	4.52	3.18	+ .152
-432.1	4.91	2.79	+ .245
-434.2	5.09	2.61	+ .290
-436.8	5.27	2.43	+ .336
-446.6	6.05	1.65	+ .564

TABLE XLIV Continued

[a] 7.527×10^{-4} mole of anthranilic acid in 50.0 ml quinoline was titrated with 0.1N tetra-n-butylammonium hydroxide in benzene-methanol at 25.0°C; the graphical representation is given by the straight line in curve(s) 1 of Figure 45.

[b] Potential in millivolts.

[c] Volume of titrant added to a particular point in the titration.

[d] Volume of titrant added to complete neutralization of the acid; V_f = 7.70 ml.

TABLE XLV

A COMPARISON OF RESULTS DERIVED FROM THE TITRATION EQUATIONS WITH OTHER MEASUREMENTS INDICATING ACID STRENGTH

No.[a]	Acid[b]	ΔHNP[c,d] (mv)	$\log \frac{V_t}{V_f - V_t}$[e]	$\log \frac{V_f - V_t}{V + V_t}$[e]	Solvent Cation[f]		Concentration[g]
				Pyridine			
1.	4-OCH_3A	-33.8	27				
2.	A	0	30		—	8(c)	0.056[h]
3.	B	6.4	33		I	10(c)	0.139-13.9 x 10^{-3}
4.	4-NO_2A	112.8	+				
5.	4-OCH_3S	200.9	++				
6.	S	231.4	++	++	I	10(g)	0.98-6.86 x 10^{-3}
					I	8(b)	0.055[h]
7.	$PyHClO_4$	406.8	+++	53	I* D	1(a)	3.9-116 x 10^{-5}

TABLE XLV Continued

No.[a]	Acid[b]	ΔHNP[c,d] (mv)	log $\frac{V_t}{V_f-V_t}$[e]	log $\frac{V_f-V_t}{V+V_t}$[e]	Solvent Cation[f]		Concentration[g]
				Quinoline			
1.	A	0	40	++	—	12(c)	0.079[h]
2.	4-NO_2A	113.5	++				
3.	4-OCH_3S	190.7	++				
4.	CF_3COOH	(307.5)[i,j]	+++	+	I I* D	12(a) 11	0.076[h] 0.04-0.12[h]
5.	5-NO_2S	322.6	+++	+			

TABLE XLV Continued

[a] Refers to the number of the curve in Figure 44 or 45.

[b] A = anthranilic; B = benzoic; S = salicylic.

[c] Taken from Table XIII (Page 247) and Table XIV (page 251). Data for benzoic and salicylic acid were originally given different values in Sets 1-3 of Table XIV. Here, the reference acid is anthranilic and the strongest acid is given the most positive ΔHNP. The values of ΔHNP for benzoic and salicylic are the mean of 3 and 2 determinations respectively.

[d] Concentration of acid: 1.50×10^{-2} mole/litre except where otherwise noted.

[e] If the plot in Figures 44 and 45 is essentially linear, the value in this column is the slope in mv per unit change in the abscissa. Slopes are positive in keeping with equation [166] or [170]. When curvature occurs, an indication is given by a plus (+) sign. When two or three of these signs are used, it means that the curvature is becoming correspondingly more pronounced. Comparisons should only be made with results in the same column (i.e., the same equation).

[f] Taken from Table XXXVII (page 408). The line from which the information is taken is also noted. The symbols —, I, I* and D refer to absence of an indication of solvent cation, partial ionization, complete ionization and partial dissociation respectively. See footnote e of Table XXXVII for complete description of symbols.

[g] Taken from Table XXXVII. The concentration (range) of the acidic solute recorded in mole/litre is that used when the measurements were taken. If different concentration units are used, this is noted.

TABLE XLV Continued

h
Mole fraction.

i
Reference acid is A, the determination of which is taken from a set completed a day earlier.

j
Concentration: 1.52×10^{-2} mole/litre.

inspects the results obtained when E vs. $\log\left(\frac{V_f - V_t}{V + V_t}\right)$ are plotted, a similar pattern is established but this time in just the opposite direction. The weakest acids (anthranilic and salicylic) give the greatest deviation from conformity to this equation, whereas for the strongest acid (pyridinium perchlorate), the result of an almost straight line enabled the calculation of a slope to be made which was not too far removed from the theoretical value of 59 mv for strong acids in water. Attention is drawn, however, to the entries of the last two columns of Table XLV which indicate from conductometric studies that even at a lower concentration $PyHClO_4$ is not fully dissociated in pyridine solution.

It is interesting to note that this pyridinium salt has a very high ΔHNP, one that is approximated by picric acid and a number of sulfonic acids which are in the $\sim$420 mv range (283). It is apparent from the results here and from the observations made by Streuli that these acids are obviously in the leveling region (completely ionized to the colvent cation) of the solvent, a condition which should prevail for acids with $pK_a(H_2O) < 1$. The generalization may not be too accurate, however, since it seems the order of acid strength is reversed from water to quinoline when trifluoracetic and 5-nitrosalicylic acids are compared (see also Table XXXVII, lines 9(a) and 11). This situation may be a reflection of the assistance to acid strength of 5-

nitrosalicylic acid in pyridine solution by an intramolecular hydrogen bond. There does not seem to be any significant contrast in the deviation shown by 4-nitroanthranilic and 4-methoxysalicylic acids in either solvent even though their ΔHNP values differ by 80-90 mv. These acids represent the strongest anthranilic and the weakest salicylic acid examined here. As far as comparisons of the titration equation results with those originally noted in Table XXXVII and briefly outlined in Table XLV are concerned, the same general pattern emerges; that is, the conformity or deviations of the acids from the titration equations is paralleled by changes in acid strength as determined by other methods. The comparison is limited in that the range of concentration and the limits of detection of the different techniques may not be the same.

In conclusion, it seems that an application of the titration equations to acid-base systems in pyridine and quinoline may be useful in giving a qualitative indication of the degree of ionization. It is not clear, however, if the extent of dissociation is also being measured. The similarity in behaviour of acid solutes in pyridine and quinoline is again confirmed. Results obtained here are consistent with the magnitudes of ΔHNP derived earlier.

Summary

(i) A comprehensive survey of information gleaned from the literature as well as from the preliminary

studies offers strong evidence that complications of acid self-association, homoconjugation and incomplete solvation of molecular species of anthranilic and salicylic acids in solvents like pyridine and quinoline are not likely to occur. Literature evidence which tended to favour the zwitterion form for anthranilic acid in basic solvents has been re-interpreted to discount this possibility. There was more reason to believe that intramolecular hydrogen bonding, stronger in salicylic acid than in anthranilic, is present in both acids. Ionization of anthranilic acid is negligible but may be quite considerable for salicylic acid.

(ii) Potentiometric titrimetry has been used to measure the relative acidities of a series of ten substituted anthranilic acids in pyridine solution. Relative acidities of a number of salicylic acids in pryidine and anthranilic and salicylic acids in quinoline have also been determined. Acid-base behaviour in pyridine and quinoline is comparable (Table XVI, page 254).

(iii) The relative-acidity data for substituted anthranilic acids in pyridine has been subjected to a statistical analysis and it was found that the extended form of the equation

$$\Delta HNP = \rho_1 \sigma_1 + \rho_2 \sigma_2$$

represented that data significantly better than the single Hammett equation

$$\Delta HNP = \rho_1 \sigma_1 \quad .$$

(iv) The results are interpreted in favour of the existence of an intramolecular hydrogen bond. The ratio $\rho_2/\rho_1 = 0.16$ gave an indication that the effect of the substituent on the acid strength of the carboxyl proton through the intramolecular hydrogen bond is about one fifth as large as the effect directly transmitted through the carboxyl carbon. The first term of the extended form of the Hammett equation was considered to be a composite expression which included the contribution to the hydrogen bond effect on acidity by the anthranilic-ion basicity. The relative importance of the latter to the over-all hydrogen bond effect was estimated. The system studied here represents another example of the value of the Hammett relationship in uncovering the importance of intramolecular hydrogen-bond interaction.

(v) The relative acid strengths of substituted anthranilic acids as determined in pyridine were compared to $pK_2(H_2O)$ values. Significant deviations from linearity were noted with the largest variance coming from those acids capable

of existing predominantly as zwitterion in aqueous solution. Because of this aqueous ionization (K_2) constants are not entirely useful for estimating the relative acidities in pyridine.

(vi) The use of the common titration equations originally derived for aqueous solutions has been discussed in their application to nonaqueous systems. They have been applied to the potentiometric titration data of a selected number of acids in both pyridine and quinoline. It is tentatively concluded that the results may be interpreted in favour of little, if any, ionization for the weakest acids (4-methoxyanthranilic, anthranilic and benzoic) while pyridinium perchlorate may be thought to be fully ionized. Similar trends are noted using data from other techniques. Pyridine and quinoline solvents behave similarly.

(vii) The relative acidity studies have shown rather conclusively that as a family salicylic acids are much stronger in pyridine and quinoline than are the anthranilic acids (Table XLV) with a considerable difference in strength ($\triangle$HNP) between the weakest and strongest member in each family respectively. There is evidence that at least one of the strongest anthranilic acids may be partially ionized (line 9(c), Table XXXVII). If

comparisons are made between $\triangle$HNP values for salicylic acids in pyridine (Table XLV) with estimated K_i and K_d values of nitrophenols in pyridine determined by Corey (lines 3(a) - (e), Table XXXVII), then the model of ionization and dissociation would seem to be a reasonable one for salicylic acids. Naturally, such comparisons are made a little difficult in that different methods may utilize somewhat different concentrations. At concentrations higher (proton magnetic resonance) than those used in decarboxylation, salicylic acid would seem to be at least partially ionized in pyridine and quinoline at room temperature whereas anthranilic acid was not.

B. DECARBOXYLATION

INTRODUCTION

The original intention of the research conducted into the acid-base behaviour of salicylic and anthranilic acids in nitrogenous media was to assist in interpreting the results of decarboxylation.

There are at least three main factors that prevent the results of acidity at room temperature from being adequately translated to conditions prevailing during decarboxylation. The wide difference in temperature ($\sim$200°C.) is one feature

which may cause significant variation in acid strength or in basicity of the solvent. The elevated temperature also affects the dielectric constant of the medium which is reduced as the temperature rises. For instance, quinoline has a dielectric constant of 9.00 and 5.05 at 25 and 238°C. respectively (97). Furthermore, the concentration of anthranilic acids used in the decarboxylation in quinoline range from ~ 0.03 - 0.1 mole/litre which is some 2 to 7 times as large as that used in the potentiometric titrations. These last two factors, that is, the lowered dielectric constant and the increased acid concentration would tend to favour less dissociation in the basic solvent at elevated temperatures. It might be recalled, however, that in the proton magnetic resonance experiments even more concentrated solutions were used and observations, interpreted as ionization phenomena, noted. Although these solutions were prepared on a mole-fraction basis, they are estimated to be between 0.35 and 0.7 mole/litre and probably closer to the larger value. At this concentration salcylic acid solutions in both pyridine and quinoline exhibited low-field proton resonances attributed to $\geq\overset{(+)}{N}-H$ (lines 8(b) and 12(b), Table XXXVII on page 408) whereas no detectable signal was observed in the same region for solutions of anthranilic acid in the same solvents (lines 8(c) and 12(c), Table XXXVII).

Unfortunately, very little is available in the way of

temperature studies on acid strength in nonaqueous solvents. The information that may be obtained is usually limited to studies rather close to room temperature or to monomer-dimer equilibria of acidic solutes. In aqueous solution ionization constants of acids are found to vary with temperature and the correlation curve is usually parabolic in nature with a flat maximum appearing usually near room temperature for most carboxylic acids (500, 501). Such is also the case for formic and acetic acids in the high dielectric-constant solvent formamide (163). Although the evidence is rather limited, particularly with respect to temperature studies involving solvents used in the present investigation, it nevertheless is clear that elevated temperatures have a negative effect on acid-base behaviour. Whether this phenomenon manifests itself simply in the form of solute-solvent intermolecular hydrogen bonding (502) or by actual ionization (160, 503) and dissociation (86c, 504), its prominence is lessened as the temperature is raised. It would be expected, therefore, that acid strengths of anthranilic and salicylic acids would be considerably reduced at the temperatures used in the decarboxylation experiments.

Despite the frequent use of basic solvents like pyridine and quinoline in decarboxylations of organic acids, it is only relatively recently that investigators have undertaken examinations to shed light on the function of these solvents

in the decompositions. In a number of studies workers have postulated in their mechanisms some form of solvent solvation, preliminary ionization or dissociation, ion-pair formation of carboxylic acids or other form of solvent involvement in the decarboxylation process (5, 7, 8, 295, 330, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349).

Fraenkel, Belford and Yankwich put forward two possibilities for solvent participation in the decarboxylation of malonic acid in quinoline (8). They offered several reasons to favour a carboxyl-carbon solvation over a reaction which proceeded through hydroxyl association with the solvent. In a later paper, however, it was presumed that the direct influence of quinoline was through an interaction with the carboxyl proton and the nitrogen of the solvent which results in a hydrogen bonded structure of the type O-H···N$\leqslant$ (153, 333). Clark has conducted an extensive study into the decomposition of numerous organic acids in a large number of nonaqueous solvents (including quinoline). His general thesis has been to accept the idea of a bimolecular reaction between the acidic solute and solvent to form an intermediate or activated complex. The co-ordination is thought to exist between the electrophilic-carbonyl carbon of the leaving carboxyl group and an unshared pair of electrons acting as a nucleophilic centre and situated on such atoms as N, O or S of the nonaqueous solvent or in the case of the melt, another solute molecule (340, 341, 342, 343, 344, 345,

346, 347). The interpretation is not always convincing, however, since rather poor nucleophiles as phenetole and dimethoxybenzene have been included in the list of solvents proposed to be involved in the bimolecular mechanism (395). There were cases where strong bases in conjunction with relatively strong acids were used or where other solvents which favoured ionization were utilized in which he invoked ionization equilibria in the decomposition (348, 349).

Decarboxylation of substituted salicylic acids have been studied in quinoline by Clark (358), Janzen (4) and Rodewald (5). Janzen began the extensive investigation of decarboxylation of 4- and 5-substituted salicylic acids at the temperature, 200°C., and found the reaction to be first order with respect to the acid, and accelerated by electron-releasing substituents. Rodewald, in continuing the work, determined activation parameters, examined basicity and steric requirements of the solvent, investigated the enthalpy-entropy relationship and found a first-order dependence with respect to quinoline in nitrobenzene-quinoline mixtures. Results were suggestive that both electron donation and electron withdrawal were effective in aiding decarboxylation. In fact the rates of decomposition were found to correlate significantly better with the extended form of the Hammett equation

$$\log \frac{k_1}{k_1^o} = \rho_1 \sigma^+ + \rho_2 \sigma \quad , \qquad [173]$$

than with the simple form of the equation possessing either one or the other terms of the right-hand side of expression [173]. Here the pseudo first-order rate constants k_1 and k_1^o refer to the substituted and unsubstituted salicylic acids. The first term, $\rho_1\sigma^+$, referred to processes such as C-H bond making and C-C bond breaking, both occurring at carbon 1 and for which Brown's sigma-plus substituent constants should apply. The second term in equation [173] emphasizes the relative importance of carboxyl-proton ionization in the reaction. All the experimental evidence could be accommodated by the following mechanism which includes a step as suggested by Bourns (365).

$$HOArCOOH + Q \underset{}{\overset{K}{\rightleftharpoons}} \underset{CXIV}{HOArCOO^{(-)}\overset{(+)}{H}Q} \qquad [174]$$

$$(a)\quad HOArCOO^{(-)}\overset{(+)}{H}Q \xrightarrow{k} HOAr + CO_2 + Q \qquad [175]$$

$$(b)\quad HOArCOO^{(-)}\overset{(+)}{H}Q \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{CXV}{HOAr\overset{(+)}{C}OO^{(-)}} \overset{H}{\diagdown} + Q \xrightarrow{k_3} HOAr + CO_2 \qquad [176]$$

Salicylic acid and quinoline are represented by HOArCOOH and Q respectively. The preliminary ionization was adequately accounted for in the second term of the extended Hammett equation; however, there was no unequivocal evidence to favour the concerted mechanism (a) over the stepwise process (b). In the former case, the rate-determining step involves the protonation of carbon 1 of the acid anion by the quinolinium ion and C-C bond breaking and C-H bond making occur in a concerted fashion. In scheme (b),

protonation of carbon 1 forms the reaction intermediate which can decompose either to products or to the ion pair (CXIV). The distinction really lay in the nature of CXV which might be considered an activated complex in the concerted mechanism and an intermediate in the stepwise pathway. A carboxyl-^{13}carbon kinetic-isotope effect, recently completed, has helped to decide in favour of a mechanism which involves the zwitterionic intermediate (CXV) (6). Isotope effects were determined in a solution of 0.02 M quinoline in nitrobenzene and in quinoline and found to increase with increasing concentration of quinoline.

