

THE RELATIVE ACIDITIES OF SUBSTITUTED SALICYLIC ACID
IN BENZENE CORRELATED WITH THE HAMMETT EQUATION

by

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ABSTRACT OF M.SC. THESIS

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The Relative Acidities of Substituted Salicylic Acids
in Benzene Correlated with the Hammett Equation

The relative acidities of fifteen 4- and 5-substituted salicylic acids were determined in benzene solution by potentiometric titration. The potentials at half-neutralization relative to that of salicylic acid were considered to measure the acidity of the substituted acids relative to the parent acid. These potentials, designated by ΔHNP , gave a significantly better correlation with Hammett's sigma constants in an equation of the form $\Delta\text{HNP} = \rho_1 \sigma_1 + \rho_2 \sigma_2$ than in a simple Hammett equation ($\Delta\text{HNP} = \rho \sigma_1$). In these equations σ_1 refers to the position of a substituent relative to the carboxyl group and σ_2 refers to its position relative to the phenol group.

The value of ρ_2/ρ_1 was found to be 0.4, indicating that the electronic effect of a substituent on the acid strength via the phenolic hydrogen-bonded path is 2/5 as great as the direct effect through the benzene ring.

These results, together with the fact that in aqueous solution there is very little if any transmission via the

phenolic group, are discussed in terms of intramolecular hydrogen bonding of salicylic acids in benzene and water.

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INTRODUCTION

The ionization constants of a series of sixteen substituted salicylic acids have recently been determined and satisfactorily correlated with Hammett's sigma constants (67) in a simple Hammett equation in the form:

$$\log \frac{K}{K_0} = \rho \sigma \quad (1)$$

where K is the ionization constant for a substituted salicylic acid and K_0 is that for salicylic acid itself. Sigma (σ) is characteristic of the substituent and of its position in the benzene ring.

Salicylic acid and salicylate ion are generally considered to possess an intramolecular hydrogen bond between the carboxyl group oxygen and the hydrogen of the phenolic group ortho to it (28). It has been suggested (55) that a system with such an intramolecular hydrogen bond should obey a modified form of the Hammett equation:

$$\log \frac{K}{K_0} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (2)$$

The symbols have the same significance as in the one-parameter equation except that σ_1 refers to the position of the substituent relative to the carboxyl group and σ_2 refers to its position relative to the phenol group.

The failure of substituted salicylic acids to obey this modified, two-parameter form of the Hammett equation in preference to the simple form could be due to one of two

reasons. Firstly, the modified equation, originally proposed for the case in which two ortho groups actually react to form conventional chemical bonds, might not apply in a case where the interaction of ortho groups is relatively weak, as in intramolecular hydrogen bonding. Secondly, if the equation is applicable in such a case, the failure of the salicylic acid-salicylate system to obey it in aqueous solution is probably an indication that here the intramolecular hydrogen bond is only quite weak or non-existent.

It was therefore decided to test the modified, two-parameter equation on a system similar to that for aqueous salicylic acid but under conditions where an intramolecular hydrogen bond was known to exist by direct evidence. This is the case for salicylic acid in solvents of low dielectric constant such as benzene (26,64).

It was therefore decided to measure the relative acidities of a series of salicylic acids in benzene by a potentiometric titration method and to determine whether a better fit is obtained to equation (2) or to equation (1).

The results are discussed in terms of hydrogen bonding.

LITERATURE REVIEW

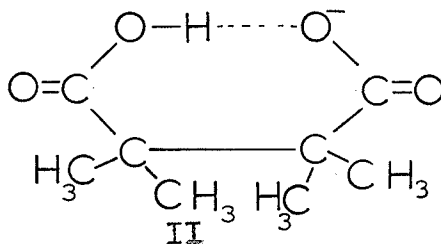
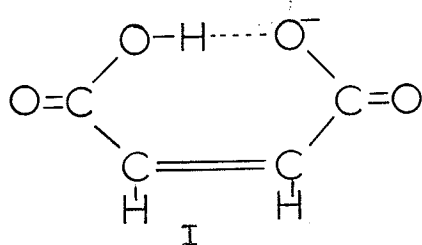
HYDROGEN BONDING IN ACIDS

Since this investigation is largely concerned with hydrogen bonding in aqueous solutions of carboxylic acids, a summary of some of the literature evidence concerning such hydrogen bonding is given. In addition to salicylic acid this will include the case of dicarboxylic acids since they resemble salicylic acid quite closely with regard to the factors that influence hydrogen bond formation.

DICARBOXYLIC ACIDS

The concept of intramolecular hydrogen bonding in aqueous solutions of dicarboxylic acids was originally proposed as an explanation of the very high ratio of first to second ionization constants for the cis form of unsaturated or cyclic acid as compared with the trans form (75,58). It has also been extended to include saturated dicarboxylic acids (30,31,32,101).

It was proposed that monoanion of these acids would be able to form more stable intramolecular hydrogen bonds than the acid. This should stabilize the monoanion relative to the acid or di-anion and as a result, K_1 , the first ionization constant should increase and K_2 should decrease (75). Structures such as:



were proposed. In the acid maleate (I), the double bond would create a conformation favorable to hydrogen bonding. In the acid anion of tetramethylsuccinic acid it was suggested that the methyl groups would push the carboxyl and carboxylate groups closer together thus enhancing hydrogen bond formation.

A number of attempts have been made to estimate the extent to which hydrogen bonding contributes to the strength of dibasic acids.

One approach to the problem is by means of a calculation of the electrostatic effect a negatively charged carboxylate group can have on the value of K_1/K_2 . Then the deviation of the observed value from the calculated one is assumed to be due to hydrogen bonding. The most successful of such methods of calculating the electrostatic factor in determining K_1/K_2 is that of Kirkwood and Westheimer (61,62) in which the molecule is treated like a spherical or ellipsoidal cavity whose dielectric constant is different than that of the solvent. Calculations made on the basis of this theory (27) have shown that, contrary to previous suggestions (75), electrostatic effects are sufficient to account for the high value of K_1/K_2 in maleic acid.

In an attempt to estimate the maximum extent which hydrogen bonding could contribute to the value of K_1/K_2 , Westheimer and Benfey (99) carried out calculations based on the values of K_1 for the unionized acid and K_E , the

dissociation constant for the corresponding mono-acid ester. By assuming that the monoester had no intramolecular hydrogen bond, they were able to calculate the maximum factor in the value of K_1/K_2 for the acid that could be attributed to hydrogen bonding. Their treatment indicates that in maleic, tetramethylsuccinic, and diethylmalonic acids hydrogen bonding can account for a maximum factor of 28, 182, and 256 respectively in the values of K_1/K_2 . However, the ratio of first to second ionization constants in these acids is found to be 20200, 6130, and 121000 respectively (75). Thus, although hydrogen bonding could have an effect, it cannot account for the high value of K_1/K_2 for these acids. However a similar calculation in the case of 2,3-di-(t-butyl)-succinic acid indicates that hydrogen bonding would be able to account for essentially the whole value of K_1/K_2 which, at 10^8 in water, is the highest such ratio observed (30).

In connection with this, it has been found (4) that for a series of dicarboxylic acids with four, six, nine, and ten carbon atoms, K_E of the mono-methyl ester is one-half K_1 of the dibasic acid. This is the statistically expected value and indicates that intramolecular hydrogen bonding is absent in these acids.

Thermodynamic treatment of the ionization of dicarboxylic acids has also been carried out. The method used is to determine whether ΔH or ΔS of ionization of the acid

under investigation deviates significantly from the trend established by acids which could not form intramolecular hydrogen bonds. Deviations are then attributed to hydrogen bonding. The interpretation of the results is not unambiguous. Thus Das and Ives (22) conclude that the acid malonate ion contains an intramolecular hydrogen bond while Ebersson and Wadsö, in an extensive investigation using thermodynamics (32), decide that if such a hydrogen bond is present it is quite weak. This latter investigation also indicates that the monoanion of 2,3-di-(t-butyl)-succinic acid does seem to possess an intramolecular hydrogen bond. On the basis of their data these authors reach the generalized conclusion that hydrogen bonding is a minor factor in affecting K_1/K_2 when this ratio is less than 10^4 and that in this case its value can be accounted for by electrostatic considerations. As the ratio of first to second ionization constants increases above this, the importance of hydrogen bonding also increases.

Most present indications are that, as steric crowding of the carboxyl groups increases, so does the value of K_1/K_2 . This has been shown to be the case in saturated dicarboxylic acids such as highly substituted succinic and malonic acids (30,31,32,101) and in 3-substituted-cis-1,2-cyclopropanedicarboxylic acids (64). The usual interpretation of this is that steric crowding of the carboxyl groups forces them closer together and thus favors hydrogen bond formation. However in the case of 1,2-disubstituted-cis-1,2-cyclopropanedicarboxylic acids, the value of K_1/K_2 decreases on increasing

the size of substituents (74). It is suggested that this is due to the carboxyl and carboxylate groups being too close together in the monoanion to form a strong intramolecular hydrogen bond and that increasing the size of the substituents aggravates this situation.

A number of studies on the rate of proton loss from the monoanions of some dicarboxylic acids have been carried out by a temperature-jump relaxation method. It is found that the rate of proton loss is in the inverse order to the values of K_1/K_2 within a given series for a number of substituted succinic, malonic, and 3-substituted cyclopropane-cis-1,2-dicarboxylic acids (48,49,76). These results have been interpreted as indicating that, as hydrogen bonding increases (assumed to be measured by K_1/K_2), proton removal becomes more difficult.

In the case of 3-substituted cyclopropane-cis-1,2-dicarboxylic acids an isotope-effect investigation has been carried out on the rate of proton removal from the monoanion, using deuterium (49). The results were not in agreement with predicted isotope effects which had been calculated on the basis of hydrogen bonding occurring in the acid anion (33).

Only a limited amount of infrared spectrophotometric data is available for deuterium oxide solutions of dicarboxylic acids, but most of it seems to be in agreement with the general trends obtained by other methods of investigation.

The infrared data indicate that an intramolecular hydrogen bond is detectable in acid maleate ion in deuterium oxide (27) but that it is quite weak (13). Evidence for hydrogen bonding in di-isopropyl hydrogen malonate is also found in the same solvent, although acid malonate itself does not seem to have such a bond (13). A number of racemic disubstituted succinic acids and their monoanions also appear to be chelated by hydrogen bonding in D_2O , although tetramethylsuccinic acid is not (31).

It is important to note the effect a change in solvent can have on intramolecular hydrogen bonding in a dibasic acid. This will be illustrated by maleic acid, which is the most thoroughly investigated example.

Both solid maleic acid (65,90) and solid acid maleate (81) have an intramolecular hydrogen bond as indicated by X-ray and infrared studies. This bond appears to be symmetric in the monoanion; that is the hydrogen atom is midway between the two oxygen atoms to which it is bound, thus indicating a strong hydrogen bond. It does not appear to be bonded to this extent in the acid (12). In carbon tetrachloride, monomethylmaleic acid shows infrared spectral indications of possessing an intramolecular hydrogen bond, but these disappear on the addition of ether (25).

Nuclear magnetic resonance studies in dimethylsulfoxide show that the acid maleate ion appears to retain its symmetrical hydrogen bond, whereas no hydrogen bond is

detectable for maleic acid (36,41). In deuterium oxide solution the hydrogen bond for maleic acid cannot be detected by infrared spectrophotometry, and that for hydrogen maleate is weak and unsymmetric (13). Finally, in dioxane solution the monoanion appears to have lost its hydrogen bond completely (27). Thus, increasing the polarity and hydrogen bonding ability of the solvent are very important factors in determining whether or not an intramolecular hydrogen bond will occur. Just because such a bond is present in one solvent does not mean that it will necessarily occur in a solution of the same compound in a more polar solvent.

The results of the discussion on dibasic carboxylic acids can be summarized as follows:

(1) For unsubstituted acids such as maleic and malonic, for 1,2-disubstituted-cis-1,2-dicarboxylic acids, and for succinic acids substituted with small groups such as methyl, stabilization of the monoanion by the formation of an intramolecular hydrogen bond does not appear to be important in aqueous solution.

(2) For highly substituted malonic and succinic acids and for 3-substituted cyclopropane-cis-1,2-dicarboxylic acids, electrostatic effects are insufficient to account for the high value of K_1/K_2 observed in these acids in water. Hydrogen bonding is proposed as a contributing factor.

(3) In the solid state both maleic acid and hydrogen maleate have intramolecular hydrogen bonds that are quite strong. As they are dissolved in increasingly polar solvents, first the acid and then the monoanion lose these hydrogen bonds.

It should be noted that in the use of the Kirkwood-Westheimer theory, the Westheimer-Benfey treatment, and thermodynamic methods, it is only possible to show that electrostatic effects are unable to account completely for the value of K_1/K_2 . Any estimates of the extent of hydrogen bonding are based on the assumption that the difference between observed acid strengths and those expected on the basis of electrostatic factors are due to hydrogen bonding. Even in the case of infrared spectral measurements, the actual results only show that the carboxylate group of an acid is partially bonded to a proton or deuteron while another acid, which is structurally unable to form intramolecular hydrogen bonds, is not. Since the measurements are being made in deuterium oxide, it cannot be unequivocally stated that the effect is intramolecular rather than intermolecular, especially since the acids which structurally could form hydrogen bonds are also the ones in which the solvent molecules that surround one carboxyl group could interfere with the other carboxyl group.

