A STUDY OF THE DECARBOXYLATION OF SUBSTITUTED

SALICYLIC ACIDS IN QUINOLINE SOLUTION

by

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ABSTRACT OF Ph.D. THESIS

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A Study of the Decarboxylation of Substituted Salicylic Acids in Quinoline Solution.

The rates of decarboxylation of a series of 4- and 5-substituted salicylic acids in quinoline solution were measured over a temperature range. The reaction is first order with respect to the acid. The reaction was also first order with respect to the quinoline as determined by measuring the rates of decarboxylation in quinoline - nitrobenzene mixtures. The relative rates were interpreted by means of the Hammett equation and its extensions and it is concluded that carboxyl O-H bond breaking and C-H bond making at carbon 1 are involved in the rate determining step.

It is also concluded that the decarboxylation of salicylic acids in quinoline involves the intramolecular proton transfer from the carboxyl group to the carbon α to the carboxyl group. The reaction proceeds by means of an ion pair formation of the acid and quinoline.

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INTRODUCTION

General Introduction

The aim of the present investigation is to determine the mechanism of the decarboxylation of salicylic acid in quinoline solution.

The mechanism of a reaction gives a description of the most favorable reaction path for the transformation of reactants into products. Generally speaking, the minimum information required to postulate a reaction mechanism is knowledge of the stoichiometric equation, the rate law, and the energy of activation.

The kinetic approach is usually considered to be the most general method of determining the reaction mechanism and is the method followed in the present investigation. Measurement of the rate of a chemical reaction implies knowledge of the stoichiometry of the reaction and of the way in which the concentration of reactants or products varies with time. Such variation may be extremely complex, but often a simple relationship such as the following can be found:

$$-\frac{dA}{dt} = kA \quad \ldots \ldots \ldots \text{ 'first order' reaction}$$

or

$$-\frac{dA}{dt} = kA^2 \quad \ldots \ldots \ldots \text{ 'second order' reaction}$$

where A is the concentration of reactant, t is the time and k is the specific rate constant.

Additional kinetic studies can supply more information as to the mechanism of a reaction by devices such as studying the effect of substituents on the rate of a given reaction, the

effect of changing solvents, the effect of changing steric factors and so forth.

Non-kinetic techniques employed to gain further insight into the mechanism of a reaction are stereochemical studies, isotopic labelling, detection of short lived intermediates and many more.

The results of kinetic measurements and other experiments furnish facts which can then be used to devise a mechanism. The mechanism is just a mental model based on experimental facts. It should be kept in mind that no matter how well a given mechanism fits the observed facts, it is always possible that some different mechanism which represents the data just as well, will be discovered later.

Theories of Reaction Rates

Arrhenius Equation

By extending the work of van't Hoff, Arrhenius showed (1) that the expression

$$\frac{d \ln k}{dT} = \frac{E_a}{RT^2} \quad \ldots \ldots \quad (1)$$

fitted the variation of the rate constant k with temperature T. The interpretation given was that an equilibrium between normal and active molecules existed. Active molecules are those capable of undergoing chemical change. A change in the temperature of the system merely shifted the position of this equilibrium. The postulated difference between 'normal' and 'active' species was solely one of energy content; the amount of energy required to transform a normal molecule into an active

one being termed the activation energy E_a. Equation (1) can
be integrated to the following equation.

$$\ln k = \frac{-E_a}{RT} + constant \ldots \ldots (2)$$

or

$$k = Ae^{-E_a/RT} \ldots \ldots (3)$$

where k is the specific rate constant, E_a is the activation
energy, T is the absolute temperature, R is the universal gas
constant and A is the constant of integration. The significant
fact about equation (2) is that it predicts that a plot of ln k
vs 1/T will yield a straight line, the slope of which is $-E_a/R$.
Thus equation (3) would permit k to be computed directly from
E_a at some temperature T if the constant A could be evaluated.

The Collision Theory

Lewis (39) attempted to interpret the constant A in
equation (3). He proposed that before chemical reaction can
occur between two molecules they must collide with each other.
He suggested that the frequency of such collisions, and hence
chemical reaction, could be related to the constant A in equation
(3). Assuming a Maxwell distribution of velocities, the fre-
quencies of collision between molecules is given by

$$z = n_a n_b \sigma_{ab}^2 \left[8\pi kT \frac{(m_a + m_b)}{m_a m_b} \right]^{1/2} \ldots \ldots (4)$$

where n_a, n_b = number of molecules a and b respectively, σ_{ab} =
mean collision diameter, and m_a, m_b = masses of a and b, respec-
tively. The rate of reaction v is given by

$$v = ze^{-E_a/RT} \ldots \ldots (5)$$

and the rate constant k is equal to

$$k = v/n_a n_b \quad \cdot \; \cdot \; \cdot \; \cdot \; \cdot \; \cdot \quad (6)$$

and thus $k = Ze^{-E_a/RT} \quad \cdot \; \cdot \; \cdot \; \cdot \; \cdot \; \cdot \quad (7)$

where Z is the collision number $\sigma_{ab}^2 \; [8\pi kT \; \dfrac{(m_a + m_b)}{m_a m_b}]^{1/2}$.

This simple treatment gives reasonable agreement with experiment for simple molecules reacting in the gas phase and for many reactions in solution. A number of reactions involving complex molecules gave an observed rate considerably lower than the calculated values (62). These discrepencies between theory and experiment were explained in terms of steric requirements for reaction. If there is a preferred orientation of molecules on the collision which leads to reaction, then the number of effective collisions may be less than that predicted by the kinetic theory and the rate of chemical reaction will be slower than that calculated by the collision theory. By choosing a suitable value for the steric factor p, the modified form of equation (7) becomes

$$k = pZe^{-E_a/RT} \quad \cdot \; \cdot \; \cdot \; \cdot \; \cdot \; \cdot \quad (8)$$

and gives reasonable agreement with experiment in a number of cases. The collision theory of reaction rates has thus equated the quantity pZ with the integration constant A in equation (3). In many cases the steric factor p is simply a correction factor to make the theory fit the experiment.

It is seen that an equation such as (8) which relates the specific rate constant k to a collision frequency Z, a steric factor p, and an Arrhenius activation energy E_a, presumes a

detailed knowledge of the nature of the collisions between the reacting molecules and the steric requirements of these collisions.

The Absolute Reaction Rate Theory

The absolute reaction rate theory has been the most successful one to date. It relates the specific rate constant to the more fundamental thermodynamic and spectroscopic properties of molecules. It was developed about thirty years ago and was expressed in its most useful form by Eyring (20). According to this theory a chemical reaction proceeds in such a way that the reactants pass through a continuous series of configurations on their way to forming products. At some point along the reaction path a critical configuration called the transition state or activated complex is reached. This configuration is the highest point of the most favorable reaction path on the potential energy surface. The assumption is made that the rate of reaction is given by the rate of decomposition of the activated complex. The concentration of activated complexes is determined by an equilibrium with the reactant molecules.

Consider a bimolecular reaction between molecules A and B leading to an activated complex C*.

$$A + B \rightleftharpoons C^* \rightarrow products \quad \ldots \ldots \quad (9)$$
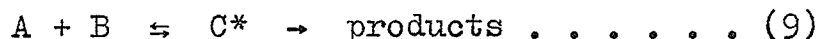
If the activated complex C* is regarded as an ordinary molecule with the one exception that motion along the reaction coordinate leads to decomposition, it can be shown by classical

statistical methods that the rate of decomposition of C* is equal to $\underline{k}\,T/h$, a universal frequency factor which depends only on temperature. $\underline{k}$ is Boltzmann's constant and h is Planck's constant. The rate of reaction (9) is therefore

$$\text{rate} = \frac{\underline{k}\,T}{h}\,[C^*] = \frac{\underline{k}\,T}{h}\,K^*\,[A]\,[B] \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where K* is defined as the equilibrium constant

$$K^* = \frac{[C^*]}{[A]\,[B]} \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The possibility of back reaction is allowed for by inserting a transmission coefficient c. It is the fraction of systems reaching the transition state which proceed to formation of products. The overall rate constant then becomes

$$k = c\,\frac{\underline{k}\,T}{h}\,K^* \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

For most ordinary reactions the transmission coefficient can be taken as unity without introducing appreciable error.

According to the principles of statistical mechanics, the equilibrium constant can be written in terms of the appropriate partition functions Q,

$$K^* = \frac{Q^*}{Q_A Q_B}\,e^{-\Delta E_o/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where ΔE_o is the difference between the zero-point energy per mole of the activated complexes and that of the reactants. Q* differs from the Q of an ordinary molecule in that the contribution of one vibrational degree, corresponding to the reaction coordinate, has been factored out and contributes to the term $\underline{k}\,T/h$. The problem of calculating the specific rate has thus

been reduced to that of evaluating the partition functions for the normal and activated states. This can be accomplished by means of the standard formulas of statistical mechanics. The partition functions for molecules in the gas phase can be calculated in a straight forward manner. However, the situation becomes much more complicated when the reaction takes place in solution since the effect of solvent on the partition functions is difficult to interpret. At present the calculation of absolute rate constants and thermodynamic parameters of activation of solution processes is virtually impossible.

Thermodynamic Formulation of Reaction Rates

If it is assumed that there is always an equilibrium between reactants and the activated complex, an equilibrium constant may be given for the reaction.

$$A + B + \ldots \rightleftharpoons C* \ldots \ldots (14)$$
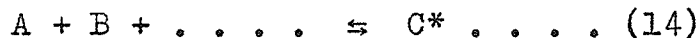
which may be treated in all respects as any other equilibrium constant and related to the standard free energy $\Delta F*$ associated with the formation of the complex

$$-\Delta F* = RT \ln K* \ldots \ldots (15)$$

where $K*$ is the equilibrium constant.

The specific rate for the reaction between A and B, as indicated in equation (12) is

$$k = \frac{k}{h} T \, K* \ldots \ldots (16)$$

when the transmission coefficient is taken as equal to unity. Substituting equation (16) into equation (15), we obtain

$$k = \frac{k}{h} T \, K* = \frac{k}{h} T \, e^{-\Delta F*/RT} \ldots \ldots (17)$$

Since $\Delta F^* = \Delta H^* - T\Delta S^*$ . . . . (18)

where ΔH^* and ΔS^* are the enthalpy and entropy of activation respectively, then equation (17) becomes

$$k = \frac{k}{h} T \, e^{-\Delta H^*/RT} \, e^{\Delta S^*/R} \quad . . . . (19)$$

The important fact in the thermodynamic formulation of reaction rates is that the free energy rather than the enthalpy of activation determines the rate of a chemical reaction.

Influence of Substituents on Reaction Rates

The Enthalpy – Entropy Relationship

Although a great deal of information can be learned about the mechanism of a reaction from its products and kinetics under various conditions, there are limitations to the amount of information which can be gleaned from the study of a single reaction. Additional information can often be obtained by studying reaction rate as a function of structure in a series of related reactions. The usual assumption made in these studies is that closely related reactions tend to have the same mechanism or else a single change in mechanism may occur somewhere within the series.

From equation (19) it can be seen that the variation in rate within a reaction series may be caused by changes in either or both the enthalpy and the entropy of activation. Four main types have been recognized:

(1) Isoentropic series. The changes in rate are due mainly to changes in enthalpy of activation since the entropy of activation is substantially constant.

(2) Isoenthalpic series. The changes in rate are due mainly to changes in entropy of activation since the enthalpy of activation is substantially constant. This type of series is not very common.

(3) Changes in rate are due to random changes in both the enthalpy and entropy of activation.

(4) _Isokinetic series_. The changes in rate are due to changes in both the enthalpy and entropy of activation, but these quantities vary in a parallel manner. A plot of ΔH^* vs ΔS^* is linear. This isokinetic relationship is very common and has been extensively reviewed by Leffler (37). As a matter of fact, an isokinetic relationship is taken to mean that a constant mechanism is in operation for the related series of reactions.

A linear relationship between ΔH^* and ΔS^* implies the following algebraic relationship:

$$\Delta H^* = \Delta H_o^* + \beta \, \Delta S^* \quad \ldots \ldots \quad (20)$$

where ΔH_o^* is the intercept or value of ΔH^* when $\Delta S^* = 0$, and β is the slope of the relationship which has the dimensions of absolute temperature. The free energy of activation is given by

$$\Delta F^* = \Delta H^* - T\Delta S^* \quad \ldots \ldots \quad (18)$$

and thus when $T = \beta$, then $\Delta F^* = \Delta H_o^*$. Since ΔH_o^* is a constant, it means that all the rates are the same at the isokinetic temperature β. Thus in order to interpret the effect of structure on rates, it is necessary to work at temperatures other than β.

The Hammett Equation

As indicated before, it is possible to obtain insight into the mechanism of a reaction by studying the effect of substituents on the rate of a given reaction. Hammett (24) has

shown that the equation

$$\log \frac{k}{k_o} = \rho\sigma \quad \ldots \ldots \quad (21)$$

can correlate the side-chain reactions of <u>meta</u> and <u>para</u> sub-
stituted benzene derivatives. k and k_o are the rate or
equilibrium constants for the reactions of the substituted
and unsubstituted derivatives, respectively, σ is the sub-
stituent constant and ρ is a constant characteristic of the
reaction. <u>Sigma</u> was defined as the logarithm of the ratio of
the acid dissociation constants for the substituted to the
unsubstituted benzoic acids in water at $25^{\circ}C$. Brown and
co-workers (9) extended the Hammett equation to include
electrophilic aromatic substitution, in which the reaction
site is on the ring instead of the side chain. This required
the introduction of a new set of <u>sigma</u> constants indicated
by σ^+. The Hammett equation correlates the structure of
certain compounds with their chemical reactivity and a know-
ledge of the sign and magnitude of the reaction constant
permits certain inferences to be made about the mechanism of
the reaction.

Many reaction series which follow the Hammett equation
are those that obey an isoentropic relationship. Under these
circumstances, using equation (19) and the fact that $\Delta S^* = \Delta S_o^*$,
it can be shown that

$$\log k - \log k_o = \frac{(\Delta H_o^* - \Delta H^*)}{2.3 \; RT} = \rho\sigma \quad \ldots \ldots \quad (22)$$

On rearranging,

$$\rho = \frac{(\Delta H_o{}^* - \Delta H^*)}{2.3\,R\,\sigma} \quad \left(\frac{1}{T}\right) \quad \ldots \ldots \quad (23)$$

Thus ρ can be expected to vary inversely as the absolute temperature.

Other reaction series correlated by the Hammett equation obey the isokinetic relationship. For these, the absolute magnitude of ρ decreases as the isokinetic temperature is approached from below. Rho is zero at the isokinetic temperature β and above β the sign of ρ is reversed and its absolute magnitude increases with temperature.

Thus any theoretical arguments based on the sign and magnitude of ρ must take into account the temperature factor.

HISTORICAL REVIEW

Decarboxylation of organic acids has long been used for the synthesis and degradation of molecules. However, it was not until about 1920 that the kinetics of decarboxylations were first studied (59).

The process of decarboxylation has been recognized as an electrophilic replacement reaction whereby a hydrogen atom replaces the carboxyl group.

$$H_1 + RCO_2H \rightarrow RH_1 + CO_2 + H \quad . . . . . \quad (24)$$
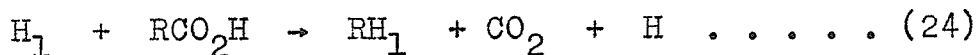
Recently, it has been demonstrated that decarboxylation can occur either by a unimolecular or a bimolecular mechanism (7, 31, 46). The mechanisms can be further classified as follows:

S_E1 Mechanism

$$RCO_2^{\ominus} \rightarrow R^{\ominus} + CO_2 \quad . . . . \quad (a)$$

$$H^{\oplus}RCO_2^{\ominus} \rightarrow RH + CO_2 \quad . . . . \quad (b)$$
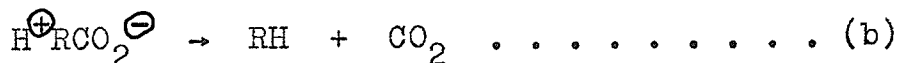
where $H^{\oplus}RCO_2^{\ominus}$ refers to the zwitterion form of the acid

S_E2 Mechanism

$$RCO_2H + H_1^{\oplus} \rightarrow RH_1 + CO_2 + H^{\oplus} \quad . . \quad (c)$$

$$RCO_2^{\ominus} + H^{\oplus} \rightarrow RH + CO_2 \quad . . . . . . \quad (d)$$
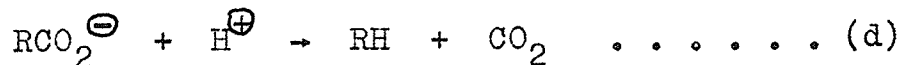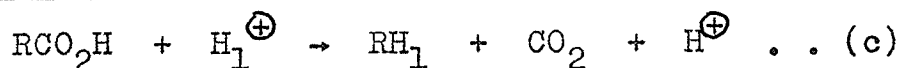
The S_E1 mechanism (a) has been firmly demonstrated by a great deal of experimental evidence. The rate determining step in this mechanism involves the loss of carbon dioxide without its bonding electron pair.

$$R-C{\overset{O}{\underset{O^{\ominus}}{\lessgtr}}} \rightarrow R^{\ominus} + CO_2 \quad . . . . . . \quad (25)$$
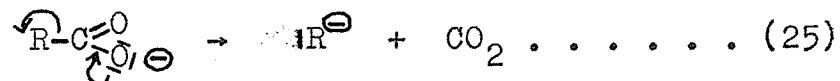
The decarboxylation proceeds from the anionic form of the acid. A carbanion intermediate is formed which then becomes protonated to form the product RH. First order kinetics should be observed and strongly electron attracting groups situated on R should facilitate the decarboxylation. A good example of mechanism (a) is the decarboxylation of trihalogen acetic acid (34,56). The main points of evidence are as Brown (7) has indicated:

(1) These acids are almost completely ionized in water.

(2) The activation energies for the decarboxylation of the acids and of their sodium salts in water are identical.

(3) The decarboxylation is approximately 10^7 times slower in the non-ionizing solvent toluene than in water.

(4) In non-aqueous solvents in which the acids are only slightly ionized, the rate is proportional to the concentration of the anion produced by added bases.

Evidence for the existence of the intermediate carbanion formed has also been indicated. For example, Pedersen (42) showed that the addition of bromine has no effect on the rate of decarboxylation of the α-nitro-isobutyrate anion even though the product is changed from 2-nitropropane to 2-bromo-2-nitropropane. He showed that the 2-nitropropane could not be brominated under the experimental conditions used. This indicates that the bromine is reacting with an intermediate formed in the decarboxylation reaction.