When attention was directed to aprotic nonbasic solvents, in particular nitrobenzene, the order of the reaction was different. For instance, decomposition of salicylic acid was found to follow second-order reaction kinetics (4). A similar result was obtained in a major study of decarboxylation of substituted anthranilic acids in nitrobenzene at 210.5°C. by Dunn and Prysiazniuk (2). Once again electron-releasing substituents favoured the reaction and it was shown that the reaction occurred in the molecular form of the acid. The Hammett equation and its extensions were used to help interpret the experimental results. It was concluded that the rate-controlling step involved attack by proton from one anthranilic acid molecule on carbon 1 of a second molecule. Although the carbon alpha to the carboxyl group was seen as the principal

reaction centre it was thought that the simple Hammett equation

$$\log \frac{k}{k_o} = \rho\sigma^+ \qquad [177]$$

did not satisfactorily correlate the rate constants because of minor participation in the transition state by the carboxyl group, in particular the ionization or breaking of the carboxyl O-H bond.

INTERPRETATION OF RESULTS

Quinoline

Reaction Order and the Hammett Relationship

The results of the decarboxylation of substituted anthranilic acids in quinoline have been recorded in pages 255 to 266.

The decompositions exhibited first-order kinetics with respect to the acid. Electron-releasing substituents were found to aid the decarboxylation.

There are a number of possible reaction schemes that may account for the observed order and substituent effects. Before considering these various possibilities with the evidence now available, it might be worthwhile to examine other information and in particular substituent effects in the light of the Hammett relationship. The data required for the correlations is recorded in Table XLVI. The logarithms of the first-order specific-rate constants were

TABLE XLVI

APPLICATION OF THE HAMMETT RELATIONSHIP TO THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN QUINOLINE AT 230.6°C.

Substituent	log k_1 [a]	± M.D. [b]	σ [c]	σ^+ [d]
4-OCH_3	-2.928	0.022	-0.268	-0.778
4-CH_3	-3.602	.069	- .170	- .311
5-CH_3	-3.975	.020	- .069	- .066
H	-4.146	.055	.000	.000
4-Cl	-4.255	.059	.227	.114
5-Cl	-4.538	.020	.373	.399
5-NO_2	-5.088	.013	.710	.674
5-CN	-5.165	-	.56	.562

[a] Derived from the average second-order specific-rate constant (k_{1av}) as recorded in Table XIX, page 261.

[b] Maximum deviation from log k_1; derived from log $k_{1\ max.}$ the latter established from values of M.D. from the average specific-rate constant as recorded in Table XIX, page 261.

[c] Hammett's substituent constants based on the ionization of substituted benzoic acids (444).

[d] Electrophilic substituent constants originally derived from solvolyses of t-cumyl chlorides (31).

first correlated with the Hammett substituent constants (σ), the equation having the form

$$\log k_1 = \rho\sigma + \log k_1^o \quad . \qquad [178]$$

The rate constant k_1 and k_1^o refer as usual to the substituted and unsubstituted anthranilic acids respectively and ρ is the reaction constant which measures the susceptibility of the reaction to nuclear substitution. Use of this particular expression, which includes an intercept ($\log k_1^o$) prevents undue weight being given to the rate constant of the unsubstituted acid. The graphical representation of the presumed relationship is depicted in Figure 46. An estimate of the error in the ordinate is also shown and is an indication of the maximum deviation associated with each point. There is no intention to show the error in the substituent constant. The plot, however, fails to exhibit the linearity expected but rather results in a distinctly concave upward appearance. Certain groups (4-OCH_3 and 4-CH_3) are showing greater electron-releasing properties than normally ascribed to the sigma substituent constants.

When the common substituent constants are replaced by sigma-plus, the Hammett equation becomes

$$\log k_1 = \rho\sigma^+ + \log k_1^o \quad . \qquad [179]$$

Correlations which involve σ^+ apply generally to reactions in which an electron deficiency is being created or destroyed at a stage of the reaction preceding or at the transition state. The upward curvature shown by the plot in Figure 46

FIGURE 46. The Hammett relationship: the correlation of the logarithm of the first-order specific-rate constants (log k_1) in the decarboxylation of substituted anthranilic acids in quinoline at 230.6°C. with sigma(σ) substituent constants. Data aretaken from Table XLVI.

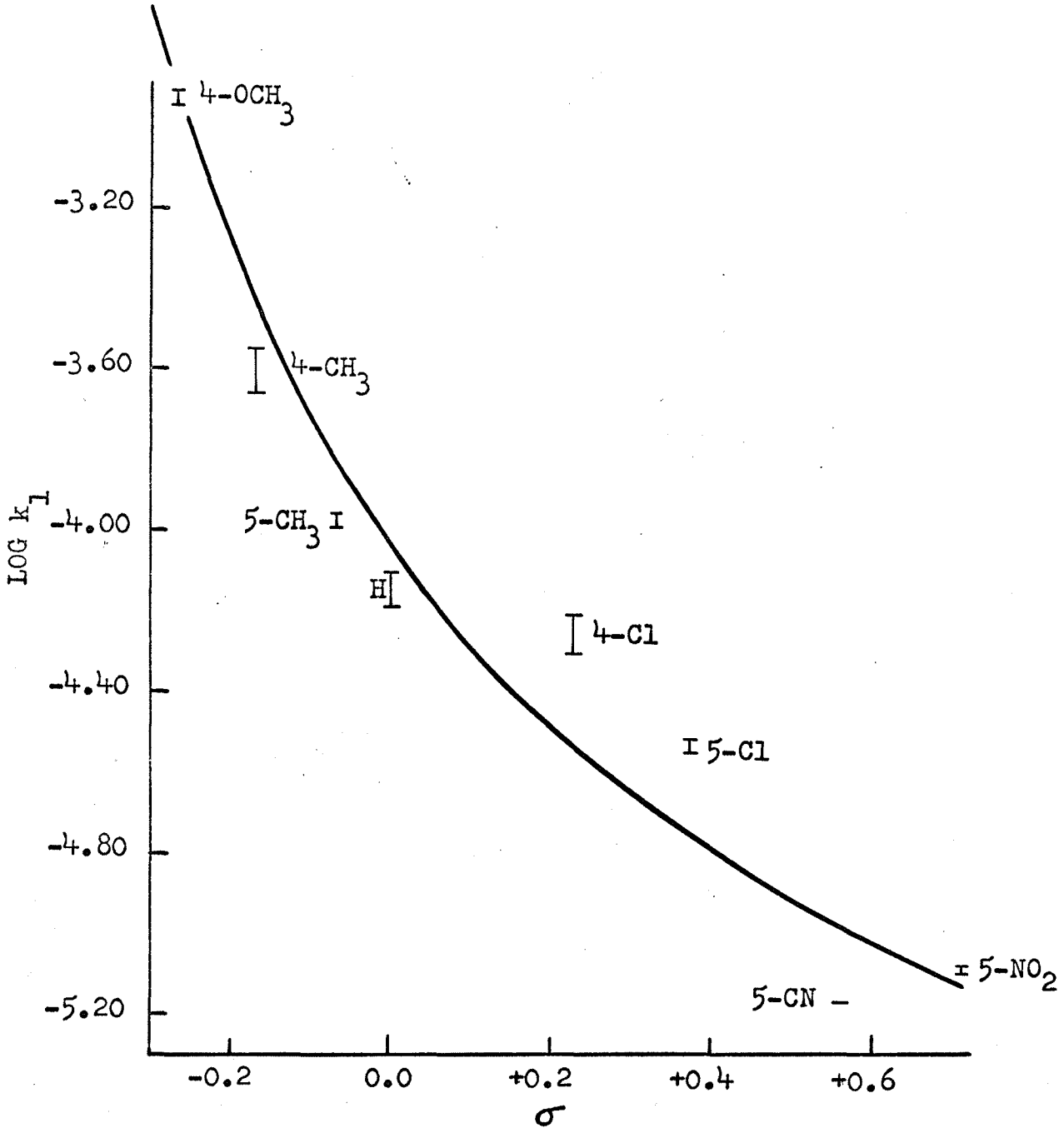

4-OCH3
-3.20
-3.60
4-CH3
LOG k1
-4.00
5-CH3
H
4-Cl
-4.40
5-Cl
-4.80
5-NO2
5-CN
-5.20
-0.2
0.0
+0.2
+0.4
+0.6
σ

FIGURE 47. The Hammett relationship: the correlation of the logarithm of the first-order specific-rate constants (log k_1) in the decarboxylation of substituted anthranilic acids in quinoline at 230.6°C. with sigma plus (σ^+) substituent constants. The reaction constant, ρ, is equal to -1.54. Data are taken from Table XLVI.

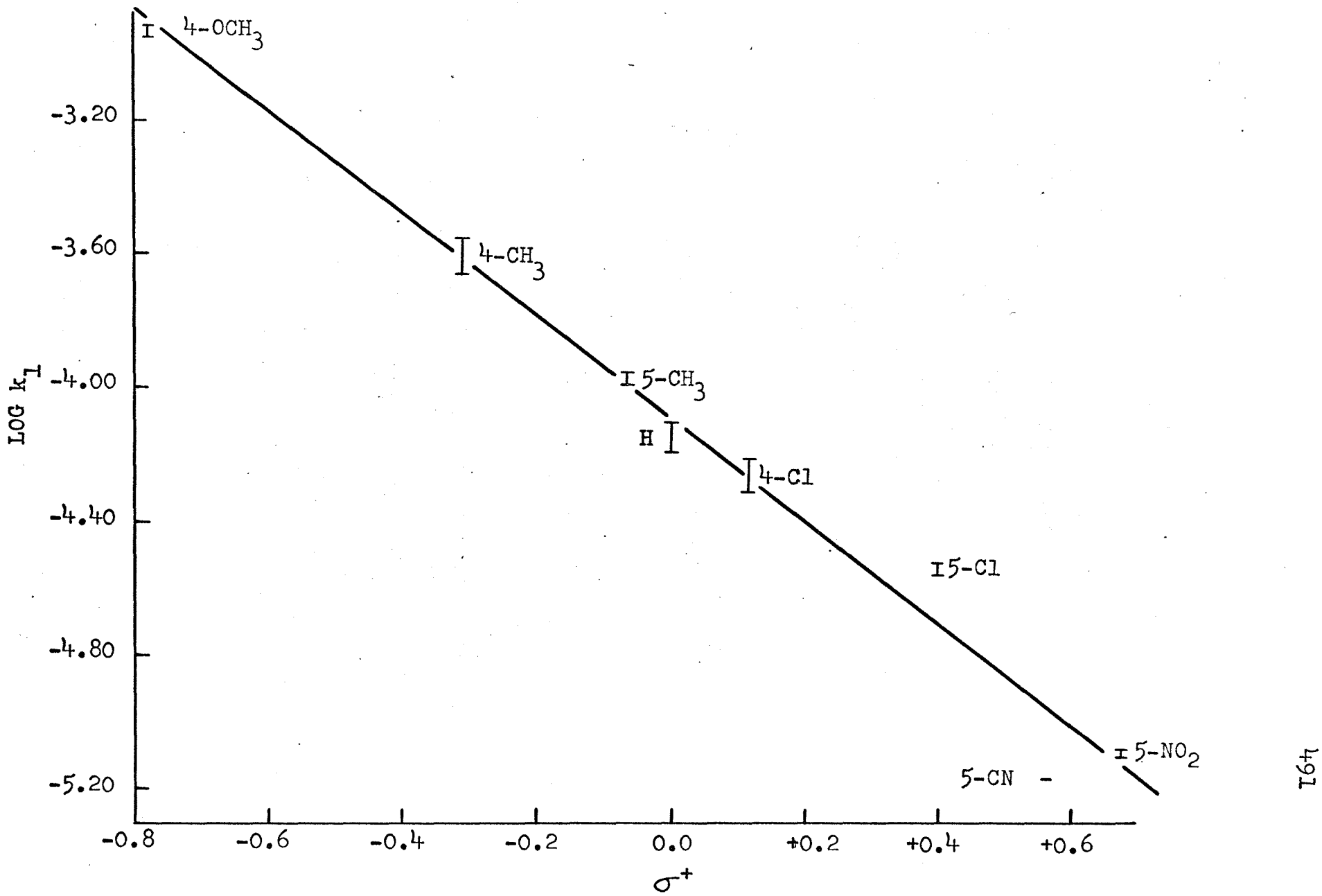

4-OCH3
4-CH3
5-CH3
H
4-Cl
5-Cl
5-NO2
5-CN
-3.20
-3.60
-4.00
-4.40
-4.80
-5.20
LOG k1
-0.8
-0.6
-0.4
-0.2
0.0
+0.2
+0.4
+0.6
σ+

TABLE XLVII

STATISTICAL ANALYSIS OF THE HAMMETT RELATIONSHIP FOR THE CORRELATION OF THE LOGARITHM OF THE PSEUDO FIRST-ORDER SPECIFIC-RATE CONSTANTS IN THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN QUINOLINE AT 230.6°C.[a]

Equation	$S_{\log k_1 . \sigma^+}$[b]	ρ[c]	S_ρ[d]	$\log k_1^o$[e]	$S_{\log k_1^o}$[f]	$r_{\log k_1, \sigma^+}$[g]
$\log k_1 = \rho\sigma^+ + \log k_1^o$	0.115	-1.54	0.09	-4.098	0.041	0.990
[179]	[A.14]	[A.4]	[A.19]	[A.4]	[A.18]	[A.46]
				-4.146[h] ($\pm$0.055)		

[a] From data recorded in Table XLVI. Figures in [ ] refer to the equation found in the Appendix that was used to calculate the parameter of that particular column. The calculated value is placed immediately above the equation number.

[b] Standard error of estimate.

[c] Slope (reaction constant).

[d] Standard error or deviation in the slope.

TABLE XLVII Continued

[e] Intercept; logarithm of the first-order specific-rate constant for anthranilic acid.

[f] Standard error in the intercept.

[g] Simple linear correlation coefficient between the two variables log k_1 and σ^+.

[h] Log k_1^o experimental; ± maximum deviation.

(68, 505, 508). A discrepancy in the sigma-plus value for the meta-cyano group has been indicated in a different substrate system and it was felt that the value should be considerably more positive (509). Because of these factors, it may not be fair to speculate on the significance of the deviation at this time.

The results obtained with the Hammett relationship in this study do not parallel those encountered by Rodewald in the decarboxylation of substituted salicylic acids in quinoline (5). In his work neither a Hammett relationship involving sigma or sigma plus correlated the data well. This led him to propose an ionization pre-equilibrium occurring prior to the rate-controlling decarboxylation. The importance of this initial step was uncovered by satisfactorily correlating the logarithm of the rate constants with a linear combination of both sigma and sigma plus substituent constants.

$$\log \frac{k_1}{k_1^o} = \rho_1 \sigma^+ + \rho_2 \sigma \qquad [173]$$

This expression has already been described briefly in the introduction to this section as well as in the Review of the Literature (page 166). Rodewald found ρ_1 and ρ_2 to have values of ~ -4 and $\sim +4$ respectively, the signs of which were in keeping with the nature of the processes which they represented (i.e., C-H bond making (C-C bond breaking of lesser importance) and carboxyl-proton ionization). It

appears that equation [173] is not required or would not correlate the data from the present investigation significantly better than the simple equation [179].

The negative value of ρ_1 in equation [179] is an indication that substituents which are electron donating favour the reaction at carbon 1. This result can be quite consistent with the assumption that a high electron density is required for a C-H bond making rate-controlling step at that site. The magnitude of rho (-1.54), however, is considerably smaller than those commonly encountered in electrophilic aromatic substitutions (68). The reaction constant is usually understood to reflect the sensitivity of the rate to changes in electron density at the reaction centre. For instance, a negative value of ρ should correspond to the development of an electron deficiency at this site. Its magnitude is often taken as a magnitude of the developing charge and of the extent to which it is able to interact with the nuclear substituent. Norman and Taylor have described ρ as a measure of the extent to which the electron pair which is used to form the new bond to the electrophile has been removed from the aromatic system at the transition state (67a). Such interpretations are often qualitatively useful but some care is needed since this simple explanation may not always be sound (56a, 63). In the present work one can be confident that the calculated rho(ρ) is distinctly different from zero but its relatively

small magnitude may be caused by the presence of one or more factors (5, 53b, 56b).

(i) The substituent is insulated from the reaction centre.

(ii) The rates of decarboxylation have been measured at or near the isokinetic temperature.

(iii) The rate of reaction is determined by concurrent processes in which the influences by substituents are opposed.

Clearly, condition (i) does not apply to the system under consideration. There is one aspect, however, that will require some clarification when the various mechanistic possibilities are being discussed later. This is the apparent insensitivity of the ionization of the carboxyl proton to substituent effects.

In order to comment on factor (ii), one requires a determination of the activation parameters, $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$, which represent the enthalpy and entropy of activation respectively. A major temperature study did not form a part of this investigation but a selected number of acids were decarboxylated at one or two lower temperatures. The enthalpy and entropy of activation were calculated using the following equations which have been given in convenient form by Bunnett (18).