SALICYLIC ACID

The case of salicylic acid is more closely related to the dicarboxylic acids with rigid structures such as maleic and cyclopropane-1, 2-dicarboxylic acids than to the non-rigid saturated acids. This is so because the groups which can undergo hydrogen bonding are attached to adjacent positions on the rigid benzene ring.

It is therefore possible that here too, as in maleic acid, the hydrogen bond which has been observed in solid salicylic acid (15) may be weakened or lost in aqueous solution. Some of the literature evidence in favor of and against this hypothesis is therefore given.

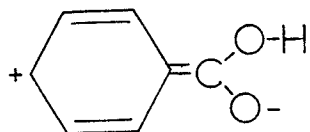
Evidence for intramolecular hydrogen bonding in aprotic solutions of salicylic acid has been found by infrared, ultraviolet, and nuclear magnetic resonance spectroscopy (26,35,64,70,78). It was found that a change in solvent from carbon tetrachloride to benzene resulted in a measurable although small decrease in the chelation of the acid, as indicated by infrared spectrophotometry (78). Thus even a small change in the ability of a solvent to interact with the acid causes a noticeable decrease in hydrogen bonding.

Direct evidence for the situation in water is quite limited, due to the difficulty in measuring effects. It has, however, been proposed on the basis of infrared measurements that both salicylic acid and salicylate ion retain strong intramolecular hydrogen bonds in deuterium oxide

solution (13). Ultraviolet spectrophotometric measurements of salicylic acid and sodium salicylate in ethanol have been interpreted as showing the retention of an intramolecular hydrogen bond in the anionic form if it is assumed to be present in the acid (98). These two studies will be dealt with in greater detail in a later section.

Some of the indirect evidence available concerning hydrogen bonding is also of interest. The original proposal of a hydrogen bond as a factor in the stabilization of salicylic acid was based on the large value of its ionization constant relative to that of para-hydroxybenzoic acid (2).

It is well known that ortho-substituted benzoic acids are usually stronger than the corresponding para-isomer (11). This is usually explained in the following way. The group ortho to the carboxyl group in the acid interferes with it sterically, turning it out of the plane of the benzene ring. This results in the loss of resonance stabilization in the acid due to the loss of structures such as:

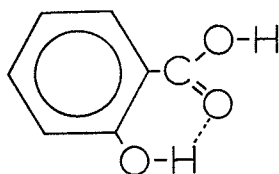


which are not very important in the anion since here the carboxyl group already has a negative charge. As a result of this loss of resonance, the anion is stabilized relative to

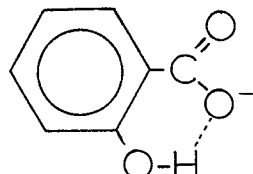
the acid and acid strength increases (11,80).

However, the acid enhancement by the ortho-hydroxy group is larger than that for any other case, while the OH group is smaller than many of them and should therefore have a smaller effect.

In order to account for this, it has been proposed (2) that the formation of an intramolecular hydrogen bond that would be stronger in the anion than the acid occurs. This would stabilize the anion relative to the acid, since structures such as (IV) would be more important than (III).



III



IV

It has been found experimentally that the strength of salicylic acid decreases less rapidly than that of p-hydroxybenzoic acid as the solvent polarity is decreased, for example by increasing the ethanol concentration in water-ethanol solutions of the acids (8). This can reasonably be interpreted as increased intramolecular hydrogen bonding in the salicylic acid as the solvent polarity is decreased, tending to offset the loss in stabilization due to decreased solvation. This also implies that on making the solvent more polar such hydrogen bonding decreases. Now this increase in hydrogen bonding in salicylic acid on decrease in the solvent polarity has, in some cases (8), been taken

as evidence of such hydrogen bonding in water. As seen from the above argument, this does not necessarily follow.

A comparison of the relative strengths of a series of benzoic acid determined in benzene with their relative strengths in alcohol, water and water-dioxane has been made (23). It was found in a plot of relative acidity in benzene versus that in the other solvents that when the other solvent was an alcohol, salicylic acid did not deviate from the straight line established by the meta-substituted acids. However, when the second solvent was water or water-dioxane, salicylic acid was stronger in these solvents than expected on the basis of the norm established by the meta-substituted acids. A possible explanation suggested for these results (23) is that, in the polar aqueous solvents, molecules of solvent hydrogen bond to the ortho group thus increasing its effective size and as a result the steric effect previously described. This would increase the acidity in these polar solvents relative to that in benzene or the alcohols.

A comparison of the conductimetric titration curves of salicylic and 2,6-dihydroxybenzoic acids in acetonitrile with those in water reveals that they are quite different in the two media. The curves obtained in acetonitrile have been interpreted in terms of greater chelation in this solvent (16).

The effect of solvent polarity on the chelation of other ortho-substituted benzene derivatives, notably phenols, is indicated in order to illustrate such solvent effects more clearly.

It has been shown by infrared measurements that changing the solvent from cyclohexane to dioxane decreases the mole fraction of ortho-iodophenol in the cis form (presumably largely hydrogen bonded) from .81 to .27 (102).

The change in nuclear magnetic resonance chemical shifts for ortho-nitro phenols, resulting from a change in solvent from chloroform to acetone has been interpreted as being due to a decrease in intramolecular hydrogen bonding (85).

The anomalously low acidities of 2,4- and 2,5-dinitrophenol in benzene relative to water is attributed to chelation (24). This conclusion is supported by a differential vapor pressure study (17) in which ortho-nitrophenol is shown to be chelated in 1,2-dichloroethane. Other studies show that o-nitrophenol undergoes little or no intramolecular hydrogen bonding in aqueous solution (71,72).

These results indicate that on going from a non-polar solvent to one which is polar, intramolecular hydrogen bonding becomes less important as competition from solvent molecules increases.

POTENTIOMETRIC TITRATIONS

The experimental object of this investigation was the determination of the relative strengths of a series of substituted salicylic acids in benzene solution. Of the more common methods of determining such relative acidities, that of potentiometric titration is well established and comparatively rapid and was therefore the method used in this investigation.

In aqueous solution potentiometric titration, using an indicator electrode that responds to pH in conjunction with a reference electrode, is a common practice. The potential at half-neutralization can readily be shown to be proportional to the logarithm of the ionization constant of an acid titrated, if it is assumed that the potential of the glass electrode follows the theoretical equation:

$$E = E_0 + \frac{RT}{F} \ln a_{H^+}$$

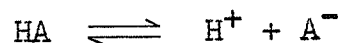
where E is the glass electrode potential, E_0 is the potential when $a_{H^+} = 1$ and F is the Faraday constant. In combination with a reference electrode:

$$E = C_1 + C_2 \log a_{H^+}$$

In both these equations a_{H^+} is the hydrogen ion activity of the solution. The constants C_1 and C_2 which arise as a result of standard potentials and constants in theoretical potential equations will not be defined since only a proportionality is being established between the potential at

half-neutralization and ionization constants.

For an acid which dissociates according to:



the expression for the ionization constant, K , is:

$$K = \frac{a_{\text{H}^+} a_{\text{A}^-}}{a_{\text{HA}}}$$

Then the expression for potential becomes:

$$E = C_1 + C_2 \log \frac{K a_{\text{HA}}}{a_{\text{A}^-}}$$

or if the concentration of acid is not high and K is not taken to be the thermodynamic ionization constant:

$$E = C_1 + C_2 \log \frac{K [\text{HA}]}{[\text{A}^-]} \quad (3)$$

Then at half-neutralization, where $[\text{HA}] = [\text{A}^-]$

$$E_{\frac{1}{2}} = C_1 + C_2 \log K \quad (4)$$

It has also been shown that the behaviour of the glass electrode in an aprotic solvent such as acetonitrile is similar to that in water, and such an electrode has in fact been calibrated in this solvent (63).

In aprotic solvents of low dielectric constant, such calibration has not been carried out. But here too, evidence exists that the glass electrode behaviour is similar to that

in water insofar as its response to hydrogen ion activity is concerned. Titration curves are normal except for deviations which occur as the result of a change in effective acid concentration because of molecular associations (46). Also, it has been found that a plot of the potential of half neutralization HNP of a series of substituted benzoic acids in a titration study in bromobenzene (dielectric constant = 5.4) against the logarithm of the ionization constants in water is a straight line (77). Similar linear correlations of potential at half neutralization in a given solvent versus logarithm of the ionization constant in water have been found for a large number of acids and bases in solvents with a wide range of dielectric constants, both protonic and aprotic (14,18,38,77,92,93,94). This can be taken as an indication that in these solvents the potential at half-neutralization is a measure of the strength of an acid or base, at least if taken with reference to some standard compound, and that such relative acidity or basicity in those solvents where such a linear relationship holds is in the same order as in aqueous solution. It should be noted that if a series of acids or bases that obeys Hammett's equation (Equation 1) in water exhibits a linear relationship between potential at half-neutralization in another solvent and logarithm of the ionization constant in water, then the values of potential at half-neutralization in this solvent also obey

Hammett's equation.

From equation (3) it can be seen that a plot of potential (E) versus $\log \frac{HA}{A}$ should be a straight line in aqueous solution. $\log \frac{HA}{A}$ can be written $\log \frac{V_e - V}{V}$ where V_e is the volume of titrant added up to the end point and V is the volume titrant at the potential E. It has been shown in a titration study (42) that a plot analogous to that of E versus $\log \frac{V_e - V}{V}$ for organic bases in ethylene dichloride was not a straight line, but curved over the whole range shown, including the region of half-neutralization. On the basis of this, it was concluded that the potential at half-neutralization does not measure the dissociation constant of the acid in this solvent. It therefore appears necessary to do such a plot in benzene solution in order to show that these conclusions do not apply in this solvent. It should be recognized that if a straight line plot is obtained in benzene, this does not prove that the potential at half-neutralization is a measure of the dissociation constant in that solvent. It does, however, increase the plausibility of an interpretation of such potentials in a manner similar to that in water. Such a linear plot of E versus $\log \frac{V_e - V}{V}$ was found for amines in solvents such as nitrobenzene, acetonitrile and ethyl acetate (42) and in these cases the potential at half-neutralization was taken as a measure of base strength. In connection with the same investigation it was stated that a linear relation between potential at half-

neutralization and Hammett sigma constants in a given solvent was evidence that in that solvent the glass electrode is measuring the activity of H^+ , since otherwise such linearity could not hold. (This is in effect stating that if the potential at half neutralization of a series of acids in a solvent is linearly related to pK_A in water, the glass electrode is responding to the same property in the two solvents and therefore HNP measures the same characteristic in the two solvents, namely acid strength.) If this is indeed the case, this lends further support to the postulate that HNP measures acid strength in at least some low dielectric constant solvents since, as has been mentioned, the HNP values of benzoic acids follow a linear relationship in bromobenzene.

In practice it is found that the values of potential at half-neutralization vary with time due to changes in liquid junction potentials and assymetry potentials of the glass electrode. It is therefore common practice (77, 94) to designate one particular acid or base as a reference compound and to determine its potential at half-neutralization whenever another compound is titrated. It is then the difference in half-neutralization potentials between the measured compound and the reference compound, designated by ΔHNP , that is considered a measure of the acid strength of that compound relative to the reference. In this way

errors due to changing electrode characteristics are largely eliminated.

The titrant used in nonaqueous titrations of acids is most commonly a quaternary ammonium hydroxide. First used by Cundiff and Markunas (19), these titrants have almost completely supplanted the alkali alkoxides previously used, since their salts are quite soluble in inert solvents.

A number of methods of preparation of these quaternary ammonium hydroxides have been proposed (20,47,73). These titrants have been quite well characterized, investigations into stability (45) and possible impurities (73) having been carried out.

Several modifications of the basic titration methods have been proposed for titrations in low dielectric solvents where high solution resistance causes measurement difficulties.

The conventional titrometers and pH meters used in most potentiometric titrations pass an amount of current between the electrodes in the course of a measurement. In solvents such as benzene this amount of current, although usually less than 10^{-10} amperes, is sufficient to cause a detectable potential drop across the electrodes because of the high resistance of the solvent.

One method of overcoming this has been to use special instruments known as vibrating-reed electrometers which pass

even less current, about 10^{-14} amperes, through the solution (46). With such a system, satisfactory titrations can be obtained. An alternative method of lowering this potential drop across the measuring electrodes has been to place these electrodes very close together, thus lowering the resistance between them (83).

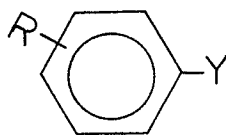
Thus it can be seen that satisfactory methods and titrants are available for potentiometric titrations in low dielectric solvents, and the determination of the relative acidities of a series of substituted salicylic acids in benzene is experimentally possible.

THE HAMMETT EQUATION

In the Introduction, the Hammett equation was mentioned as the method used to correlate the acid strengths of a series of substituted salicylic acids with the corresponding substituents. In addition, a modified form of this equation was indicated as being applicable to intramolecularly hydrogen bonded systems.

The Hammett equation provides a means of relating the reaction rate or equilibrium constants of substituted benzene derivatives to their structures.