The S_E1 mechanism (b) where the decarboxylation proceeds from the free acid also has considerable experimental proof for its existence. It occurs in the acids which are

capable of zwitterion formation or where internal hydrogen
bonding is possible. As in mechanism (a), first order kinetics
should be obeyed and a carbanion formed as an intermediate.
Hammick and co-workers (25) indicated that the decarboxylation
of α-picolinic, quinaldinic and iso-quinaldinic acids are a
good example of mechanism (b). There is good indication that
the decarboxylation probably proceeds through the zwitterion
form. They showed that the methylbetaine (I) of the acid
decarboxylated readily and therefore the analogous zwitterion
(II) is probably the form of the acid that decarboxylates.

$$+ CO_2 \quad \cdots \quad (26)$$

I   II   III
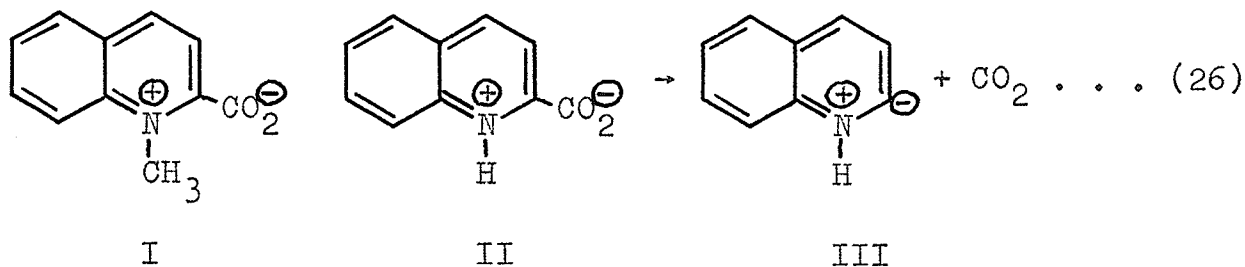
Some of the evidence offered for the existence of the carbanion
intermediate (III) was obtained by decarboxylating quinaldinic
acid in quinoline. α,α'-Diquinolyl was produced in small
yield.

$$+ H_2 \quad \cdots \quad (27)$$

III   α,α'-Diquinolyl
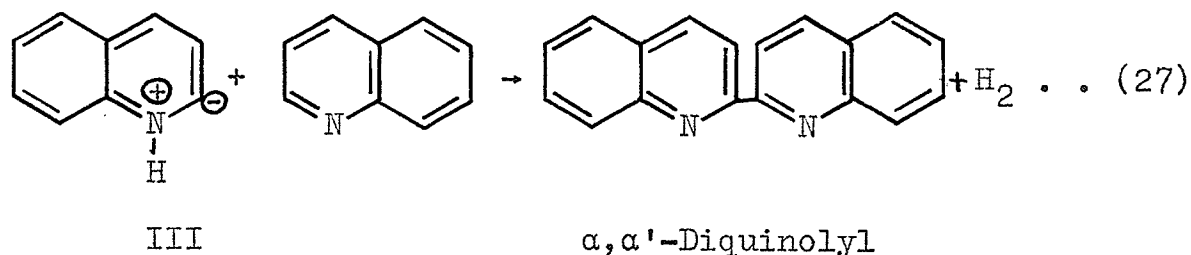
β-Keto acids are believed to decarboxylate from an
internally hydrogen-bonded form. An example of this mechanism
is the decarboxylation of α,α-dimethylacetoacetic acid (43).
Pedersen first suggested the decarboxylation of the zwitterion.

$$CH_3 - \overset{\underset{\oplus}{OH}}{\underset{\|}{C}} - \overset{\underset{CH_3}{|}}{\underset{|}{C}} - \overset{O}{\underset{CO_2^{\ominus}}{C}} \rightarrow CH_3 - \overset{|}{\underset{OH}{C}} = C \overset{CH_3}{\underset{CH_3}{\diagdown}} + CO_2 \qquad \cdot\cdot(28)$$
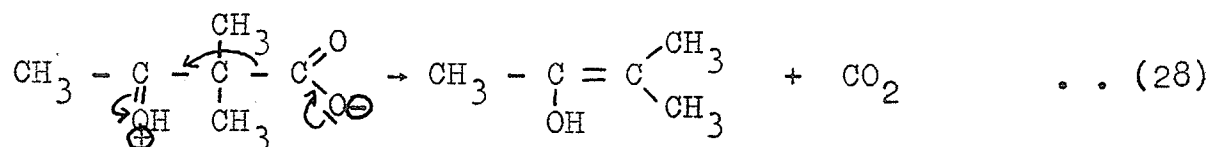
However, Westheimer and Jones (58) found that the rate of decarboxylation of α,α-dimethylacetoacetic acid is very little affected by the dielectric constant of the solvent. They therefore concluded that the zwitterion could not be an intermediate since its formation should be favored in a high dielectric constant medium and instead suggested a hydrogen-bonded intermediate such as (IV).

$$H_3C - \underset{\underset{H}{\overset{\|}{O}}}{C} \overset{\overset{CH_3}{\diagup}\underset{}{\overset{C}{\diagdown}}\overset{CH_3}{}}{} \underset{\overset{|}{O}}{C} = O \rightarrow CO_2 + HO - \overset{\underset{}{\overset{CH_3}{|}}}{C} = C \overset{CH_3}{\underset{CH_3}{\diagdown}} \qquad \cdot\cdot(29)$$

IV
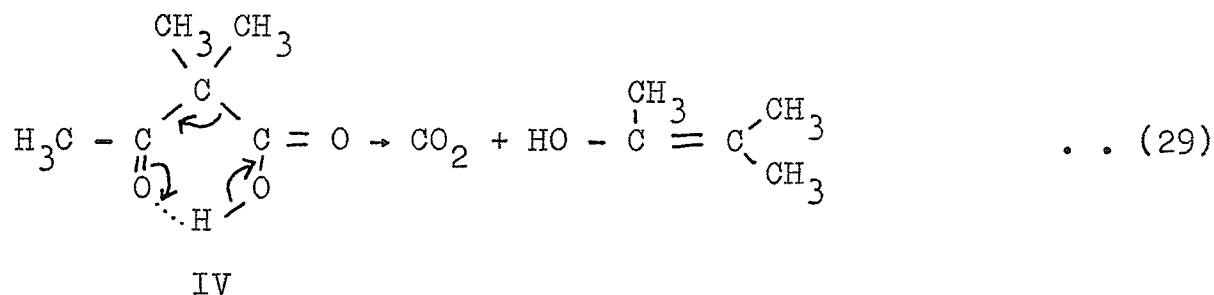
The net result of the studies on the unimolecular decarboxylation reactions is that the decarboxylation of the acid seems to take place from the anionic form.

There are more examples of the unimolecular decarboxylation reactions but since the author is primarily concerned with the bimolecular mechanisms, the reader is referred to B.R. Brown (7) for a more comprehensive review of the S_E1 reaction mechanisms.

Since 1948, evidence has been accumulating suggesting that decarboxylation may occur by the S_E2 mechanism (c) or (d).

The rate determining step is attack by the proton at the carbon
α to the carboxyl group. In mechanism (c), it is proton attack
on the free acid whereas in (d) it is proton attack on the
anion of the acid. Thus, second (or psuedo first) order
kinetics will be observed and substituents in R which increase
the electron density on the carbon α to the carboxyl group
will facilitate the reaction.

In 1948, Schenkel and Schenkel-Rudin (46) first
suggested mechanism (c) as a possibility in the decarboxylation
of anthracene-9-carboxylic acid since it is more easily
decarboxylated in acidic solvents than in basic ones.

The S_E2 mechanism was also substantiated by the work
of Brown and Hammick (8) who investigated the kinetics of the
decarboxylation of hydroxy benzoic acids. The rates were meas-
ured in resorcinol solution over a temperature range of 110-240
degrees. They noted a fall in activation energy and an increase
in rate with increasing ortho and para substitution with
hydroxyl groups. These results support the conclusion that
with these acids the decarboxylation is an S_E2 type reaction
where an increase in the electron density on the carbon α to the
carboxyl group facilitates proton attack in the rate deter-
mining step. Schubert (48) investigated the kinetics of
decarboxylation of 2,4,6-trihydroxy benzoic acid in perchloric
acid solution. He found that in the range of 0.135 - 38.2 °/o
perchloric acid, the kinetics were consistent with the rate-
controlling step being a first order decomposition of free acid
or the reaction of the anion of the acid with a proton released

from the solution. Willi (60, 61) showed that the decarboxyla-
tion rates of 4-methyl, 4-methoxy, 4-hydroxy and 4-amino-
salicylic acids in aqueous hydrochloric acid solution increase
with increasing electron-donating power of the substituents.
When the logarithms of the rate constants were plotted against
Brown's sigma constants (9), a good linear relationship was
observed. He concluded that the reaction was a bimolecular
substitution reaction of the anion with a proton. However, it
could be equally well interpreted as a unimolecular decomposi-
tion of the free acid. This situation arises because
kinetically it is impossible to distinguish between mechanisms
$S_E 2$ (d) and $S_E 1$ (b) as indicated below:

$$S_E 1 \text{ (b)} \qquad RCO_2 H \xrightarrow{k_1} RH + CO_2$$
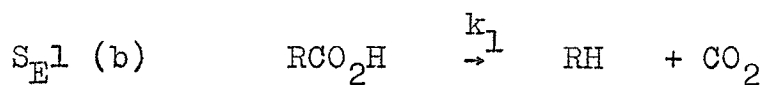
and rate = $k_1 [RCO_2 H]$ . . . . . . (30)

but, for a weak acid:
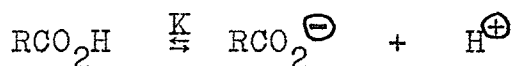
$$RCO_2 H \overset{K}{\rightleftharpoons} RCO_2^{\ominus} + H^{\oplus}$$

and $\qquad [RCO_2 H] = \dfrac{[RCO_2^{\ominus}][H^{\oplus}]}{K}$ . . . . . . (31)

and therefore substituting (31) in (30), we obtain

rate = $k_1/K \; [RCO_2^{\ominus}][H^{\oplus}]$ . . . . . . (32)

and obviously this equation (32) is identical to that for the
$S_E 2$ mechanism (d) in equation (33):

$$S_E 2 \text{ (d)} \qquad RCO_2^{\ominus} + H^{\oplus} \xrightarrow{k_2} RH + CO_2$$
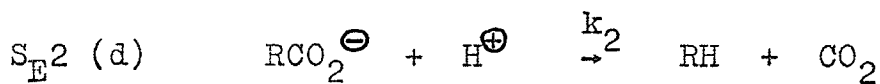
and rate = $k_2 [RCO_2^{\ominus}][H^{\oplus}]$ . . . . . . (33)

Lynn and Bourns (41) have indicated that a concerted mechanism whereby C-H bond making and C-C bond breaking at the carbon α to the carboxyl group is involved in the decarboxylation of 4-hydroxysalicylic acid. This conclusion was arrived at because a C^{13} isotope effect was observed in the decarboxylation of 4-hydroxysalicylic acid in aqueous perchloric acid solutions and also in acetic acid - sodium acetate buffer solutions of varying concentrations. Liquori and Ripamonte (40) concluded that p-aminosalicylic acid decarboxylates in the free acid form. However, as is usually the case, it could also fit a S_E2 (d) mechanism. Janzen (33) studied the decarboxylation of a series of substituted salicylic acids in quinoline and suggested an internal replacement of the carboxyl group by a proton in the decarboxylation process.

Schubert (47) showed that the decarboxylation of mesitoic acid in 80-100 % sulfuric acid followed the following rate expression:

$$\text{rate} = k \ [H_3O^+][\text{acid}] \ . \ . \ . \ . \ . \ (34)$$

He concluded that the probable rate determining step is the reaction between the conjugate acid of mesitoic acid and water. Bothner-By and Bigeleisen (6) and Stevens (51) have observed a C^{13} isotope effect in the decarboxylation of mesitoic acid. This indicates that C-C bond breaking must be involved in the rate determining step.

Stevens (52) did not find any C^{13} isotope effect in the decarboxylation of anthranilic acid and arrived at the conclusion that the rate determining step involved the attack of a proton on the carbon α to the carboxyl group. Prysiazniuk (45) decar-

boxylated a series of meta and para substituted anthranilic acids in nitrobenzene and concluded that the rate determining step was the attack by proton from one anthranilic acid molecule on the carbon α to the carboxyl group of the second molecule.

The view that decarboxylation can occur by the S_E2 mechanism is thus supported by many kinetic studies. However, no evidence as to the exact nature of the carboxylic entity exists, whereas the evidence for the S_E1 mechanism always indicate that the carboxyl group is in the anionic form preceding decarboxylation.

The role played by the solvent quinoline in various decarboxylation reactions has been studied by Yankwich and Clark.

Clark (12) studied the decarboxylation of β-resorcylic acid in amines and glycols. The amines used were quinoline and 8-methylquinoline. His interpretation of the mechanism was that the rate determining step of the reaction involved the formation of a transition complex between the carboxyl carbon atom of the free acid and the unshared pair of electrons on the nitrogen atom of the amine. This is the same bimolecular mechanism advanced by Clark for the decarboxylation of several other unstable acids in quinoline and 8-methylquinoline (13, 14, 15, 16). This postulate was first advanced by Yankwich (21) for the decarboxylation of malonic acid in quinoline solution but in later publications (63, 64) he maintained that malonic acid solvation in quinoline occurred through the carbonyl hydrogen atom of the free acid.

OBJECT OF THE PRESENT INVESTIGATION

The author proposed to extend Janzen's (33) investigations concerning the reaction mechanism for the decarboxylation of salicylic acid in quinoline solution. Janzen determined the rates of decarboxylation for a series of meta and para substituted salicylic acids in quinoline solution at 200°C. The reaction was first order with respect to salicylic acid. Application of the Hammett equation failed to give a clear indication as to the nature of the mechanism. Essentially what Janzen found was that salicylic acid, 4-nitrosalicylic acid and all the 5-substituted salicylic acids decarboxylated at about the same rate. Strong electron-releasing substituents in the para position such as 4-amino, 4-hydroxy, 4-methoxy and 4-ethoxy increased the rate of decarboxylation about ten times. However, these four para-substituted acids all decarboxylated at the same rate.

It was proposed to determine the rates of decarboxylation of the salicylic acids over a range of temperature and thus obtain information which was not available to Janzen. This temperature study would make possible the following observations:

(1) It would then be possible to determine the enthalpy - entropy relationship of the various substituted salicylic acids. This would show whether or not the series of salicylic acids were decarboxylating by the same mechanism.

(2) The Hammett equation should be applicable if an isoentropic or isokinetic relationship existed in the series of

22

substituted salicylic acids. Should these acids obey such a relationship, then it would be possible to correlate the decarboxylation rates with the structure of the acid.

(3) If an isokinetic relationship were observed, it would be possible to determine whether the experimental temperature was far enough away from the isokinetic temperature so that the substituents on salicylic acid would have an effect on the rate. This would be an especially important fact to know since Janzen found that, in general, the rates of decarboxylation of salicylic acid were fairly insensitive to varying substituents.

It would also be desirable to ascertain the role of quinoline in the decarboxylation reaction. This could be done by finding the order with respect to quinoline in an inert solvent. If it were found that quinoline was involved prior to or in the rate determining step, it would then become desirable to get a more accurate picture of its function. This aspect could be examined by using substituted quinolines and pyridine as solvents for the decarboxylation reaction of salicylic acid.

EXPERIMENTAL

Materials

Quinoline (synthetic, Matheson Coleman and Bell) was dried over barium oxide (Barium and Chemicals, Inc.) and then distilled at atmospheric pressure. The fraction at 234-235°C (uncorr.) was collected and stored over barium oxide. The index of refraction was 1.6229 at 25°C. (lit. value, $n_D^{24.9}$ 1.6245).

Pyridine (Baker Analyzed Reagent) was dried over barium oxide (Barium and Chemicals, Inc.) and then distilled at atmospheric pressure. The fraction 114-115°C was collected and stored over barium oxide. The index of refraction was 1.5081 at 22°C. (lit. value, n_D^{21} 1.5092).

6-Methoxyquinoline (Eastman Organic Chemicals) was used directly without any further purification. The index of refraction was 1.6209 at 22°C.

The melting points of the solids were determined in a Hershberg melting point apparatus (26) using conventional short Anschutz enclosed-scale thermometers. Janzen (33) had checked the calibrations of these thermometers against a platinum resistance thermometer. The silicone fluid in the apparatus was heated internally by a resistance wire controlled by means of an autotransformer.

6-Nitroquinoline (Aldrich Chemical Co., Inc.) was used directly without any further purification. The melting point was 150.5-153.0°C. (lit. value, 150°C)[28].

<u>8-Hydroxyquinoline</u> (B.D.H. Analar) was used directly without any further purification. The melting point was 73-74°C. (lit. value 73-74°C)[28].

<u>4-Methylsalicylic acid.</u> The method employed was an adaptation of that used for the preparation of bromo-2-nitrobenzoic acids used by Erickson, Dechary and Pullig (19). Fifty grams (0.329 moles) of 4-methyl-2-nitroaniline was stirred with 130 ml. of concentrated hydrochloric acid and 180 ml. of water for a period of about one hour. A solution of 33 gm. of sodium nitrite in 100 ml. water was added slowly over a period of 1 1/2 hours. The temperature was kept below 10°C during this time. A cuprous cyanide solution was freshly prepared by mixing 81 gm. sodium cyanide in 330 ml. of water with 53 gm. of anhydrous copper sulfate and this solution was then cooled to a temperature of 30°C. While this solution was stirred, a small portion of the diazonium solution was added. It was necessary to heat the solution to a temperature of 60°C before the reaction started. The diazonium solution was then added in small portions at this temperature until the reaction was complete. The reddish brown precipitate of the 4-cyano-3-nitrotoluene was then collected by filtration. This compound was then refluxed for five hours with a solution of 250 ml. each of water, concentrated sulfuric acid and glacial acetic acid. This solution was cooled overnight, made alkaline with ammonium hydroxide, filtered, and reacidified with hydrochloric acid. On dissolving 22 gm. (0.122 moles) of the 4-methyl-2-nitrobenzoic acid in 25 ml. of ethanol, 1 gm. of palladium on charcoal was added and the compound was then catalytically

Flow Sheet for the Preparation of 4-Methylsalicylic Acid.
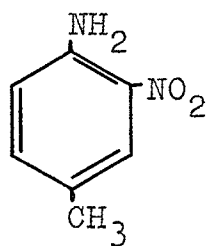
4-Methyl-2-nitroaniline
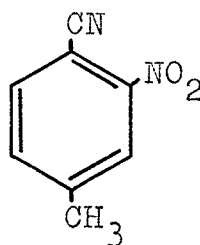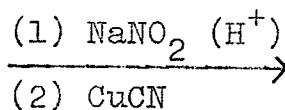
$\xrightarrow{\begin{array}{c}(1)\ NaNO_2\ (H^+)\\ (2)\ CuCN\end{array}}$

4-Cyano-3-nitrotoluene

$\xrightarrow[\text{reflux}]{H^+,\ aq.,}$

4-Methyl-2-nitrobenzoic acid

$\xrightarrow{Pd-H_2\ (\text{ethanol})}$

4-Methyl-2-aminobenzoic acid

$\xrightarrow{\begin{array}{c}(1)\ NaNO_2\ (H^+)\\ (2)\ \text{heat}\end{array}}$
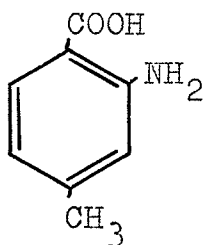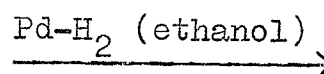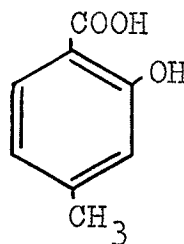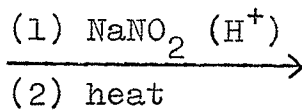
4-Methylsalicylic acid

hydrogenated over a period of 45 minutes. After the evaporation of the alcohol solution to 125 ml., the addition of 200 ml. water resulted in the precipitation of the 4-methyl-2-aminobenzoic acid. Twelve grams (0.080 moles) of this acid were added to a cold solution of 70 ml. concentrated sulfuric acid and 100 ml. water. This mixture was cooled to $-2^{o}C$ by stirring it on a salt water-ice bath. While keeping the temperature at $0^{o}C$, a solution of 5 gm. sodium nitrite dissolved in 50 ml. water was slowly added. The clear diazonium solution was then slowly dropped into a boiling solution of 150 ml. concentrated sulfuric acid and 100 ml. water. 4-Methylsalicylic acid was precipitated on cooling, and after two crystallizations from aqueous alcohol 6 gm. (0.040 moles) were recovered with a melting point of $170.0-172.0^{o}C$. (lit. value, $176^{o}C$[41], $177^{o}C$[60]).
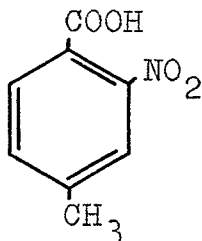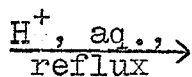
4-Bromosalicylic acid. The method employed was an adaptation of that used for the preparation of bromo-2-nitrobenzoic acids used by Erickson, Dechary and Pullig (19). One hundred and fifty grams (1.087 moles) of 2-nitroaniline were dissolved in 900 ml. glacial acetic acid. While this was stirred, a solution of 120 gm. bromine in 115 ml. glacial acetic acid was added over a period of two hours at a temperature of about $15^{o}C$. The light yellow precipitate of 4-bromo-2-nitroaniline was filtered, washed with acetic acid, and then stirred for 15 minutes in 1.5 liters of water. The 4-bromo-2-nitroaniline was stirred for 1/2 hour at room temperature with 246 gm. concentrated sulfuric acid and 1370 ml. water. The solution was then cooled to less than $5^{o}C$ and a solution of 43.6 gm. sodium nitrite in 342 ml.