For data at only two temperatures, the Arrhenius activation energy, E, can be obtained by

$$\log k_2 - \log k_1 = \frac{E}{4.576} \frac{(T_2 - T_1)}{T_2 T_1} \quad , \qquad [180]$$

where k_2 and k_1 are rate constants at the absolute temperatures T_2 and T_1 respectively. The enthalpy of activation can be secured from the Arrhenius activation energy by subtracting RT.

$$\triangle H^{\ddagger} = E - RT \qquad [181]$$

R has the value 1.987 cal/deg and T was taken as the absolute temperature midway between the two values chosen in [180]. By using the equation

$$\frac{\triangle S^{\ddagger}}{4.576} = \log k - 10.753 - \log T + \frac{E}{4.576T} \quad , \qquad [182]$$

the entropy of activation may be calculated. In using this expression, the specific-rate constant in each case was that determined at 230.6°C. The derived activation parameters are shown in Table XLVIII. Included for purposes of comparison are values determined for the decomposition of salicylic acids which bear the same nuclear substituents as the anthranilic acids. The values of $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$ for the latter acids should be considered as provisional since only one determination was made at the temperature other than 230.6°C. and the rate constants were determined graphically as usual, but without including any blank correction. On the other hand, the data derived by Rodewald were from rate constants determined from at least two

TABLE XLVIII

ACTIVATION PARAMETERS IN THE DECARBOXYLATION OF ANTHRANILIC AND SALICYLIC ACIDS IN QUINOLINE SOLUTION

Substituent	$k_1 \times 10^5$ (sec^{-1}) [a] T_1	[b] T_2	Anthranilic Acids $\Delta H^{\ddagger}$ (k cal/mole)	Anthranilic Acids $\Delta S^{\ddagger}$ (cal/deg mole)	Salicylic Acids [c] $\Delta H^{\ddagger}$ (k cal/mole)	Salicylic Acids [c] $\Delta S^{\ddagger}$ (cal/deg mole)
H	1.58[d]	7.14	22.5	-33.9	33.4	-7.00
4-CH_3	1.56[e]	25.0	21.9	-32.6	30.7	-10.3
4-OCH_3	31.6 [f]	118.	19.6	-34.2	32.6[g]	-0.485[g]
5-Cl	2.16[h]	2.90	13.3	-54.0	31.2	-10.9

[a] No blank correction; rate constants determined from only one run.

[b] Temperature: 230.6°C.

[c] Reference (5).

[d] Temperature: 200.2°C; acid concentration: 4.376×10^{-3} mole/100 ml solvent.

TABLE XLVIII Continued

[e] Temperature: 220.4°C; acid concentration: 1.207×10^{-3} mole/10.0 ml solvent.

[f] Temperature: 200.2°C; acid concentration: 2.495×10^{-3} mole/10.0 ml solvent.

[g] Value for 4-ethoxysalicylic acid.

[h] Temperature: 200.4°C; acid concentration: 1.704×10^{-3} mole/10.0 ml solvent.

measurements at each temperature and over 4 to 6 different temperatures.

The isokinetic temperature, β, is given by the algebraic relationship

$$\Delta H^{\ddagger} = \beta \Delta S^{\ddagger} + \Delta H_o^{\ddagger} \quad , \qquad [183]$$

where $\Delta H_o^{\ddagger}$ is the intercept or value of $\Delta H^{\ddagger}$ corresponding to $\Delta S^{\ddagger} = 0$ (18, 359, 510). Combining the common equation involving the free energy of activation,

$$\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad , \qquad [184]$$

with equation [183] leads to

$$\Delta F^{\ddagger} = \Delta H_o^{\ddagger} - (T - \beta)\Delta S^{\ddagger} \quad . \qquad [185]$$

When $\beta = T$, $\Delta F^{\ddagger} = \Delta H_o^{\ddagger}$ and the rate constants for all the acids are the same within the precision of the relationship. At this temperature $\rho = 0$ for the reaction series which is described by the Hammett equation. The application of the data in Table XLVIII in the form of equation [183] does not adequately test the isokinetic relationship since the first three acids listed are grouped closely together, which is clearly discerned if the numbers are plotted, while the value for 5-chloroanthranilic acid is the only one which shows significant differences. Tentatively, however, a line was drawn visually through the points in a plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ (not shown) and an isokinetic temperature of ~394°A.

(~121°C.) determined. Since the working temperature is much higher than this (230°C.) it would seem that the sign of ρ is mechanistically significant. It would be well to emphasize once again that a more thorough examination of the entropy-enthalpy relationship would have to be conducted. For one thing the isokinetic relationship is usually lacking the precision which is required in making generalizations as to the nature of the reaction or mechanism (18, 511). Also there is considerable controversy over the validity of linear entropy-enthalpy plots as an adequate demonstration of the existence of an isokinetic relationship and for the simultaneous occurrence of Hammett and isokinetic relationships (18, 56b, 63, 359, 510, 512). One feature is clear from the data in Table XLVIII, however, and that is that the reaction is controlled or governed mostly by the entropy of activation. If the apparent variations in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ among the various acids are real, then the system represents a case where the Hammett equation holds when the entropy effects are not constant but vary in a parallel fashion with the enthalpy of activation.

The remaining factor (iii), which can contribute to a resultant reaction constant of relatively small magnitude, is a distinct likelihood. The possibility that the ortho-amino group might be involved as a reaction site in the decarboxylation was really not examined, at least not in an application of the extended form of the Hammett equa-

tion which might have uncovered interactions such as chelation that may affect the acidity or removal of the carbon dioxide molecule. Rodewald showed that the decarboxylation process for salicylic acids did not involve carbon 2 which possesses a phenolic group. From the evidence considered in the acidity studies anthranilic acid should have a weaker intramolecular hydrogen bond than salicylic acid. At room temperature it was found that the indirect effect of the substituents on the acid strengths of substituted anthranilic acids in pyridine accounted for a little less than 1/5 the total effect on the carboxyl group. At elevated temperatures intramolecular hydrogen bonding would be considerably weakened and in all probability nonexistent.

As mentioned in the introduction to this section the term, $\rho\sigma^+$, can refer to processes that involve both C-H bond making and C-C bond breaking for which sigma plus substituent constants should apply. Equation [179] may then be rewritten

$$\log k_1 = (\rho_{C-H} + \rho_{C-C})\sigma^+ + \log k_1^{\circ} , \quad [186]$$

where ρ_{C-H} and ρ_{C-C} are measures of the susceptibility of C-H bond making and C-C bond breaking to nuclear substitution respectively. The influence of substituents are opposed in these two cases with ρ_{C-H} and ρ_{C-C} bearing negative and positive signs respectively. It seems reasonable, therefore, that if competitive C-C bond rupture is important, then the magnitude of ρ could be considerably decreased.

Mechanism of the Decarboxylation

With the information now available one may more adequately consider the various reaction schemes or mechanisms that can account for the observed order and possible substituent effects.

(i) The acids exist essentially in the zwitterionic form or this form is in equilibrium with the nonpolar molecule. Decarboxylation would involve a rate-determining C-C cleavage of the zwitterion followed by a relatively fast intramolecular C-H bond-making step (e.g., see page 130).

(ii) The unionized acid might undergo a slow heterolysis of the C-C bond thereby forming a carbanion intermediate and a transitory protonated carbon dioxide entity (see page 126 for further comments).

(iii) The acids may be completely ionized in quinoline and decarboxylation could proceed spontaneously from the anion or the rate may involve a concurrent or stepwise process of proton (quinolinium ion) attack at carbon 1 and release of the molecule of carbon dioxide (e.g., see page 127).

(iv) A more reasonable interpretation than (iii) as far as acid strengths are concerned would be to expect a preliminary ionization equilibrium to exist and then

decarboxylation of the ion-pair to occur by a concerted or stepwise process (e.g., see pages 167 and 168).

(v) Another possibility is to suppose that quinoline assists in the decomposition not by ionizing the acid molecule to an ion pair but by an action which is limited to intermolecular hydrogen bonding between the carboxyl proton and the lone pair of electrons on the quinoline nitrogen. Although the reaction centre would primarily involve carbon 1, the overall process could be envisaged to encompass atoms which would also include the carbon, hydroxyl oxygen and proton of the carboxyl group in the form of a four-centre reaction. Multicentre-type reactions are not uncommon (52c).

There are a number of reasons for not favouring reaction scheme (i) as a plausible explanation of the experimental results. The most important one is undoubtedly the evidence which has been gleaned from the literature on acidity studies and that derived in this investigation. It is not likely that anthranilic acid would exist as the zwitterion in quinoline solution at 230°C. Furthermore, if zwitterion were present in quinoline and its relative concentration for the different acids followed the same order as in aqueous solution then, for instance, anthranilic and 4-methyl-

anthranilic acids would have been expected to decarboxylate more easily than 4-methoxyanthranilic acid in quinoline (see Table XLII on page 449 and reference (12)). A mechanism described in (i) would inevitably involve a carbanion intermediate which might adequately be stabilized by a strong electron-withdrawing group such as an ortho $-\overset{(+)}{N}H_3$ substituent. Closely related to this is the decarboxylation of quinaldinic acid in quinoline which has been explained on the basis of a dipolar-ion tautomer formed from the carboxylate-α-imino system (313, 314, 315, 316). It was found, however, that electron-releasing substituents accelerated the decomposition of anthranilic acids in quinoline, a condition which is not consistent with a reaction centre which develops an anionic charge in the rate-controlling step.

The mechanism envisaged by (ii) is not reasonable since cleavage of a neutral molecule into positive and negative fragments would be a relatively difficult process; in fact, there is apparently no evidence which supports the idea that in decarboxylations proton removal from the carboxyl group occurs after the C-C fission. This led Brown and Hammick to propose an empirical rule which stated that the carboxyl group is usually in the anionic form prior to the decarboxylation (316). Included in this interpretation would be zwitterions or forms containing at least the carboxyl-group proton hydrogen bonded internally to a basic moiety in the molecule (299) (see also pages 124-133 in this dissertation). Further-

more, the scheme described in ii would accommodate substituent effects of a similar nature to those required for process (i) and opposite to what is observed in this investigation. It would also not be clearly understood why the decarboxylation should occur when the acid is in the unionized form by a first-order process (as presented by ii) in quinoline but by second-order kinetics in nitrobenzene (2).

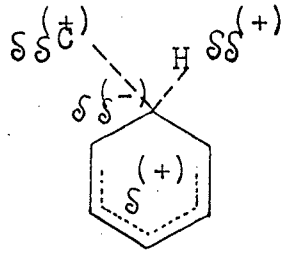
With reference to possibility (iii) it is unlikely that substituted anthranilic acids will exist as the conjugate bases in quinoline solution. The evidence has been presented earlier and is quite convincing (see in particular Table XXXVII on page 408). Also, the substituent effects do not follow the order expected for strong electron-withdrawing groups which might assist the cleavage of the C-C bond.

The scheme presented in (iv) is the same one which satisfactorily explained the experimental results of the decarboxylation of salicylic acids in quinoline (5) and which has briefly been outlined in the introduction to this section. The active species involved in the decarboxylation would be the anion and the fact that electron-releasing substituents enhance the decomposition of anthranilic acid in quinoline could be reconciled by a rate-controlling proton attack on carbon 1 of the anion. What should also be required, however, is that the extended form of the Hammett equation should apply which reflects both the sub-

stituent effects on the ionization equilibrium and a developing carbonium centre at carbon 1. The Hammett treatment of the data in the present study, however, showed that a good correlation was obtained with the use of only a single substituent constant, sigma plus. Apparently then, a preliminary ionization cannot be occurring prior to the decarboxylation proper. The result is consistent with what is now known about the relative acid strengths of anthranilic and salicylic acids in pyridine and quinoline solutions. It becomes clearer now that the apparent insensitivity of substituent effects to the ionization of the carboxyl group must be a result of the inability of inductive and mesomeric influences of the substituent to reach the carboxyl group through carbon 1 of the benzene ring. A reaction constant of -1.54 is an indication that the electrophile (i.e., the carboxyl proton) has in fact interacted with the aromatic nucleus in the transition state, thereby obtaining a share in the electron pair which ultimately will form the new C-H bond. If this is the case, the O-H bond must be broken or at least weakened in the stages leading to the transition state. Insensitivity to this latter process must mean that ionization is not occurring as a preliminary equilbrium (this interpretation is given for salicylic acid decompositions in quinoline) but rather that the aromatic character of the ring is being modified or deformed so as to alter the sp^2 character of carbon 1 and, therefore, reduce any resonance

effect or inductive relay of substituent influences to the carboxyl group.

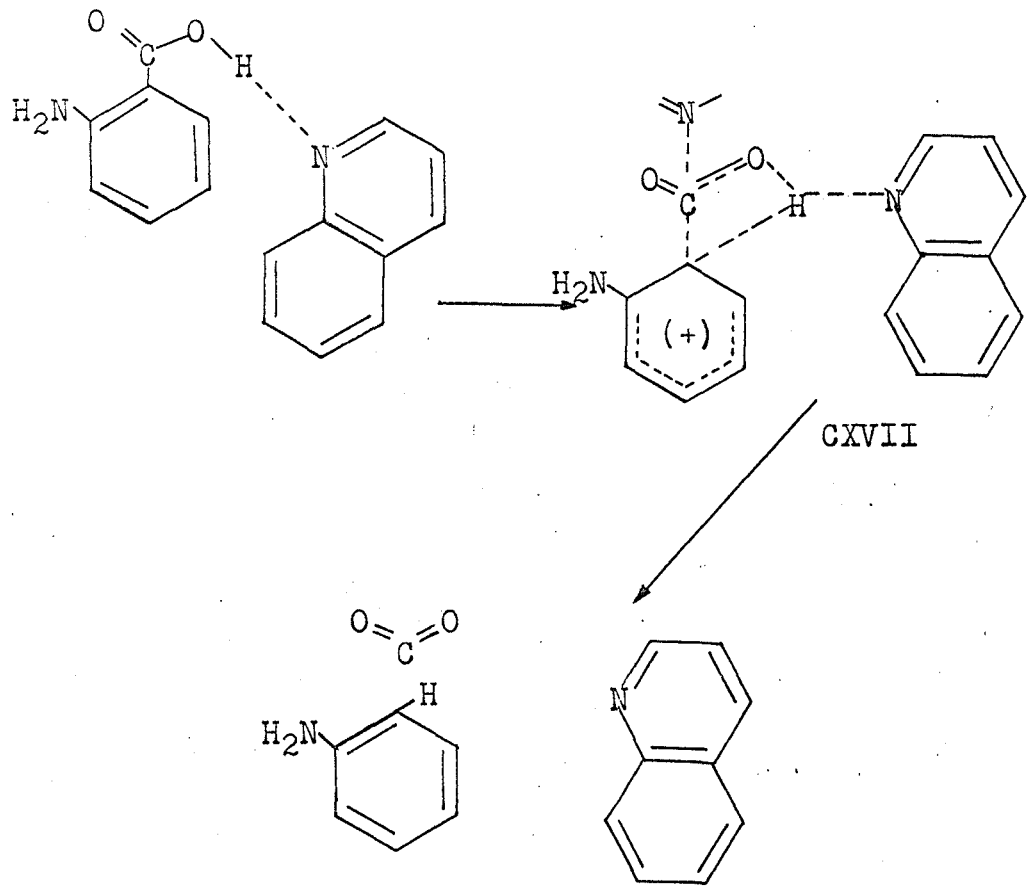
It appears that, in discounting the first four reaction schemes, one is left with only mechanism (v) as the most reasonable interpretation that may be given in accommodating all the information gathered with regard to the decomposition of anthranilic acids in quinoline. It is suggested that a molecule of solvent interacts with the carboxyl proton via an intermolecular hydrogen bond and assists an intramolecular-proton transfer to carbon 1 in a concerted fashion such that C-C cleavage has occurred to the same or lesser extent than C-H bond making. It would be expected that the original sp^2 hydridization of carbon 1 has been modified substantially to an sp^3 state (CXVI). The residual molecule forms a pentadienate cationic system.



CXVI

If C-C cleavage had progressed significantly by the time the transition state were reached, then a slight deposition of negative charge ($\delta\delta^{(-)}$) at carbon 1 should reduce the electron deficiency at the cationic centre sufficiently so that the reaction is not particularly sensitive to substituent

effects. The proposed mechanistic pathway is depcted in equation [187] . It may be termed an electrophilic substitution by an internal mechanism ($S_E i$).

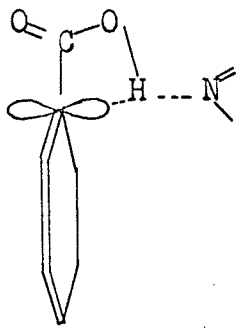


[187]

It is possible that another solvent molecule solvates the carboxyl carbon (as emphasized by Clark; see page 149), which becomes momentarily electron deficient, and assists the release of carbon dioxide. Fraenkel et al. have given reasons for considering this type of solvation in the decarboxylation of malonic acid in quinoline (8). Although not shown in [187] the ortho-amino group may help to stabilize

CXVII through mesomeric interaction.

The conformation of the carboxyl group during the decarboxylation is of particular interest. It might be thought that the group maintains a co-planarity with the aromatic nucleus. On the other hand the carboxyl moiety may be rotated about the C-C axis until it is perpendicular to the aromatic plane (CXVIII).



CXVIII

There are a number of features or considerations which tend to favour the latter interpretation and these are supported in part by an examination of Fisher - Taylor - Hirschfelder models.

(i)Direct resonance interaction of para substituents to the carboxyl carbon would be reduced and consequently electronic influences, mesomerically at least, on the proton acidity would not be felt.

(ii)The lack of overlap of the pi electrons of carbon 1 and the carboxyl carbon weakens the C-C bond.

(iii)The carboxyl proton may assume a position such that the solvent molecule is able to enter the region

facing the aromatic ring with the least steric interference from the ortho-amino group or ortho-hydrogen.