Hammett (43,44) proposed a quantitative relationship between the nature of a substituent R and the reactivity of the reacting side chain Y for compounds of the form:



The equation is most widely applied in the form:

$$\log \frac{K}{K_0} = \rho \sigma \quad (1)$$

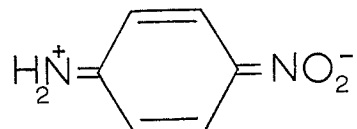
where K and K_0 are the rate or equilibrium constants for the substituted and unsubstituted benzene derivative respectively. Sigma (σ) is the substituent constant and depends solely on the nature and position of the substituent R . Rho (ρ) is the reaction constant and depends on the reaction, the conditions under which it takes place, and the nature of the side chain Y .

Sigma, which is a measure of the electronic effect of the substituent group R on the reaction center Y , is given numerical values by setting rho equal to one for the reaction in which Y is the carboxyl group and K and K_0 refer to the thermodynamic ionization constants of substituted and unsubstituted benzoic acid in aqueous solution at 25°C respectively.

Then:

$$\sigma = \left[\log \frac{K}{K_0} \right]_{\text{Benzoic Acid}} \quad (5)$$

The basic equation (5) has been modified for cases in which direct resonance interaction between the substituent group and the reaction center can occur. For example, in 4-nitroaniline structures such as:



which will increase the acidity of the anilinium ion are possible. Such structures have no counterpart in 4-nitrobenzoic acid and consequently sigma for the 4-nitro group will not adequately account for the strength of 4-nitroanilinium ion as an acid.

Therefore, new values of sigma are defined for such situations. Sigma minus (σ^-) values are defined for cases in which the reaction center is strongly electron-releasing and the substituent para to it is strongly electron-withdrawing. Its values are obtained from reactions in which this is the case (10,34) and it is used under the same conditions. Similarly, sigma plus (σ^+) values are defined and used in the case where the substituent is strongly electron-releasing and the reaction center is strongly electron-withdrawing (96).

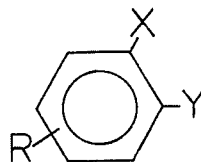
Modifications of this basic Hammett equation have been proposed (55,56) for more complex molecules.

When there are several substituents on the benzene ring in positions which do not interfere with the reaction

center, the equation becomes:

$$\log \frac{K}{K_0} = \rho \sum \sigma \quad (6)$$

In compounds of the type:

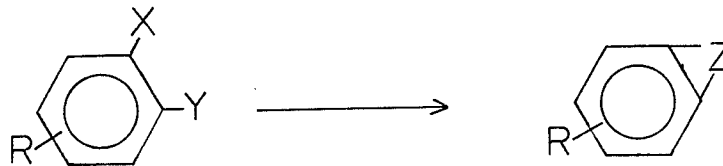


where X remains the same throughout the series of compounds and does not react directly with Y, the proposed equation is:

$$\log \frac{K}{K_0} = \rho \sigma + x \quad (7)$$

where x is a constant (55). This equation is obeyed by the ionization constants of a series of substituted ortho-toluic acids (86).

Another possibility arises when two ortho groups react to form the reaction center:



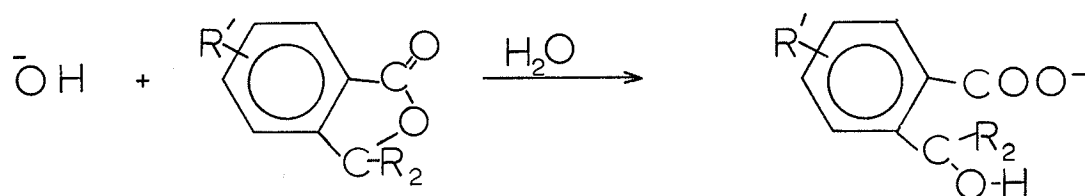
In this case the substituent R can affect the reaction center by two paths. The equation for such a situation is:

$$\log \frac{K}{K_0} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (2)$$

where σ_1 refers to the position of R relative to one point of attachment of Z to the benzene ring and σ_2 (σ_2) refers to the other point of attachment (56). As

mentioned in the introduction this equation has also been proposed for the case in which the ortho interaction is the formation of a hydrogen bond (56), although no examples of such a situation have been found.

The applicability of equation (2) has been shown in the case of the alkaline hydrolysis of substituted phthalide and its derivatives (54).



Equation (2) applied in the general form

$$\log \frac{K}{K_0} = \sum \rho_i \sigma_i \quad (8)$$

has also been suggested for the case where several substituted aromatic rings are in non-equivalent positions relative to the reaction site. Here $\sigma_i = \sigma_1, \sigma_2, \dots$ refer to the substituents in the various rings and $\rho_i = \rho_1, \rho_2, \dots$ measure the susceptibility of the reaction to the effect of the substituents in the corresponding rings. The relative rates of decomposition of potassium salts of certain meta and para substituted dibenzhydroxamic acids are reported to follow this equation (84).

In the present investigation of the relative acidities of substituted salicylic acids in benzene, equation (1) and equation (2) are correlated with the data to see which gives

the more significant fit, and the results are compared with the situation in aqueous solution.

EXPERIMENTAL

MATERIALS AND PREPARATIONS

Table 1 lists the acids used in this investigation, together with their source of preparation, melting point, and literature melting points. All commercially available acids were recrystallized from water while the solvent used in those prepared is given in the preparation description. Melting points were determined using Anschutz immersion thermometers.

The syntheses of acids prepared in the process of this investigation are described below.

4-Methylsalicylic acid was prepared by the diazotization and subsequent hydrolysis of 4-methylanthranilic acid. The sulfate salt of 4-methylanthranilic acid (Aldrich Chemicals) was made by dissolving 7.1 gm (.047 moles) of the acid in a mixture of 70 ml of water and 70 ml of sulfuric acid. The salt mixture was cooled to 0°C and was treated with a solution of 4.5 gm of sodium nitrite in 12 ml of water, added slowly over a period of an hour. The diazotized solution was poured into 250 ml of boiling water, boiled for 10 minutes, and then cooled. The crude product was collected, 6 gm being obtained. Two recrystallizations from water, the first using decolorizing charcoal, were carried out. The final yield was 2.1 gm (30% of theoretical) with a melting point of 176.8-177.8°C

TABLE 1. Substituted Salicylic Acids

Substituent	Source	Melting Point °C	
		Observed	Literature
5-Bromo	Matheson, Coleman + Bell	168.8-169.8	177 (69) 166.5-167.5 (88)
4-Bromo	Prepared	212.6-214.0	212 (79) 206.0-207.0 (87)
5-Chloro	Matheson, Coleman, + Bell	174.6-175.1	172 (69) 167-168 (105)
4-Chloro	Prepared	217.1-217.5	207 (79) 221(51)
5-Fluoro	Prepared	180.3-181.2	178.5-179.5 (95)
4-Fluoro	Prepared	188.2-189.8	186(53) 185(106)
5-Iodo	Aldrich Chemicals	199.3-200.4	195(21)
5-Nitro	Eastman Organic Chemicals	232.9-233.8	228(3)
4-Nitro	L. Light & Co.	226.4-228.2	229-230(91) 234.8-235.3(57)
5-Cyano	Prepared	221.6-222.0	224-225(28)
4-Cyano	Prepared	224.6-226.0	227-229 (9) 228-229 (67)

continued

TABLE 1 CONTINUED

Substituent	Source	Melting Point °C	
		Observed	Literature
5-Methyl	Matheson, Coleman, +Bell	148.3 - 150.0	148-150 (60) 146-147 (105)
4-Methyl	Prepared	176.8 - 177.8	168-171 (82) 177 (100)
5-Methoxy	Kung (67)	145.1 - 145.9	145.7-146.2(57)
4-Methoxy	Prepared	161.1 - 162.2	157(40) 160-161 (6)
Salicylic	May + Baker	159.1 - 160.1	156-158 (60)

(lit. 169-171°C (82), 177°C (100)).

4-Methoxysalicylic acid was prepared by methylating 4-hydroxysalicylic acid. A solution of 7.1 gm (.046) moles of 4-hydroxysalicylic acid (Aldrich Chemicals) was refluxed in 40 ml of 10% sodium hydroxide. Fifteen ml of dimethylsulfate and 40 ml of 10% sodium hydroxide were added, alternatively, in small portions over a period of three hours. The solution was acidified and the crude product obtained was refluxed for an hour in 50 ml of 10% sodium hydroxide in order to decompose any ester impurities. The product was recrystallized from water and then water-ethanol. The final yield was 2.6 gm (33% of theoretical) with a melting point of 161.1-162.2°C (lit. 157°C (40), 160-161°C(6)).

The preparation of 4-bromosalicylic acid was via a Sandmeyer reaction in which diazotized 4-aminosalicylic acid was allowed to react with cuprous bromide.

The preparation of the cuprous bromide, analogous to that for cuprous chloride in reference (1), was carried out as follows. A hot solution consisting of 78 gm copper sulfate pentahydrate and 38.5 gm (.37 moles) of sodium bromide in 400 ml of water was treated with 25.5 gm sodium bisulfite and 18 gm of sodium hydroxide in 100 ml of water. The solution was cooled, filtered, and the washed precipitate was dissolved in 120 ml of freshly distilled 48% hydrobromic acid and 35 ml of water. This cuprous bromide solution was used immediately.

To carry out the Sandmeyer reaction, 38.5 gm (.25 moles) of 4-aminosalicylic acid (Aldrich Chemicals) in a solution of 40 ml water and 120 ml of freshly distilled hydrobromic acid at 0°C were treated with 18 gm of sodium nitrite in 50 ml of water. Addition of the sodium nitrite solution was carried out over a period of 1.5 hours and was continued until a positive starch-iodide test was obtained. The clear, diazotized solution was poured into a solution of cuprous bromide at 0°C. The resulting mixture was stirred for 10 minutes and then warmed to 50° for 15 minutes. It was cooled and filtered, and the solid was allowed to dry. The crude yield was 36.5 gm. One half of this amount was dissolved in ether and filtered, a large amount of solid remaining insoluble. The ether solution was twice treated with charcoal and filtered. The ether was evaporated and the residue was recrystallized twice from water-ethanol. The yield was 4.0 gm (15% theoretical) with a melting point of 212.6-214.0°C (lit. 212°C (79), 206.0-207.0°C (87)). A mixed melting point with some previously prepared 4-bromosalicylic acid (87) showed no depression.

4-Chlorosalicylic acid was prepared from 4-chloroanthranilic acid by diazotization and hydrolysis. The sulfate salt of 4-aminosalicylic acid was prepared by the slow addition of concentrated sulfuric acid to a suspension of 10 gm (.058 moles) of the acid (Aldrich Chemicals) in 100 ml of water.

The resulting clear solution precipitated the salt on cooling. This solution, cooled to 0°C, was treated with 5.0 gm of sodium nitrite in 15 ml of water, added dropwise over a period of 1 hour. The clear diazonium solution was poured into 200 ml of boiling water, boiled for 15 minutes, cooled, and filtered. Five gm of crude product were obtained. This was dissolved in ether, treated with charcoal, and filtered. The ether solution was extracted with aqueous sodium hydroxide, which was then acidified with dilute sulfuric acid. The product was recrystallized from water-ethanol, giving a final yield of 1.5 gm (15% of theoretical) with a melting point of 217.1-217.5°C (lit. 207°C (79), 211°C (51)).

5-Fluorosalicylic acid was prepared by a modified Reimer-Tiemann reaction (105). A mixture of 22 gm (.20 moles) of 4-fluorophenol (Aldrich Chemicals), 100 gm of carbon tetrachloride, 66 ml of 30% potassium hydroxide, and 2 gm of copper (British Drug House "precipitated") was stirred under reflux for two days. The excess carbon tetrachloride was distilled off after acidification of the solution with dilute hydrochloric acid. The remaining hot solution had a brown oily layer of the phenol at the bottom of the flask. The aqueous layer was decanted, cooled, and filtered. Product which was dissolved in the phenol was recovered by repeated extractions of the phenol layer with boiling water until the aqueous solution failed to yield product on cooling.

The phenol was separated from each aqueous extract by filtration. The total yield of crude product was 6.0 gm. The dry product was dissolved in ether and a small amount of residue was filtered off. The ether was evaporated and the product was recrystallized from water. A final yield of 2.5 gm (8% of theoretical) was obtained, with a melting point of 180.3-181.2°C (lit. 178.5-179.5°C (95)).

4-Fluorosalicylic acid was prepared by the oxidation of the cupric salt of 4-fluorobenzoic acid (59). This cupric salt was prepared by treating 4-fluorobenzoic acid with basic cupric carbonate, the latter compound being prepared by alternative method (a) in reference (39).

The 4-fluorobenzoic acid used was prepared by the oxidation of 4-fluorotoluene. A suspension of 10 gm (.091 moles) of 4-fluorotoluene (Matheson, Coleman & Bell) in a solution of 10 gm of magnesium sulfate and 45 gm of potassium permanganate in 1.5 liters of water, was stirred at 75-80°C for two days. The solution was treated with sodium bisulfite to destroy excess potassium permanganate, filtered, and acidified. Six and a half gm of product were obtained which melted at 184-186°C, unrecrystallized (lit. for 4-fluorobenzoic acid is 186°C (89)).