Flow Sheet for the Preparation of 4-Bromosalicylic Acid.
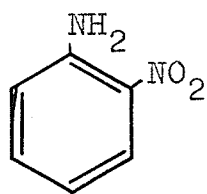
2-Nitroaniline
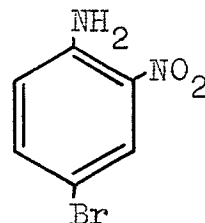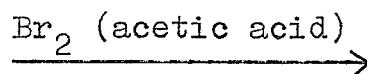
Br$_2$ (acetic acid) →

4-Bromo-2-nitroaniline

(1) NaNO$_2$ (H$^+$)
(2) CuCN →

4-Bromo-1-cyano-2-nitrobenzene

H$^+$, aq.,
reflux →

4-Bromo-2-nitrobenzoic acid

FeSO$_4$·7H$_2$O (NH$_4$OH) →
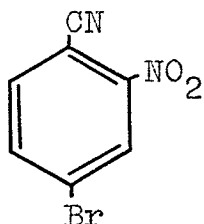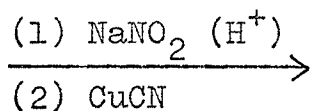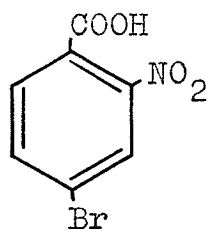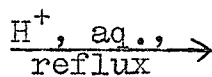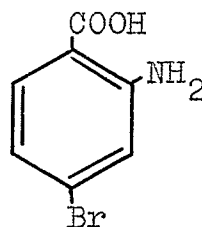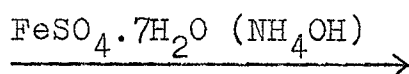
4-Bromo-2-aminobenzoic acid

(1) NaNO$_2$ (H$^+$)
(2) reflux →
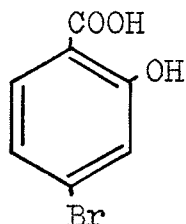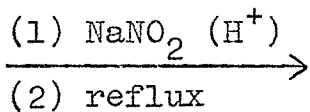
4-Bromosalicylic acid

water was added over a period of 2 hours. This clear diazonium solution was decanted from a small residue and added to a stirred hot solution of cuprous cyanide prepared by mixing 218.4 gm. anhydrous copper sulfate with 290 gm. sodium cyanide in 1680 ml. water. The light brown precipitate of 4-bromo-1-cyano-2-nitrobenzene which settled out after cooling was extracted with several portions of methanol. This compound was hydrolyzed by refluxing it for 1 1/2 hours in a solution of 330 gm. concentrated sulfuric acid and 150 ml. water. The precipitate of 4-bromo-2-nitrobenzoic acid which formed was added to 700 ml. of a 10 ^{o}/o sodium hydroxide solution, filtered, and reacidified. The recovered acid was dissolved in a solution of 200 ml. concentrated ammonium hydroxide, 100 gm. of $FeSO_4 \cdot 7H_2O$ and 200 ml. water. The solution was brought to a boil and then allowed to cool. A very fine black inorganic precipitate was removed by filtration. The filtrate was then acidified and the white precipitate of 4-bromoanthranilic acid which settled out was then recrystallized from aqueous ethanol. Seven grams (0.032 moles) of the 4-bromoanthranilic acid were stirred with 30 ml. of concentrated hydrochloric acid and 50 ml. water for 1/2 hour. The solution was cooled to a temperature of less than 5°C and then 2.5 gm. sodium nitrite dissolved in 25 ml. water was added over a period of 1/2 hour. This diazonium solution was then slowly poured into a boiling solution of 50 ml. concentrated sulfuric acid and 30 ml. water. 4-Bromosalicylic acid was precipitated on cooling, and after two recrystallizations from aqueous ethanol 5 gm.

(0.023 moles) were recovered with a melting point of 206.0-207.0°C. (lit. value, 212°C[30], 214°C[29]).

Some of the remaining acids were synthesized by Janzen (33) and the others were obtained commercially. These are listed in Table I along with any pertinent information.

TABLE I

Substituted Salicylic Acids

Subst.	Source	Melting Points, $^{\circ}C$	
		Observed	Literature
$4NH_2$	Matheson, Coleman, Bell	140d	146-7[49]
$5NH_2$	Matheson, Coleman, Bell**	286-7 (water)*	280[28], 283[28]
4OH	Eastman Organic Chemical**	223.6-.8(toluene)*	213[4], 226d[17]
5OH	Eastman Organic Chemical ***	206.2-.8d	200[53], 202-3[18]
4OEt	Eastman Organic Chemical***	155.2-.7	154[35]
5Cl	Matheson, Coleman, Bell	174.0-.6 (aq. alc)*	176[32]
5Br	Matheson, Coleman, Bell	167.8-168.4	164[3]
$5NO_2$	Eastman Organic Chemical***	231.7-232.2	228-9[2]
$4NO_2$	Janzen****	234.8-235.3	226[54], 229-230[50], 235[10]
H	Merck, U.S.P. (Bulk)	159.8-.9	159[28]
$5OCH_3$	Janzen****	145.7-146.2	143.5[23], 145-6[5]
$5CH_3$	Janzen****	149.6-150.6	146-7[65], 152[11], 153[11]

*   Solvent used in recrystallizations

**   Practical grade

***   White label grade

****   Prepared by Janzen (33)

APPARATUS

Apparatus for Manometric Runs

The manometric system used for the study of the rates of decarboxylation for some of the acids is shown on page 31.

The reaction vessel (V) used was that designed by Janzen (33) and is shown on page 30. It was designed to hold 5 ml. of solution and about 15 ml. vapour which could be thermostated entirely throughout a run. The tubing that connected the reaction chamber and the manometer was of 2 mm. dimension so that a minimum volume of gas was exposed to variations in room temperature. A 2 cm. long piece of 6 mm. tubing was inserted next to the reaction chamber so as to minimize the amount of condensed liquid which could rise up the capillary and into the manometer.

The reaction vessel was kept to within $\pm$ 0.05°C of the required temperature by means of a manostated thermostat as shown on page 31. The thermostat consisted of a 2-litre flask containing a liquid which was gently refluxed so that the vapours bathed the reaction vessel. The thermostat was heated with an electric heating mantle regulated by an autotransformer. The liquid used in the thermostat was phenyl-ether for the temperature range 210°-230°C, nitrobenzene for the 160°-200°C range and bromobenzene for the 93°-150°C range. An iron-constantan thermocouple (K) inserted in a thermocouple well (W) recorded the temperature in the thermostat. The difference in potential created by the hot and cold junction

REACTION VESSELS

V, MANOMETRIC   Y, GRAVIMETRIC
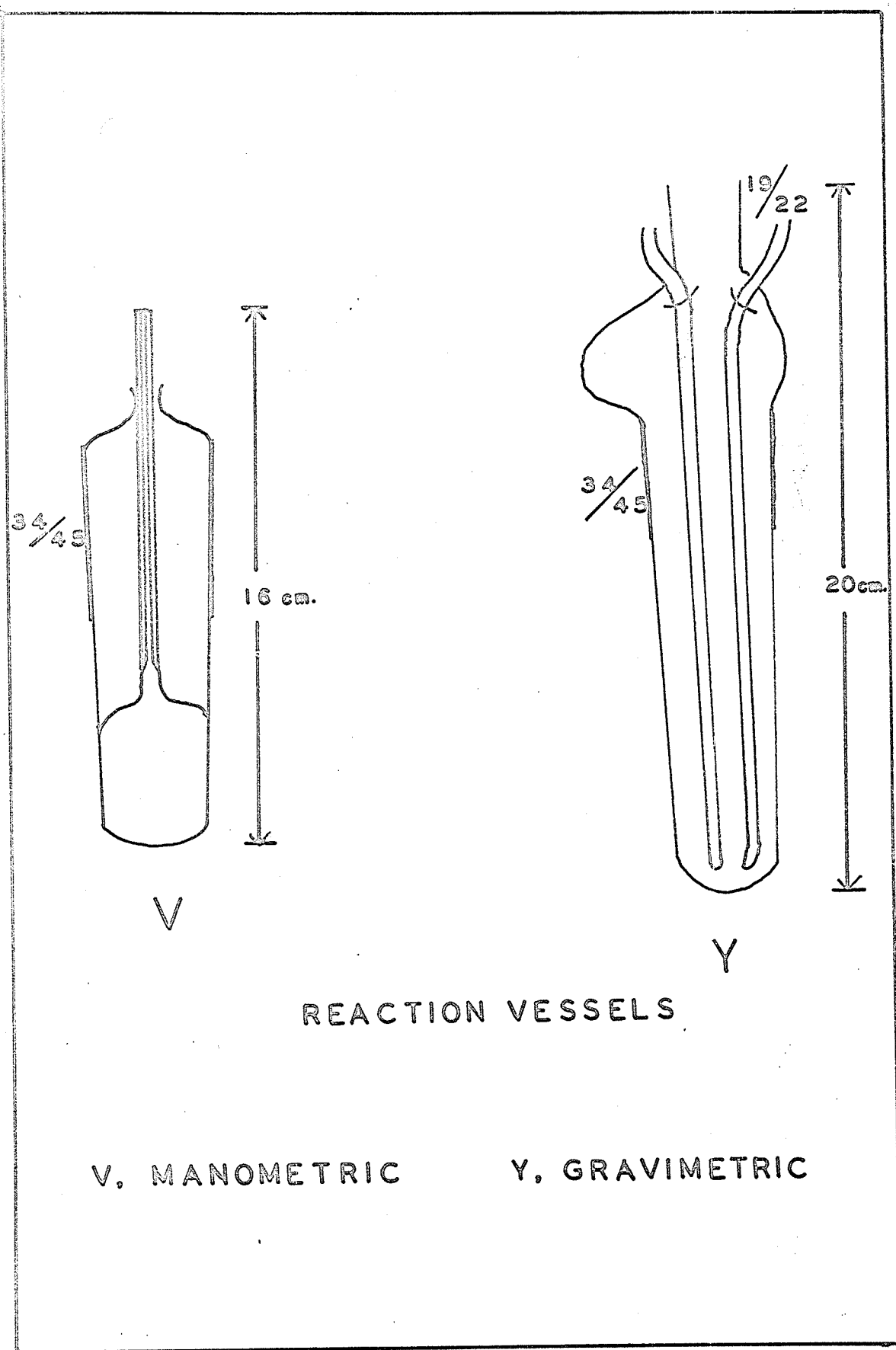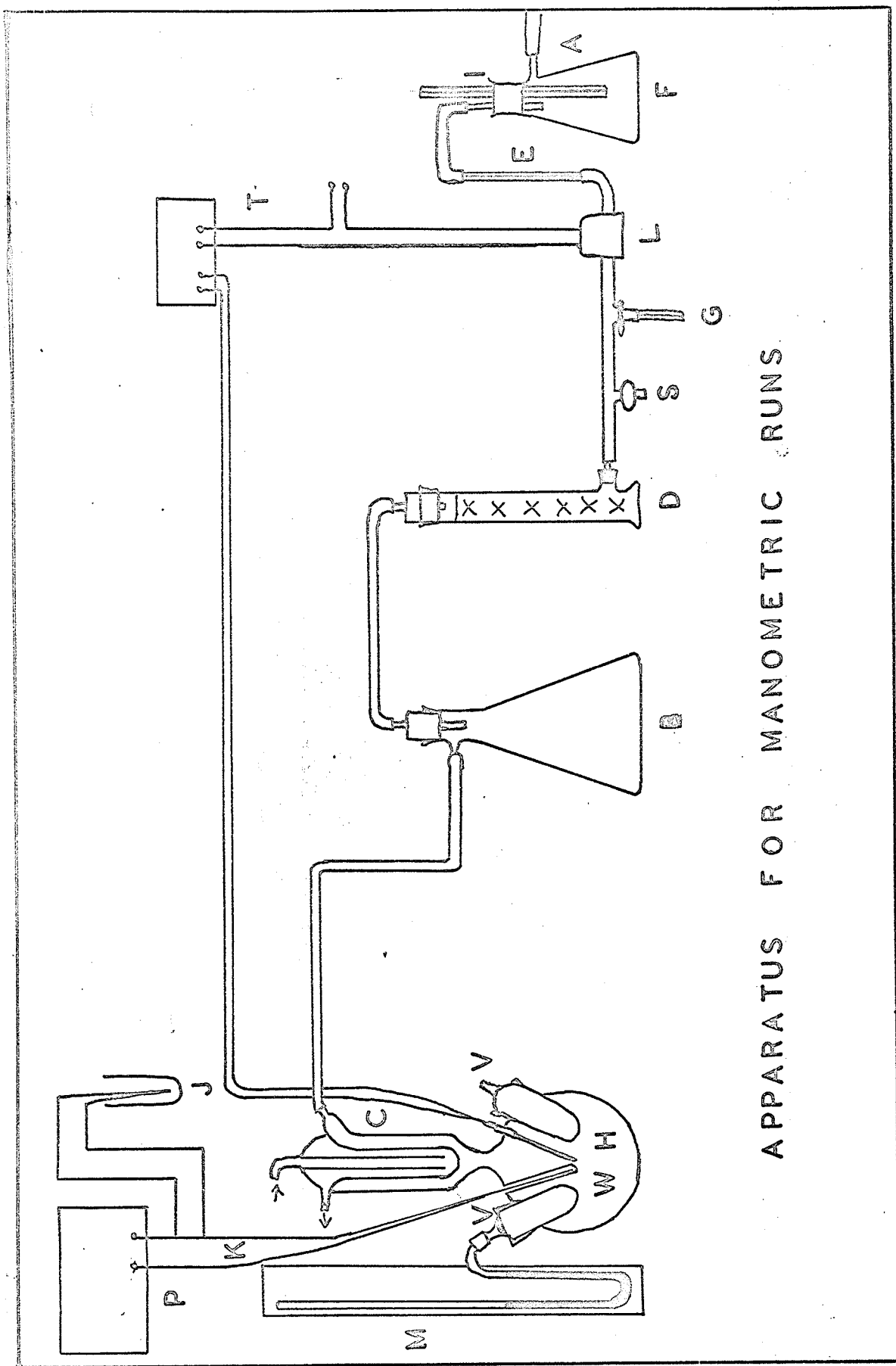
Figure 1

APPARATUS FOR MANOMETRIC RUNS

Figure 2

of the thermocouple was measured by a Tinsley portable poten-
tiometer type 3184D (P).

A constant and reproducible temperature was obtained
in the thermostat by employing a thermister system. The
thermister controlled the pressure in the thermostat. The
manostating system was connected through a condenser (C) to
the thermostat. The source of low pressure was the building
vacuum line connected to a flask (F) which was provided with
a capillary leak (I). When the thermister probe (H) activated
the thermister relay (T), the valve (L), a Honeywell solenoid
gas valve, opened the system to the low pressure flask and the
pressure in the thermostat was decreased accordingly. As the
temperature decreased to the desired temperature, the ther-
mister probe now deactivated the relay and the gas valve was
closed. The pressure and temperature now once again increased
and the cycle repeated itself. It was a simple matter to
obtain any desired temperature by merely adjusting the ther-
mister controller to a new temperature. To avoid surging and
excess overshooting a ballast flask (B) and a capillary (E)
were inserted between the thermostat and the low pressure
flask. At higher pressures, the system was found to function
more satisfactorily if the system was provided with a small
leak (G). A drying tower (D) filled with Drierite placed be-
tween the atmosphere and the system kept water vapour from
entering the thermostat. The system was opened to the atmos-
phere through a stopcock (S).

Apparatus for Gravimetric Runs

The gravimetric method was also used to determine the rates of decarboxylation for some of the acids. It was used exclusively for the slower rates at the lower temperatures and the faster rates at the higher temperatures. It was also used as a check for the manometric runs.

The reaction vessel (Y) page 30, was that used by Janzen (33). The reaction vessel was kept at $\pm$ 0.2°C of the desired temperature in the thermostat already described in the manometric runs.

The absorption train, as shown on page 34 consisted of a condenser (O), a n-butylphthalate bubbler (Q), a drying tube containing anhydrone (R), a two-way stopcock (T), absorption tubes containing ascarite and a small amount of anhydrone (X,X), another two-way stopcock (T), an anhydrone U-tube (Z), and an ascarite U-tube (U). The condenser was of a Liebig and Graham type combination. The condenser, along with the n-butylphthalate bubbler eliminated organic vapours from the train. The drying tube (R) removed water vapour which may have entered the system when the apparatus was opened. The two-way stopcocks (T,T) were used to direct the gas stream to either absorption tube. The U-tubes (Z) and (U) prevented atmospheric vapour and carbon dioxide from entering the absorption tubes. The incoming nitrogen which was used to sweep the carbon dioxide out of the reaction vessel and along the train was first passed through anhydrone (X') and ascarite (U') U-tubes.
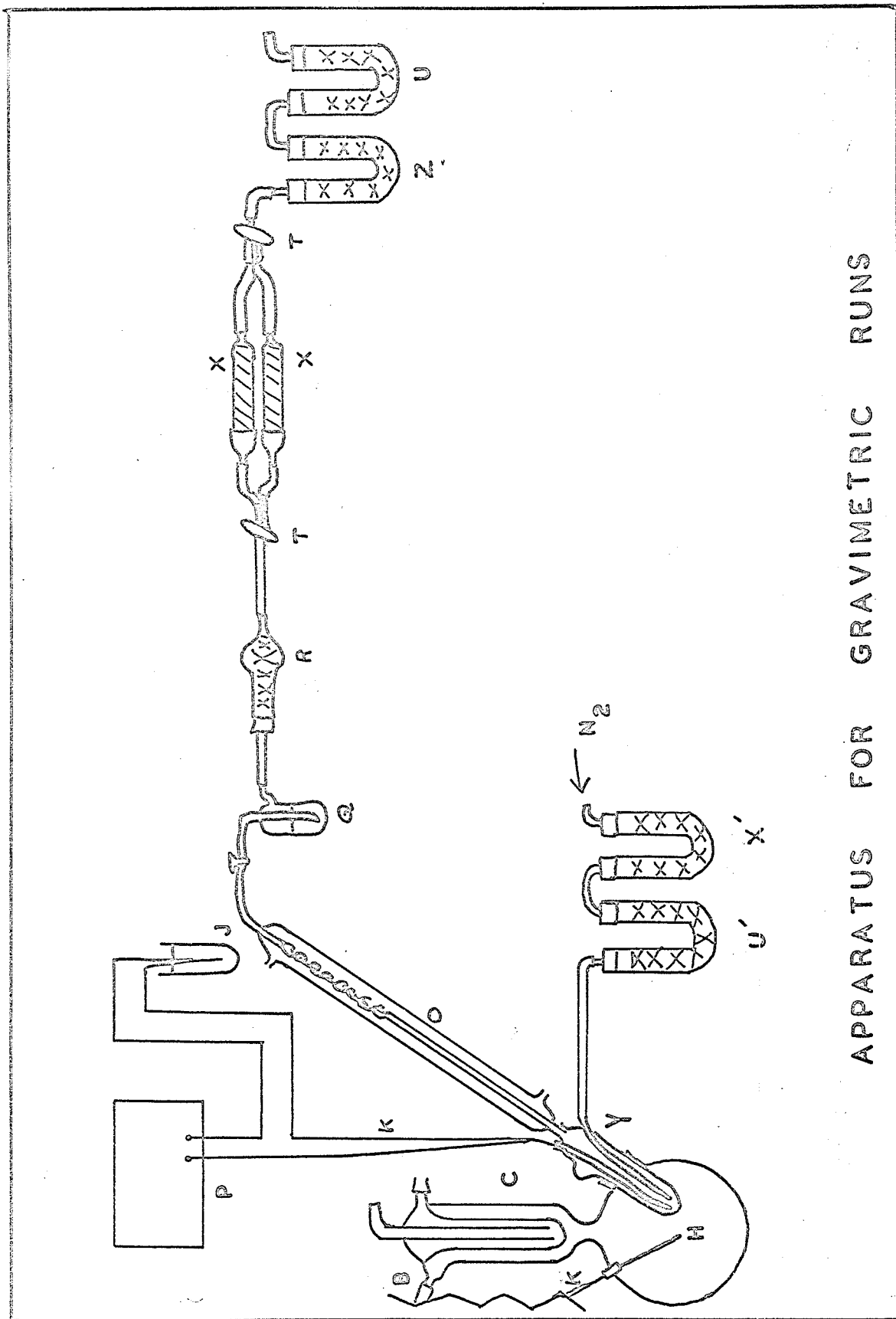
APPARATUS FOR GRAVIMETRIC RUNS

Figure 3

PROCEDURE

Manometric

The reaction vessel was cleaned with a solution of hot chromic acid. It was rinsed with water, acetone and ether and allowed to dry in a vacuum oven over-night. The acid to be decarboxylated was weighed on a Mettler balance in a special 15 ml. weighing bottle. Eleven ml. of quinoline were added and the solution was then heated up to a temperature close to that in the thermostat. The reaction vessel was placed into the thermostat and allowed to heat up to the desired temperature before the solution was injected. Five ml. of quinoline solution was then injected into the reaction chamber by means of a hypodermic syringe fitted with a 4 inch needle. After 500 seconds an open-end manometer of 2 mm. capillary was attached to the capillary of the reaction vessel with a piece of Tygon tubing. The pressure was then taken as a function of time. An electric second counter was used to indicate the time. Readings were generally taken up to about three half lives and after reaction was complete a final pressure reading was taken. This final pressure reading was taken as being proportional to the initial concentration.