(iv) The proximity of the pi-electron lobe at carbon 1 may assist in the intramolecular proton transfer from O to C.

(v) Any possible intramolecular hydrogen bonding between the ortho-amino group and the carbonyl oxygen is thereby precluded. The only interacting mechanism left to this group may be a resonance stabilizing effect on the transition state.

A mechanism envisaged by equation [187] is consistent with the following experimental observations.

(i) It predicts the observed pseudo first-order kinetics.

$$\frac{d(CO_2)}{dt} = k_1 [RCOOH] [Quinoline]^n \qquad [188]$$

where the pseudo first-order specific-rate constant,

$$k' = k_1 [Quinoline] \qquad [189]$$

and n=1 is assumed. It is possible that the order with respect to quinoline is higher than unity.

(ii) The mechanism does not prescribe a preliminary ionization equilibrium which is in keeping with evidence of the acidity of anthranilic acids in the basic solvent and the fact that an extended form of the Hammett equation appears not to be required.

(iii) As seen in Table XLVIII both the enthalpy and entropies of activation are lower than those representing comparable substrate systems in the decarboxylation of salicylic acids in quinoline. Solvent-solute interactions can adequately explain this difference (92b, 513). An effect which leads to stronger binding between the acid and the solvent molecule will lower the enthalpy of activation. It should also cause a restriction or increased constraint in the transition compared to the reactant state. The value of $\Delta S^{\dagger}$ is much more negative than would be expected if the activated complex involved only minor rearrangement of solvent molecules. Interaction must be strong enough to result in a solvent-concentration dependence of the reaction rate. The relatively large negative entropy of activation is undoubtedly well accommodated by postulating the intervention of only a single solvent molecule but, as stated earlier, this interpretation may have to be modified to include a higher kinetic order with respect to quinoline.

(iv) The application of the Hammett equation in the form

$$\log k_1 = \rho\sigma^{+} + \log k_1^{o} \qquad [179]$$

was found to be successful and is also consistent with the described mechanism which proposes the reaction centre at carbon 1. The relatively small

negative value for rho may be explained reasonably on the basis of concurrent C-C bond breaking and C-H bond making, processes that are oppositely affected by substituents and which cause a cancellation in the magnitude of the reaction constant.

There are a number of reaction systems from the literature that parallel in many respects the mechanistic interpretation given here to the decarboxylation of substituted anthranilic acids in quinoline solution.

It is of interest to note that Janzen did offer a mechanism for the decarboxylation of salicylic acids in quinoline which bears some resemblance to the one described here (4). At that stage of the work in the salicylic acid-quinoline system, however, inconsistencies in the Hammett relationship were not clearly explained. Fraenkel et al. postulated an intramolecular proton transfer together with carboxyl-carbon solvation in the decarboxylation of malonic acid in quinoline (8). Krueger has also discussed the possibility of intramolecular proton attack in the decarboxylation of deuterated anthranilic acid in the melt (514).

Wiberg and Shryne studied the kinetics and substituent effects of the thermal rearrangement of α-phenylethyl chlorocarbonates in toluene and dioxane and postulated a cyclic transition state or ionic intermediate (51d, 515). The protodeboronation of areneboronic acids in aqueous sulfuric

acid solution was examined by Nahabedian and Kuivila (516). A number of competitive reaction schemes were discussed that depended on the substrate reactivity and acid concentration. One that was favoured was described in terms of a pre-equilibrium attack by bisulfate ion on boron followed by an intramolecular proton transfer to carbon 1. Reaction rates were correlated with the Hammett equation using sigma-plus substituent constants. One further example of a mechanism, which involved a species capable of internal proton transfer to the ring carbon, is found in the pH-dependence study of the decarboxylation of p-hydroxycinnamic acid (517).

Nitrobenzene

Reaction Order and the Hammett Relationship.

The results of the decarboxylation of substituted anthranilic acids in nitrobenzene have been recorded on pages 266 to 278.

The decomposition of anthranilic acids in nitrobenzene at 200.2°C. was found to be second order with respect to anthranilic acid which confirms the earlier work of Dunn and Prysiazniuk (2). Nuclear substituents which donate electrons were found to promote the decarboxylation, a result similar to that observed in the decarboxylation of anthranilic acids in quinoline.

The data necessary for correlating the series of substituted anthranilic acids in the Hammett relationship are

presented in Table XLIX. The interdependence of the logarithm of the second-order specific-rate constant was checked first with respect to the Hammett substituent constant in the equation

$$\log k_2 = \rho\sigma + \log k_2^{\circ} \quad , \qquad [190]$$

where k_2 and k_2° refer respectively to the substituted and unsubstituted anthranilic acids and the term $\rho\sigma$ has the usual significance. A plot of the data given in Figure 48 is seen to exhibit a concave upward appearance similar to the results obtained in the quinoline decarboxylations. The maximum deviation in log k_2 related to each point is also shown in the figure. For the purpose at hand the substituent constant is depicted without error. It is clear that certain groups are displaying abnormally large electron-releasing properties not in keeping with influences usually associated with the ionization of the carboxyl proton.

If the correlation of the form

$$\log k_2 = \rho\sigma^{+} + \log k_2^{\circ} \qquad [191]$$

is applied to the data, one observes from the plot in Figure 49 that sigma-plus substituent constants serve particularly well. The derived values of the slope (ρ) and intercept (log k_2°) were obtained by the method of least squares and are recorded in Table L along with their standard deviations. Other statistical parameters such as the standard error of

TABLE XLIX

APPLICATION OF THE HAMMETT RELATIONSHIP TO THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN NITROBENZENE AT 200.2°C.

Substituent	log k_2[a]	± M.D.[b]	σ[c]	σ^+[d]
5-Cl	-5.038	0.003	0.373	0.399
4-Cl	-4.764	.002	.227	.114
H	-4.410	.050	.000	.000
4-F	-4.364	.006	.062	- .073
5-CH_3	-4.199	.001	- .069	- .066
4-CH_3	-3.670	.054	- .170	- .311
4-OCH_3	-2.652	.030	- .268	- .778
4-NH_2	-1.219	.043	- .66	-1.3[e]
	(-1.135)[f]			

a Derived from the average second-order specific-rate constant (k_{2av}) as recorded in Table XXIII, page 273.

b Maximum deviation from log k_2; derived from log k_{2max}, the latter established from values of M.D. from the average specific-rate constant as recorded in Table XXIII.

c Hammett's substituent constants based on the ionization of substituted benzoic acids (444).

d Electrophilic substituent constants originally derived from solvolyses of t-cumyl chlorides (31).

e Estimated from data of other electrophilic reactions; see reference (31).

f Derived from k_2 which was obtained from the Arrhenius equation; see Table XXIII. This value was not used in the application of the Hammett relationship.

FIGURE 48. The Hammett relationship: the correlation of the logarithm of the second-order specific-rate constants)log k_2) in the decarboxylation of substituted anthranilic acids in nitrobenzene at 200.2°C. with sigma (σ) substituent constants. Dataare taken from Table XLIX.

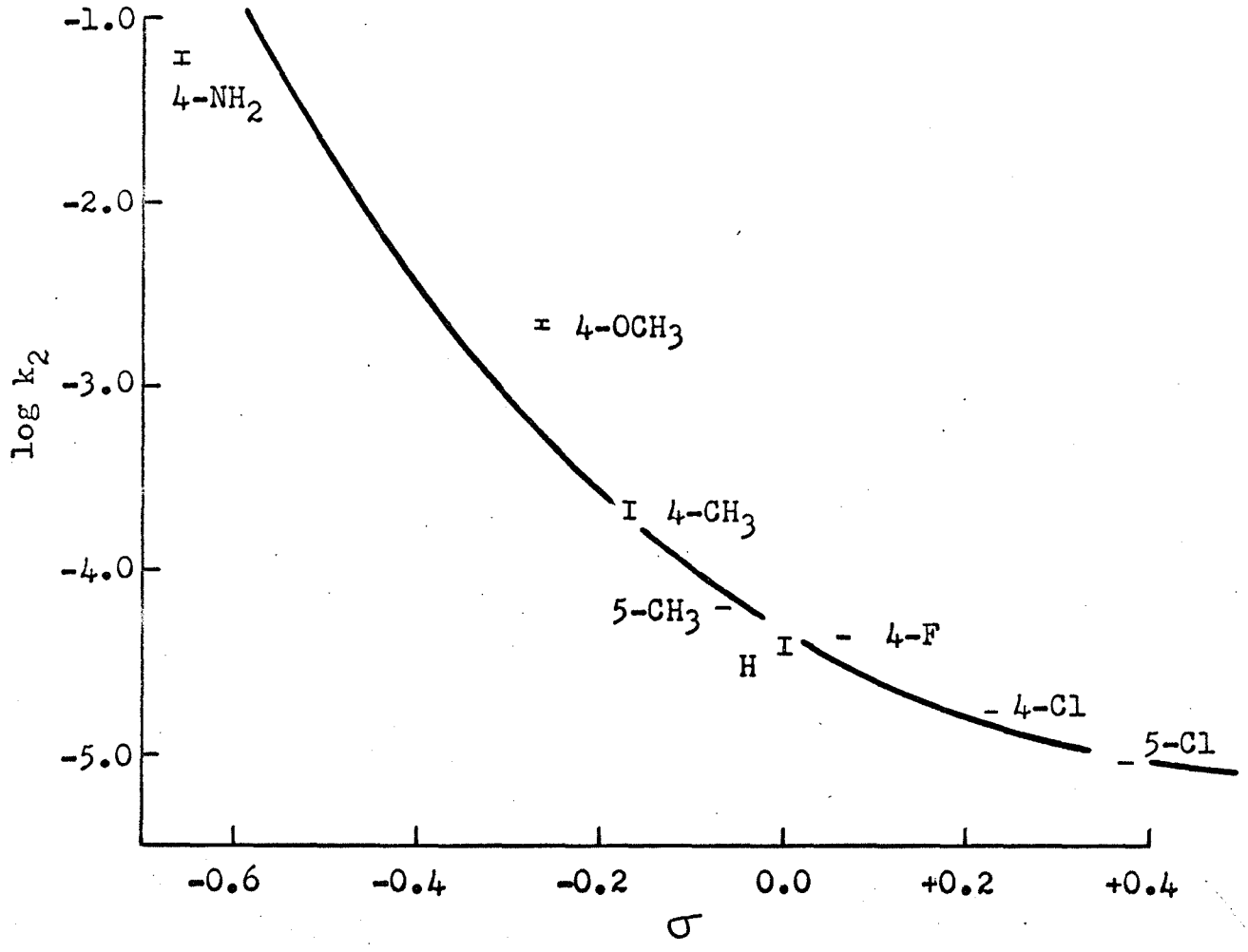

-1.0
-2.0
-3.0
-4.0
-5.0
log k_2
4-NH_2
4-OCH_3
4-CH_3
5-CH_3
H
4-F
4-Cl
5-Cl
-0.6
-0.4
-0.2
0.0
+0.2
+0.4
σ

FIGURE 49. The Hammett relationship: the correlation of the logarithm of the second-order specific-rate constants (log k_2) in the decarboxylation of substituted anthranilic acids in nitrobenzene at 200.2°C. with sigma-plus (σ^+) substituent constants. The reaction constant, ρ, is equal to -2.32. Data are taken from Table XLIX.

* Value of log k_2 for 4-aminoanthranilic acid derived from the Arrhenius equation.

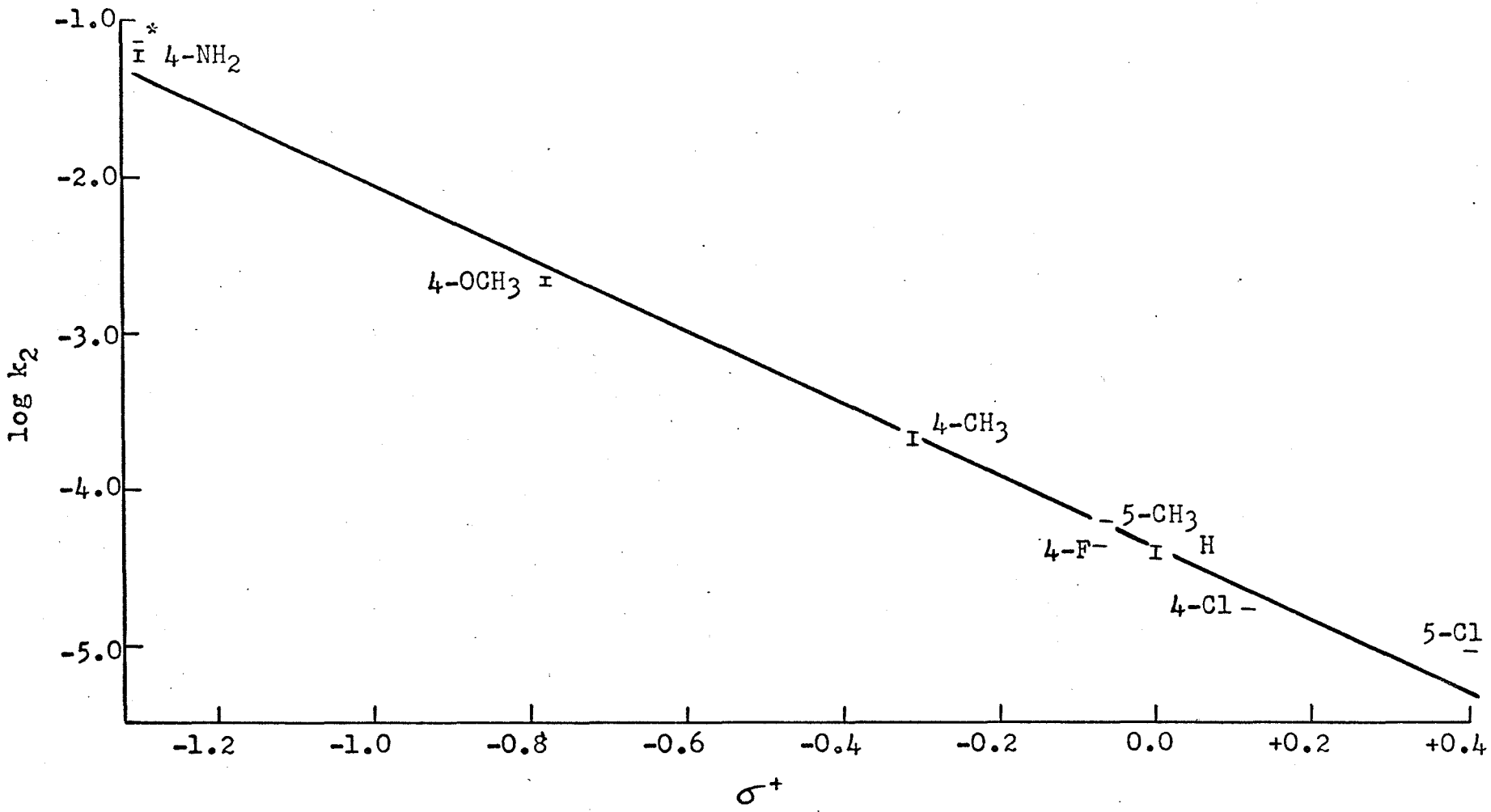

-1.0
-2.0
-3.0
-4.0
-5.0
log k_2
4-NH_2
4-OCH_3
4-CH_3
5-CH_3
4-F
H
4-Cl
5-Cl
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
+0.2
+0.4
σ^+

TABLE L

STATISTICAL ANALYSIS OF THE HAMMETT RELATIONSHIP FOR THE CORRELATION OF THE LOGARITHM OF THE SECOND-ORDER SPECIFIC-RATE CONSTANTS IN THE DECARBOXYLATION OF SUBSTITUTED ANTHRANILIC ACIDS IN NITROBENZENE AT 200.2°C.[a]

Equation	$S_{\log k_2}$[b]	σ^+ ρ[c]	$S\rho$[d]	$\log k_2^o$[e]	$S_{\log k_2^o}$[f]	$r_{\log k_2, \sigma^+}$[g]
$\log k_2 = \rho\sigma^+ + \log k_2^o$	0.152	-2.32	0.11	-4.375	0.060	0.994
[191]	[A.14][a]	[A.4]	[A.19]	[A.4]	[A.18]	[A.46]
				-4.410[h] (± 0.050)		

a From the data recorded in Table XLIX. Figures in [ ] refer to the equation found in the Appendix that was used to calculate the parameter of that particular column. The calculated value is placed immediately above the equation number.

b Standard error of estimate.

c Slope (reaction constant).

d Standard error or deviation in the slope.

e Intercept; logarithm of the second-order specific-rate constant for anthranilic acid.

f Standard error in the intercept.

g Simple linear correlation coefficient between the two variables $\log k_2$ and σ^+

h $\log k_2^o$ experimental (± maximum deviation).

estimate and correlation coefficient are also included.