The 4-fluorosalicylic acid was prepared by dissolving 5.0 gm (.036 moles) of 4-fluorobenzoic acid in 100 ml of diphenyl ether. The solution was heated to 180°C where 5 gm

of basis cupric carbonate were slowly added with stirring over a period of 10 minutes. A blue-green precipitate was formed which turned brown on heating to 230°C. Stirring was continued at this temperature for 1.5 hours, after which the mixture was cooled, diluted with ether, and filtered. The brown copper complex that remained was decomposed by treating it with hydrogen chloride-saturated ether. The ether solution was filtered, washed with sodium bicarbonate solution, then with water, and was evaporated after drying with calcium chloride.

The salicylic acid was separated from the benzoic acid in the residue by an extraction process. The acid mixture was dissolved in 50 ml of chloroform and agitated with 200 ml of .3 molar aqueous ferric chloride. The organic layer was separated and the violet-black aqueous solution was extracted with three 30 ml portions of chloroform. The aqueous solution was acidified with hydrogen chloride gas and extracted with two 25 ml portions of chloroform. The chloroform was evaporated. The three chloroform extracts of the ferric chloride solution were combined, evaporated to 50 ml and extracted in the same manner as the original chloroform solution. The residues obtained from the two sets of extractions were combined and recrystallized from ethanol-water, with the use of decolorizing charcoal. The final yield was 0.4 gm (7% of theoretical) with a melting

point of 188.2-189.8°C (lit. 186°C (53), 185°C (106)). A mixed melting point with the 4-fluorobenzoic acid showed a 15°C depression.

4-Cyanosalicylic acid was prepared by a Sandmeyer reaction on 4-aminosalicylic acid. Twenty-five gm (.16 moles) of 4-aminosalicylic acid (Aldrich Chemicals) were treated with 150 ml of 1:1 sulfuric acid and water and stirred for an hour. The resulting salt was cooled to less than 5°C and diazotized by the slow addition of 11 gm of sodium nitrite dissolved in 30 ml of water. A suspension of 7.5 gm cuprous cyanide in 200 ml of water was dissolved by the addition of potassium cyanide. The cold diazonium solution was rapidly poured into the cyanide solution at room temperature. The mixture was heated to 60°C with stirring for 1/2 hour, cooled, filtered, and allowed to dry. The solid was extracted with four portions of 150 ml ether. The extracts were combined, evaporated to 100 ml, and extracted with aqueous K₂CO₃. The carbonate solution was acidified and filtered, yielding 0.8 gm of product. Recrystallization from water using decolorizing charcoal resulted in 0.2 gm (1% of theoretical) of product with a melting point of 224.6-226.0°C (lit. 227-229°C (9), 228.0-229.0°C (67)).

5-Cyanosalicylic acid was prepared by refluxing 5-iodosalicylic acid with cuprous cyanide in dimethyl formamide (37).

A mixture of 100 ml of dimethylformamide, 9.0 gm cuprous cyanide, and 23.0 gm (.087 moles) of 5-iodosalicylic acid (Aldrich Chemicals) was refluxed for two days. The resulting brown-green mixture was poured into a solution of 20 gm of ferric chloride hexahydrate, 60 ml of concentrated hydrochloric acid and 60 ml of water. The mixture was heated at the boiling point for half an hour, cooled, and extracted with four portions of 200 ml ether. The extracts were combined and the ether was evaporated. The solid was washed with sodium bisulfite to remove iodine. The crude yield was 7.5 gm. The product was recrystallized from water. The yield was 6.0 gm (42% of theoretical) with a melting point of 220°C with apparent immediate resolidification of the liquid (lit. 224-225°C (28)).

During titrations the neutralization equivalent was found to be low, only 92% of the expected value. Special attempts were made to purify the product. Several recrystallizations from water or water-ethanol were carried out. Also, since it was observed that 5-iodosalicylic is much more soluble in benzene than is 5-cyanosalicylic acid, the cyanoacid was extracted with boiling benzene. After a final recrystallization from water the melting point was 221.6-222.0°C. The melt appeared to resolidify almost immediately and decomposed at 260°C. It was found that the titration was still low to the same extent as before these purifications.

The benzene used as the solvent for the acids in the titrations was purified in the following way. An amount of benzene (1.5 liters) was shaken with 150 ml portions of sulfuric acid until the benzene layer was colourless. The benzene was washed repeatedly with distilled water until the latter was neutral to litmus. It was dried over calcium chloride for two hours to remove most of the water and then stored for two days over drierite. Distillation was carried out, the first 100 ml being discarded and the fraction boiling over a 0.5°C temperature range being collected.

Tetrabutylammonium hydroxide, the basic titrant used in the titrations, was prepared in a methanol-benzene solution. It was prepared by the silver oxide method modified to prevent any silver oxide from dissolving (20). Forty gm (.15 moles) of tetrabutylammonium iodide (Eastman Organic Chemicals) were dissolved in 100 ml of absolute methanol (Fisher reagent) in a flask filled with nitrogen. The solution was cooled to 0°C and 21 gm (.091 moles) of silver oxide (Fisher purified) were added to the cold solution. It was stirred for two hours after which 400 ml of dry benzene were added. The solution was then filtered through a sintered porcelain filter under a nitrogen atmosphere. It was transferred to a 1 liter volumetric flask and, after warming to room temperature, was made up to a liter with benzene. The concentration was approximately 0.1 normal.

POTENTIOMETRIC TITRATIONS

The apparatus consisted of a Radiometer pH-4 pH meter set to read voltage directly, a Radiometer G202B glass electrode, and a Radiometer K-100 calomel electrode. The calomel electrode was modified by replacing the aqueous KCl in the salt bridge with KCl-saturated methanol. The tall-form beaker used as the titration vessel was kept at constant temperature in a water bath thermostated at $25.0 \pm .1^{\circ}\text{C}$.

In order to shield the electrodes from electrical interference, a perforated steel cylinder was placed around the titration vessel. In addition, sodium chloride was added to the temperature bath to make the water a conductor and therefore an additional electrical shield. Both the metal shield and the bath water were grounded, as were the electrode holder and the pH meter.

In order to reduce the resistance of the titration solution, the electrodes were placed in their holders at an angle which brought the bulb of the glass electrode to within one or two millimeters of the tip of the liquid junction of the calomel electrode. The titrations were done with the electrodes in this position.

An additional procedure for reducing the solvent resistance was the addition of a quantity of tetrabutylammonium iodide to the solution to be titrated. This served

both to increase the conductance of the solution, and therefore to stabilize the measurements, and to make the ionic environment more constant.

Titrations were carried out with a 10 ml automatically-zeroing burette calibrated in units of .05 ml. The burette was protected from atmospheric moisture and carbon dioxide by drierite and ascarite-filled tubes and was filled from a reservoir containing the titrant, which was similarly protected. The titrated solution was stirred with a magnetic stirrer.

In many cases, the titrated acid was dissolved in the benzene by warming the solution, which was afterward cooled and allowed to equilibrate in the constant temperature bath. In some cases, specifically the 5-nitro, 5-cyano, and 4-chlorosalicylic acids, the acid did not dissolve completely until one or two ml of titrant had been added.

The glass electrode was stored in distilled water when not in use. Before being used, it was carefully wiped dry. After a titration, the glass electrode was washed with ethanol, then distilled water, and placed in distilled water until further use. The calomel electrode was flushed with a small amount of methanolic KCl solution both before and after a titration. It was also washed with ethanol and dried after a titration.

The titrations were carried out by adding an amount of

titrant to the solution of acid in benzene, stirring for one to two minutes, depending on the amount of titrant added, and then balancing the instrument with the stirrer turned off. The balance button was kept on long enough to confirm the fact that no change in potential was occurring.

The end point could easily be determined by inspection since the potential change here was of the order of 100 millivolts for the addition of 1 drop of titrant. The volume of titrant at half-neutralization could then be determined from that at the end point. From the half-neutralization volume, the half-neutralization potential (HNP) was obtained by interpolating between the potentials for the volumes on either side of half-neutralization. Special precautions were taken to add only small amounts of titrant in the vicinity of half neutralization in order to reduce the error in interpolating between two volumes.

As indicated in the theoretical section, the potentials at half-neutralization are taken relative to a reference compound. For the salicylic acids measured in these experiments, the parent acid was the reference compound and two or three titrations of it were carried out on each day that measurements were made. They were averaged for any one day and the difference between the half-neutralization potential of this reference acid and that of a substituted acid was designated as Δ HNP. The value of Δ HNP was then considered a measure of the strength of the substituted acid relative to the unsubstituted parent compound.



RESULTS

EXPERIMENTAL DATA

The data obtained from the titrations are given in this section.

An example of a typical titration of salicylic acid in benzene is given. The curves for the substituted acids resemble those of the parent compound in every respect and are therefore not included. The data for the titration is given in Table 2 and the graph of potential (E) versus volume of titrant added is given in Figure 1. Figure 2 is a plot of potential versus $\log \frac{V_e - V}{V}$ where V_e is the volume of titrant added at the end point and V is the volume added at potential E. The data are plotted to 80% titration since after this, potential begins to change fairly rapidly and the values are not too reliable. Table 3, Figure 3, and Figure 4 give the corresponding information for a titration carried out on salicylic acid in aqueous solution using aqueous sodium hydroxide as the titrant and the same electrodes as in the benzene titrations. This titration in aqueous solution was done so that a comparison could be made with the titrations in benzene.

As seen from Figures 2 and 4, neither plot is actually a completely straight line as predicted by equation (3). Deviation from linearity could perhaps be attributed to changes in ionic strength during titration. The straight lines drawn in the two figures allow a better comparison

to be made of the extent of deviation from linearity in the two solvents but are not in themselves considered significant.

Up to approximately 65% neutralization ($\log \frac{V_e - V}{V} \approx 0.25$), Figure 2 is as near to being linear as Figure 4. Beyond this, the plot in benzene shows increasing deviation from linearity while Figure 4, the plot in aqueous solution, does not deviate significantly until 75% neutralization.

A situation similar to that in Figure 2 was found with other titrations of salicylic acid in benzene which were tested in this manner. Thus, in contrast to the situation in ethylene dichloride previously discussed, it can be concluded that the behaviour of the glass electrode in benzene is similar to that in water up to and beyond the half-neutralization point.

In connection with these titration curves it should be mentioned that, as can be seen from Table 2, salicylic acid exhibits two large potential breaks near the end point, separated by a region of approximately 0.1 ml where the potential change is less rapid. This also occurred for all the substituted salicylic acids although it did not appear in the titration in aqueous solution or in a titration of benzoic acid in benzene, which was carried out for comparison with the salicylic acids. In the case of the salicylic acids, the second potential change was generally

the larger, and was the one taken as the endpoint. No explanation for this behaviour has been found.

The titration data and the titration curve for the benzoic acid are given in Table 4 and Figure 5. It can be seen from the data that there is only one large potential change at the end point. Also the shape of the titration curve is slightly different than for salicylic acid.

TABLE 2. The titration data for salicylic acid in benzene at a concentration of 7.39×10^{-3} molar and with a half-neutralization potential of -121.3 millivolts.

Volume titrant (ml)	Potential (millivolts)
1.00	+ 36.3
1.50	+ 12.3
2.00	- 13.1
2.52	- 37.7
3.01	- 66.3
3.50	- 91.7
3.75	-104.4
3.90	-112.2
4.00	-116.3
4.10	-121.8
4.25	-127.2
4.50	-136.3

continued

TABLE 2 CONTINUED

Volume titrant (ml)	Potential (millivolts)
5.00	-152.2
5.51	-166.5
6.05	-179.5
6.50	-190.8
7.00	-206.4
7.50	-229.6
7.75	-255.7
7.80	-260.3
7.84	-274.4
7.86	-282.8
7.91	-302.1
7.93	-343.5
7.96	-427.3
7.99	-479.2
8.03	-513.1
8.06	-537.7
8.08	-630
8.11	-645.5
8.51	-666.8

FIGURE 1. The titration curve of salicylic acid in benzene from data in Table 2. Potential (E) versus volume of titrant added (V).