Gravimetric

Ten ml. of quinoline were placed in the reaction vessel and the nitrogen flow was adjusted to a satisfactory rate. The absorption train was then connected to the vessel as indicated in the diagram on page 34. The iron-constantan

thermocouple was introduced into the reaction vessel well
and the temperature was then adjusted to the desired tem-
perature by means of the thermister controller. When the
system had come to equilibrium a pellet of about 0.2 gm.
of the acid to be decarboxylated was dropped into the
reaction vessel. The absorption tubes were weighed at
intervals. A hydraulic pellet press was used to shape the
acid into a pellet.

RESULTS AND OBSERVATIONS

Rate Constants

It was found that the decarboxylation of salicylic acid in quinoline followed first order kinetics. The rate expression is

$$-\frac{dc}{dt} = kc \quad \ldots \ldots \ldots (35)$$

where c = concentration of the reacting acid, k = specific rate constant and t = time.

In the manometric runs

$$-\frac{dc}{dt} \quad \alpha \quad \frac{dP}{dt} \quad \ldots \ldots \ldots (36)$$

and $\quad c \quad \alpha \quad [P_\infty - P_t]$,

where P_∞ = final pressure reading and P_t = pressure of carbon dioxide at time t.

Then

$$\frac{dP}{dt} = k[P_\infty - P_t] \quad \ldots \ldots \ldots (37)$$

This equation can be rearranged to

$$\frac{dP}{[P_\infty - P_t]} = k\,dt \quad \ldots \ldots \ldots (38)$$

which integrates to

$$\log[P_\infty - P_t] = \frac{-kt}{2.303} + \log[P_\infty - P_0] \quad \ldots \ldots (39)$$

where P_0 = initial pressure.

The slope of the plot $\log[P_\infty - P_t]$ vs t is equal to $-k/2.303$. The specific rate constant, k, for each run was calculated from the slope of the best straight line through the points of the $\log[P_\infty - P_t]$ vs t plot. This was done with

an I.B.M. computer. Table II gives a list of pressure read-
ings for a typical manometric run. The first order plot
corresponding to these readings is shown on page 40.

Gravimetrically, a similar kinetic expression can be
derived,

$$\log [X_\infty - X_t] = \frac{-kt}{2.303} + \log X_\infty \quad \ldots \ldots \quad (40)$$

where X_t = number of moles of carbon dioxide weighed at time
t and X_∞ = initial moles of acid used. The concentration of
acid was calculated at room temperature on the basis of the
acid weighed and the quinoline added as solvent. This con-
centration was checked in several cases by allowing the run to
go to completion. The number of moles carbon dioxide recovered
was over 95 °/o of the theoretical calculation. The same
method as in the manometric runs was used to calculate the
specific rate constants. Table III lists the weights of carbon
dioxide for a typical gravimetric run. The corresponding first
order plot is shown on page 42.

It was found that the manometric runs did not agree
with those obtained gravimetrically when the specific rate
constant exceeded about 12×10^{-4} sec.$^{-1}$. At higher rates,
the specific rate constants obtained manometrically dropped
off sharply with an increase in temperature and approached a
limiting value of about 20×10^{-4} sec.$^{-1}$. For example, in
run no. 365, the gravimetric method showed that the reaction
was completed after about 700 seconds, whereas use of the
manometric method indicated continued evolution of carbon
dioxide up to 3,000 seconds. Weissberger (57) has indicated

TABLE II

TYPICAL MANOMETRIC RUN NO. 187

0.052 M. Salicylic Acid in Quinoline at 230°C

Time (sec.)	Pressure (mm. Hg)	$[P_\infty - P_t]$	Log $[P_\infty - P_t]$
550	30.0	272.6	2.436
650	50.7	251.9	2.401
750	70.0	232.6	2.367
850	88.5	214.1	2.331
950	106.0	196.6	2.294
1,050	121.5	181.1	2.258
1,150	137.0	165.6	2.219
1,250	151.3	151.3	2.180
1,350	163.5	139.1	2.143
1,450	175.5	127.1	2.104
1,550	186.9	115.7	2.063
1,650	197.7	104.9	2.021
1,800	210.9	91.7	1.962
2,000	226.1	76.5	1.884
2,200	238.5	64.1	1.807
7,300 (t_∞)	302.6 (P_∞)		

Figure 4

PLOT OF LOG $(P_\infty - P_t)$ vs t FOR RUN 187 SALICYLIC ACID

AT 230°C

LOG $(P_\infty - P_t)$

t (sec.)

40
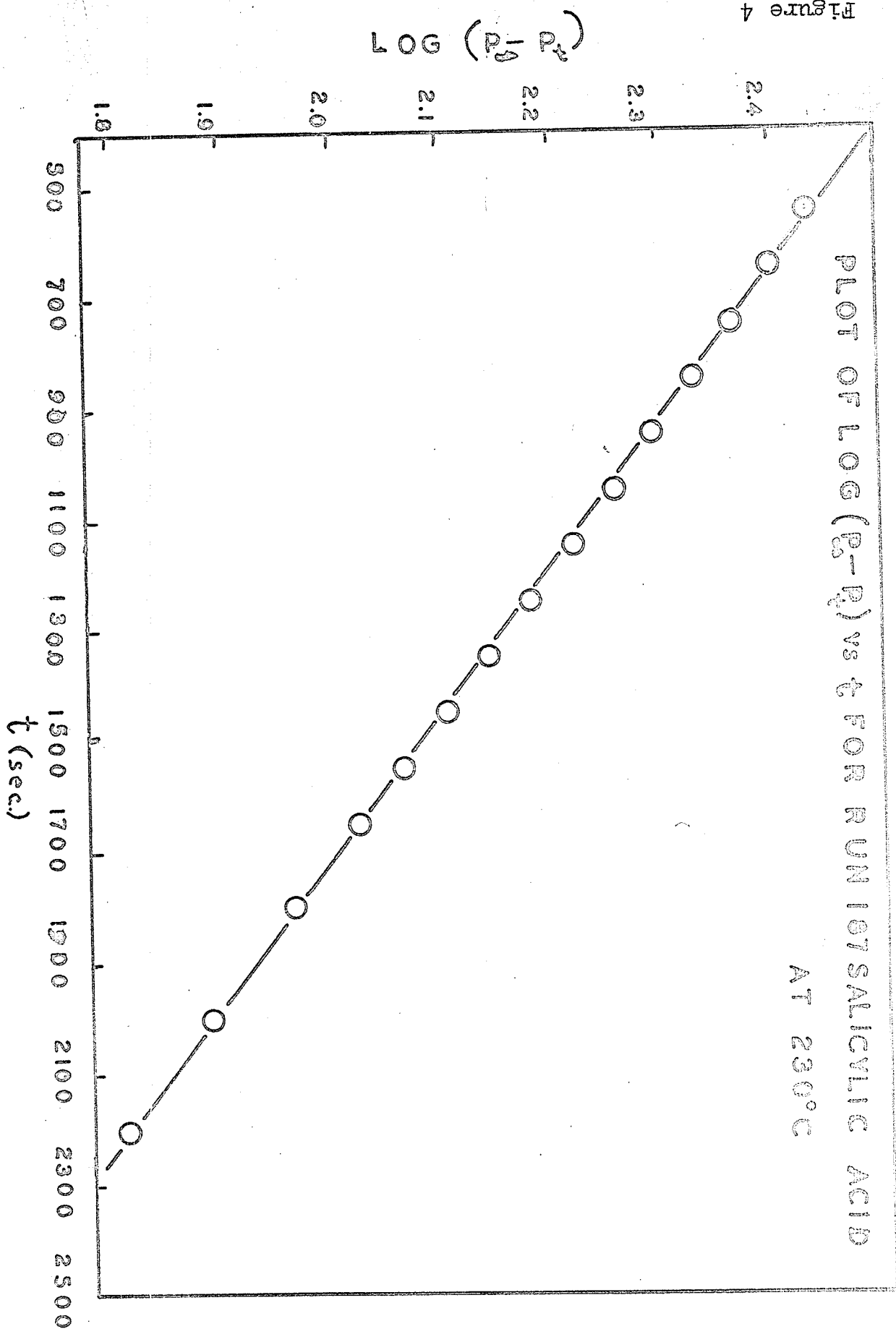
TABLE III

TYPICAL GRAVIMETRIC RUN* NO. 385

0.109 M. Salicylic Acid in Quinoline at 230°C

Time (sec.)	CO_2 Weights (gm.) $[X_t]$	$[X_\infty - X_t]$	Log $[X_\infty - X_t]$
0	0	0.0433	−1.363
125	0.0046	0.0387	−1.412
275	0.0098	0.0335	−1.475
425	0.0145	0.0288	−1.541
575	0.0180	0.0253	−1.597
725	0.0211	0.0222	−1.654
875	0.0238	0.0195	−1.710
1,025	0.0261	0.0172	−1.764
1,225	0.0290	0.0143	−1.845
1,475	0.0320	0.0113	−1.947

* In calculating X_∞, the first reading was subtracted from the theoretical value of X_∞. This allowed enough time for the system to come to temperature equilibrium.

Figure 5

PLOT OF LOG $(X_\infty - X_t)$ vs t FOR RUN 385,

SALICYLIC ACID (230°C)

42
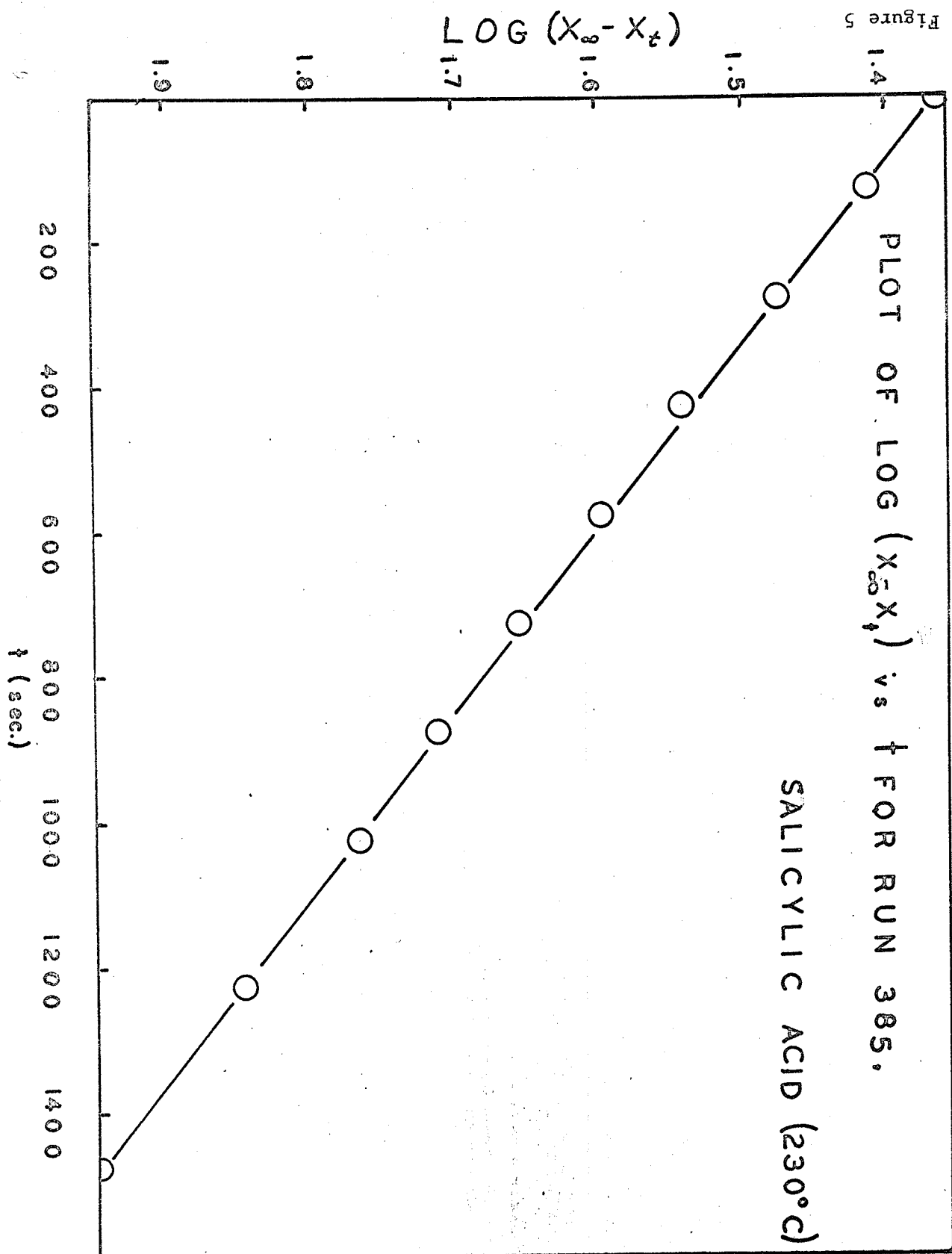
that unless the solution is stirred rapidly this type of behavior is common in manometric kinetics. A supersaturated solution is formed which then results in a lag in rate of gas evolution. Therefore, at high reaction rates, the manometric method merely records the rate of evolution of gas from the supersaturated solution rather than the rate of reaction. This phenomenon explained the constant rates of decarboxylation (k was approximately equal to 16×10^{-4} $sec.^{-1}$) observed by Janzen (33) for the 4-amino, 4-hydroxy and 4-alkoxysalicylic acids in quinoline solution at $200^{\circ}C$.

This problem was not encountered in the gravimetric method because nitrogen gas was used to sweep the carbon dioxide out of the reaction vessel.

Table IV lists the observed rates of decarboxylation of salicylic acid and thirteen substituted salicylic acids.

TABLE IV

Rates of Decarboxylation of Substituted Salicylic Acids in Quinoline

Temp. $^{\circ}C$	Substituent	Run No.	Rate x 10^4 (sec. $^{-1}$)	Standard Error	Average Rate $\pm$ max. dev.
93	4NH$_2$	304*	0.5788	0.0077	
		305*	0.4761	0.0167	0.5275 $\pm$ 0.514
100		310*	1.041	0.027	
		311*	1.138	0.039	1.089 $\pm$ 0.048
110		302*	3.407	0.045	
		303*	3.296	0.041	3.352 $\pm$ 0.056
120		296*	9.355	0.061	
		297*	9.321	0.048	9.338 $\pm$ 0.017
126		405*	12.54	0.20	
		406*	14.06	0.22	13.30 $\pm$ 0.76
130	4OH	298*	0.6183	0.0038	
		299*	0.6111	0.0059	0.6147 $\pm$ 0.036
140		288*	1.668	0.024	
		289*	1.556	0.028	1.612 $\pm$ 0.056
150		292*	4.150	0.016	
		293*	3.798	0.039	3.974 $\pm$ 0.176
160		284*	11.12	0.27	
		285*	9.699	0.571	10.41 $\pm$ 0.71
180		368*	44.34	0.64	
		369*	45.80	0.67	45.07 $\pm$ 0.73
190		365*	77.06	2.20	
		367*	80.81	1.70	78.94 $\pm$ 1.88

TABLE IV cont'd

Temp. °C	Substituent	Run No.	Rate x 10^4 (sec. $^{-1}$)	Standard Error	Average Rate ± max. dev.
130	4OEt	300*	0.1347	0.0023	
		301*	0.1275	0.0032	0.1311 ± 0.036
140		290*	0.3885	0.0050	
		291*	0.4070	0.0040	3.978 ± 0.093
150		294*	1.031	0.013	
		295*	1.013	0.014	1.022 ± 0.009
160		282*	2.880	0.026	
		283*	2.674	0.073	2.777 ± 0.103
170		278*	6.410	0.259	
		279*	5.204	0.510	5.807 ± 0.603
180		370*	14.22	0.07	
		371*	15.06	0.19	14.64 ± 0.42
190		362*	27.74	0.44	
		363*	31.70	0.60	29.72 ± 1.98
200	$4CH_3$	236	3.535	0.055	
		237	3.680	0.067	3.608 ± 0.072
210		254	7.004	0.086	
		255	6.705	0.117	6.855 ± 0.150
220		250	12.67	0.167	
		251	13.20	0.170	12.94 ± 0.27
230		374*	27.55	0.23	
		395*	27.09	0.06	27.32 ± 0.23
200	4Br	232	3.547	0.094	
		233	3.227	0.101	3.387 ± 0.160

TABLE IV cont'd

Temp. °C	Substituent	Run No.	Rate x 10^4 (sec.$^{-1}$)	Standard Error	Average Rate ± max. dev.
210	4Br	246	6.433	0.111	
		247	6.362	0.124	6.398 ± 0.036
220		248	11.48	0.157	
		249	11.16	0.173	11.32 ± 0.16
230		389*	24.22	0.25	
		393*	23.02	0.19	23.62 ± 0.60
200	4NO$_2$	276*	0.3879	0.109	
		277*	0.4324	0.113	0.4102 ± 0.222
210		264	0.8792	0.0090	
		265	0.8340	0.0093	0.8566 ± 0.0226
220		179	2.148	0.013	
		182	2.266	0.012	
		268	2.020	0.014	
		269	2.223	0.021	2.164 ± 0.144
230		144	4.950	0.123	
		145	4.528	0.035	
		266	4.470	0.031	
		267	4.980	0.074	4.732 ± 0.262
200	5NO$_2$	7**	1.148	0.008	
		8**	1.028	0.012	
		9**	0.9909	0.0144	1.056 ± 0.092
210		262	1.860	0.022	
		263	2.126	0.017	1.993 ± 0.133

TABLE IV   cont'd

Temp. °C	Substituent	Run No.	Rate x 10^4 (sec. $^{-1}$)	Standard Error	Average Rate ± max. dev.
220	5NO$_2$	176	3.821	0.018	
		177	3.869	0.019	
		178	4.105	0.037	3.932 ± 0.173
230		140	7.670	0.044	
		174	7.707	0.041	
		175	8.298	0.067	7.891 ± 0.407
200	5CH$_3$	272	1.457	0.023	
		319	1.343	0.021	
		320	1.269	0.010	1.363 ± 0.094
210		256	3.007	0.031	
		257	3.192	0.053	3.099 ± 0.092
220		252	5.657	0.052	
		253	5.996	0.115	5.827 ± 0.170
230		386*	12.16	0.08	
		387*	11.48	0.07	11.82 ± 0.34
200	5Br	218	1.483	0.007	
		219	1.533	0.024	1.508 ± 0.025
210		208	3.506	0.031	
		209	3.357	0.036	
		212	3.333	0.025	3.399 ± 0.107
220		196	6.120	0.061	
		197	6.350	0.055	
		198	6.561	0.080	6.344 ± 0.224