It may be recalled that the kinetic runs associated with 4-aminoanthranilic acid proved particularly troublesome (page 276). Dunn and Prysiazniuk also commented on the difficulty of obtaining suitable rate constants for the acid which decarboxylated very rapidly at the temperature used (2). They resorted to calculating the rate constant from the observed half lives. In this investigation the Arrhenius relationship was used to check the value at the higher temperature (200.2°C.) determined directly. An asterisk in the plot of Figure 49 marks the location of the point corresponding to the indirectly derived value of log k_2 which is seen not to vary too significantly from the value obtained in the usual way. The point for 4-amino-anthranilic acid is reasonably well accommodated by the linear plot in the figure as are the other two neighbouring acids (4-methoxy- and 4-methylanthranilic) all of which possess relatively strong resonance electron-donating capacities. This observation is assurance that the value of log k_2 for the 4-amino acid can be accepted as being reliable in the Hammett relationship. The point corresponding to 5-chloroanthranilic acid is really the only one which perhaps deviates significantly from the line. This may be a result of reasons discussed previously (page 490).

Dunn and Prysiazniuk in the original work on this system acknowledged the predominant importance of carbon 1 in the

transition state although a contribution from the site of the carboxyl proton of lesser importance could not be discounted. In fact deuterated anthranilic acid decarboxylated two to three times slower than anthranilic acid indicating that proton transfer must be involved in the rate-controlling step. Available to this study, but not to the above workers, were 4-methoxy- and 4-methylanthranilic acids which, together with 4-aminoanthranilic, are crucial in any test of the Brown and Okamoto modification of the Hammett equation. It appears that the results here signify that the latter equation adequately correlates the data but one is still left with the notion that the weakening or breaking of the O-H bond should be affected by nuclear substituents and therefore reflected in an extended form of the Hammett equation noted earlier (page 483) which incorporates terms describing carbon 1 processes and carboxyl proton ionization.

The possibility that one reaction site is the amino group or more specifically an $NH_3^{(+)}$ group has been discounted by Dunn and Prysiazniuk on the basis of the Hammett equation application involving sigma constants related to the ionization of the ammonium ion. They also determined the rates of decarboxylation of N-substituted anthranilic acids. Rates increased relative to anthranilic when substituents were methyl and phenyl while the rate for N-acetylanthranilic acid was decreased. The results are in agreement with

the interpretation that the decarboxylation must take place from the neutral acid rather than the zwitterion. The mesomeric electron-donating capacity of the ortho-amino group would have been destroyed if it were protonated.

The determination of activation parameters for the decarboxylation of anthranilic acid in nitrobenzene affords some further important information. Limited data, which are available for only anthranilic and 4-aminoanthranilic acids, are presented in Table LI. Equations [180], [181] and [182] on page 497 were used in the calculations except in one instance. Rather than giving undue weight to any one rate constant, the Arrhenius activation energy for the decarboxylation of anthranilic acid was estimated graphically using the equation

$$\log k_2 = \log A - \frac{E}{2.303RT} \quad , \qquad [192]$$

that is, by plotting $\log k_2$ against $\frac{1}{T}$. R has the value 1.987 cal/deg. The quantity A is a constant labelled the frequency or pre-exponential factor. E is calculated from the slope of the best straight line drawn visually through the three points.

$$\text{slope} = -\frac{E}{4.576} \quad . \qquad [193]$$

TABLE LI

ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF ANTHRANILIC AND 4-AMINOANTHRANILIC ACIDS IN NITROBENZENE SOLUTION

Acid	Temperature (°C.)	k_2[a] x 10^4 (litre/mole sec)	$\Delta H^{\ddagger}$ (k cal/mole)	$\Delta S^{\ddagger}$ (cal/deg mole)
AA[b]	180	0.110[c]		
	200.2	.389[d]		
	210.5	.617[c]	23.8[e]	-29.3[f]
4-NH_2AA	149.5	123.[d]		
	169.7	263.[d]	13.1[g]	-36.8[h]

a Second-order specific-rate constant.

b Anthranilic acid.

c Reference (2).

d This investigation; see Table XXIII, page 273.

e Value of T used in equation [181] was 468.4°A. The Arrhenius activation energy, E, was graphically determined. See text for details.

f Value of k_2 and corresponding T used in equation [182] were 0.389 x 10^{-4} litre/mole sec and 473.4°A.

g Value of T used in equation [181] was 432.8°A. The Arrhenius activation energy was determined by using equation [180].

h Value of k_2 and corresponding T used in equation [182] were 123 x 10^{-4} litre/mole sec and 422.7°A.

Mechanism of the Decarboxylation.

Since nitrobenzene does not possess labile hydrogens capable of being involved in proton transfer, the hydrogen must come from anthranilic acid itself, just as in quinoline decarboxylations, except here a bimolecular reaction will most likely consist of an intermolecular proton attack.

(i) The reaction may involve a proton transfer from an unionized anthranilic acid molecule to carbon 1 of an anthranilate anion. It is also possible that a proton (solvated?) may attack an unionized acid molecule. These reaction schemes imply that an ionization equilibrium is operative in nitrobenzene. A concerted or stepwise mechanism may then follow.

(ii) The mechanism may involve the reaction of two unionized acid molecules in a stepwise or synchronous manner. The rate-controlling processes may include

(a) hydrogen-oxygen bond breaking

(b) carbon-carbon bond breaking

or (c) carbon-hydrogen bond making.

It is possible that the proton transfer is in fact intramolecular and that the second molecule of anthranilic acid functions only as a basic centre in assisting the movement of hydrogen.

The earlier work of Dunn and Prysiazniuk helped to

resolve a number of questions regarding the nature of decarboxylation of anthranilic acid in the aprotic nonbasic solvent (2). They dealt with factors such as whether the proton transfer occurred inter- or intramolecularly, whether the neutral acid or zwitterion was involved and thus whether the proton was donated from the carboxyl or from the amino group. For reasons given earlier the intervention of zwitterionic reactants may be disregarded.

Reaction scheme (i) proposes the establishment of an ionization equilibrium prior to the actual decarboxylation. Considerable evidence, however, favours the contrary. The low basicity of nitrobenzene is well documented (100). Murray-Rust and co-workers found that perchloric acid was appreciably dissociated in nitrobenzene by conductivity measurements whereas even very strong (aqueous) acids such as hydrochloric, benzenesulfonic and trinitrobenzoic were very weak electrolytes in nitrobenzene (518). Witschonke and Kraus found that pyridinium picrate had a dissociation constant of 5.54×10^{-5} at 25°C. in nitrobenzene (69). Kolthoff et al. determined spectrophotometrically the dissociation of picric acid in nitrobenzene and found it to have a value of 3.5×10^{-8} at room temperature (449). These are all very strong acids in aqueous solution but possess small dissociation constants in nitrobenzene. Dissociation and/or ionization of much weaker acids like anthranilic would be negligible particularly at elevated

temperature. The moderately high dielectric constant of nitrobenzene at room temperature (ϵ = 34.8 at 25°C. (97)) is considerably reduced as the temperature rises and may approach a value of 15-16 at 200°C. An indication may be obtained by extending to this temperature the smooth curve formed by four values of the dielectric constant between 25° and 130°C. (97).

The results of the Hammett treatment pointed out that an extended form of the equation was not required. Substituent effects should have affected the ionization if the latter had occurred. This result also favours the interpretation that an ionization pre-equilibrium may be disregarded.

The more attractive reaction scheme must involve the interaction of two unionized acid molecules. The concave upward Hammett plot obtained by correlating log k_2 with sigma substituent constants (Figure 48) pointed out that O-H bond breaking cannot be the only factor involved. The deuterium-isotope effect (k_H/k_D = 2-3), however, does indicate that the O-H bond must at least be weakened in the transition state (2). The successful application of the Hammett equation using sigma-plus substituent constants together with the magnitude and sign of rho obtained suggest that both C-C bond breaking and C-H bond making are important prior to and in the transition state. If the C-C bond is weakening synchronously with C-H bond making then some degree

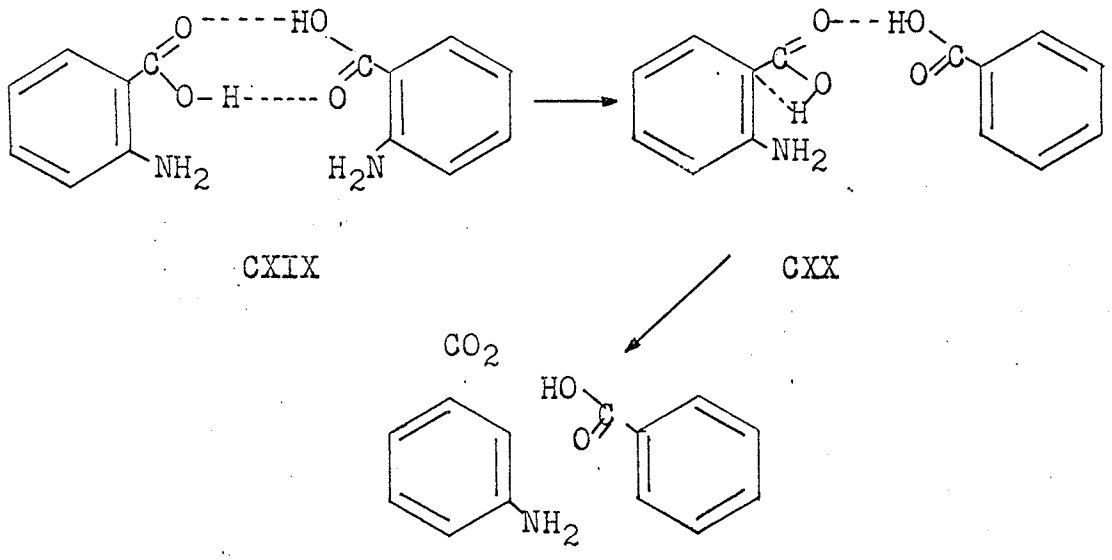
of cancellation may be occurring in the observed rho as seen from the equation

$$\log k_2 = (\rho_{C-H} + \rho_{C-C})\sigma^+ + \log k_2^o \quad . \quad [194]$$

On the basis of the substituent effects C-H bond making is relatively more important at the transition state while C-C bond cleavage may have progressed somewhat less in comparison prior to reaching the activated complex. The mesomeric interaction by substituents is probably somewhat less than that expected from a fully developed Wheland intermediate (67a) but large enough to alter the sp^2 character of carbon 1. This latter effect along with possible weakening of the C-C bond prior to or at the transition state is consistent with the observation that acidity effects seem to be relatively unimportant in the decarboxylation. It offers an explanation for the somewhat paradoxial situation where a deuterium-isotope effect indicates the importance of O-H bond breaking whereas substituent effects do not, because the latters' influences are insulated from the carboxyl proton.

When mechanism (ii) was proposed, it was suggested that conceivably either an intramolecular or intermolecular hydrogen transfer was possible. The former possibility was originally put forward by Dunn and Prysiazniuk but what was envisaged was that in the two molecules existing as dimer (CXIX) in solution, one -O-H...O = C$\swarrow$ bond became

severed and intramolecular hydrogen transfer was able to proceed (CXX)(2).

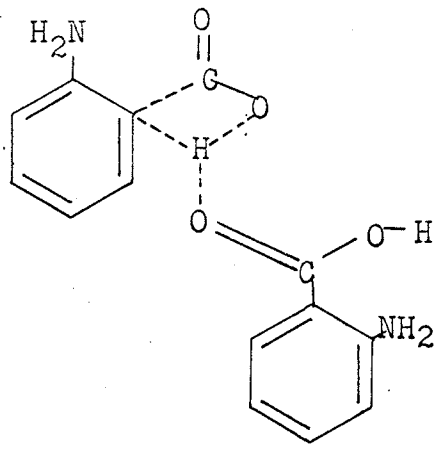


CXIX CXX [195]

There are a number of reasons for not favouring this interpretation as depicted. The above workers also did not prefer this scheme but preferred the intermolecular transfer since it was thought that extensive dimerization in nitrobenzene close to the boiling point is unlikely. For instance, the monomer - dimer equilibrium of benzoic acid in benzene favours the monomeric form as the temperature is raised (475). A consideration of values of $\Delta S^{\ddagger}$ and the frequency factor, A, from equation [192] for anthranilic decarboxylation in nitrobenzene lends support to the idea that dimerization cannot be important. The two quantities have respective values of -29.3 cal/deg mole and 1×10^7 litre/mole sec. If the reactant molecules existed in dimeric form, one might not have expected the structure

of the transition state to impose a rather large additional rigidity in order to reconcile the large negative $\Delta S^{\ddagger}$. It must be remembered, however, that the sign and magnitude of this latter parameter may not only signify a loss of freedom of the reactant molecules in the activated complex, but may also reflect the additional loss of freedom of motion by solvating molecules as the activated complex carries developing charges whereas the reactants do not (519). In this case perhaps the frequency factor may be used to give additional information. The value quoted for A in this work is abnormally low and it is interesting to note that it is virtually the same as that derived for the association of benzoquinone and cyclopentadiene to form the diene adduct, cyclopentadiene - benzoquinone, in nitrobenzene (21-42°C.) (520).

With some confidence, therefore, dimerization of reactant molecules may be neglected from consideration. This does not preclude however that an intramolecular proton transfer occurs. The molecule of anthranilic acid not undergoing decarboxylation may be responding in a manner similar to a molecule of quinoline as proposed for the decarboxylation of anthranilic acids in that solvent. Anthranilic acid possesses a number of basic sites including the amino group, the carbonyl and hydroxyl oxygens. For purposes of illustration only, structure (CXXI) involving the carboxyl oxygen is given below.

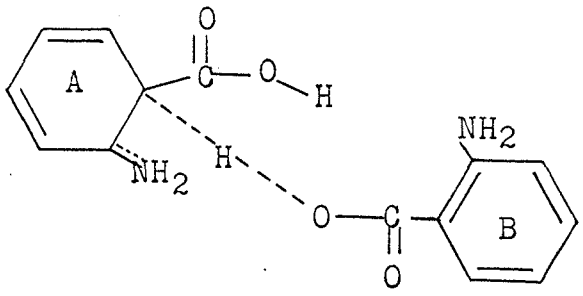


CXXI

Naturally more rigid conformations may be described in which amino or carboxyl groups not directly in interaction with reaction centre processes nevertheless help to hold the complex together. Since no bond is thought to form between a basic site of one molecule and the carboxyl proton of the other, it would be expected that perturbations of electron density at, for example, the carbonyl oxygen by nuclear substituents would not influence the transfer significantly or at least not show up as an obvious substituent effect. The reaction would consist of synchronous bond breaking and making with perhaps the C-C bond being considerably weakened in the transition state relative to C-H bond making. The ortho-amino group may help to stabilize the transition state. The considerations given to the conformational position of the leaving group in the decarboxylation in quinoline may also apply here (see page 509). A weakness of the above description is the questionable basicity of any site in the anthranilic

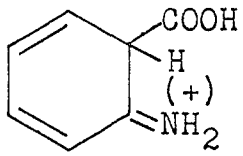
acid molecule and the over-all steric requirements.

The decarboxylation reaction may involve an intermolecular proton attack by one anthranilic acid molecule to carbon 1 of the other species. It was this mechanism that was favoured by Dunn and Prysiazniuk and for which they proposed the transition state (CXXII).



CXXII

The deuterium - isotope effect (k_H/k_D = 2-3) indicated that the O-H bond may only be weakening in the transition state and C-H bond making just beginning to form in molecule A. They suggested that the transition state rests somewhere between the reactants and the intermediate (CXXIII)



CXXIII

so that C-C bond cleavage has not as yet begun. Since the

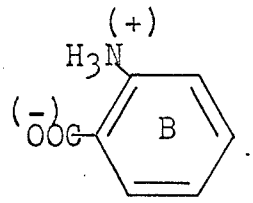
superiority of the Hammett correlation with sigma plus has been shown in this investigation, one must be able to offer some explanation for the fact that the ionization or O-H bond cleavage is seemingly not affected by nuclear substituents (molecule B).

Carboxyl - ^{13}carbon kinetic - isotope effect studies have not been conducted on the present acid - solvent system. Stevens and co-workers found no isotope effect in the melt, in aqueous or in aqueous acid-catalyzed decarboxylations of anthranilic acid (289). More recently Dunn and Buccini found isotope effects in the decarboxylation of 4-methoxy-anthranilic acid in strongly acidic solutions but when pH = 4 was reached the effect was zero (6). Results in these media, however, do not necessarily apply to the decomposition of the same acids in nitrobenzene or to that matter in quinoline. The closest comparable system would be salicylic acids in quinoline. At 196°C. the carboxyl - ^{13}carbon kinetic - isotope effect was found to be 2.2% showing that C-C bond cleavage was at least partially rate determining (6).

There seems to be at least two requirements for adequate support of the intermolecular proton-transfer mechanism.

(i) The transfer of the proton from the carboxyl group of B to carbon 1 of molecule A must be accompanied by a transfer of the proton from the departing carboxyl group in A to the ortho-amino group of B.

B momentarily becomes a zwitterion (CXXIV)

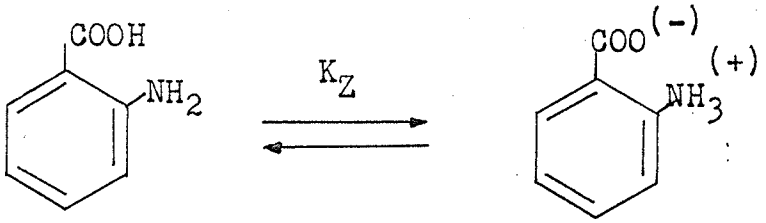


CXXIV

which can revert intramolecularly to neutral anthranilic acid.