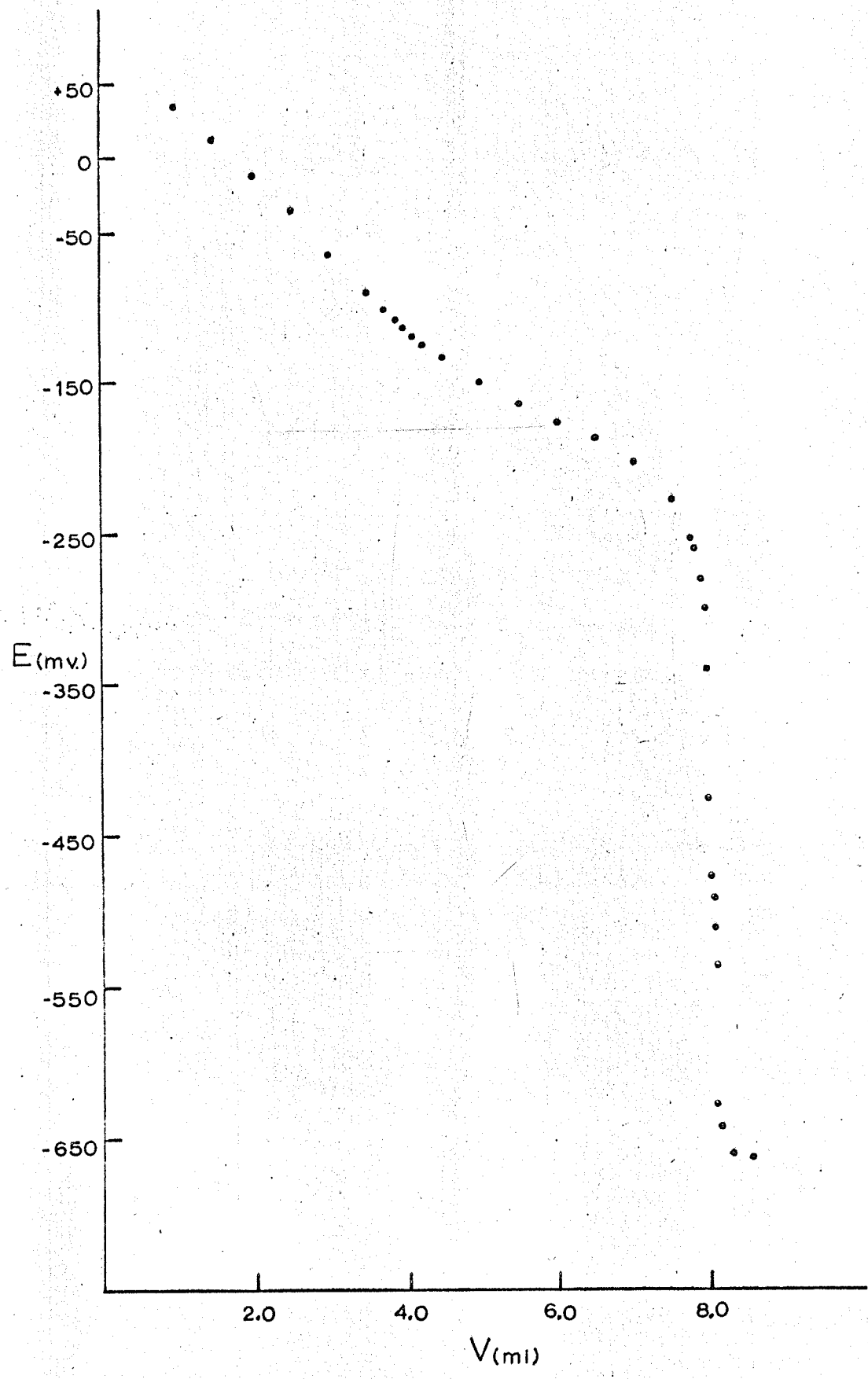


FIGURE 2. A plot of potential versus
 $\log \frac{V_e - V}{V}$ for salicylic acid in
benzene from data in Table 2.

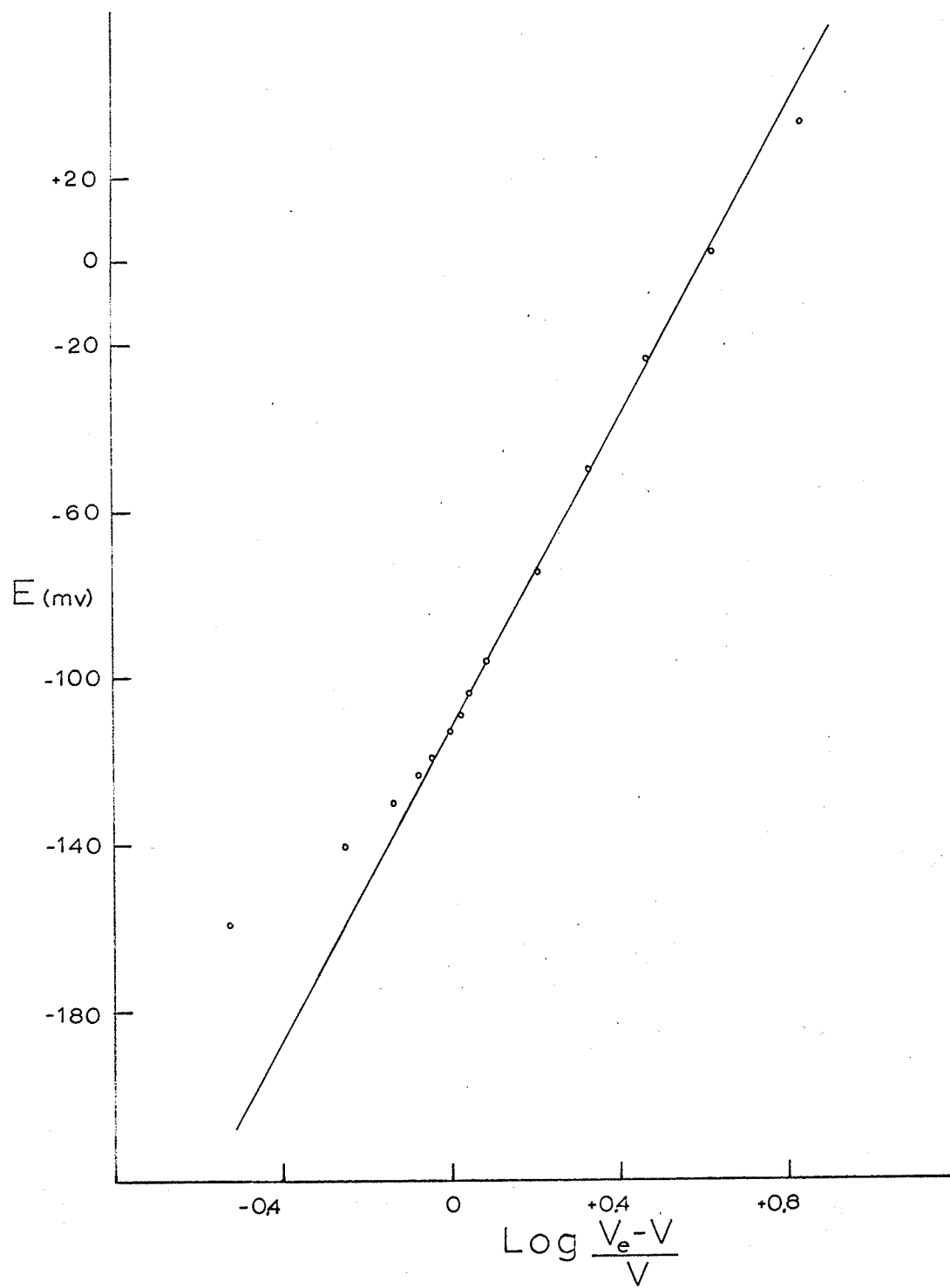


TABLE 3. The titration of salicylic acid in water at a concentration of 22.76×10^{-3} molar.

Volume titrant (ml)	Potential (mv)
0.0	+194.2
0.50	+192.2
1.00	+190.3
1.99	+185.6
2.50	+181.8
3.00	+178.2
3.50	+174.4
4.00	+170.8
4.20	+168.5
4.40	+166.9
4.80	+163.9
5.00	+162.2
5.51	+157.9
6.02	+153.2
7.00	+142.3
7.50	+135.1
8.00	+127.1
8.50	+114.0
8.64	+109.7

continued

TABLE 3 CONTINUED

Volume titrant (ml)	Potential (mv)
9.00	+ 95.9
9.16	+ 83.0
9.24	+ 72.8
9.36	+ 54.2
9.41	+ 35.8
9.47	- 10.3
9.51	-161.9
9.57	-221.5
9.61	-243.0
9.90	-283.4
10.50	-309.6

FIGURE 3. The titration curve of salicylic acid
in water from data in Table 3.
Potential (E) versus volume of
titrant (V).

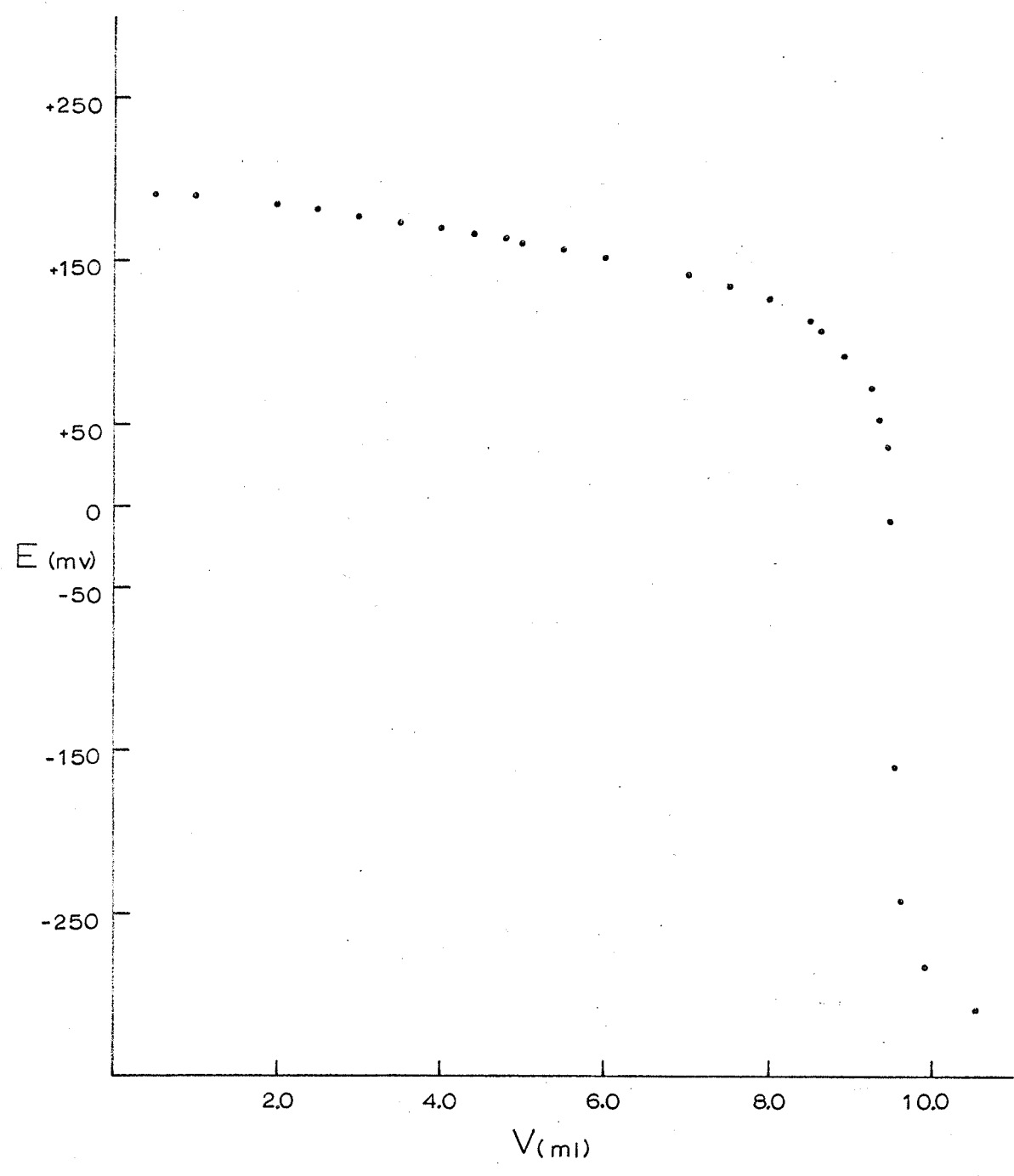


FIGURE 4. A plot of potential versus $\log \frac{V e^{-V}}{V}$ for salicylic acid in water from data in Table 3.

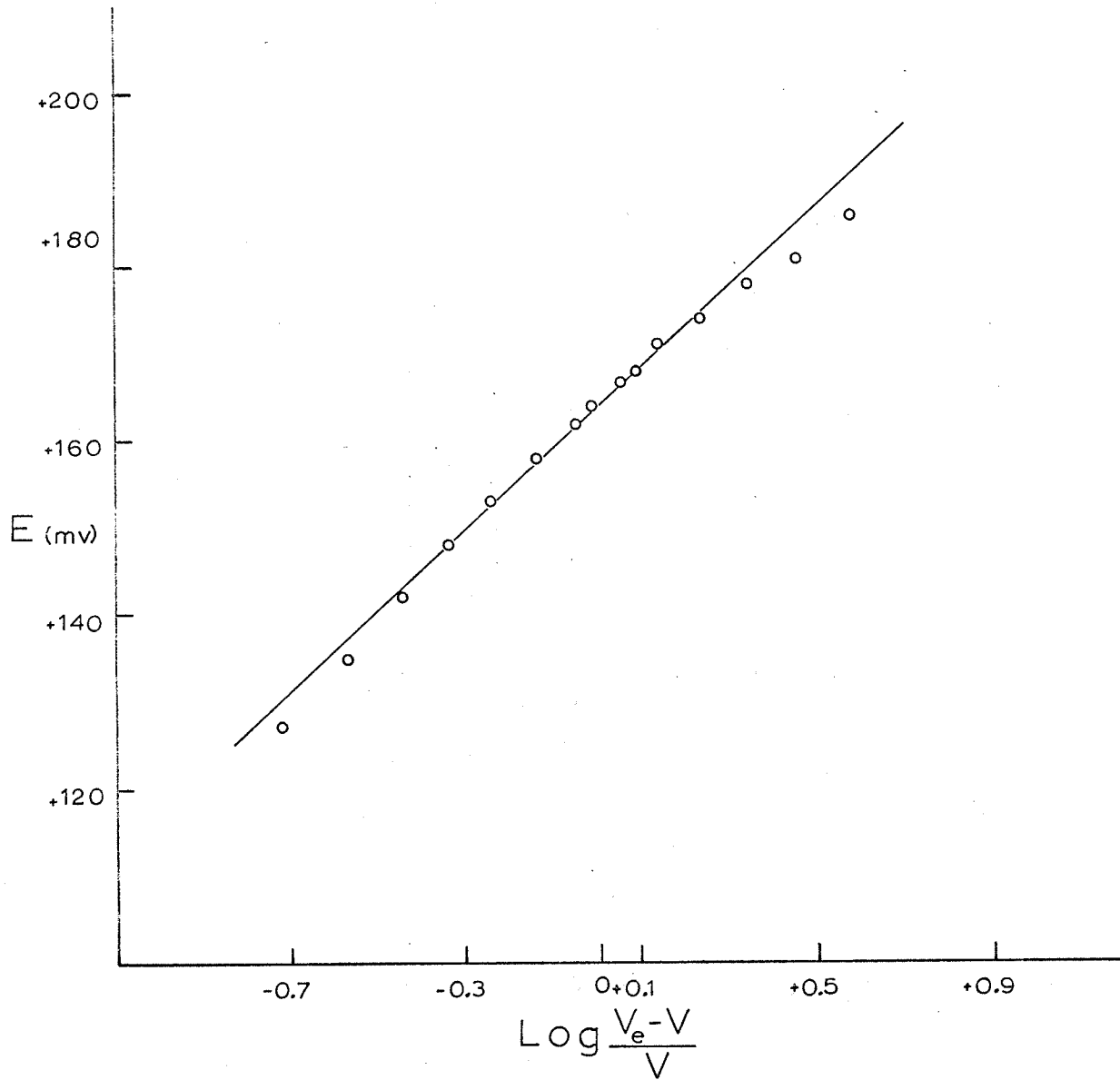


TABLE 4. The titration of benzoic acid in benzene at a concentration of 13.64×10^{-3} molar.