TABLE IV   cont'd

Temp. $^{\circ}$C	Substituent	Run No.	Rate x 10^4 (sec. $^{-1}$)	Standard Error	Average Rate $\pm$ max. dev.
230	5Br	382*	12.58	0.16	
		384*	11.09	0.06	11.84 $\pm$ 0.75
200	5Cl	230	1.524	0.013	
		231	1.595	0.031	1.559 $\pm$ 0.035
210		214	3.059	0.020	
		215	3.270	0.050	
		216	3.472	0.062	3.267 $\pm$ 0.208
220		168	6.139	0.101	
		169	6.704	0.127	
		192	6.170	0.097	6.338 $\pm$ 0.366
230		380*	11.42	0.26	
		381*	12.78	0.10	12.10 $\pm$ 0.68
200	5OH	228	1.801	0.011	
		229	2.058	0.019	1.929 $\pm$ 0.128
210		213	4.006	0.042	
		315	4.071	0.057	4.039 $\pm$ 0.032
220		166	7.674	0.064	
		167	7.469	0.041	
		193	8.190	0.108	7.778 $\pm$ 0.412
230		378*	16.87	0.03	
		379*	19.47	0.13	18.17 $\pm$ 1.30

TABLE IV   cont'd

Temp. °C	Substituent	Run No.	Rate x 10^4 (sec.$^{-1}$)	Standard Error	Average Rate $\pm$ max. dev.
200	5NH$_2$	238	1.682	0.013	
		239	1.831	0.021	1.757 $\pm$ 0.074
210		396*	3.690	0.071	3.690 $\pm$ 0.000
220		163	7.293	0.099	
		164	7.794	0.165	
		165	7.763	0.121	7.617 $\pm$ 0.324
230		390	16.38	0.45	
		391	15.34	0.20	15.86 $\pm$ 0.52
200	5OCH$_3$	224	2.171	0.020	
		225	2.284	0.029	2.228 $\pm$ 0.056
210		206	4.412	0.089	
		207	4.641	0.074	4.527 $\pm$ 0.114
220		194	8.376	0.130	
		195	9.047	0.078	
		199	7.966	0.087	8.429 $\pm$ 0.618
230		376*	19.16	0.11	
		377*	19.98	0.11	19.57 $\pm$ 0.41
180	H	76*	0.1993	0.0028	
		77*	0.1956	0.0029	
		79*	0.2005	0.0169	0.1985 $\pm$ 0.0029
200		220	1.135	0.007	
		2**	1.089	0.007	

TABLE IV cont'd

Temp. $^{\circ}C$	Substituent	Run No.	Rate x 10^4 (sec. $^{-1}$)	Standard Error	Average Rate $\pm$ max. dev.
	H	3**	1.056	0.006	
		43**	1.050	0.019	1.082 $\pm$ 0.053
220		183	4.753	0.061	
		184	4.905	0.074	
		185	4.930	0.059	4.863 $\pm$ 0.110
230		186	8.544	0.099	
		187	8.692	0.070	
		191	8.677	0.106	
		385*	9.106	0.069	8.755 $\pm$ 0.351
200	5OCH$_3$[1]	325	2.176	0.016	
	5OCH$_3$[2]	326	2.497	0.037	

*Determined gravimetrically. All others determined manometrically.

**Results obtained by Janzen (33).

1 Dissolved in 0.197 M hydroquinone solution in quinoline.

2 Dissolved in 0.078 M benzoyl peroxide solution in quinoline.

Test for a Free Radical Mechanism

Since varying substituents had very little effect on the rate of decarboxylation of salicylic acid, it was possible that a free radical mechanism was operating. Most free radical reactions are initiated by small quantities of reactive free radicals and retarded by inhibitors which react with active radicals and form less active radicals or nonradicals. The decarboxylation of 5-methoxysalicylic acid in run no. 326 was

carried out in the presence of an initiator such as benzoyl
peroxide to test for a free radical reaction. Similiarly the
5-methoxysalicylic acid in run no. 325 was decarboxylated in
the presence of a retarder such as hydroquinone also intended
to test for a free radical mechanism. It was noted that
neither the initiator or retarder had any appreciable effect
on the rate of decarboxylation of 5-methoxysalicylic acid in
quinoline and hence, the possibility of a free radical
mechanism was eliminated.

Activation Parameters

As shown in the theory of absolute reaction rates,
the specific rate constant k of any reaction can be given by
the expression:

$$k = \frac{k\ T}{h}\ e^{\Delta S*/R}\ e^{-\Delta H*/RT} \quad \ldots \ldots \ (41)$$

where $\underline{k}$ = Boltzmann constant

T = Absolute temperature

h = Planck's constant

$\Delta S*$ = Entropy of activation

$\Delta H*$ = Heat of activation

Rearrangement of equation (41) yields the following expression:

$$\ln k/T = \ln \underline{k}/h + \Delta S*/R - \Delta H*/RT \ \ldots \ldots \ (42)$$

If, as is usually the case, $\Delta S*$ does not vary greatly with the
temperature, a plot of ln k/T vs 1/T will give an approximate
straight line of slope $-\Delta H*/R$. The plots for the various
acids which were decarboxylated are shown on pages 51a and 51b.
The enthalpies of activation were calculated by means of a
least squares plot. The calculations were carried out by an
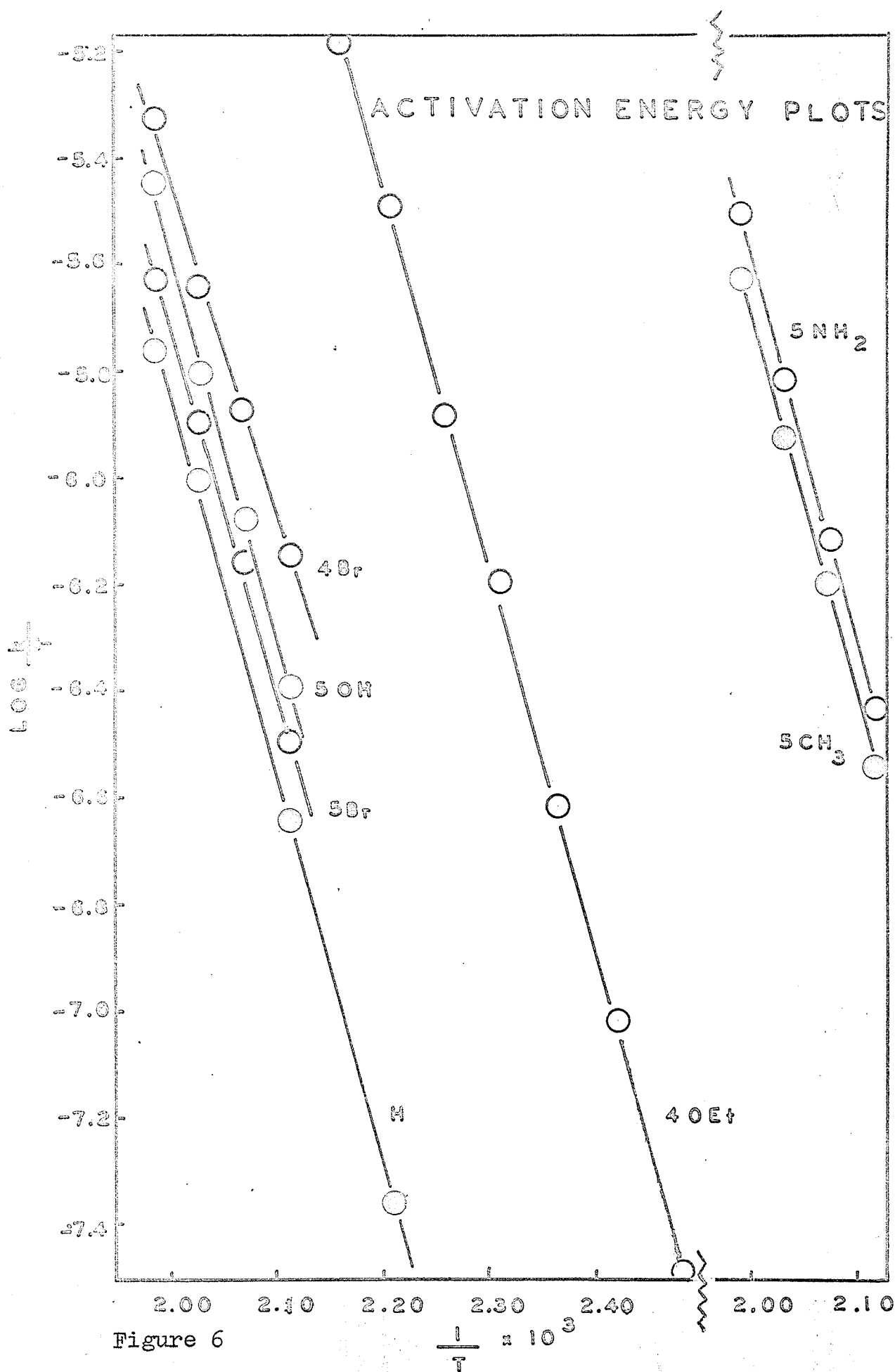
Figure 6
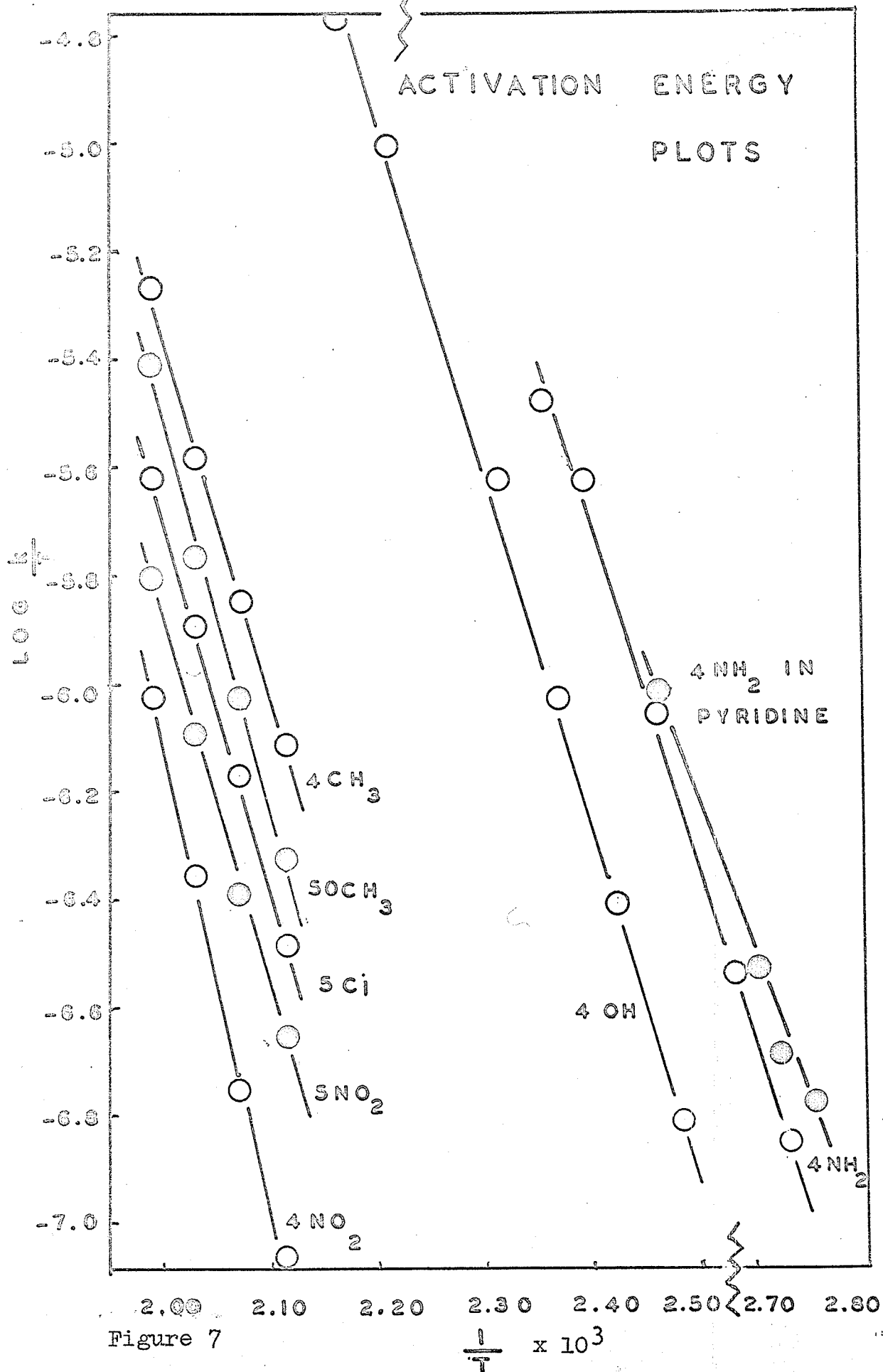
Figure 7

I.B.M. computer. The entropies of activation were calculated from the intercept of the plot ln k/T vs 1/T. From equation (42) it can be seen that the intercept $b = \ln \underline{k}/h + \Delta S^*/R$ and thus

$$\Delta S^* = R(b - \ln \underline{k}/h) \quad . \quad . \quad . \quad . \quad . \quad (43)$$

Table V gives the results of these calculations.

TABLE V

Activation Parameters

Subst.	ΔH^* (k cal/mole)	Standard Error	ΔS^* (cal/mole deg)	Standard Error
$4NH_2$	28.5	0.8	−0.707	2.03
4OH	29.5	0.5	−5.18	1.17
4OEt	32.6	0.4	−0.485	0.954
$4CH_3$	30.7	0.8	−10.3	1.65
4Br	29.3	0.9	−13.5	1.89
$4NO_2$	38.2	0.8	+1.14	1.72
$5NO_2$	30.7	0.8	−12.8	1.60
$5CH_3$	32.9	0.8	−7.55	1.68
5Br	31.1	0.9	−11.1	1.77
5Cl	31.2	0.8	−10.9	1.55
5OH	33.7	1.3	−5.24	2.59
$5NH_2$	33.6	0.6	−5.61	1.23
$5OCH_3$	32.6	1.2	−6.18	2.43
H	33.4	0.4	−7.00	0.765

Using a different method for determining rates (volumetric) and only a 20° range in temperature, Clark (12) determined the activation parameters for the decarboxylation of 4-hydroxysalicylic acid in quinoline. The value obtained for the enthalpy of activation was 34.5 ± 1.8 k cal./mole and that for the entropy of activation was +5.89 ± 4.26 eu./mole.

As shown in Table V, the present investigation shows an enthalpy of activation equal to 29.5 ± 0.5 k cals./mole and the entropy of activation equal to -5.18 ± 1.17 eu./mole. This study was carried out over a 60° temperature range. Combining the kinetic results obtained by Clark and those in the present investigation, the value for the enthalpy of activation is 29.6 ± 2.8 k cals./mole and the entropy of activation is -4.96 ± 6.57 eu./mole. These values for the combined data are well within the experimental error of the author's results. The plot of ln k/T vs 1/T gives an excellent correlation coefficient of -0.998 for the author's results and -0.996 for the combined results. Therefore it seems that the results obtained in the present investigation are valid. The significance of the correlation coefficients was tested by application of Student's t test (36). t was equal to 57.7 and 40.2 in the author's results and the combined results, respectively. In both cases, the correlation coefficients were highly significant at the 0.1 °/o level.

The Enthalpy - Entropy Relationship

As indicated in the introduction, Leffler (37) has

shown it is possible to determine whether a series of
compounds are reacting by the same mechanism by plotting
ΔH^* vs ΔS^*. If they are operating by the same mechanism
a linear relationship between ΔH^* and ΔS^* should be
observed. The plot is shown on page 56a. For the sake
of neatness, Figure 8 only shows the error limits in ΔH^*
and ΔS^*. However, as Leffler and Grunwald (38) have
pointed out, the actual error contour of ΔH^* vs ΔS^* is a
highly eccentric ellipse whose major axis is inclined to
the entropy axis at a slope equal to the mean experimental
temperature. An example of this error contour is shown
for 5-methoxysalicylic acid. The results indicate a fairly
good linear relationship except for the 4-amino, 4-hydroxy
and 4-ethoxysalicylic acids. Neglecting these three acids,
the plot of ΔH^* vs ΔS^* has a correlation coefficient of
0.982 and the isokinetic temperature is equal to 286 $\pm$ 48
degrees Centigrade.

Since the isokinetic temperature is considerably
higher than the experimental temperatures, the substi-
tuents on salicylic acid should have an effect on the
rate of decarboxylation. However, an examination of Fig-
ures 6 and 7 shows that apart from the 4-hydroxy, 4-ethoxy
and 4-amino acids, the rates are all much the same. The
constant rate is particularly noticeable if only the
5-substituted acids are considered, as is recommended by

PLOT OF $\Delta H^{\ddagger}$ vs $\Delta S^{\ddagger}$
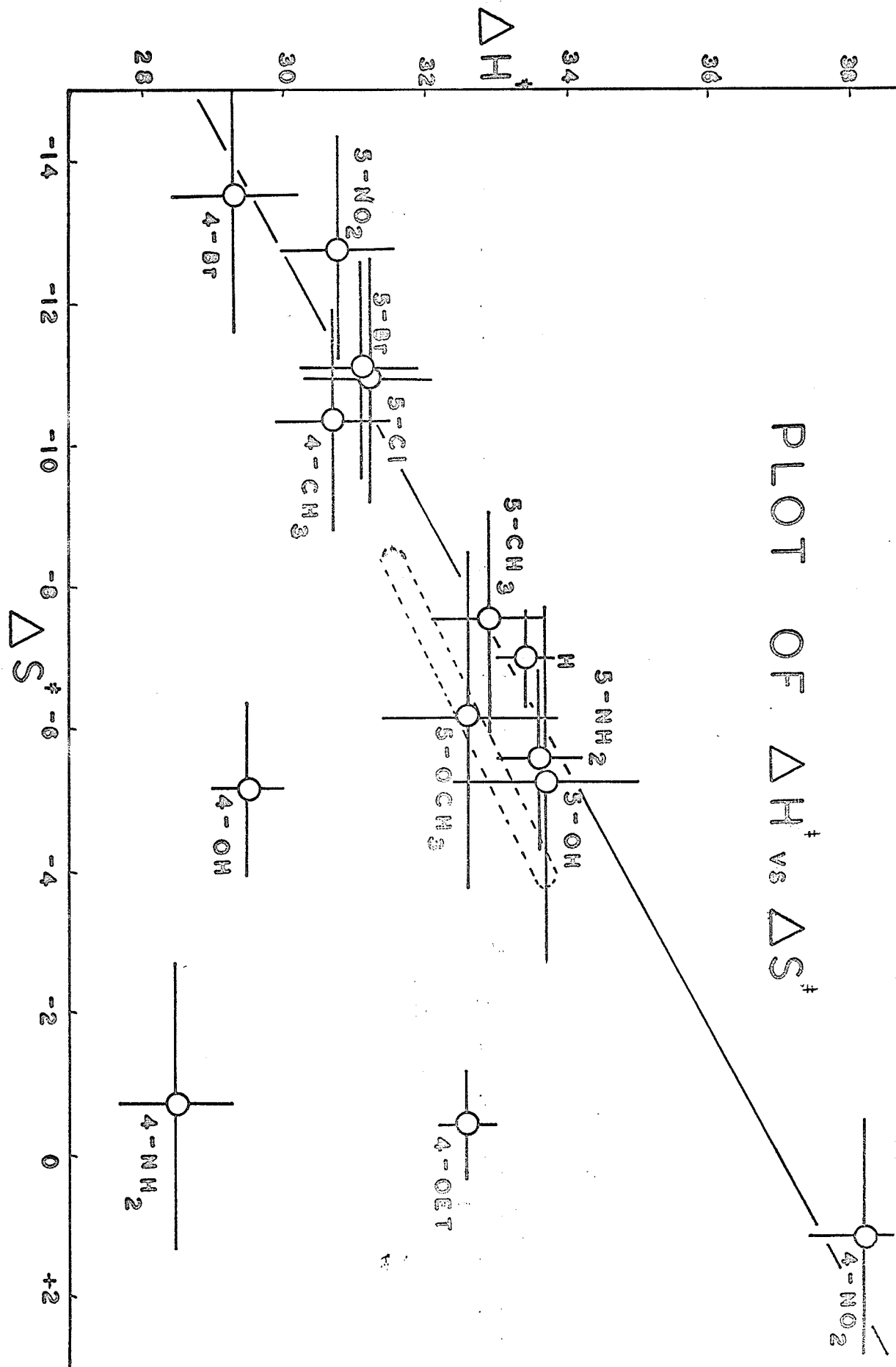
Figure 8

vanBekkum, Verkade and Wepster (55). Re-examination
of Figure 8 shows that the variation in ΔH^* and ΔS^* is
barely outside the probable error of the measurements,
so that for these acids the rates of decarboxylation are
the same, not only at the calculated isokinetic tempera-
ture, but at any temperature. The facts that the rates
are the same at temperatures other than the calculated
isokinetic temperature suggests that the apparent iso-
kinetic relationship is not real. Thus the insensitivity
of the rates towards varying substituents cannot simply
be due to the fact that the rates were measured at the
isokinetic temperature, but must have some other origin.