(ii) The bond between carboxyl group and carbon 1 of A must be weakening concurrently so that electronic influences of substituents are not being picked up by the departing carboxyl proton.

If a species such as CXXIV were involved in the overall decomposition, its formation could be likened to the nonpolar-dipolar tautomeric equilibrium commonly present in aqueous solution (12).

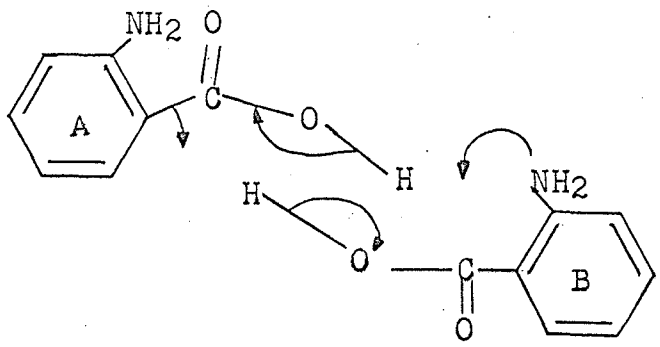


[196]

In order that substituent effects can be rendered unimportant in equation [196], the values of K_Z would have to be all very similar for the series of anthranilic acids. For the

acids used in this decarboxylation study their K_Z values (aqueous) varied from 0.1 for 4-fluoroanthranilic acid to 3.0 for 5-methyl anthranilic acid (12) (see page 448 in this dissertation for details about calculations) which is a 30-fold difference in equilibrium constants. Naturally an aqueous system can not be expected even to crudely approximate the situation envisaged as arising in the decarboxylation. One piece of evidence does support the notion that the catalysis by the second molecule of anthranilic acid (i.e., B) may be bifunctional in character as depicted above and that is that the rate of decarboxylation of p-aminobenzoic acid is only about one fifth the rate of anthranilic acid (2),

With all these factors under consideration structure (CXXII) resembling the proposed transition state may be redrawn



CXXV

to show the necessary electron shifts (CXXV) required of the two reactant molecules in the over-all process. The decomposition, therefore, may be described briefly as taking

place via an intermolecular proton transfer from the carboxyl group of one molecule to carbon 1 of the second anthranilic acid molecule. As the transition state is reached the C-C bond has weakened considerably, proton transfer from O(A) to N(B) is beginning to occur and the carboxyl proton from B is commencing to gain a share in the electron pair which ultimately will form the C-H bond at carbon 1.

The description is consistent with the following experimental observations.

(i) It predicts kinetically that the reaction is second-order with respect to anthranilic acid;

$$\frac{d(CO_2)}{dt} = k_2 \left[RCOOH\right]^2 \quad , \qquad [197]$$

where k_2 is the second-order specific-rate constant.

(ii) The large negative entropy of activation (Table LI) in the decarboxylation supports the proposed transition state which is constrained (cyclic structure) significantly relative to the reactants. It may also reflect an activated complex which is developing partial charges and causing an additional loss of freedom of any solvating molecules.

(iii) The Hammett equation as applied in the form

$$\log k_2 = \rho\sigma^+ + \log k_2^o \qquad [191]$$

was found to correlate the rate data in the decarboxylation. The principal reaction centre is therefore carbon 1. The sign of rho signifies that electron-releasing substituents favour the reaction, consistent with C-H bond making, but the indication is given that C-C bond breaking is important enough to affect a cancellation in the magnitude of this parameter.

(iv) Evidence presented earlier (2) such as the deuterium kinetic-isotope effect, the decarboxylation of N-substituted anthranilic acids and the rate of p-aminobenzoic acid relative to anthranilic are consistent with the proposed mechanism.

There are a number of reaction schemes from literature sources which possess some characteristics of the mechanism described for the decarboxylation of anthranilic acid in nitrobenzene. Schubert studied the decarboxylation of mesitoic acid (2,4,6-trimethylbenzoic) in 82-100 per cent sulfuric acid over the temperature range 50-90°C. and postulated a pre-equilibrium hydronium-ion attack on the carbonyl oxygen followed by a rate-controlling bimolecular proton transfer to carbon 1 of the resulting conjugate acid by a water molecule. A cyclic transition step was proposed (323). Eaborn and co-workers have examined detritiation and desilylation in concentrated trifluoroacetic acid

solutions (521). For example, p-chlorophenyltrimethylsilane reacted with trifluoroacetic acid (80-100 mole per cent region) in a slow proton attack at carbon 1 of the aromatic nucleus resulting in a cyclic intermediate followed by a rapid desilylation step. Norman and Taylor have described numerous other cases where cyclic intermediates or transition states have been postulated in similar systems (67b).

SUMMARY

(1) The preparation of 5-cyanoanthranilic acid is reported for the first time. The two immediate precursors, 2-acetamido-5-cyanotoluene and 2-acetamido-5-cyanobenzoic acid, also apparently have not been reported previously. The same applies to the isomeric products, 2-acetamido-4-cyanotoluene and 2-acetamido-4-cyanobenzoic acid. The preparation of the 4-cyano derivative of anthranilic acid, however, has not been suitably established.

(2) The presence of pyridinium ion in solutions of salicylic and trifluoroacetic acids in pryridine and quinoline is reasonably assured. Anthranilic acid in the two solvents did not exhibit a low-field resonance signal in the vicinity usually attributed to the resonating $\gtrless\overset{(+)}{N}-H$. The absence of such a signal was interpreted as probably the result of weak solute-solvent interaction. A more detailed summary of the work utilizing proton magnetic resonance measurements is given on pages 299 to 302.

(3) The ultraviolet absorption spectrophotometric investigations of salicylic and anthranilic acids in pyridine led to a number of conclusions, mainly

that

(i) taken as a family, the anthranilic acids may be considered as either partially ionized or that the solutes exist chiefly as solvated species through solute-solvent intermolecular hydrogen bonding.

(ii) salicylic acids may be considered to be partially dissociated.

(iii) the spectral characteristics of anthranilic acids do not favour the zwitterionic form.

The more complete summary of information derived from the spectrophotometric study is presented on pages 388 to 390.

(4) The results of the potentiometric titrimetry of substituted salicylic, anthranilic and miscellaneous acids in pyridine and quinoline solutions together with other evidence allowed the following more important interpretations to be advanced.

(i) Acid-base behaviour of salicylic and anthranilic acids in these basic solvents is not complicated by solute self-association, homoconjugation or incomplete solvation of molecular species. Intramolecular hydrogen bonding appears to be considerably stronger in salicylic acid than in anthranilic acid.

(ii) The substantial difference in $\triangle$HNP between the strongest anthranilic acid and the weakest salicylic acid in both solvents indicated that salicylic acids are considerably stronger than the anthranilic acids.

(iii). The relative acidities of a series of substituted anthranilic acids were measured in pyridine and the data found to significantly correlate with an extended form of the Hammett equation which takes into account the contribution to acid strength made by the intramolecular-hydrogen bond.

(iv) Acid strengths of anthranilic acids in aqueous solution do not adequately represent the order of acid strengths as measured by the half-neutralization potential in pyridine. This is a direct consequence of the zwitterionic equilibrium present in aqueous solution.

A more thorough summary related to potentiometric studies is given on pages 475 to 479.

(5) The following synopsis refers to the decarboxylation studies of substituted anthranilic acids conducted in quinoline and nitrobenzene solution.

Quinoline

(i) The decarboxylation of substituted anthranilic

acids in quinoline at 230.6°C. followed first-order kinetics with respect to the acid. Electron-releasing nuclear substituents were found to favour the decarboxylation.

(ii) The activation parameters, $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$, were calculated from the decarboxylation data of selected acids determined at two temperatures. Tentatively, it is found that enthalpy of activation changes are compensated by changes in the same direction for the entropy of activation which suggests the presence of an isokinetic relationship.

(iii) The Hammett relationship was successfully applied to the rate-constant data when the latter were correlated with sigma-plus substituent constants. This result is consistent with a reaction scheme that does not involve an ionization pre-equilibrium.

(iv) The sign and magnitude of rho in the Hammett equation is seen to reflect a composite effect in which C-C bond breaking and C-H bond making at carbon 1 compete, being oppositely affected by nuclear substituents.

(v) The various reaction schemes that were put forward were critically discussed in the light of all the experimental evidence. The most favourable

interpretation of the nature of the mechanism is that the reaction proceeds in concerted fashion by way of a four-centre process. A solvent molecule assists the intramolecular proton transfer from the carboxyl group to carbon 1 of the aromatic nucleus. It appears that at the transition state C-C bond fission has advanced to a lesser extent than C-H bond making. The mechanism is seen to contrast that proposed for the decarboxylation of salicylic acids in quinoline.

Nitrobenzene

(i) The decomposition of substituted anthranilic acids in the aprotic solvent, nitrobenzene, at 200.2°C. was confirmed to be second order. Electron-donating nuclear substituents aided the decarboxylation.

(ii) The activation parameters, $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$, were calculated for anthranilic and 4-amino-acids anthranilic/and the magnitudes are consistent with the proposed mechanism.

(iii) The Hammett equation using sigma-plus substituent constants correlated the rate-constant data particularly well. Implications are drawn from this result in dealing with possible reaction sites and various bond making and bond breaking

processes.

(iv) The probability of ionization or dissociation and dimerization of anthranilic acids in nitrobenzene at 200°C. was shown to be slight. The two most likely reaction schemes involve the interaction of two unionized molecules. In the first place the proton attacking carbon 1 comes from the same molecule (intramolecular) with the second anthranilic acid molecule functioning only as a basic centre in assisting the proton transfer from the hydroxyl oxygen to carbon 1. The second mechanism envisages that the C-H bond making step predominates in the transition state but the process is really concerted with bond breaking and making and electronic rearrangements occurring over an extended cyclic transition state.

SUGGESTIONS FOR FUTURE WORK

(1) The final step in the attempted synthesis of 4-cyanoanthranilic acid should be re-examined and a quantitative analysis made of any product.

(2) Further studies may be pursued in order to place acid-base behaviour in basic solvents such as pyridine and quinoline on a more quantitative basis (i.e., actual determination of ionization and dissociation constants).

(i) A number of suggestions for future work in acidity studies utilizing proton magnetic resonance techniques have already been put forward (see page 301).

(ii) An indicator spectrophotometric method should be screened as a possible approach in studying acid-base equilibria of salicylic and anthranilic acids in pyridine and quinoline. Two papers that may be examined in this regard deal with acid-base behaviour in glacial acetic acid (160) and ethylenediamine (136).

(iii) The method of measuring half-neutralization potentials during titrations has been a very useful procedure for indexing the relative strengths of anthranilic and salicylic acids. In order to determine an acidity scale on an absolute basis, however, it is important that quantitative

potentiometric equilibrium studies be made using electrodes in solutions that contain only the pure acid or the acid and its salt. In this way complications which have been outlined earlier (498) are removed. Quantitative measurements in electromotive-force cells of hydrochloric acid in anhydrous pyridine and quinoline solutions using the glass electrode have been conducted (250). A number of procedures might be checked for their applicability to the systems at hand, in particular the acid-base studies in glacial acetic acid (160), acetonitrile (128, 179) and ethylenediamine (166).

(3) A more thorough study of titration curves of anthranilic and salicylic acid in pyridine and quinoline might be conducted particularly as they may apply to ionization and dissociation phenomena of the acid titrated and the salt that results on titration. The discussion of Kolthoff and Bruckenstein (160) and Schaap et al. (105) may be useful in this regard.

(4) There are a number of approaches that may be taken to advance additional information as to the mechanism of decarboxylation of substituted anthranilic acids in quinoline and nitrobenzene solutions.

Quinoline

(i) A carboxyl-^{13}carbon kinetic-isotope study should be made to examine the relative importance of C-C bond cleavage in the concerted mechanism.

(ii) A carboxyl-deuterium kinetic-isotope study may help to uncover the relative importance of C-H bond making or O-H bond cleavage.

(iii) A number of N-pyridyl and N-quinolylanthranilic acids have been prepared (534, 535, 536) and N-(3-pyridyl) anthranilic acid has been decarboxylated in the solid state (537). It would be interesting to study the rates of decarboxylation of these acids (and others prepared by methods described in the sources quoted) in nitrobenzene with the view of examining if the nitrogen moiety on the pyridyl or quinolyl radical is conformationaly able to assist in proton transfer in the decarboxylation process.

(iv) A determination of the order with respect to quinoline might be made by decarboxylating the acids in nitrobenzene-quinoline solutions. An isotopic study paralleling that done for 4-methylsalicylic acid in quinoline-nitrobenzene and quinoline solutions might also prove useful (6).

(v) A more thorough study of the solvent dependence of reaction rates might be made, which would include factors like basicity, substituent effects, steric hindrance and dielectric constant variations.

(vi) If the decarboxylation of anthranilic and salicylic acids were carried out in a relatively high boiling and strongly basic solvents (e.g., butylpiperidines) which would promote ionization, then possible variations may be observed in the reaction mechanisms. In fact one might find that anionic decarboxylation becomes the exclusive mode of decomposition in both acid systems.

Nitrobenzene

(i) A carboxyl-^{13}carbon kinetic-isotope effect should be made to examine how important C-C bond breaking is in the decarboxylation.

(ii) The decarboxylation of salicylic acid in nitrobenzene was found to be second order with respect to the acid (4). A study of decompositions of substituted salicylic acids in nitrobenzene might be informative since ionization phenomena may become more important with the stronger acids.

APPENDIX

STATISTICAL TREATMENT OF EXPERIMENTAL DATA

The following is an account of the statistical methods in regression, variance and correlation that were utilized in this work. The worded description is purposely limited in most areas but reference is made to adequate and more detailed descriptions found in standard sources. The various equations have been referred to earlier in tables presented in the Discussion (i.e., XLI, XLVII and L). Introduced in the appropriate places in these tables was the number of the equation(s) which was used to arrive at that particular figure or set of values in the table.

In using the various statistical models for linear (single or multiple) regressions it was assumed that each Y_i was an observation on a random variable Y, which was normally distributed and dependent linearly on one or more fixed values X_1, X_2, etc. (522a). These independent variables were considered to have been measured without error (523a). Experimentally, the dependent variable was either the differential half-neutralization potential ($\triangle$HNP) in the potentiometric titrations or the logarithm of the first- or second-order rate constant in the decarboxylation studies (log k) while the independent or fixed variable was the substituent constant (σ, σ^- or σ^+). The slope or regression coefficient, represented by b, in the

following treatment stands for the reaction constant ρ, corresponding to either acid-base studies or experiments in decarboxylation. The intercept a is interjected as log k°, that is, the logarithm of the first- or second-order specific-rate constant for the unsubstituted anthranilic acid. It may also be considered to stand for $(\triangle HNP)_{o}$, that is, the acidity of anthranilic acid relative to benzoic acid in pyridine solution.

I. SIMPLE AND MULTIPLE LINEAR REGRESSION

(a) One independent variable (X) with zero intercept (a = 0) (522a).

The line of regression has the function form

$$Y = bX \qquad [A.1]$$

The regression coefficient or slope parameter (b) is obtained in the usual way by minimizing the sum of the squares of the deviations of the observations (Y) from their mean values.

$$b = \frac{\sum XY}{\sum X^2} \qquad [A.2]$$

In this latter expression and also in all other equations bearing summation signs, it will be understood that X and Y represent the i^{th} values X_i and Y_i respectively.

(b) One independent variable (X) with intercept ($a \neq 0$) (522a).

For the line of regression of the form

$$Y = a + bX \ , \qquad [A.3]$$

the normal regression equations,

$$a\,n + b\sum X = \sum Y$$
$$a\sum X + b\sum X^2 = \sum XY\ , \qquad [A.4]$$

may be solved for intercept (a) and slope (b). Here n refers to the number of observations (Y) made. The former parameter may also be found from

$$a = \bar{Y} - b\,\bar{X} \qquad [A.5]$$

where $\bar{Y}$ and $\bar{X}$ refer to the mean values of the respective variables.

(c) Two independent variables (X_1 and X_2)with zero intercept (a = 0) (522a).

The multiple regression equation is of the form

$$Y = b_1 X_1 + b_2 X_2 \qquad [A.6]$$

The (sample) partial regression coefficients (b_1 and b_2) (523a, 524a) are obtained by solving the equations

$$b_1 \sum X_1^2 + b_2 \sum X_1 X_2 = \sum X_1 Y \qquad [A.7]$$
$$b_1 \sum X_1 X_2 + b_2 \sum X_2^2 = \sum X_2 Y$$

Once these two parameters are made available, the calculated values of Y (i.e., $\tilde{Y}$), may be secured by solving a series of individual equations of the form

$$\tilde{Y} = b_1 X_1 + b_2 X_2 \qquad [A.8]$$

II. STANDARD ERROR OF ESTIMATE

A common statistical quantity, which is used in calculations of standard errors of regression coefficients and intercepts and the analysis of variance, is called the estimate of the variance of the observations Y (522a). It may be described in slightly different terms: the

experimental error variance of the observed Y values (525a), mean square deviation from regression (524b) or the variance about the regression line (523a). It is usually symbolized by $S^2_{Y.X}$, $S^2_{Y.X_1X_2}$, etc. depending upon whether the regression equation involves one or more independent variables. Contained in its expression is the quantity

$$\sum (Y - \tilde{Y})^2$$

which is the sum of the squares of the differences between observed (Y) values and those calculated ($\tilde{Y}$) by inserting the computed values of a, b_1, b_2, etc. (i.e., sum of squares of the deviations from the estimated regression equation). The square root, $S_{Y.X}$, is described as the standard error of estimate (523a, 526a), the standard deviation of Y holding X constant (526a) or (sample) standard deviation from regression (524b). The following expressions are presented in the order which corresponds to the regression equations recorded in I; thus the same notation here (i.e., II(b) refers to the respective equation in I(b). The standard error of estimate is obtained by taking the square root of the expressions noted below.