Volume titrant (ml)	Potential (mv)
1.00	-244.2
2.00	-288.3
2.50	-310.5
2.70	-319.9
2.91	-327.0
3.10	-335.2
3.25	-341.2
3.40	-345.5
3.50	-349.2
3.61	-352.4
3.76	-360.3
4.20	-366.8
5.01	-378.3
6.01	-394.9
6.52	-413.3
6.71	-430.3
6.83	-450.5
6.87	-466.4
6.89	-476.5
6.91	-489.9

continued

TABLE 4 CONTINUED

Volume titrant (ml)	Potential (mv)
6.93	-506.8
6.95	-527.5
6.97	-557.9
7.00	-663
7.02	-708.5
7.05	-721.7
7.17	-764.2
7.50	-778.9

Table 5 lists the results of the titrations done in the course of this work. The titrations have been divided into sets, each set having been titrated in a single day. All the substituted acids in a set have as their reference potential the average of the parent acid's HNP values which were determined in that set. The symbol TBAI is used to represent tetrabutylammonium iodide. The heading "Vol. titrant" represents the amount of titrant added to the end point. The "Conc. acid" and "Conc. TBAI" headings represent the initial concentrations of these compounds in moles per liter $\times 10^3$, while the "Vol. benzene" is the amount of benzene in which the acid and the iodide were dissolved.

FIGURE 5. The titration curve of benzoic acid in benzene from Table 4. Potential (E) versus volume of titrant (V).

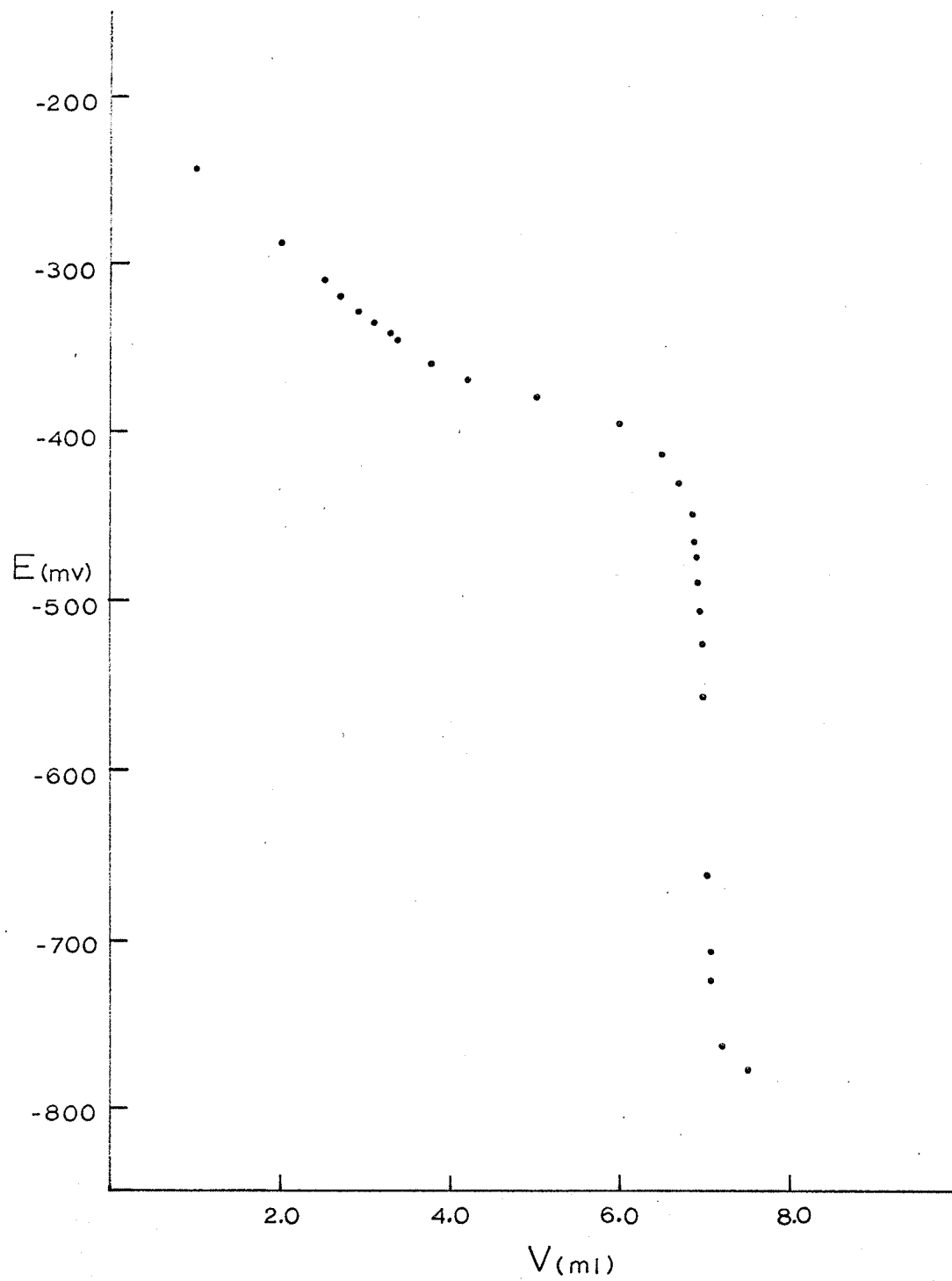


TABLE 5. Results of the potentiometric titrations of salicylic acid.

Set	Substituent	Conc. acid (Mx10 ³)	Conc. TBAI (Mx10 ³)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
1	5-Bromo	7.48	2.76	8.25	100	-42.7
	H	7.38	2.70	8.00	100	-117.8
5-Bromo	H	7.38	2.72	8.07	100	-124.0
	H	7.48	2.71	8.26	100	-42.1
	H	7.38	2.72	8.14	100	-121.3
2	4-Nitro	5.46	2.71	6.03	100	- 0.2
	H	5.45	2.70	5.95	100	-140.8
3	H	5.47	2.72	6.02	100	-141.4
	4-Nitro	5.46	2.72	6.14	100	- 2.9
4	H	6.50	2.73	7.21	100	-134.5
	4-Nitro	6.58	3.12	7.21	100	+ 3.2
	4-Nitro	6.57	2.68	7.44	100	+ 1.9
	H	6.52	2.69	7.23	100	-135.5
5	5-Methyl	6.72	2.68	3.84	50	-149.7
	H	6.76	2.75	3.88	50	-127.8
	5-Methyl	6.71	2.70	3.84	50	-152.4
	H	6.99	2.69	4.05	50	-130.9
	5-Methyl	6.67	2.69	3.83	50	-151.0
	H	6.92	2.66	3.90	50	-125.0

continued

TABLE 5 CONTINUED

Set	Substituent	Conc. acid (Mx10 ³)	Conc. TBAI (Mx10 ³)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
6	H	7.31	2.68	4.11	50	-126.2
	4-Methyl	7.20	2.75	4.16	50	-166.3
	4-Methoxy	7.31	2.72	4.16	50	-172.0
	H	7.27	2.71	4.12	50	-131.5
7	H	7.28	2.72	4.14	50	-128.0
	4-Methoxy	7.19	2.72	4.07	50	-179.3
	H	7.31	2.70	4.02	50	-133.2
8	5-Chloro	14.53	5.43	7.98	50	-33.4
	H	14.51	5.44	7.88	50	-108.6
	5-IODO	14.52	5.42	8.02	50	-35.8
	H	14.51	5.45	7.95	50	-110.3
9	4-Chloro	14.40	5.43	7.86	50	-50.9
	5-Methoxy	14.52	5.42	7.92	50	-110.4
	H	14.44	5.43	7.86	50	-109.6
	4-Methyl	14.46	5.42	8.06	50	-143.5
4-Methoxy	H	14.56	5.44	7.88	50	-151.3
	H	14.48	5.41	7.78	50	-111.8
	5-Methoxy	14.54	5.41	7.83	50	-114.3
	4-Methyl	14.47	5.42	7.95	50	-145.2
H	14.46	5.42	7.77	50	-112.6	

continued

TABLE 5 CONTINUED

Set	Substituent	Conc. acid (Mx10 ³)	Conc. TBAI (Mx10 ³)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
10	5-Cyano	14.49	5.48	7.84	50	+ 40.5
	H	14.48	5.47	7.82	50	-108.7
	4-Chloro	14.51	5.43	7.89	50	- 51.2
	H	14.47	5.40	7.77	50	-104.8
11	H	14.49	5.40	7.25	50	-109.3
	4-Methyl	14.55	5.48	7.48	50	-143.2
	5-Methoxy	14.55	5.48	7.30	50	-108.7
	H	14.44	5.40	7.24	50	-109.0
12	H	14.45	5.42	7.24	50	-111.1
	5-Iodo	14.61	5.42	7.33	50	- 40.2
	5-Chloro	14.48	5.42	7.35	50	- 38.4
	4-Chloro	14.48	5.45	7.30	50	- 50.2
	H	14.47	5.45	7.25	50	-110.9
13	H	14.54	5.46	7.39	50	-119.1
	5-Bromo	14.52	5.41	7.38	50	- 43.8
	4-Methoxy	14.49	5.45	7.34	50	-163.3
	H	14.51	5.42	7.42	50	-121.2
14	5-Chloro	14.67	5.42	7.56	50	- 47.5
	H	14.48	5.41	7.35	50	-119.3
	5-Fluoro	14.54	5.42	7.30	50	- 59.3
	5-Iodo	14.59	5.40	7.41	50	- 44.8
	H	14.52	5.42	7.34	50	-120.7
	5-Methoxy	14.55	5.42	7.36	50	-115.9
	4-Bromo	14.56	5.43	7.29	50	- 47.6
	H	14.52	5.43	7.36	50	-119.6

continued

TABLE 5 CONTINUED

Set	Substituent	Conc. acid (Mx103)	Conc. TBAI (Mx103)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
15	5-Methyl	14.49	5.42	7.30	50	-137.0
	H	14.48	5.43	7.32	50	-120.6
	4-Bromo	14.52	5.88	7.30	50	-47.7
	5-Fluoro	14.47	5.41	7.41	50	-60.0
	H	14.51	5.47	7.33	50	-118.2
16	H	14.47	5.50	7.35	50	-117.0
	5-Iodo	14.60	5.43	7.40	50	-51.2
	4-Methyl	14.49	5.46	7.56	50	-153.1
	5-Fluoro	14.49	5.42	7.43	50	-65.9
	H	14.51	5.47	7.41	50	-118.6
17	H	14.55	5.45	7.37	50	-120.2
	5-Chloro	14.55	5.46	7.46	50	-50.1
	4-Bromo	14.53	5.52	7.32	50	-51.2
	5-Fluoro	14.49	5.84	7.42	50	-63.9
	H	14.94	5.44	7.35	50	-120.2
18	4-Chloro	14.48	5.44	7.29	50	-57.5
	4-Methoxy	14.56	5.47	7.38	50	-163.3
	H	14.49	5.44	7.36	50	-120.4
18	5-Bromo	14.54	5.45	7.37	50	-44.7
	5-IODO	14.60	5.46	7.38	50	-49.0
	4-Bromo	14.52	5.44	7.30	50	-50.1
	H	14.55	5.41	7.35	50	-116.2
	4-Chloro	14.52	5.45	7.36	50	-55.4

continued

TABLE 5 CONTINUED

Set	Substituent	Conc. acid (Mx10 ³)	Conc. TBAl (Mx10 ³)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
18	5-Fluoro	14.53	5.43	7.41	50	- 58.8
19	H	14.44	5.41	7.38	50	-119.5
	5-Chloro	14.55	5.41	7.37	50	- 44.5
	4-Chloro	14.57	5.42	7.28	50	- 57.8
	5-Fluoro	14.50	5.44	7.35	50	- 61.8
	H	14.42	5.41	7.30	50	-119.5
20	H	7.27	5.43	7.35	100	-157.5
	5-Cyano	7.26	5.42	6.66	100	- 8.6
	5-Nitro	7.26	5.43	7.34	100	+ 26.1
	H	7.25	5.43	7.38	100	-153.4
	5-Nitro	7.25	5.43	7.25	100	+ 28.1
21	H	7.25	5.44	7.31	100	-153.4
	5-Nitro	7.26	5.43	7.29	100	+ 24.6
	5-Cyano	7.28	5.45	6.55	100	- 8.0
	H	7.25	5.42	7.23	100	-157.5
	5-Nitro	7.25	5.42	7.22	100	+ 24.0
22	4-Cyano	6.16	5.44	4.71	50	- 17.0
	H	6.12	5.42	4.73	50	-150.6
	4-Cyano	6.15	5.42	4.64	50	- 16.2
	H	6.18	5.41	4.80	50	-149.9
23	H	5.79	5.42	9.00	100	-152.5
	5-Cyano #	5.79	5.42	8.10	100	- 8.0
	H	5.81	5.41	9.00	100	-153.9

continued

Prepared by Kung (28)