The absence of any variation of rate with sub-
stitution at the 5-position indicates that these substi-
tuents are not able to transmit any electronic influence
to the reaction site. On the other hand, the 4-substi-
tuents, especially the 4-hydroxy, 4-ethoxy and 4-amino,
are able to transmit electronic influences to the reaction
site as evidenced by the fact that they react at different
rates. This might at first sight suggest that the
4-substituted acids react by a different mechanism from
the 5-substituted ones, but it will be shown later that
all acids can be accommodated by a single mechanism.

Order with Respect to Quinoline

It was desirable to ascertain whether the solvent

quinoline was involved prior to or in the rate determining step of the decarboxylation process. It was found that nitrobenzene was a suitable inert solvent. The extent of decarboxylation of 4-methylsalicylic acid in this solvent was negligible over a period of one day at a temperature of $220^{\circ}C$. The order with respect to quinoline was determined by adding progressively larger amounts of quinoline to the nitrobenzene and then determining the rates of decarboxylation of 4-methylsalicylic acid in these solutions. The decarboxylations followed first order kinetics as shown on page 59. The final results are shown in Table VI.

TABLE VI

Rates of Decarboxylation of 4-Methylsalicylic Acid in Nitrobenzene-Quinoline Mixtures at a Temperature of $220^{\circ}C$

Run No.	Rate x 10^4 (sec.$^{-1}$)	Stand. Error	Concentration* Quinoline (m/l)	Conc. Acid* (m/l)	k_1 x 10^4
336	6.139	0.112	1.61	0.165	
337	6.812	0.075	1.61	0.132	4.0
338	8.949	0.067	8.00×10^{-1}	0.123	11.2
339	10.25	0.142	4.46×10^{-1}	0.135	23.0
340	12.63	0.154	2.45×10^{-1}	0.183	51.6
341	9.996	1.467	1.35×10^{-1}	0.144	74.2
342	7.928	0.087	5.87×10^{-2}	0.149	135.1
343	4.611	0.049	2.69×10^{-2}	0.154	171.2
344	2.367	0.015	1.26×10^{-2}	0.144	187.7
349	3.565	0.020	1.99×10^{-2}	0.146	179.4
350	1.913	0.015	9.98×10^{-3}	0.140	191.8

* The concentrations were calculated at $220^{\circ}C$.

PLOT OF LOG $(X_3 - X_t)$ vs t FOR RUN 350.

4-METHYL SALICYLIC ACID

(2 2 0° C)

t (sec)

LOG $(X_3 - X_t)$

Figure 9
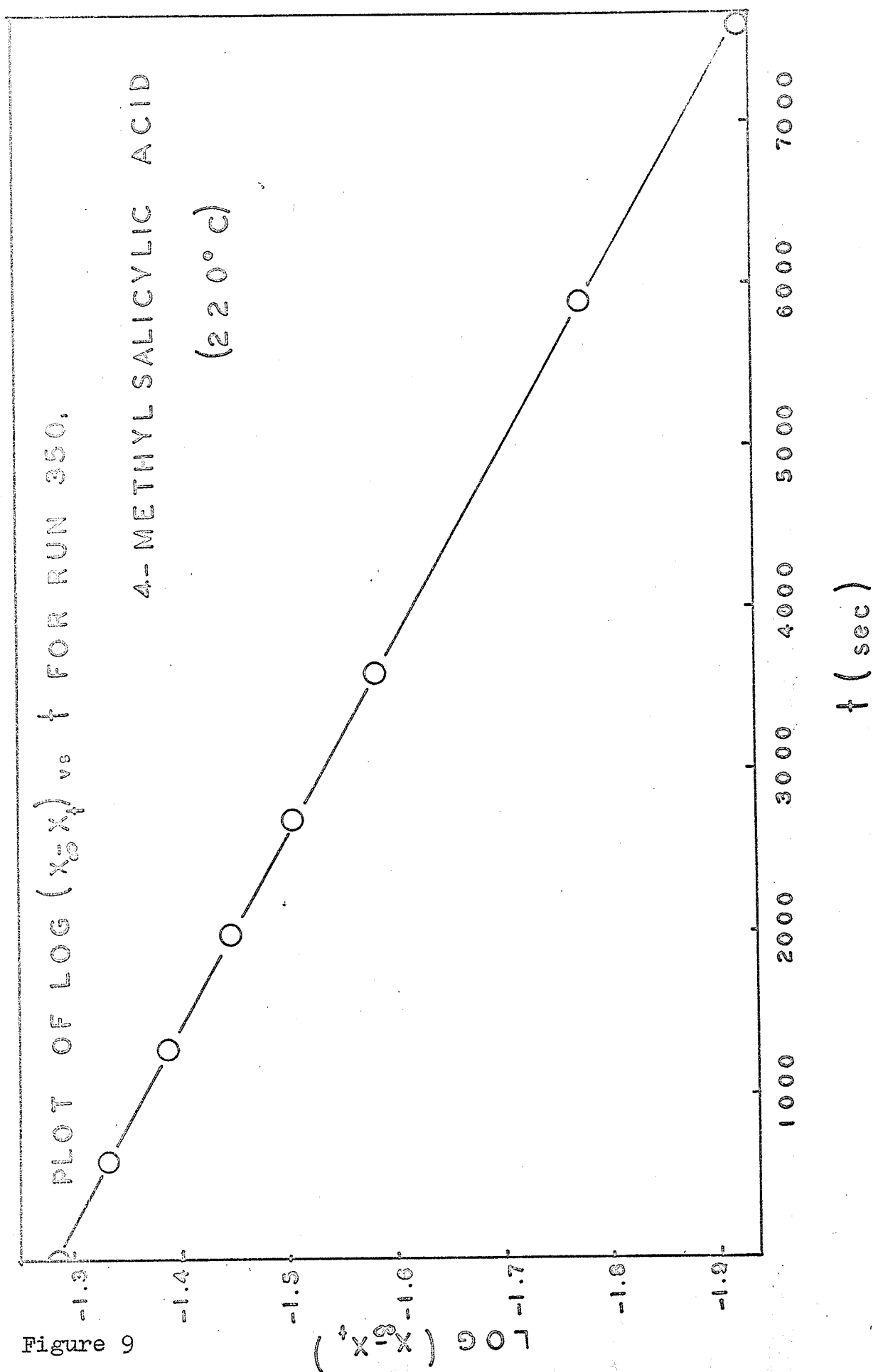
TABLE VI   cont'd

Run No.	Rate x 10^4 (sec.$^{-1}$)	Stand. Error	Concentration Quinoline (m/l)	Conc. Acid (m/l)	k_1 x 10^4
351	0.9824	0.0061	5.35 x 10^{-3}	0.154	183.6
352	1.442	0.199	7.58 x 10^{-3}	0.147	190.3
373	0.9547	0.036	4.85 x 10^{-3}	0.086	196.9

The effect of increasing concentration of quinoline on the rate of decarboxylation is shown by plotting rate vs concentration of quinoline as shown on page 61. The shape of the curve suggests that the catalytic effect of the quinoline is opposed by some other retarding factor as the concentration of quinoline is increased. The retarding factor is probably due to the decreasing dielectric constant of the medium as the quinoline concentration is increased. However, as shown on page 62, at conditions where the acid is approximately five to thirty times in excess of the quinoline concentration, a linear relationship is obtained. A correlation coefficient of 0.998 is obtained in this region. It is over this range where the order of the reaction with respect to quinoline is determined. The order is determined from the slope of the best straight line which is calculated from a least squares plot. The order is equal to 1.0 ± 0.0. Therefore, the rate expression becomes:

$$\frac{d[CO_2]}{dt} = k' [Acid] = k_1 [Quinoline][Acid] \quad . \quad . \quad (44)$$

where the pseudo rate constant

$$k' = k_1 [Quinoline] \quad . \quad . \quad . \quad . \quad . \quad (45)$$

On rearrangement,

$$k_1 = k' / [Quinoline] \quad . \quad . \quad . \quad . \quad . \quad (46)$$

RATES OF DECARBOXYLATION OF
4-METHYL SALICYLIC ACID IN
QUINOLINE - NITROBENZENE
MIXTURES AT 220°C

Figure 10

RATES OF DECARBOXYLATIONS OF
4-METHYLSALICYLIC ACID IN
QUINOLINE – NITROBENZENE
MIXTURES AT 220°C

CONC. QUINOLINE IN NITROBENZENE (m/l)
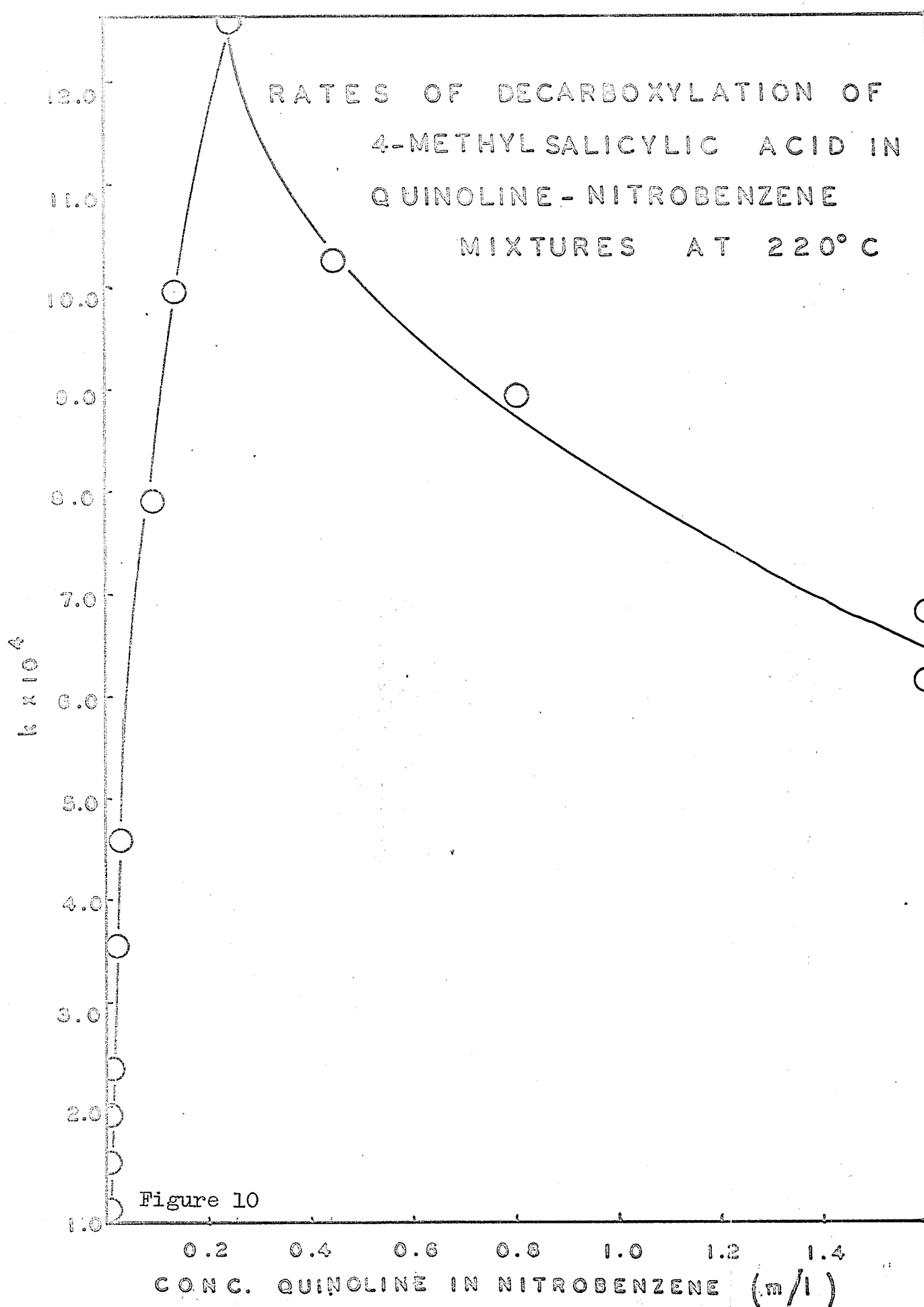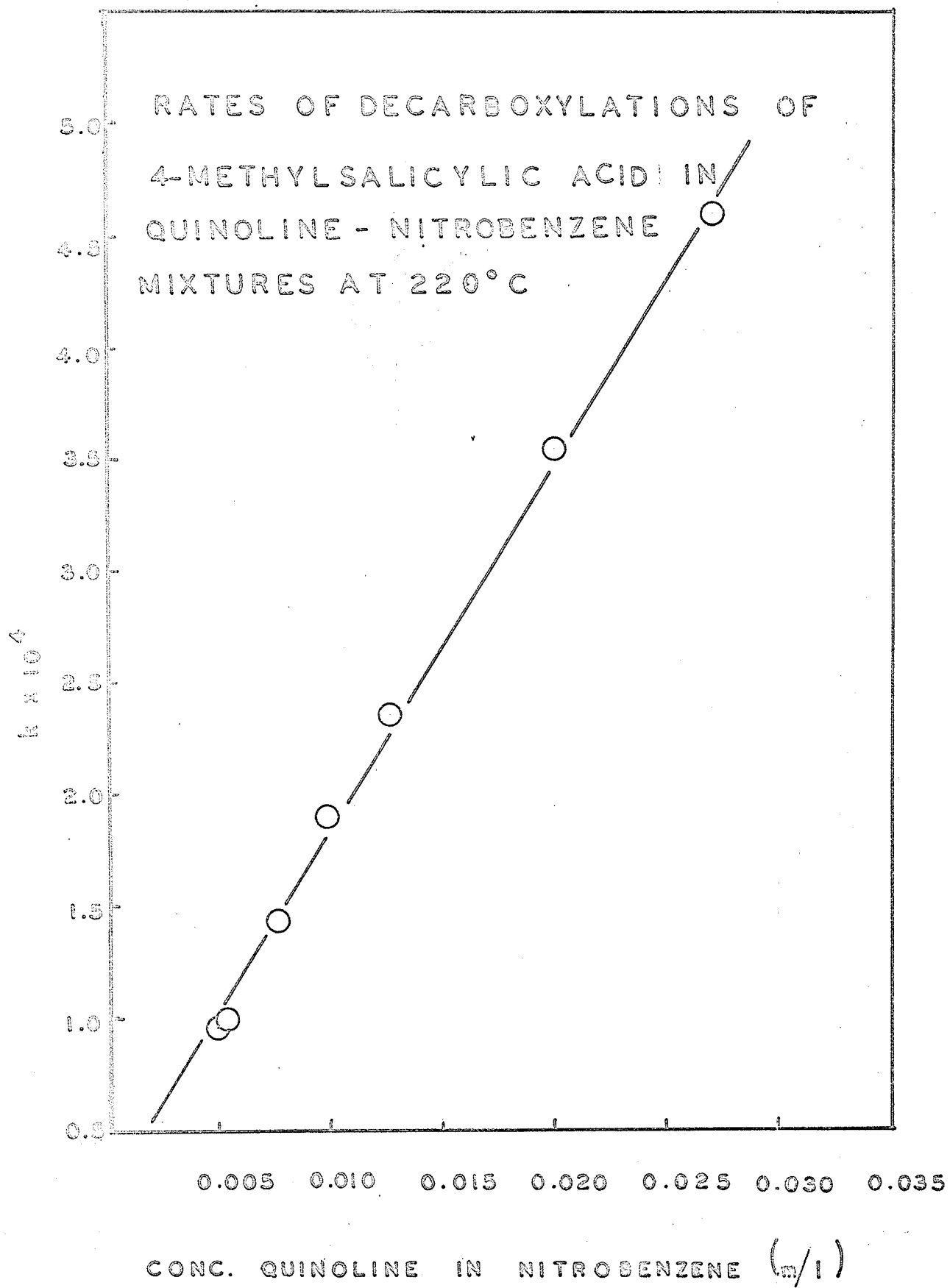
Figure 11

As shown in Table VI, the value of k_1 over this concentration range is equal to $(185.9 \pm 14.6) \times 10^{-4}$. The maximum deviation noted in k_1 is about the extent of experimental error observed in the rate measurements.

Effect of Substituted Quinolines and Pyridine

Since the quinoline is involved prior to or in the rate determining step, it was decided to determine what effect changing electron density on the nitrogen atom would have on the rate of decarboxylation of salicylic acid. This was studied by decarboxylating salicylic acid in 6-nitro, 6-methoxy and 8-hydroxyquinolines. The decarboxylations showed first order kinetics and the rates are tabulated in Table VII. It was noted that electron-donating groups on quinoline enhanced the rate of decarboxylation. This substituent effect cannot be attributed to dielectric effects since the 6-nitro and 6-methoxyquinolines both have a dielectric constant greater than quinoline.

TABLE VII

Rates of Decarboxylation of Salicylic Acid in Various Substituted Quinoline Solutions at a Temperature of $220^\circ C$

Solvent	Run No.	Rate x 10^4 (sec.$^{-1}$)	Standard Error	Average Rate x 10^4
6-nitro-quinoline	415	3.820	0.023	
	416	4.011	0.029	3.916 ± 0.096
Quinoline	183	4.753	0.061	
	184	4.905	0.074	
	185	4.930	0.059	4.863 ± 0.110

TABLE VII   cont'd

Solvent	Run No.	Rate x 10^4 (sec.$^{-1}$)	Standard Error	Average Rate x 10^4
8-hydroxy-quinoline	417	6.046	0.030	
	418	5.954	0.043	6.000 ± 0.046
6-methoxy-quinoline	423	6.093	0.035	
	424	6.298	0.095	6.146 ± 0.053

The effect of steric hindrance in the decarboxylation of 4-aminosalicylic acid was studied by carrying out the reaction in pyridine. The reaction showed first order kinetics as indicated on page 65. The kinetic results are shown in Table VIII.