(a)
$$S^2_{Y.X} = \frac{\sum (Y - \tilde{Y})^2}{n-k} = \frac{\sum (Y - \tilde{Y})^2}{n-1} \qquad [A.9]$$
$$(a=0)$$

where n = number of observations Y,

k = number of independent variables (526b)

$n-k$ = number of degrees of freedom

and
$$\tilde{Y} = b\,X \qquad [A.10]$$

Equation [A.9] may be expanded to a form more convenient for computation (522a, 527).

$$S^2_{Y.X} = \frac{\sum Y^2 - \frac{(\sum XY)^2}{\sum X^2}}{n-1} \qquad (a=0) \qquad [A.11]$$

(b) $$S^2_{Y.X} = \frac{\sum(Y - \tilde{Y})^2}{n-k-1} = \frac{\sum(Y - \tilde{Y})^2}{n-2} \qquad (a \neq 0) \qquad [A.12]$$

where $n-k-1$ = number of degrees of freedom

and $$\tilde{Y} = a + b X \qquad [A.13]$$

Thus (522a)

$$S^2_{Y.X} = \frac{\sum Y^2 - a\sum Y - b\sum XY}{n-2} \qquad (a \neq 0) \qquad [A.14]$$

(c) $$S^2_{Y.X_1X_2} = \frac{\sum(Y - \tilde{Y})^2}{n-k} = \frac{\sum(Y - \tilde{Y})^2}{n-2} \qquad (a = 0) \qquad [A.15]$$

where $$\tilde{Y} = b_1X_1 + b_2X_2 \qquad [A.8]$$

Thus $$S^2_{Y.X_1X_2} = \frac{\sum Y^2 - b_1\sum X_1Y - b_2\sum X_xY}{n-2} \qquad (a = 0) \qquad [A.16]$$

III. STANDARD ERROR--REGRESSION COEFFICIENT AND INTERCEPT

It is useful to obtain an estimate of the standard deviation or error associated with the slopes or partial regression coefficients (S_b) and intercepts (S_a) that have been computed from the various equations outlined in I. Here, as in II, the same order of presentation is maintained so that, for example, the standard deviation for the partial

regression coefficient, S_{b_1}, of equation [A.6] in I(c) will be found under III(c) (i.e., equation [A.25]). It is more convenient in calculations to make use of the square of the standard error of regression coefficient and intercept (variances) from which S_b and S_a may easily be obtained.

(a) The expression for the square of the standard deviation (variance) of b in the case of the simplest linear functional relationship (i.e., $Y = bX$) has the form (522a, 527)

$$s_b^2 = \frac{s^2_{Y.X}}{\sum X^2} \quad . \qquad [A.17]$$

(b)

(i) The estimated variance of the intercept a is expressed by (527, 528a)

$$s_a^2 = \frac{s^2_{Y.X} \sum X^2}{n\sum X^2 - (\sum X)^2} \quad . \qquad [A.18]$$

where n = number of observations Y.

(ii) Also (522a, 524b, 527, 528a)

$$s_b^2 = \frac{s^2_{Y.X}\, n}{n\sum X^2 - (\sum X)^2} \quad . \qquad [A.19]$$

(c) With regression in two variables a method of solution for the standard deviation of the partial regression coefficients is adopted where certain elements, c_{ij} (sometimes known as Gaussian multipliers) are first calculated (522a, 523b, 524a, 526b). From the solution of two sets of equations,

$$c_{11}\, S(X_1^2) + c_{12}\, S(X_1X_2) = 1$$
$$c_{11}\, S(X_1X_2) + c_{12}\, S(X_2^2) = 0 \qquad [A.20]$$

and

$$c_{21}\, S(X_1^2) + c_{22}\, S(X_1X_2) = 0$$
$$c_{21}\, S(X_1X_2) + c_{22}\, S(X_2^2) = 1 \quad , \qquad [A.21]$$

the elements c_{11}, c_{12}, c_{21} and c_{22} may be obtained. The notations, $S(X_1^2)$, $S(X_2^2)$ and $S(X_1X_2)$ are defined by the following equations.

$$S(X_1^2) = \sum X_1^2 - \frac{(\sum X_1)^2}{n} \qquad [A.22]$$

$$S(X_2^2) = \sum X_2^2 - \frac{(\sum X_2)^2}{n} \qquad [A.23]$$

$$S(X_1X_2) = \sum X_1X_2 - \frac{\sum X_1 \sum X_2}{n} \qquad [A.24]$$

Estimates of S_{b_1} and S_{b_2} are now possible by using the expressions

$$S_{b_1}^2 = S^2_{Y.X_1X_2}\, c_{11} \qquad [A.25]$$

and $$S_{b_2}^2 = S^2_{Y.X_1X_2}\, c_{22} \quad . \qquad [A.26]$$

The standard error in the partial regression coefficient may also be obtained directly by solving for c_{11} and c_{22} in terms of the notations in equation [A.20] and [A.21] (11).

Thus $$S_{b_1}^2 = \frac{S^2_{Y.X_1X_2}\; S(X_2^2)}{S(X_1^2)\, S(X_2^2) - \left[S(X_1X_2)\right]^2} \qquad [A.27]$$

and $$S^2_{b_2} = \frac{S^2_{Y.X_1X_2}\, S(X_1^2)}{S(X_1^2)\, S(X_2^2) - \left[S(X_1X_2)\right]^2} \qquad \left[A.28\right]$$

Since the elements or multipliers, c_{11}, c_{22}, etc. are required for setting confidence intervals or making tests of significance as well as for estimating S_b, they may also be used to calculate the partial regression coefficients themselves (b_1 and b_2) by combining the latter with S(XY) values in the equations (522a, 523b, 524a)

$$b_1 = c_{11}\, S(X_1Y) + c_{12}\, S(X_2Y)$$
$$b_2 = c_{21}\, S(X_1Y) + c_{22}\, S(X_2Y) \qquad \left[A.29\right]$$

rather than utilizing equations [A.10].

IV. t STATISTIC AND ANALYSIS OF VARIANCE

Variability in the computed parameters (a, b_1 and b_2) is to be expected because of inherent or uncontrollable factors of experimental error. Naturally the reliability of any estimated parameter will be enhanced as the amount of data (i.e., number of observations Y) from which they are calculated increases. There is, however, a limitation to the number of observations that can be made because of limited resources of compounds studied, time, etc. so that it is often necessary to use statistical tests of significance and perhaps establish confidence limits, if required, on the sample statistics a, b_1 and b_2 (525b).

Among the common tests of significance those involving the 't' statistic and analysis of variance (F test) are frequently used. In this investigation, there was a need to examine whether the data were represented significantly better by a linear regression equation which incorporated an extra independent variable or, in another instance, whether the introduction of an intercept was justified. The general pattern will again be followed (to the extent to which it is feasible); that is, the tests that were conducted are presented in the order in which the regression equations were introduced in section I. A few examples will be dealt with in some detail in an attempt to add further clarification to the description already presented in the interpretation of results in the Discussion.

(a), (b)

(i) In determining whether the experimental data is better represented by

$$Y = a + bX \qquad [A.3]$$

than by the equation with zero intercept

$$Y = bX \qquad [A.1]$$

the relationship or t distribution

$$t = \frac{a - \alpha}{S_a} \qquad [A.30]$$

can be used for the adoption of a null hypothesis (H_o) that the intercept, a, is equal to a specified value α_o (i.e., $H_o: \alpha = \alpha_o$) which, for this purpose, is taken to be equal

to zero (523a, 527, 528a, 529). Here a and S_a represent the calculated estimates of the intercept obtained from the usual least squares method ([A.4]) and standard error in that intercept ([A.18]). The right-hand side of equation [A.30] follows a t distribution with n-2 degrees of freedom where n is the number of observations or samples.

Thus if $H_o: \alpha = 0$,

$$t = \frac{a - 0}{S_a} \quad . \qquad [A.31]$$

Critical values of t may be selected from tables at the confidence level (probability) that one wishes to consider (523c, 524a). Naturally, the choice of significance will depend upon the nature and importance of the investigation being studied but Brookes, Betteley and Loxston have included the following useful table in their book which indicates divisions that are generally accepted (525b). Jaffe has tested the significance of numerous applications of the extended Hammett equation (e.g., generally possessing two independent variables or sigma substituent constants) over the simple expression as formulated by its originator. As a limit of significance for, say, rejecting the inclusion of a second partial regression coefficient, b_2, he recommended the 95% confidence level (46, 47). A similar interpretation will be given to the confidence tests in this study and Table A.I has, therefore, been modified as shown.

Returning once more to equation [A.31], if a value of

TABLE A.I

Divisions of Significance Levels[a]

Probability	Conclusion	Symbol
Greater than 0.1	NOT SIGNIFICANT, H_o accepted.	N.S.
Between 0.1 and 0.05	POSSIBLY SIGNIFICANT, some doubt cast on H_o but further evidence sought before rejection.	P.S.(N.S.)[b]
Between 0.05 and 0.01	SIGNIFICANT, H_o rejected; if the result is very important confirm with further evidence.	S*
Between 0.01 and 0.001	HIGHLY SIGNIFICANT, H_o confidently rejected.	S**
Less than 0.001	VERY HIGHLY SIGNIFICANT, H_o rejected and it is very unlikely that the conclusion is incorrect.	S***

[a] Reference (525b); the notation is changed slightly.

[b] Reference (46, 47).

t in excess of the selected critical value is obtained, then the result is evidence that the data do not support the hypothesis that the intercept is zero and, therefore, H_o is rejected. In this case, equation [A.3] would be preferred over the simpler one [A.1]. In comparing the calculated t value (equation [A.31]) with the tabulated t value, the foregoing may conveniently be summarized symbolically for the case of n-2 degrees of freedom and probability of 0.05.

$$\text{If } |t| \geq t_{0.05(n-2)} \quad ; \text{ reject } H_o \qquad [A.32]$$

$$\text{or if } |t| < t_{0.05(n-2)} \quad ; \text{ unable to reject } H_o \qquad [A.33]$$

As an example consideration might be given to a statistical analysis made in the present study of the potentiometric titration data of substituted benzoic acids in pyridine experimentally determined by Streuli and Miron (10). They were fitted to the equation

$$Y = a + bX \qquad [A.3]$$

or specifically

$$\Delta HNP = a + \rho\sigma \quad . \qquad [A.34]$$

By introducing the computed values of a and S_a as recorded in Table XLI on page 432 into equation [A.31], H_o: $\alpha = 0$ is tested.

$$t = \frac{8.52}{3.99} = 2.14 \qquad [A.31]$$

At the 95% confidence level with n-2 degrees of freedom the tabular value $t_{0.05(12)} = 2.18$ (522b). Since the result (N.S.) represents conditions given by [A.33], H_o cannot be rejected

since the evidence is insufficient to maintain that the intercept differs from zero more than can be attributed to experimental error. The relative acidity data is, therefore, suitably represented by the simple equation

$$\triangle \text{HNP} = \rho\sigma \qquad . \qquad [A.35]$$

For interest, the intercept a would have been 'significant' if the confidence level between 0.1 to 0.05 had been accepted. The statistical test is supported further by chemical intuition and by reason of the mathematical formulation of equation [A.35]. Since $\triangle$HNP really represents a relative measure of acidity of meta- and para-substituted benzoic acids which is equivalent to an expression like $\log \frac{K}{K_o}$ (data for the equilibrium constants is more readily obtainable in aqueous solution), then the presence of an intercept in the regression equation would not have been considered tenable.

(ii) An analysis of variance in regression also provides a method for arriving at the results described in the example given immediately above. It is perhaps a more direct way since it removes the necessity of knowing the standard deviation of the parameter a, b_1 or b_2 and much of the pertinent information can be obtained when $S_{Y.X}$ or $S_{Y.X_1X_2}$ is calculated. Dunn and co-workers (2, 12) and Jaffe *et al.* (46, 47, 530, 531) have used the techniques of variance analysis extensively in establishing the significance of extended forms of the Hammett relationship when compared to

simpler expressions. Youden has presented, most clearly, a simple example of one way of conducting the examination (527). A measure of the goodness of fit of the line is given by the deviations from either regression line described by equations [A.34] and [A.35]. The formulas and calculations necessary for a simple analysis of variance are summarized in Table A.II. The treatment has considerable similarity to ones given by Youden (527) and Jaffe and Jones (46).

The variance ratio represented in line 2.1 of Table A.II, namely

$$F = \frac{S - S'}{\frac{S'}{n-k-1}} \qquad [A.36]$$

$$= \frac{\text{mean square for reduction in the deviations (S) due to a (improvement)}}{\text{mean square for deviations from single regression, } a \neq 0}, \qquad [A.37]$$

follows an F distribution with 1 and n-2 degrees of freedom. The denominator of the right-hand side of the expression [A.36] is taken to be the error in the variance analysis. For a line constrained to pass through the origin the variance is S/n-1 (line 1.2). If the fit is improved by the introduction of the constant a in the regression equation, then one obtains a smaller variance $S'/n-2$ (line 3.2). The quantity $(S - S')$ is a measure of this improvement or reduction in the sum of squares, S, due to a and in the F ratio comparison is made to the mean square $S'/n-2$ (error). In order to test this improvement the hypothesis (H_o) to be

TABLE A.II

Analysis of Variance[a]

No.	Equation	Source of Variation	D.F.[b]	S.S.[c]	M.S.[d]	F[e]	$F_P(\nu_1, \nu_2)$[f]
1.1	$Y = bX$	Deviations from single regression, $a = 0$	n-k	$\sum Y^2 - \frac{(\sum XY)^2}{\sum X^2}$ (S)	$\frac{S}{n-k}$		
1.2	$\Delta HNP = \rho\sigma$		n-1	$\sum(\Delta HNP)^2 - \frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2}$	$\frac{S}{n-1}$		
1.3			13	3506	270		
2.1		Reduction in S due to a	1	(line 1.1 - 3.1) $- \frac{(\sum XY)^2}{\sum X^2} + a\sum Y + b\sum XY$ (S-S')	$\frac{S-S'}{1}$	$S-S'/\frac{S'}{n-k-1}$	
2.2			1	$- \frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2} + a\sum \Delta HNP + \rho \sum (\sigma \Delta HNP)$		$S-S'/\frac{S'}{n-2}$	
2.3			1	966	966	4.56(N. S.)	$P_{0.05}(1, 12) = 4.75$ $P_{0.10}(1, 12) = 3.18$
3.1	$Y = a + bX$	Deviations from single regression, $a \neq 0$	n-k-1	$\sum Y^2 - a\sum Y - b\sum XY$ (S')	$\frac{S'}{n-k-1}$		
3.2	$\Delta HNP = a + \rho\sigma$		n-2	$\sum(\Delta HNP)^2 - a\sum \Delta HNP - \rho \sum (\sigma \Delta HNP)$	$\frac{S'}{n-2}$		
3.3			12	2540	212		

TABLE A.II Continued

[a] Represents an analysis of variance for the potentiometric titration data of relative acidities of m- and p-substituted benzoic acids in pyridine (10).

[b] Degrees of freedom; total number of observations (compounds), n = 14; k = number of independent variables (i.e., k = 1).

[c] Sum of the squares of deviations; includes the formula used in the calculation; the notation S and S' is similar to that used by Youden (527) but the classification here has been reversed.

[d] Mean square: S.S./D.F.

[e] Variance ratio, calculated by dividing the mean square of that line by the mean square for the error. As an estimate of error the deviations from single regression ($a \neq 0$) are used; N.S. indicates not significant at the 95% confidence level.

[f] Variance ratio obtained from tables (522c, 523d) where P indicates the probability or significance reached by the test with degrees of freedom ν_1 and ν_2 in the numerator and denominator respectively.

examined here is that a = 0, that is, the line goes through the origin. Once again the level of confidence is taken to be 95%.

$$\text{If } F \geq F_{0.05\,(\nu_1,\,\nu_2)}\text{; reject } H_o \qquad [A.38]$$

$$\text{or if } \quad F < F_{0.05(\nu_1,\nu_2)}\text{; unable to reject } H_o \qquad [A.39]$$

where ν_1 and ν_2 refer to the degrees of freedom associated with the numerator and denominator in expression [A.36]. The computed variance ratio for line 2.3

$$F = \frac{966}{212} = 4.56 \qquad [A.36]$$

may be compared to the critical value from tables (522) (line 2.3),

$$F_{0.05\,(1,\,12)} = 4.75 \qquad [A.40]$$

This result (N.S.) represents conditions given by [A.39], therefore, it cannot be concluded that the intercept differs from zero significantly enough to reject the simple equation [A.35] over [A.34]. (One notes that at the 90% significance level the result would have been significant and H_o could have been rejected). Expressed differently, one would have accepted the hypothesis that the line goes through the origin if it were found that the one degree of freedom associated with (S - S') took out considerably more than its proportionate share of S, that is, the portion of the total sum of squares that should be accounted for by the linear regression (a = 0) (527). To understand how this share of S arises, one can interrelate the sources of

variation about the fitted line conveniently by use of the simple expression (46, 525a).

total S.S. = S.S. due to single regression—
S.S. due to deviations from single regression [A.41]

(a), (b), (c)

In the experimental work conducted in this study the potentiometric titration data were fitted to the three following equations:

$$\Delta HNP = \rho\sigma \qquad [A.35]$$

$$\Delta HNP = \rho\sigma + a \qquad [A.34]$$

$$\Delta HNP = \rho_1\sigma_1 + \rho_2\sigma_2 \qquad [A.42]$$

(i) If the t statistic is utilized as a measurement of significance, then a test that the parameters a and $\rho_2(b_2)$ (from equations [A.34] and [A.42] respectively) are different from zero may be made. The former problem, that of testing the hypothesis H_o: $\alpha = 0$ is handled identically to that outlined in the first part of IV and in particular, equations [A.31], [A.32] and [A.33].