TABLE 5 CONTINUED

Set	Substituent	Conc. acid (Mx10 ³)	Conc. TBAl (Mx10 ³)	Vol. titrant (ml)	Vol. benzene (ml)	HNP (mv)
24	H	5.83	5.46	9.07	100	-151.2
	5-Chloro	5.81	5.42	8.97	100	-80.9
	H	5.80	5.47	8.94	100	-152.1
	4-Methoxy	5.83	5.47	9.06	100	-192.8
25	H	5.83	5.45	8.98	100	-153.0
	5-Cyano	5.82	5.45	8.21	100	-10.7
	H	5.82	5.45	8.96	100	-151.5
	5-Cyano	5.83	5.42	8.18	100	-8.4
26	H	7.23	5.42	5.59	50	-144.0
	4-Fluoro	7.26	5.47	5.64	50	-106.4
	H	7.24	5.44	5.60	50	-147.5
27	H	7.27	5.44	5.60	50	-144.0
	4-Fluoro	7.23	5.41	5.56	50	-105.3
	H	7.31	5.46	5.61	50	-142.1
	4-Fluoro	7.27	5.42	5.61	50	-107.2
28	5-Nitro	13.96	5.44	7.18	50	+39.8
	H	13.99	5.43	7.23	50	-134.7

The values of ΔHNP for the various substituted acids were determined as previously described. Table 6 gives the mean values of ΔHNP for these acids together with their standard deviations, defined by:

$$\text{Standard deviation} = \left[\frac{\sum (\Delta\text{HNP} - \overline{\Delta\text{HNP}})^2}{n} \right]^{\frac{1}{2}}$$

where n is the number of values of ΔHNP for a given acid and $\overline{\Delta\text{HNP}}$ is the mean value of ΔHNP for that acid.

In the case of 4-cyanosalicylic acid, where $n = 2$, the deviation was taken as the difference between the two values of ΔHNP .

In the course of these titrations a number of variable conditions were encountered which might conceivably affect the results.

Table 7 shows HNP and ΔHNP values for a number of salicylic acids titrated under different experimental conditions. The "Conc. acid" and "Conc. TBAI" headings refer to the initial concentration of the titrated acid and the tetrabutylammonium iodide respectively. The "Conc. methanol" refers to the methanol introduced into the titrated solution by the titrant solvent which, for purposes of preparation and stability, contains 10% methanol. The concentration given is that at the half-neutralization point in ml per ml of solution. The set number refers to the set in Table 5 from which each titration was taken.

TABLE 6. The mean value of Δ HNP for substituted salicylic acids determined from Table 5.

Substituent	n	Δ HNP (mv)	Standard Deviation
5-Bromo	4	+ 76.8	2.1
4-Bromo	4	+ 70.3	1.7
5-Chloro	6	+ 72.8	2.1
4-Chloro	6	+ 60.4	3.0
5-Fluoro	6	+ 57.5	2.9
4-Fluoro	3	+ 37.6	1.5
5-Iodo	5	+ 71.1	3.0
5-Nitro	5	+179.8	2.7
4-Nitro	4	+138.5	1.3
5-Cyano	6	+145.4	2.1
4-Cyano	2	+133.6	0.8
5-Methyl	4	- 21.6	2.8
4-Methyl	5	- 34.6	1.8
5-Methoxy	4	+ 0.6	2.5
4-Methoxy	6	- 43.2	2.7

TABLE 7. The effect of varying experimental conditions on the values of HNP and Δ HNP for substituted salicylic acids.

Substituent	Conc. acid (Mx10 ³)	Conc. TBAI (Mx10 ³)	Conc. methanol (ml/ml solution x 10 ³)	Set	HNP	Δ HNP
5-Chloro	5.80	5.42	4.11	24	- 80.9	+ 70.7
	14.48	5.42	6.41	12	- 38.4	+ 72.6
	14.55	5.46	6.49	17	- 50.1	+ 70.1
4-Methoxy	5.83	5.47	4.16	24	-192.8	- 41.2
	7.31	2.72	3.83	6	-172.0	- 43.2
	7.18	2.73	3.71	7	-179.3	- 48.7
	14.56	5.47	6.43	17	-163.3	- 43.1
5-Cyano	5.79	5.42	3.75	23	- 8.0	+145.2
	5.82	5.45	3.78	25	- 10.7	+141.6
	14.49	5.48	8.75	10	+ 40.5	+147.3

The examples chosen represent the maximum variation in the concentration of acid, methanol, and tetrabutylammonium iodide that occurred during these titrations.

A change in the concentration of the acid being titrated has been reported (97) to change the value of HNP. Table 7 indicates that this was also the case in the present investigation. In addition to acid concentration other variables that might affect the value of HNP are the concentration of tetrabutylammonium iodide and the amount of methanol introduced by the titrant. These three variables generally all change when conditions vary. For example, if the concentration of acid is changed, a different volume of titrant is required to neutralize it and therefore a different amount of methanol is added to the solution. The value of HNP tends to change even if the same experimental conditions are maintained. This is especially pronounced if the titrations were determined a considerable time apart. For example, the titrations of 5-chlorosalicylic acids indicated in sets 12 and 17 of Table 7 were done under the same experimental conditions but their HNP values differ by almost 12 millivolts. These two sets were determined almost two months apart while sets 23 and 25 for 5-cyanosalicylic acid in which the HNP values differ by less than 3 millivolts, were titrated two days apart.

In order to determine whether the values of Δ HNP for the acids in Table 7 also are affected by variations in

conditions, it is necessary to know to what extent differences in these values can be attributed to experimental error. In order to make an estimation of the experimental error which can be associated with ΔHNP , the reproducibility of HNP for salicylic acid within individual sets is examined. Since experimental conditions are the same within a given set, and the time factor is not important, any deviation in HNP values must be attributed to experimental error inherent in the method. The following procedure was used to obtain an estimation of this error.

The deviation of each HNP value for salicylic acid in a set from the mean value in that set was calculated. These deviations were summed and averaged for all values of salicylic acid in all sets. This mean deviation of HNP in the different sets from the mean HNP in those sets was found to be 1.5 millivolts. Then, making the reasonable assumption that a similar experimental error exists in the substituted salicylic acids, an experimental error of 3 millivolts is estimated for ΔHNP . This deviation is inherent in the apparatus and method and is not a result of changes in experimental conditions.

Thus if two values of ΔHNP for a single acid do not differ by more than 6 millivolts, it can be concluded that the deviation is due to experimental error and not changes in titration conditions. Occasionally two values of ΔHNP

for a given acid may not agree within 6 millivolts. This larger deviation may still be the result of experimental error since in order to illustrate the largest such deviations that could occur, the maximum deviations in HNP within each set should be used in the calculations rather than deviations from the mean value. This latter procedure, however, gives a better indication of the experimental error that can usually be expected.

From Table 7 it can be seen that in all these examples, except for the 4-methoxysalicylic acid in sets 7 and 24, the values of Δ HNP for a given acid agree within 6 millivolts. In the exception mentioned, there are indications that this larger deviation is due to large experimental error in the value in set 7 rather than the result of different conditions in sets 7 and 24. This can be seen from the facts that Δ HNP for set 6, in which the conditions are the same as in set 7, differs from that of the latter by 5.5 millivolts while its deviation from set 24 is only 2.0 millivolts. Also set 17, in which acid and methanol concentrations as well as HNP differ from these values in set 24 even more than they do in sets 6 and 7, has a value of Δ HNP which differs from that of set 24 by only 1.9 millivolts. Thus the large deviation in Δ HNP between sets 7 and 24 cannot be due to different experimental conditions, but is probably the

result of a large experimental error, and since it is set 7 that deviates most from sets 6 and 17 rather than 24, the error is probably in set 7.

In connection with this it should be noted that the important thing in these tests is not that these variables will not affect Δ HNP at all, but rather that any change in them as a result of the different conditions encountered in the present investigation can be neglected. For example, it is to be expected that the introduction of a large amount of methanol into the titrated solution will change the value of Δ HNP, since the solvent is effectively different. However, as has already been concluded, the changes in methanol concentration encountered in the examples in Table 7 do not change Δ HNP significantly.

Thus, since the different experimental conditions for the titrations in Table 7 represent the maximum variation in these conditions encountered in this investigation, the fact that the Δ HNP values obtained under these different circumstances generally agree within experimental error, means that the conditions for all titrations can be considered to be effectively the same insofar as influencing Δ HNP is concerned.

STATISTICAL TREATMENT OF EXPERIMENTAL DATA

The values of Δ HNP for the salicylic acids in

Table 6 were fitted to the modified Hammett equation in the form:

$$\Delta \text{HNP} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (9)$$

where, for a 4-substituted salicylic acid, sigma 1 (σ_1) is sigma para (σ_p) and sigma 2 (σ_2) is sigma meta (σ_m) for the substituent. Similarly, for a 5-substituted salicylic acid, σ_1 is σ_m and σ_2 is σ_p . In the case of the 5-nitro and 5-cyano acids, σ_2 was σ^- (sigma minus), since here these strongly electron-withdrawing groups are para to the electron-releasing hydroxy group. The values of sigma constants were taken from the compilation of Hine (50). In order to fit the data to equation (9), the normal regression equations in two variables (5) were solved. For equation (9), these take the form

$$\begin{aligned} \rho_1 \sum \sigma_1^2 + \rho_2 \sum \sigma_1 \sigma_2 &= \sum \sigma_1 \Delta \text{HNP} \\ \rho_1 \sum \sigma_1 \sigma_2 + \rho_2 \sum \sigma_2^2 &= \sum \sigma_2 \Delta \text{HNP} \end{aligned} \quad (10)$$

where the summation is carried out over all the acids. These equations were solved using the data in Table 8. It was found that ρ_1 was 148.1 millivolts and ρ_2 was 59.3 millivolts.

The variance, S_{ext}^2 , of the calculated from the experimental values of ΔHNP was obtained from the equation:

TABLE 8. Values of ΔHNP (from Table 6) and the substituent constants of substituted salicylic acids used in the one and two-parameter Hammett equations.

Substituent	ΔHNP	σ_1	σ_2
5-Bromo	+ 76.8	+0.391	+0.232
4-Bromo	+ 70.3	+0.232	+0.391
5-Chloro	+ 72.8	+0.373	+0.227
4-Chloro	+ 60.4	+0.227	+0.373
5-Fluoro	+ 57.5	+0.337	+0.062
4-Fluoro	+ 37.6	+0.062	+0.337
5-Iodo	+ 71.1	+0.352	+0.276
5-Nitro	+179.8	+0.710	+1.27
4-Nitro	+138.5	+0.778	+ .710
5-Cyano	+145.4	+0.56	+1.000
4-Cyano	+133.6	+0.660	+0.56
5-Methyl	- 21.6	-0.069	-0.170
4-Methyl	- 34.6	-0.170	-0.069
5-Methoxy	+ 0.6	+0.115	-0.268
4-Methoxy	- 43.2	-0.268	+0.115

$$S_{\text{ext}}^2 = \frac{\sum (y - \tilde{y})^2}{n-2} \quad (11)$$

where n is the number of acids, y is the experimental value of ΔHNP for a given acid, and \tilde{y} , the calculated value of ΔHNP for the same acid, is given by:

$$\tilde{y} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (12)$$

where ρ_1 and ρ_2 are 148.1 and 59.3 respectively. A value of 63.0 was found for S_{ext}^2 .

Table 9 gives experimental and calculated values of ΔHNP . The deviations in \tilde{y} were calculated from the deviations in ρ_1 and ρ_2 . The calculation of these deviations in ρ_1 and ρ_2 is given in the following treatment. Figure 6 is a plot of the experimental values of ΔHNP versus the calculated values, using the data in Table 9. This figure gives a graphical indication of how well equation (9) fits the data.