TABLE VIII

Rates of Decarboxylation of 4-Aminosalicylic Acid in Pyridine Solution

Run No.	Temperature $^{\circ}$C	Rate x 10^4 (sec.$^{-1}$)	Standard Error
407	110	3.341	0.468
408	110	3.760	0.015
409	110	3.663	0.046
438	97	1.089	0.010
440	94	0.7606	0.0020
439	90	0.6138	0.0030

By determining the rates of decarboxylation, over a temperature range, it was possible to determine the enthalpy of activation and also the entropy of activation. The activation energy plot is shown on page 53. The enthalpy of

PLOT OF LOG$(X_\infty - X_t)$ vs t FOR RUN 440

4-AMINOSALICYLIC ACID IN PYRIDINE

LOG $(X_\infty - X_t)$

t (sec.)
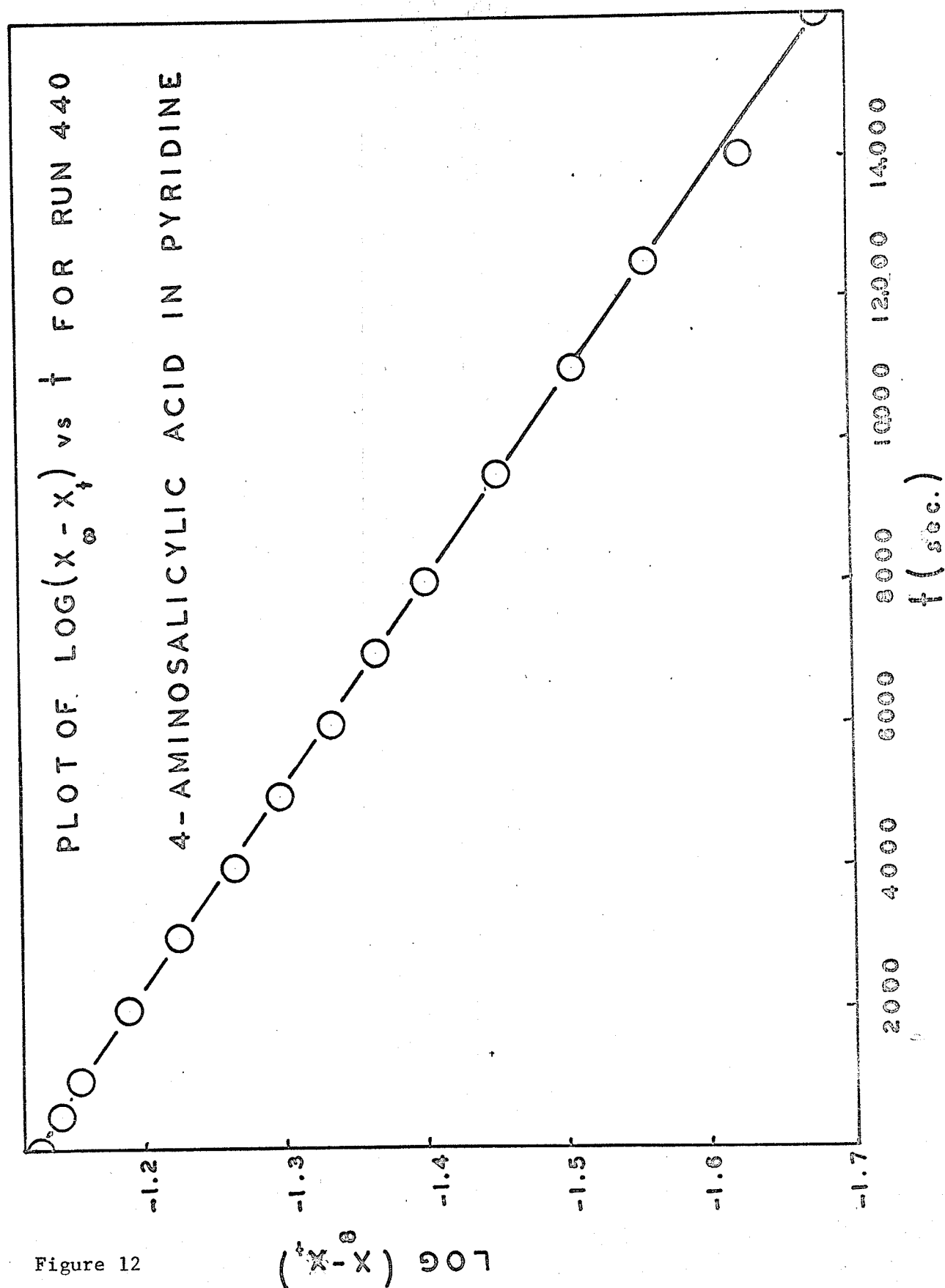
Figure 12

activation $\Delta H^* = 24.9 \pm 1.8$ k cal./mole and the entropy of activation $\Delta S^* = -9.84 \pm 4.58$ cal./mole degree. The fact that ΔH^* has been decreased from 28.5 k cal./mole in quinoline to 24.9 k cal./mole in pyridine indicates that the solvent is involved prior to or in the rate determining step of the decarboxylation process. Also, the decreased value for ΔS^* from -0.707 cal./mole degree in quinoline to -9.84 cal./mole degree in pyridine, indicates a more highly ordered arrangement in the transition state of the reaction compared to that in quinoline. Because of the magnitude of the experimental errors in ΔH^* and ΔS^*, it is necessary to use this data only as an indication of the mechanism in operation for the decarboxylation process.

DISCUSSION

The Hammett Equation

The Hammett plot on page 68 shows that the rates
of decarboxylation are very little influenced by varying
the substituents on salicylic acid except for the 4-amino,
4-hydroxy and 4-ethoxysalicylic acids. van Bekkum, Verkade
and Wepster (55) have proposed that the meta- substituted
compounds should define rho. On this basis, the value of
rho would be approximately zero. This insensitivity re-
quires one of three conditions:

(1) The substituent is insulated from the reaction centre.

(2) The rates are measured at or near the isokinetic
temperature.

(3) The rate is determined by two processes which are
oppositely influenced by substituents.

It is obvious that (1) does not apply to this re-
action. It was shown in the enthalpy - entropy discussion
of the results that the rates were not measured at the
isokinetic temperature. This leaves (3) as the correct
interpretation.

In salicylic acid the three likely reaction sites
may be numbered as shown below:
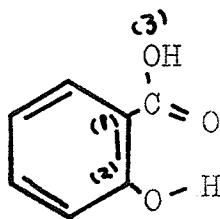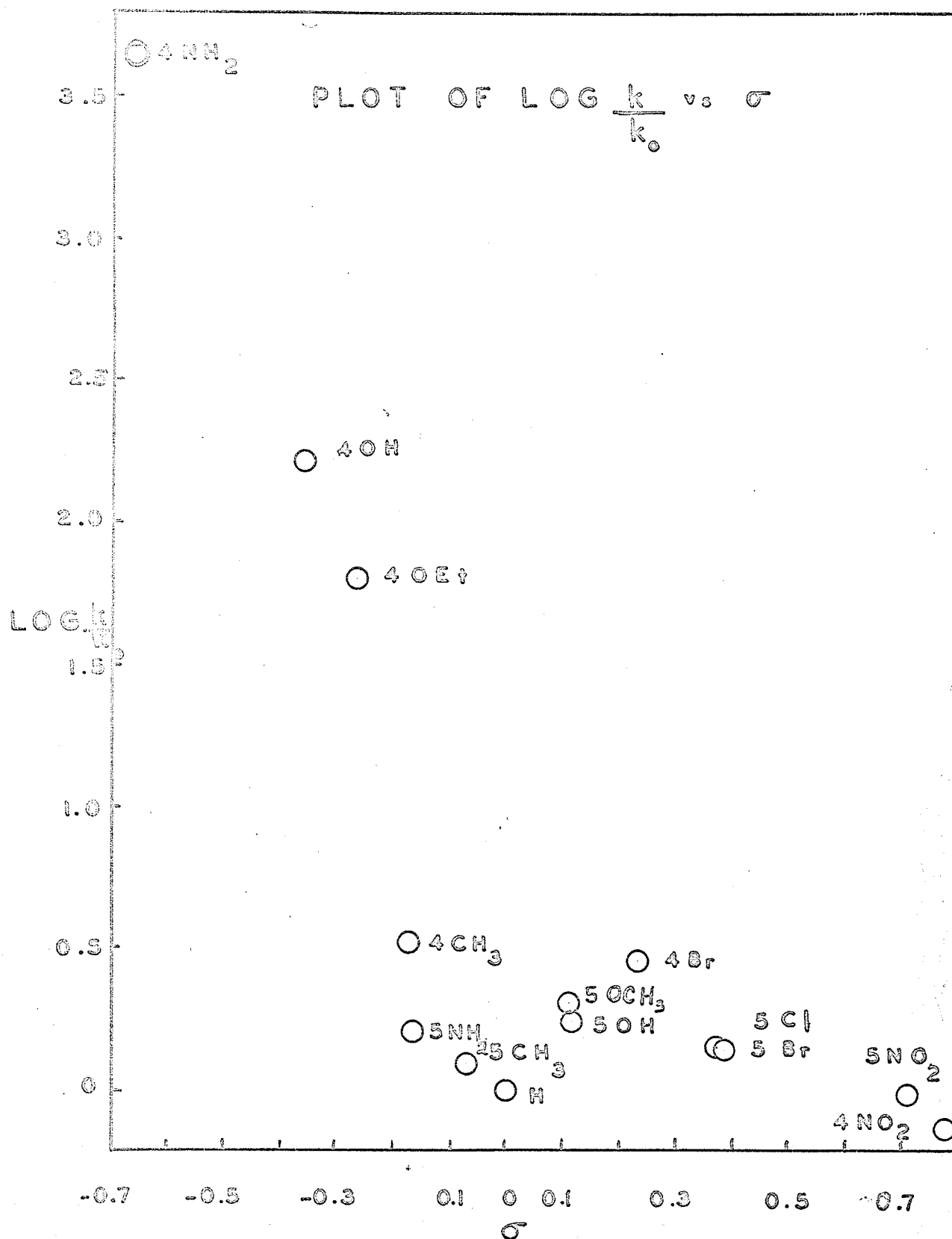
Figure 13

Since chelation occurs in salicylic acid, it seems possible that a substituent might affect a reaction occurring on the carboxyl group by two paths; namely through carbon 1 and carbon 2. This would result in a Hammett equation of the form:

$$\log k/k_0 = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad \ldots \ldots \quad (47)$$

Since a 5-substituent is _meta_ to carbon 1 and _para_ to carbon 2, the equation may be written:

$$\log k/k_0 = \rho_1 \sigma_m + \rho_2 \sigma_p \quad \ldots \ldots \quad (48)$$

Hence, in order that log k should remain constant for all the 5-substituted acids;

$$\rho_1/\rho_2 = -\sigma_p/\sigma_m \quad \ldots \ldots \ldots \quad (49)$$

and $-\sigma_p/\sigma_m$ must be constant for all 5-substituents. Since this is not the case, the proposed two opposing processes can not involve carbon 1 and carbon 2 but must both involve carbon 1.

One of the processes at carbon 1 is quite likely to be C-H bond making. The other could be C-C bond breaking or O-H bond breaking. O-H bond breaking is an acid ionization and so Hammett's σ should apply. C-H bond making and C-C bond breaking are substitution reactions on an aromatic ring and hence Brown's σ^+ should apply. For 5-substituents σ and σ^+ are all approximately the same, but for 4-substituents they are not and hence for the 4-substituents the opposing effects of the substituents might not cancel. The Hammett relationship should then be:

(a) for O-H bond breaking,

$$\log k/k_0 = \rho_1 \sigma^+ + \rho_3 \sigma \quad \cdots \cdots \quad (50)$$

(b) or for C-C bond breaking,

$$\log k/k_0 = \rho_1 \sigma^+ + \rho_1' \sigma^+ = (\rho_1 + \rho_1')\sigma^+ \quad \cdots \quad (51)$$

Equation (51) shows that a linear relationship should hold when $\log k/k_0$ is plotted against σ^+. As shown on page 70a this is not the case and hence equation (50), where C-H bond making and O-H bond breaking are involved, must be the correct interpretation. It is also possible that C-H bond making and C-C bond breaking are both involved at site 1 as well as O-H bond breaking at site 3. In this case, ρ_1 in equation (50) would be composed of rho for C-H bond making plus rho for C-C bond breaking at site 1. On rearranging equation (50),

$$\frac{\log k/k_0}{\sigma} = \rho_3 + \rho_1\left(\frac{\sigma^+}{\sigma}\right) \quad \cdots \cdots \quad (52)$$

A plot of $\dfrac{\log k/k_0}{\sigma}$ vs $\dfrac{\sigma^+}{\sigma}$ should yield a straight line of slope equal to ρ_1 and the intercept giving the value for ρ_3. These results are tabulated in Table IX on page 71. The plot is shown on page 72. Within experimental error, a fairly good linear relationship is observed. It should be noted that any small error in the sigma values will be multiplied by rho and thus cause considerable error in the plotted points. The plot has a correlation coefficient of -0.916 and $\rho_3 = +4.064$ and $\rho_1 = -4.011$. Equation (50) was also solved by means of an I.B.M. computer and the results obtained were $\rho_1 = -4.212 \pm 0.622$ and $\rho_3 = +3.983 \pm 0.838$. The negative value of ρ_1 indicates that electron releasing substituents favor the reaction at carbon 1. This is consistent with the assumption made that C-H bond making occurs at carbon 1 since a high electron density at this
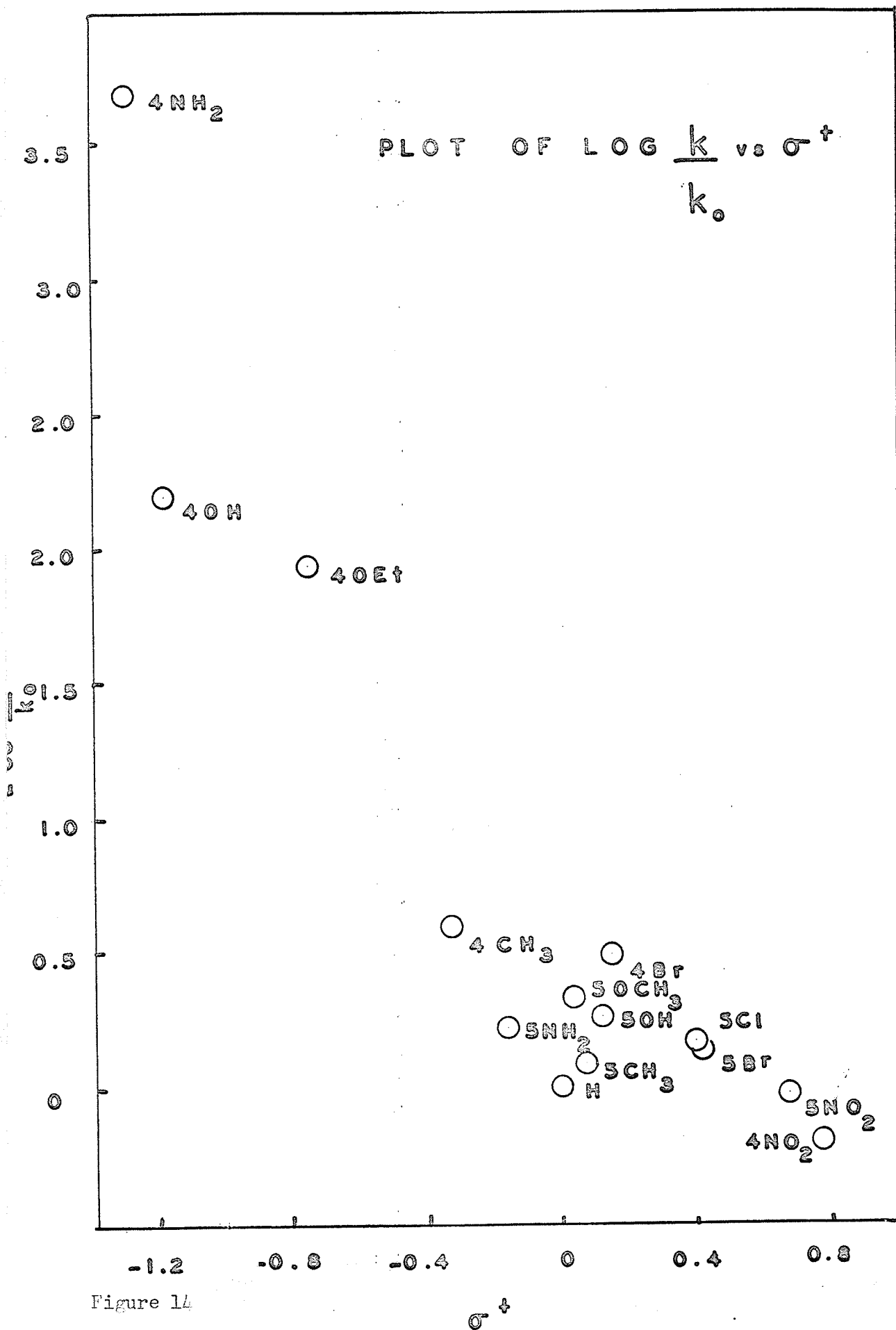
PLOT OF LOG $\dfrac{k}{k_o}$ vs σ^+

Figure 14

site should favor such a reaction. The positive value of ρ_3 is also consistent with the assumption that O–H bond breaking occurs at site 3. Generally, the absolute magnitude of ρ in aromatic substitution reactions is much larger than ρ in acid ionizations. This is because in the former the reaction site is on the ring and hence more sensitive to substituent effects, whereas in the latter it is on the side chain making it less sensitive to substituent effects.

Since the absolute values of ρ_1 and ρ_3 are approximately the same in the present investigation, this suggests that in the transition state O–H bond breaking is of greater importance than C–H bond making.

TABLE IX

HAMMETT PLOT AT 200°C

Subst.	σ	σ^+	Log k/k_0	$\dfrac{\text{Log } k/k_0}{\sigma}$	σ^+/σ
$4NH_2$	−0.660	−1.30	+3.661*	−5.54	+1.97
$4OH$	−0.357	−0.92	+2.216*	−6.21	+2.58
$4OEt$	−0.268	−0.78	+1.797*	−6.71	+2.91
$4CH_3$	−0.170	−0.31	+0.523	−3.08	+1.82
$4Br$	−0.232	0.150	+0.496	+2.14	+0.647
$4NO_2$	0.778	0.790	−0.136	−0.175	+1.02
$5NO_2$	0.710	0.674	−0.010	−0.014	+0.949
$5CH_3$	−0.069	−0.066	+0.101	−1.46	+0.957
$5Br$	0.391	0.405	+0.144	+0.368	+1.04
$5OH**$	0.121	0.121	+0.251	+2.07	+1.00
$5Cl$	0.373	0.399	+0.159	+0.426	+1.07
$5NH_2$	−0.161	−0.16	+0.211	−1.31	+0.994
$5OCH_3$	0.115	0.047	+0.314	+2.73	+0.409

Figure 15
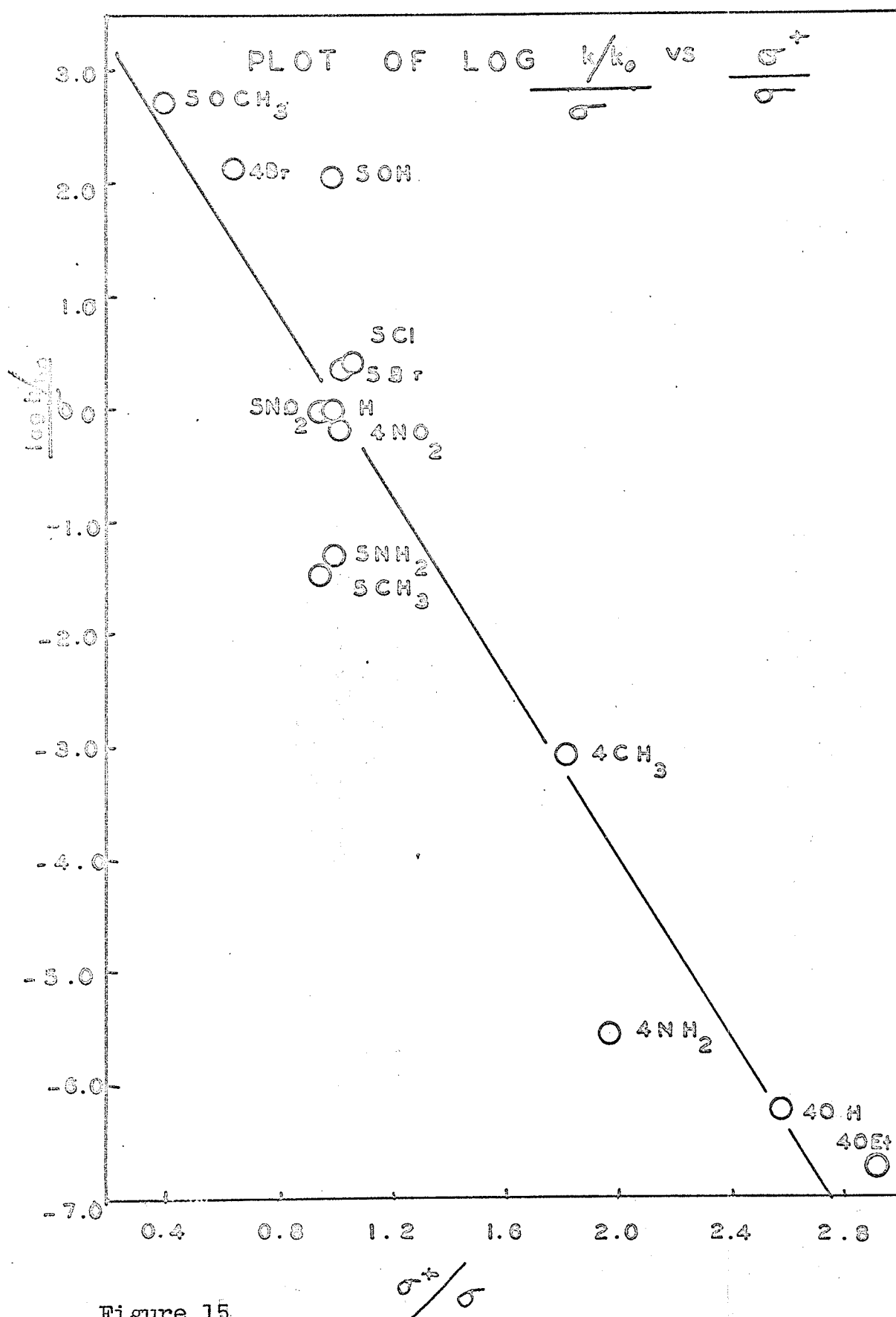
* Values extrapolated to $200^{\circ}C$.