Further, the t distribution

$$t = \frac{b_2 - \beta}{s_{b_2}} \qquad [A.43]$$

with n-2 degrees of freedom may be used to test the hypothesis (523a, 524b, 529).

$$H_o : \beta = 0 \qquad [A.44]$$

Equation [A.43] then becomes

$$t = \frac{b_2}{s_{b_2}} \qquad [A.45]$$

Here, b_2 and S_{b_2} represent the calculated estimates of the partial regression coefficient and the standard error in that coefficient. Introducing the computed values into [A.45],

$$t = \frac{\rho_2}{s_{\rho_2}} = \frac{22.0}{5.62} = 3.91 \qquad [A.45]$$

At the 95% confidence level with n-2 degrees of freedom the tabular value is $t_{0.05\ (8)} = 2.31$ (522b). The result is, therefore, significant; in fact, it is highly significant (S**) (Table XLI, page 432) since even at $t_{0.005\ (8)}$ the tabular value is only 3.83. The hypothesis that the partial regression coefficient ρ_2 is zero can confidently be rejected and the conclusion accepted that the equation [A.42] bearing the two independent variables represents the data best of the three equations [A.35], [A.34] and [A.42].

(ii) In multiple linear regressions like equation [A.42], the use of the t statistic [A.45] necessitated knowing the Gaussian multiplier c_{22} in order to calculate S_b. An analysis of variance permits a testing of the significance of the equation bearing the two substituent constants without this knowledge. The example presented here will involve equations [A.35], [A.34] and [A.42], the results of which are summarized in Table A.III. The first portion of this Table (sets 1-3) involves the analysis of the first two equations and is identical to the presentation in Table

TABLE A.III

ANALYSIS OF VARIANCE[a]

No.	Equation	Source of Variation	D.F.[b]	S.S.[c]	M.S.[d]	F[e]	F_P[f]
1.1	$Y = bX$	Deviations from single regression, $a = 0$	$n-k$	$\sum Y^2 - \frac{(\sum XY)^2}{\sum X^2}$ (S)	$\frac{S}{n-k}$		
1.2	$\Delta HNP = \rho\sigma$		$n-1$	$\sum(\Delta HNP)^2 - \frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2}$	$\frac{S}{n-1}$		
1.3			9	654	73		
2.1		Reduction in S due to a	1	(line 1.1 - 3.1) $-\frac{(\sum XY)^2}{\sum X^2} + a\sum Y + b\sum XY$ (S-S')	$\frac{S-S'}{1}$	$S-S'/\frac{S'}{n-k-1}$	
2.2			1	$-\frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2} + a\sum \Delta HNP + \rho\sum(\sigma \Delta HNP)$	$S-S'/S'/n-2$	$S-S'/\frac{S'}{n-2}$	
2.3			1	174	174	2.90 (N. S.)	$F_{0.05}$ $F_{0.25}$
3.1	$Y = a + bX$	Deviations from single regression, $a \neq 0$	$n-k-1$	$\sum Y^2 - a\sum Y - b\sum XY$ (S')	$\frac{S'}{n-k-1}$		
3.2	$\Delta HNP = (\Delta HNP)_o^g + \rho\sigma$		$n-2$	$\sum(\Delta HNP)^2 - a\sum \Delta HNP - \rho\sum(\sigma \Delta HNP)$	$\frac{S'}{n-2}$		
3.3			8	480	60.0		
4.1		Reduction in S due to b_2X_2	1	(line 1.1 - 5.1) $-\frac{(\sum XY)^2}{\sum X^2} + b_1\sum XY + b_2\sum X_2Y$	$\frac{S-S''}{1}$	$S-S''/\frac{S''}{n-k}$	
4.2			1	$-\frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2} + \rho_1\sum(\sigma \Delta HNP) + \rho_2\sum(\sigma \bar{\Delta} HNP)$ (S-S'')		$S-S''/\frac{S''}{n-2}$	
4.3			1	436	436	16.1 (S**)	$F_{0.05}$ ($F_{0.005}$(

TABLE A.III

ANALYSIS OF VARIANCE[a]

on	Source of Variation	D.F.[b]	S.S.[c]	M.S.[d]	F[e]	$F_{P(\nu_1, \nu_2}$[f]
	Deviations from single regression, a = 0	n-k	$\sum Y^2 - \frac{(\sum XY)^2}{\sum X^2}$ (S)	$\frac{S}{n-k}$		
		n-1	$\sum(\Delta HNP)^2 - \frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2}$	$\frac{S}{n-1}$		
		9	654	73		
	Reduction in S due to a	1	(line 1.1 - 3.1) $-\frac{(\sum XY)^2}{\sum X^2} + a\sum Y + b\sum XY$ (S-S')	$\frac{S-S'}{1}$	$S-S'/\frac{S'}{n-k-1}$	
		1	$-\frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2} + a\sum \Delta HNP + \rho\sum(\sigma \Delta HNP)$	$S-S'/\frac{S'}{n-2}$	$S-S'/\frac{S'}{n-2}$	
		1	174	174	2.90 (N. S.)	$F_{0.05}$ (1, 8) $F_{0.25}$ (1, 8)
	Deviations from single regression, $a \neq 0$	n-k-1	$\sum Y^2 - a\sum Y - b\sum XY$ (S')	$\frac{S'}{n-k-1}$		
$NP)_o^g + \rho\sigma$		n-2	$\sum(\Delta HNP)^2 - a\sum \Delta HNP - \rho\sum(\sigma \Delta HNP)$	$\frac{S'}{n-2}$		
		8	480	60.0		
	Reduction in S due to b_2X_2	1	(line 1.1 - 5.1) $-\frac{(\sum XY)^2}{\sum X^2} + b_1\sum XY + b_2\sum X_2Y$	$\frac{S-S''}{1}$	$S-S''/\frac{S''}{n-k}$	
		1	$-\frac{(\sum \sigma \Delta HNP)^2}{\sum \sigma^2} + \rho_1\sum(\sigma \Delta HNP) + \rho_2\sum(\sigma \bar{\Delta} HNP)$ (S-S'')		$S-S''/\frac{S''}{n-2}$	
		1	436	436	16.1 (S**)	$F_{0.05}$ (1, 8) = $F_{0.005}$(1, 8) =

TABLE A.III Continued

No.	Equation	Source of Variation	D.F.[b]	S.S.[c]	M.S.[d]	F[e]
5.1	$Y = b_1X_1 + b_2X_2$	Deviations from double regression, a = 0	n-k	$\Sigma Y^2 - b_1\Sigma XY - b_2\Sigma X_2Y$ (S")	$\frac{S"}{n-k}$	
5.2	$\Delta HNP = \rho_1\sigma_1 + \rho_2\sigma_2$		n-2	$\Sigma(\Delta HNP)^2 - \rho_1\Sigma(\sigma\Delta HNP) - \rho_2\Sigma(\sigma^-\Delta HNP)$	$\frac{S"}{n-2}$	
5.3			8	218	27.2	

TABLE A.III Continued

Source of Variation	D.F.[b]	S.S.[c]	M.S.[d]	F[e]	$F^{f}P(\nu_1, \nu_2)$
Deviations from double regression, a = 0	n-k	$\Sigma Y^2 - b_1\Sigma XY - b_2\Sigma X_2Y$ (S")	$\frac{S"}{n-k}$		
$\rho_2\sigma_2$	n-2	$\Sigma(\Delta HNP)^2 - \rho_1\Sigma(\sigma\Delta HNP) - \rho_2\Sigma(\sigma^-\Delta HNP)$	$\frac{S"}{n-2}$		
	8	218	27.2		

TABLE A.III Continued

[a] Represents an analysis of variance for the potentiometric titration data of relative acidities of substituted anthranilic acids in pyridine in this investigation for single and multiple linear regression.

[b] Degrees of freedom; total number of observations (compounds), n = 10; k = number of independent variables.

[c] Sum of the squares of deviations; includes the formula used in the calculation; the notation S, S' and S'' follows a similar representation used by Youden (527) although the order of classification is not the same.

[d] Mean square: S.S./D.F.

[e] Variance ratio, calculated by dividing the mean square of that line by the mean square for the error. With reference to sets 1, 2 and 3 the estimate of error is given by the deviations from single regression ($a \neq 0$) while in reference to sets 1, 4 and 5 the estimate of error is given by the deviations from double regression ($a = 0$); N.S. indicates not significant at the 95% confidence level; S** refers to a highly significant result (99-99.9%).

[f] Variance ratio obtained from tables (522c, 523d) where P indicates the probability or significance reached by the test with degrees of freedom ν_1 and ν_2 in the numerator and denominator respectively.

[g] $(\triangle HNP)_o$ stands for the differential half-neutralization potential of unsubstituted anthranilic acid with reference to benzoic acid.

A.II since the same problem is being investigated. The summary here, however, is presented in its entirety for completeness. A description related to the method of variance analysis has already been given (IV(a),(b)) and will not be repeated. The interpretation given to the results is approached in a similar manner.

An inspection of Table A.III indicates that even though there is a reduction in S due to the inclusion of parameter a, it is not significant enough to reject the validity of representing the data by the simple Hammett equation (line 1.1). This result upholds that derived from the use of the t statistic for the intercept a (see Table XLI page 432). When the analysis includes consideration of an equation with two independent variables (line 5.2), however, the reduction in S due to the introduction of b_2X_2 is highly significant as seen by the F column in line 4.3. The conclusion reached is that one can be confident that, statistically, the extended form of the Hammett equation [A.42] represents the data best of all.

V. SIMPLE AND MULTIPLE CORRELATION COEFFICIENTS

Generally speaking, statistical analyses of experimental work in the physical sciences usually involve problems of regression. The nature of this work has lent itself to a consideration of various statistical models for linear (single or multiple) regression. The forms of the equations relating the several variables were anticipated from either

a chemical sense or from previous formulations and the usual assignment was to determine necessary constants or parameters. However, there is another approach available for examining if a (linear) relationship exists between observations which comes under the general heading of correlation analysis (522a,d, 523e, 524c, 526c, 528a, 529, 532).

The method is more commonly used in cases where there is no reason to believe that there is a dependence of one variable on the other. It is applied most correctly when bivariate (multivariate) distributions are involved; that is, the sampling is made from a bivariate population (or multivariate population if more than two variables are considered) in which a random pair of measurements constitutes an observation. In other words, the variable X does not retain its fixed characteristic as was understood previously in the regression analysis. Regardless of the foregoing, the linear correlation coefficient, as it is usually named, is often quoted in work related to examinations of linear free energy relationships of which the Hammett equation is a particularly important example (2, 12, 22, 46, 47, 531).

(i) When only two variables are involved the degree of linear association is given by the simple correlation coefficient r (532, 532a),

$$r = \frac{n\sum XY - \sum X \sum Y}{\left[n\sum X^2 - (\sum X)^2\right]^{1/2}\left[n\sum Y^2 - (\sum Y)^2\right]^{1/2}} \qquad [A.46]$$

where n = number of pairs of observations, or equivalently by (523e, 526c, 528a, 529).

$$r = \frac{\sum(X - \bar{X})(Y - \bar{Y})}{\left[\sum(X - \bar{X})^2 \sum(Y - \bar{Y})^2\right]^{1/2}} \quad , \qquad [A.47]$$

where $\bar{X}$ and $\bar{Y}$ represent the means of the respective variables. The (sample) linear correlation coefficient is independent of units of measurement and, therefore, the variables X and Y are no longer intended to imply an independent and a dependent variable (524c, 526c). The coefficient is also known by the name of simple correlation, total correlation and product-moment correlation coefficient (523e, 526c, 529) and can have the value

$$-1 \leqslant r \leqslant 1 \quad . \qquad [A.48]$$

If r has a value near 1 or -1, the variables are said to be highly correlated. A negative linear correlation means that as one variable decreases the other increases while a positive correlation is one in which one variable increases as the other also increases.

In this study equation [A.46] was used where the degree of association was examined for variables such as substituent constants (i.e., σ and σ^+) and the logarithms of the rate constants in decarboxylation (log k) or the relative acidity constant in nonaqueous potentiometric titrations (ΔHNP). The correlation coefficient has also proven useful in measuring the degree of linear association between substituent constants (i.e., σ and σ^-) when both have

been incorporated in multiple-parameter Hammett equations. Jaffe, in extensive examinations on the validity of extended forms of the Hammett equation, has suggested that a correlation coefficient of $r_{12} > 0.9$ between substituent constants σ_1 and σ_2 be arbitrarily taken as the limit of usefulness (47) in using an equation such as [A.42]. Most of the apparent inconsistent results in applying multiple-parameter equations to experimental data have been removed by acknowledging the simple suggestion given by Jaffe.

Once a linear correlation coefficient is obtained, workers may then consider testing various hypotheses about the degree of correlation existing between the two variables, the most common of which is the hypothesis that no correlation exists between the two variables (i.e., r = 0) (523e). Tables are available which give for various numbers, n, of pairs of observations, the probability of obtaining a given value of r (523f, 526d, 528b). At the level of significance chosen, for n-2 degrees of freedom, the observed or computed value of r_{XY} is considered to be significantly different from zero if it exceeds the tabular value. For an example, the two substituent constants σ (σ_1) and σ^- (σ_2) which were applied to the potentiometric-titration data in the form of equation [A.42], had a correlation coefficient $r_{\sigma,\sigma^-} = 0.578$. At the 95% confidence level and n-2 = 8 degrees of freedom

$$r_{\sigma,\sigma^-}(0.05, 8) = 0.632 \qquad [A.49]$$

which may be taken to mean here a lack of confidence in the correlation although the tabular value

$$r_{\sigma,\sigma^-}\ (0.10,\ 8) = 0.549 \qquad [A.50]$$

indicated significance at the 90% level. If the suggestion made by Jaffe is accepted that only pairs of substituent constants having correlation coefficients < 0.9 are useful in testing the reliability of equations such as

$$\Delta HNP = \rho_1\sigma_1 + \rho_2\sigma_2 \quad , \qquad [A.42]$$

then the probability test ([A.49] and [A.50]) was not really needed. It did add, however, further emphasis that the number of compounds, which were represented by the pairs of substituent constants with correlation coefficient $r_{\sigma,\sigma^-} = 0.578$, is suitable for testing the significance of having equation [A.42] represent the data.

(ii) When three variables are involved, an examination of the degree of association can be made by utilizing the multiple (linear) correlation coefficient R (522a, 523b, 526b, 533b). Ostle has remarked that R may be looked upon as a measure of the degree of joint linear association among all the variables, both dependent and independent, that are under consideration (523b). The value of R obtained is greater than or always at least as large as any simple correlation coefficient which expresses the degree of linear association between Y and only one of the other variables (X's). It is given in general terms by (522a,

533b)

$$R^2_{1.23} = 1 - \frac{(n-k)\, S^2_{1.23}}{(n-1)\, S_1^2} \qquad [A.51]$$

or

$$R_{1.23} = \left[1 - \frac{(n-k)\, S^2_{1.23}}{(n-1)\, S_1^2} \right]^{1/2} \qquad [A.52]$$

where n = number of groups of three variables,

k = number of variables being considered,

$S^2_{1.23}$ = variance about the regression line described earlier (see I(c))

and S^2_1 = variance of variable 1 when no account is taken of the relation between 2 or 3 and 1.

The quantity $R^2_{1.23}$ is known as the coefficient of multiple determination (533b). The coefficient of multiple linear correlation may have the values

$$0 \leqslant R \leqslant 1 \qquad [A.53]$$

where a perfect correlation would be indicated by 1.

Specifically, equation [A.51] would become

$$R^2_{Y.X_1X_2} = 1 - \frac{(n-3)\, S^2_{Y.X_1X_2}}{(n-1)\, S^2_Y} \qquad [A.54]$$

$$= 1 - \frac{(n-3)\left[\dfrac{\sum Y^2 - b_1\sum XY - b_2\sum X_2Y}{(n-2)}\right]}{(n-1)\left[\dfrac{\sum Y^2 - \dfrac{(\sum Y)^2}{n}}{(n-1)}\right]} \qquad [A.55]$$

where Y, X_1 and X_2 could be represented experimentally by

ΔHNP, σ and σ^- respectively. Just as was done with the simple linear correlation coefficient, R may be tested for the hypothesis that no linear correlation exists among the variables and tables are available to give R values at different probability levels (523f, 526d).

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