** The σ^{+} value for 5-OH was set equal to σ since no other value is available. A better estimate would probably be obtained by using the same value as that for the 5-OCH$_3$.

The Enthalpy — Entropy Relationship

The Hammett equation arrived at in equation (50) is consistent with the observed enthalpy — entropy relationship. As indicated in the introduction, most of the reaction series which obey the Hammett equation are those which obey an isoentropic or isokinetic relationship. Thus each opposing process described in equation (50) should obey an isoentropic or isokinetic relationship.

In one process the relationship is correlated with σ and in the other with σ^+. Whether the relationship is isoentropic or isokinetic, the enthalpy of activation will vary as the substituent is varied. Since σ and σ^+ are all approximately the same for the 5-substituents and not for the 4-substituents, one would predict that the opposing effects of the 5-substituents on the enthalpies of activation might cancel out whereas they would not necessarily do so in the case of the 4-substituents. This is experimentally observed.

Thus an extended Hammett equation such as (50) predicts that an overall isokinetic relationship may not be observed even though each opposing process might individually obey such a relationship.

Mechanism

Any proposed mechanism for the decarboxylation of salicylic acid in quinoline solution must account for the following experimental facts:

(1) It must predict second order kinetics; first order with respect to acid and first order with respect to quinoline. Pseudo first order kinetics would be predicted when the solvent is quinoline.

(2) It must account for the fact that the catalytic effect of quinoline on the rate of decarboxylation of 4-methyl-salicylic acid in quinoline - nitrobenzene mixtures is offset by a retarding process as the concentration of quinoline is increased.

(3) It must predict that C-H bond making and O-H bond breaking are involved prior to or in the rate determining step of the decarboxylation process since this was the conclusion reached by application of the Hammett equation and its extensions.

(4) It must account for the enhanced decarboxylation rates when the electron density on the nucleophilic nitrogen atom of quinoline is increased by electron donating groups and decreased with electron withdrawing groups.

(5) The mechanism must be consistent with the fact that the activation energy and the entropy of activation for the decarboxylation of 4-aminosalicylic acid is decreased on going from quinoline to pyridine as the solvent.

A mechanism consistent with all these experimental facts is discussed below.
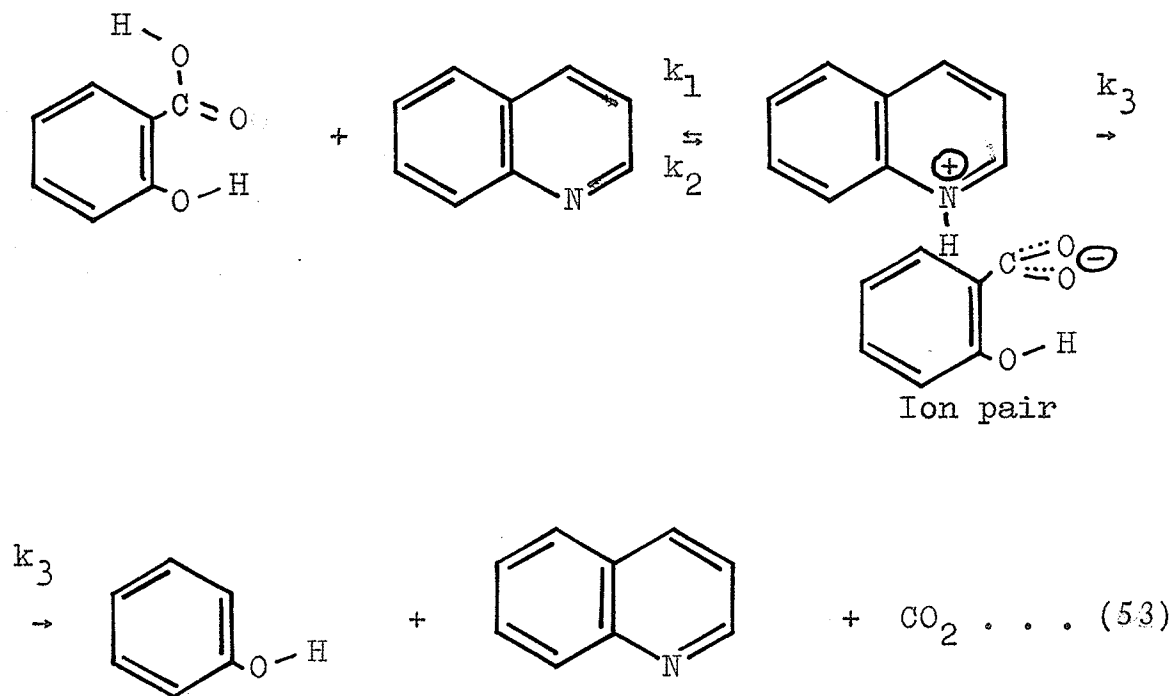
The reasons for choosing this mechanism are as follows:

(1) The mechanism will predict the observed pseudo first order kinetics.

$$\frac{d[CO_2]}{dt} = \frac{k_1 k_3}{k_2} \quad [RCOOH][Quinoline] \quad . \quad . \quad . \quad . \quad (54)$$

$$= k' \; [RCOOH] \quad . \quad . \quad . \quad . \quad (55)$$

where the pseudo first order rate constant

$$k' = \frac{k_1 k_3}{k_2} \; [Quinoline] \quad . \quad . \quad . \quad . \quad (56)$$

(2) The mechanism will accommodate the behavior of the rates of decarboxylation of 4-methylsalicylic acid in

nitrobenzene - quinoline mixtures. The rate is determined
by the concentration of ion pairs and the rate at which
they decompose. Since the more polar solvent nitrobenzene
favors ion pair formation, the rate observed in a mixture
of high nitrobenzene concentration should be greater than
that observed in pure quinoline. This is observed experi-
mentally. Also, the concentration of ion pairs, and hence
the rate of decarboxylation, should be determined by two
opposing factors. Increasing concentration of quinoline
should increase the rate of reaction since it shifts the
ion pair equilibrium to the right but at the same time ion
pair formation should be hindered as the dielectric con-
stant of the medium is decreased. The figure on page 61
shows the catalytic effect at low quinoline concentration
and also the retarding effect due to the dielectric con-
stant of the medium as the concentration of quinoline is
increased.

(3) The mechanism predicts that O-H bond breaking and C-H
bond making are involved prior to or in the rate determin-
ing step. This was the conclusion reached in discussion
of the Hammett plot and its extensions.

(4) The mechanism can also account for the fact that as the
electron density on the nucleophilic nitrogen atom of
quinoline is increased, the rate of decarboxylation be-
comes greater. Increasing electron density on the nitro-
gen will facilitate O-H bond breaking and thus shift the
ion pair equilibrium to the right. It will also hinder
C-H bond making. The experimental results can be

explained on the basis that the increased rate due to the increased concentration of ion pairs more than compensates for the decreased rate due to C-H bond making becoming more difficult.

(5) Finally, the following line of reasoning could accommodate the fact that the activation energy and the entropy of activation for the decarboxylation of 4-aminosalicylic acid is decreased on going from quinoline to pyridine as the solvent.

Since the basicity of pyridine is only slightly less than that of quinoline (22), the decrease in ion pair formation will not be very great. However, the C-H bond making process will be facilitated not only because of the decreased basicity of pyridine but also the smaller size of the pyridinium ion allows stronger interaction with the anion of the acid. Thus the activation energy for the decarboxylation reaction should be lower in pyridine than in quinoline. Also, since the pyridinium ion interacts more strongly with the acid in the transition state, it will be more highly ordered and the entropy of activation should become less than in quinoline.

Conclusions

To summarize, the decarboxylation of salicylic acids in quinoline involves the intramolecular proton transfer from the carboxyl group to the carbon α to the carboxyl group. The transfer of this proton is aided by the quinoline. The reaction proceeds by means of an ion pair formation of the acid and quinoline. Both O-H bond breaking and C-H bond making are involved in this reaction.

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APPENDIX

The external examiner, Dr. A.N. Bourns, has indicated that he is not in agreement with certain of the interpretations given to the experimental results.

His objections center upon the extent of ionization of the salicylic acids in both the pure quinoline solution and the quinoline-nitrobenzene mixtures. He argues that the acids should be completely ionized under most of our conditions because:

(1) The author's proposal that they are not leads to an unreasonably large value of ρ = +4 for the ionization.

(2) The decrease in rate observed as quinoline replaces nitrobenzene in the solvent is too great to be accounted for as a medium effect upon the ionization.

Dr. Bourns has therefore suggested a different mechanism for the decarboxylation reaction. This mechanism assumes that all of the acids are completely in the ionized form in quinoline solution, and mainly so in quinoline-nitrobenzene solution beyond the inflection point. The mechanism is outlined below:
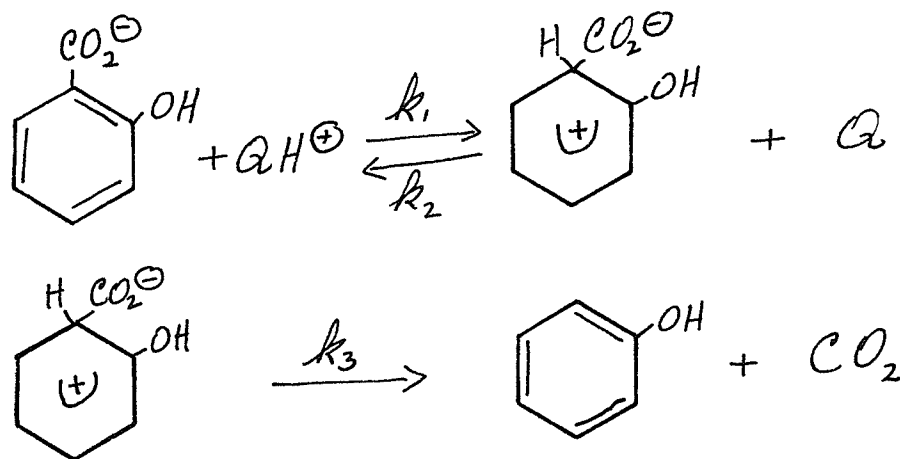
At low concentrations of quinoline in nitrobenzene, the
formation of the zwitterionic intermediate is rate determin-
ing ($k_3 \gg k_2[Q]$) and the rate increases linearly with
quinoline concentration because of an increase in concentra-
tion of the reactive carboxylate ion. Above 0.3 m/l the acid
is essentially all in the ionized form and the rate starts to
drop as the zwitterionic intermediate is increasingly diverted
back to reactants by reaction with excess quinoline. In
quinoline solution, $k_2[Q] \gg k_3$ and the C-C bond rupture step
is now completely rate determining. Dr. Bourns' suggested
explanation for the observed effect of substituents on decar-
boxylation rate is that the influence of the substituents on
k_1/k_2, the equilibrium constant for formation of the inter-
mediate, and on k_3, the rate constant for its decomposition,
are opposed. Stock and Brown (1) have cited this as a factor
which can result in discrepancies in the $\log k/k_H = \rho \sigma^+$
relationship. Dr. Bourns also suggested that equation (50) is
an expression of the Yukawa and Tsuno (2) four parameter
equation:

$$\log k/k_H = \rho \sigma + \rho r \Delta \sigma^+$$

where $\Delta \sigma^+ = \sigma^+ - \sigma$. This equation can be rewritten as

$$\log k/k_H = (\rho - \rho r) \sigma + \rho r \sigma^+$$

which is equation (50) with $\rho_3 = \rho - \rho r$ and $\rho_1 = \rho r$.

(1) Stock, L.M., and Brown, H.C., ''Advances in Physical
    Organic Chemistry'', Academic Press, London and New York,
    1963, p. 133-134.

(2) Yukawa, Y., and Tsuno, Y., Bull. Chem. Soc., (Japan), 32,
    971.

There are several reasons which indicate that the mechanism as suggested by Dr. Bourns may not be compatible with all the experimental evidence. They are as follows:

1. The first point concerns the numerical value of approximately +4 obtained for $\underline{rho}$ in the ionization step of our proposed mechanism. Dr. Bourns suggests that a smaller value of approximately +1 would be more reasonable and indicates that this has been found to be the case for several such systems (3). These $\underline{rho}$ values for the ionization of carboxylic acids as listed by Jaffé (3) are mainly for equilibria in aqueous media at approximately room temperature. As Jaffé (3) has indicated, the value of $\underline{rho}$ generally increases with decreasing dielectric constant of the media. Table X below lists the Hammett $\underline{rho}$ constants obtained for benzoic acid under various conditions.

<div align="center">

TABLE X

</div>

Acidity Constants of	ρ	Dielectric Constant
1. Benzoic acid in water at 25°	+1.000	78.5
2. Benzoic acid in methanol at 25°	+1.537	32.6
3. Benzoic acid in ethanol at 25°	+1.957	24.3

It can be seen from the above Table that ρ becomes much more sensitive to the dielectric constant at the dielectric constant of the medium is decreased. On the

(3) Jaffe, H.H., $\underline{Chem}$. $\underline{Revs}$., $\underline{53}$, 191 (1953).

overall average it is found that on going from water to methanol as solvent, the value of ρ increases 0.012 units per dielectric constant unit. Similiarly, on going from methanol to ethanol as solvent, the value of ρ increases 0.051 units per dielectric constant unit. Therefore, it is logical to assume that the sensitivity of ρ should increase even more on going from ethanol to quinoline as solvent since the dielectric constant of quinoline is about half that of ethanol. In view of these facts, the experimental value of +4 obtained for ρ in the ionization step of our proposed mechanism not only becomes quite plausible but should in fact be predicted on the basis of known chemical facts.

Finally, as Jaffé (3) has indicated, it is usually true that ρ varies with the temperature. Since the present investigation was carried out at 200°C, it would not really be valid to compare the value of ρ at this temperature with those obtained at room temperature for similiar systems. It is thus possible that temperature effects alone could account for the value of +4 obtained for ρ in our present investigation. Therefore it is not valid to eliminate the ionization stage in our proposed mechanism on the basis that the value of rho is too high for such an ionization step.

2. The second objection raised by Dr. Bourns is that the decreased rate at higher quinoline concentrations in nitrobenzene is too large to be simply a medium effect. This view does not seem to be substantiated by the

chemical literature. For instance, it is known (4) that the dissociation constant of benzoic acid is 10^{-6} times as large in ethanol as in water. This effect is accounted for largely by the difference in dielectric constants and solvating power between the two solvents. Such an immense effect would surely be large enough to account for differences in rate observed for the decarboxylation of 4-methylsalicylic acid in quinoline-nitrobenzene mixtures.

3. The complete dissociation of the acids into ions in quinoline solution is an assumption not in agreement with known facts concerning ionization processes in low dielectric constant solvents. Kolthoff and Bruckenstein (5) have discussed acid-base equilibria in nonaqueous solutions. From this discussion it is clear that dissociation into ions is not extensive in solvents with low dielectric constants. For example, the largest dissociation constants observed in acetic acid is of the order 10^{-5}. Ions which exist in these solvents do so mainly in the form of ion pairs. This view is consistent with the mechanism proposed by the author.

4. Dr. Bourns did not comment upon the experimental results observed when substituted quinolines were used as solvents. According to his mechanism, electron releasing

(4) ''Treatise on Analytical Chemistry'', Part I, Volume I, Interscience, New York, 1964, p. 496.

(5) ''Treatise on Analytical Chemistry'', Part I, Volume I, Interscience, New York, 1964, p. 475-542.

substituents should favor quinolinium ion formation and hence decrease the concentration of zwitterionic intermediate. This would decrease the rate of decarboxylation. Since the opposite effect was observed experimentally, it would appear that the proposed mechanism is not capable of explaining these results. Because the purpose of any mechanism is to accommodate all the experimental evidence with as simple a picture as possible, it appears that the mechanism proposed by the author is more satisfactory.

5. The enhanced rates of decarboxylation for the acids with strong electron releasing substituents are not satisfactorily accounted for by the mechanism put forward by Dr. Bourns. He proposes that most substituents have no effect on the rate because they have opposite effects upon bond making and bond breaking at carbon 1, and suggests that the observed rates can be accounted for by the Yukawa and Tsuno equation. However, by this interpretation the effects of all substituents should cancel whereas, in fact, they do not. Our mechanism accounts for the lack of cancellation by the 4-amino, 4-hydroxy and 4-ethoxy substituents by making the opposed effects occur on carbon 1, where σ^+ applies, and on the carboxyl group, where σ applies. Among the substituents used in this investigation σ and σ^+ differ significantly only for the 4-amino, 4-hydroxy and 4-ethoxy groups.

It should also be noted that the Yukawa and Tsuno equation was actually employed for electrophilic

side-chain reactions rather than electrophilic aromatic substitution reactions. In fact, Stock and Brown (6) indicate that the good correlations of log k/k_H with the σ^+ constants in the case of electrophilic aromatic substitution reactions cannot be significantly bettered by the four parameter equation. On this basis, it should not be necessary to use the Yukawa and Tsuno equation for the mechanism put forward either by Bourns or the author since in both cases electrophilic aromatic substitution is involved. In view of all the above facts, it would seem that our interpretation of substituent effects would at least account specifically for the enhanced rates of decarboxylation observed for the strongly electron releasing substituents in the para position.

In conclusion, it should be noted that our mechanism does not rule out the possibility of zwitterionic intermediate formation in the final step of the mechanism. In fact, by analogy with other electrophilic substitution reactions, it seems highly probable that such an intermediate would be formed. Dr. Bourns has suggested that his mechanism, in which this zwitterionic intermediate is formed, could be tested for by measuring the carboxyl carbon isotope effect at high and low quinoline concentrations. A carbon isotope effect should

(6) Stock, L.M., and Brown, H.C., ''Advances in Physical Organic Chemistry'', Academic Press, London and New York, 1963, p. 144-145.

be found only at high quinoline concentrations. Our mechanism makes no particular prediction as to carbon isotope effects since it can accommodate either the presence or absence of such effects. In fact, it was the author's intention for future work to test for a carbon isotope effect and thereby elucidate the final step in our proposed mechanism. However, it should be quite clear that the finding of this carbon isotope effect would not rule out our mechanism. It would only be necessary to include the formation of a zwitterionic intermediate in the final step of our mechanism.

In the final analysis, the criticisms raised by Dr. Bourns can only be resolved by actually measuring the extent of ionization of salicylic acid in quinoline solution.