The deviations in ρ_1 and ρ_2 , designated by S_{ρ_1} and S_{ρ_2} respectively, can be calculated from equations of the form:

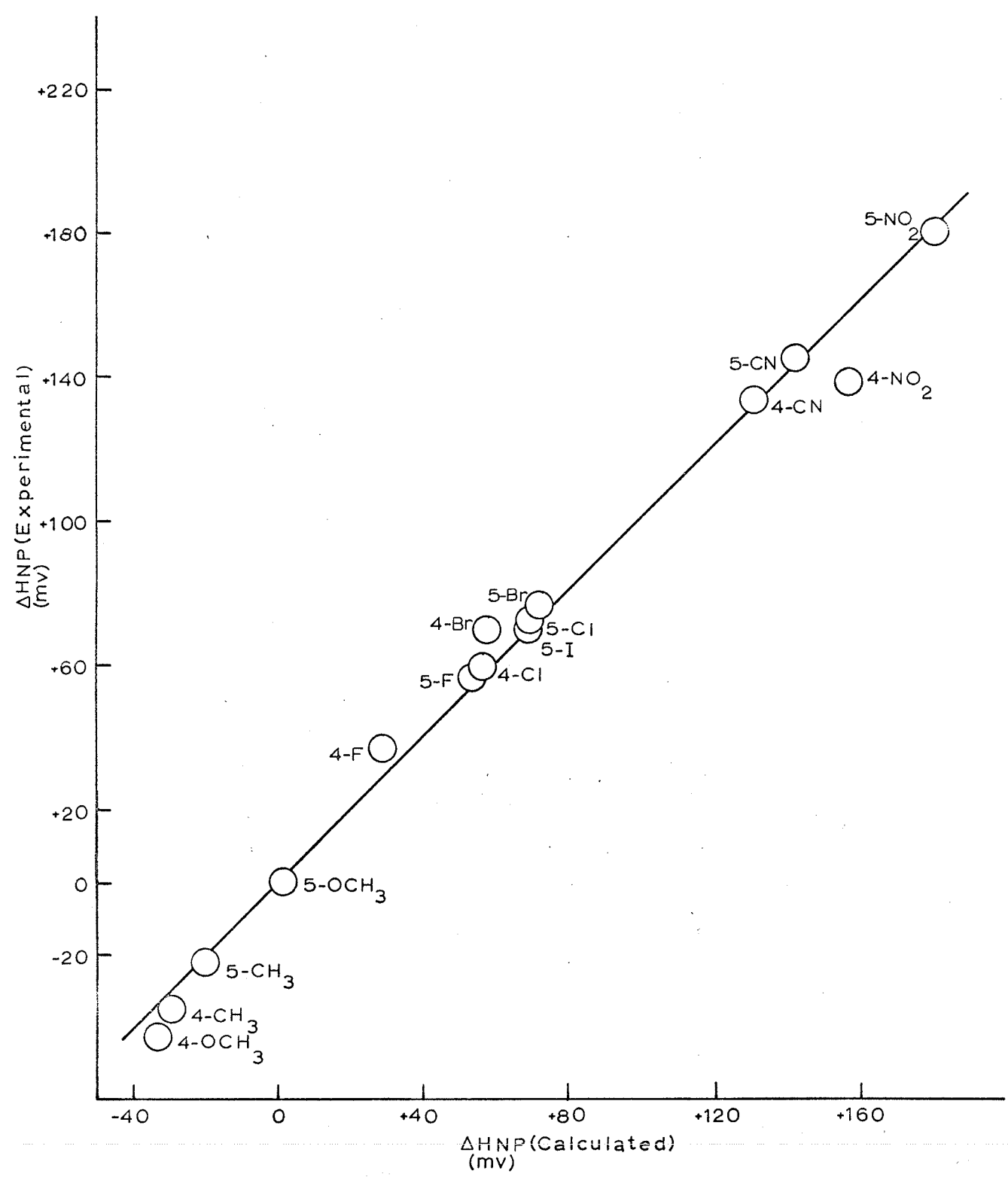
$$S_{\rho_1}^2 = \frac{-(\sum \sigma_2^2 - (\sum \sigma_2)^2/n) S_{\text{ext}}^2}{(\sum \sigma_1 \sigma_2 - \sum \sigma_1 \sum \sigma_2/n)^2 - (\sum \sigma_1^2 - (\sum \sigma_1)^2/n)} \quad (13)$$

Similarly $S_{\rho_2}^2$ can be calculated by exchanging σ_1 and σ_2 in equation (13). The values obtained were:

TABLE 9. Values of Δ HNP, experimental (Table 6) and calculated on the basis of equation (12). All values are in millivolts.

Substituent	Δ HNP Experimental	Deviation	Δ HNP Calculated	Deviation
5-Bromo	+ 76.8	2.1	+ 71.7	5.9
4-Bromo	+ 70.3	1.7	+ 57.6	5.4
5-Chloro	+ 72.8	2.1	+ 68.7	5.6
4-Chloro	+ 60.4	3.0	+ 55.7	5.2
5-Fluoro	+ 57.5	2.9	+ 53.6	4.0
4-Fluoro	+ 37.6	1.5	+ 29.1	3.2
5-Iodo	+ 71.1	3.0	+ 68.5	5.8
5-Nitro	+179.8	2.7	+180.5	17.2
4-Nitro	+138.5	1.3	+157.3	13.6
5-Cyano	+145.4	2.1	+142.2	13.6
4-Cyano	+133.6	0.8	+130.9	11.2
5-Methyl	- 21.6	2.8	- 20.3	2.0
4-Methyl	- 34.6	1.8	- 29.3	2.4
5-Methoxy	+ 0.6	2.5	+ 1.1	3.3
4-Methoxy	- 43.2	2.7	- 32.9	3.7

FIGURE 6. A plot of experimental values of ΔH_{NP} versus values calculated on the basis of the two-parameter Hammett equation. Data from Table 9.



$$S_{\rho_1} = 10.3$$

$$S_{\rho_2} = 7.8$$

Therefore the Hammett equation becomes:

$$\Delta \text{HNP} = (148.1 \pm 10.3) \sigma_1 + (59.3 \pm 7.8) \sigma_2 \quad (14)$$

A similar treatment was carried out for the simple Hammett equation in the form :

$$\Delta \text{HNP} = \rho \sigma_1 \quad (15)$$

using the equation $\rho \sum \sigma_1 = \sum \Delta \text{HNP}$ to obtain ρ . A value of 220.2 millivolts was obtained for ρ . The variance was defined in a manner similar to that for the two parameter equation:

$$S_{\text{ext}}'^2 = \frac{\sum (y - \tilde{y}')^2}{n-2} \quad (16)$$

where the symbols have the same meaning as in equation (10) except that \tilde{y}' , the calculated value of ΔHNP , is defined by:

$$\tilde{y}' = \rho \sigma_1 \quad (17)$$

where ρ is 220.2.

The deviation in ρ was found from:

$$S_{\rho}^2 = \frac{S_{\text{ext}}'^2}{\frac{\sum \sigma_1^2 - (\sum \sigma_1)^2}{n}} \quad (18)$$

The value of $S_{\text{ext}}'^2$ was 337.4 and S_{ρ} was 15.6. Table 10

TABLE 10. Values of ΔHNP , experimental (Table 6) and calculated on the basis of equation (17). All values are in millivolts.

Substituent	ΔHNP Experimental	Deviation	ΔHNP Calculated	Deviation
5-Bromo	+ 76.8	2.1	86.1	6.1
4-Bromo	+ 70.3	1.7	51.1	3.6
5-Chloro	+ 72.8	2.1	82.1	5.8
4-Chloro	+ 60.4	3.0	50.0	3.5
5-Fluoro	+ 57.5	2.9	74.2	5.2
4-Fluoro	+ 37.6	1.5	13.6	1.0
5-Iodo	+ 71.1	3.0	77.5	5.5
5-Nitro	+179.8	2.7	156.3	11.0
4-Nitro	+138.5	1.3	171.3	12.1
5-Cyano	+145.4	2.1	123.3	8.7
4-Cyano	+133.6	0.8	145.4	10.3
5-Methyl	- 21.6	2.8	-15.2	1.1
4-Methyl	- 34.6	1.8	-37.4	2.6
5-Methoxy	+ 0.6	2.5	+25.3	1.8
4-Methoxy	- 43.2	2.7	-59.0	4.2

gives the experimental and calculated values of ΔHNP . The deviation in the calculated value was obtained from the deviation in ρ .

Figure 7 is a plot of the experimental value of ΔHNP versus σ_1 , using the data in Table 8, and a value for ρ of 220.2.

It has been indicated (56) that if σ_1 and σ_2 are linearly correlated, data which would be adequately represented by a one-parameter equation will fit a two-parameter equation. If σ_1 and σ_2 are linearly related.

$$\sigma_2 = c \sigma_1 \quad (19)$$

Then if the data fit the equation

$$\Delta \text{HNP} = \rho \sigma_1 \quad (15)$$

a fit will also be obtained for the equation

$$\Delta \text{HNP} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (9)$$

in which

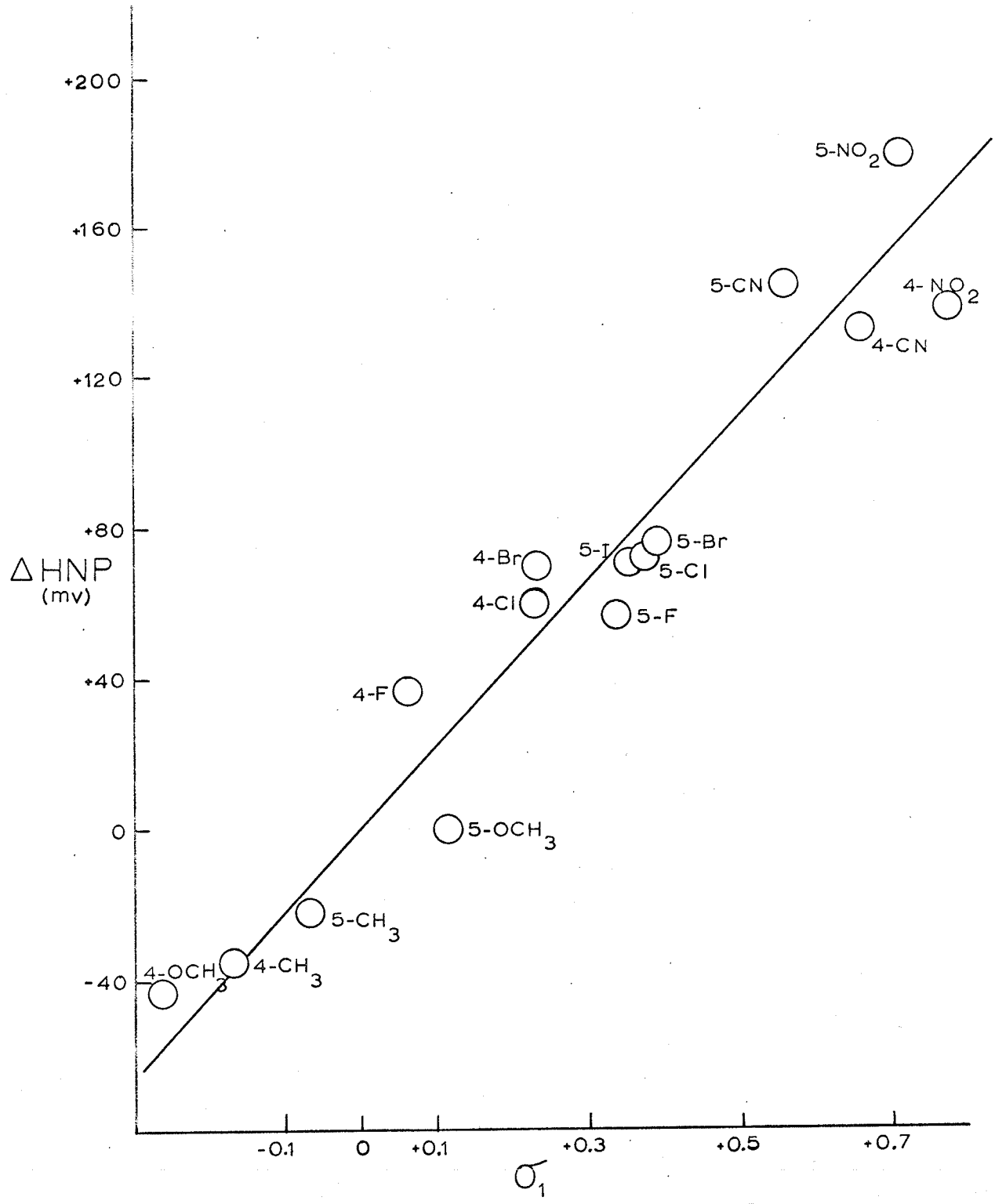
$$\rho_1 + c\rho_2 = \rho \quad (21)$$

Jaffe (56) proposed that this would be the case if the linear correlation coefficient between σ_1 and σ_2 has a value greater than 0.9.

The linear correlation coefficient between σ_1 and σ_2 , $r_{\sigma_1\sigma_2}$, is defined by:

$$r_{\sigma_1\sigma_2} = \frac{n \sum \sigma_1 \sigma_2 - \sum \sigma_1 \sum \sigma_2}{(n \sum \sigma_1^2 - (\sum \sigma_1)^2)^{\frac{1}{2}} (n \sum \sigma_2^2 - (\sum \sigma_2)^2)^{\frac{1}{2}}} \quad (22)$$

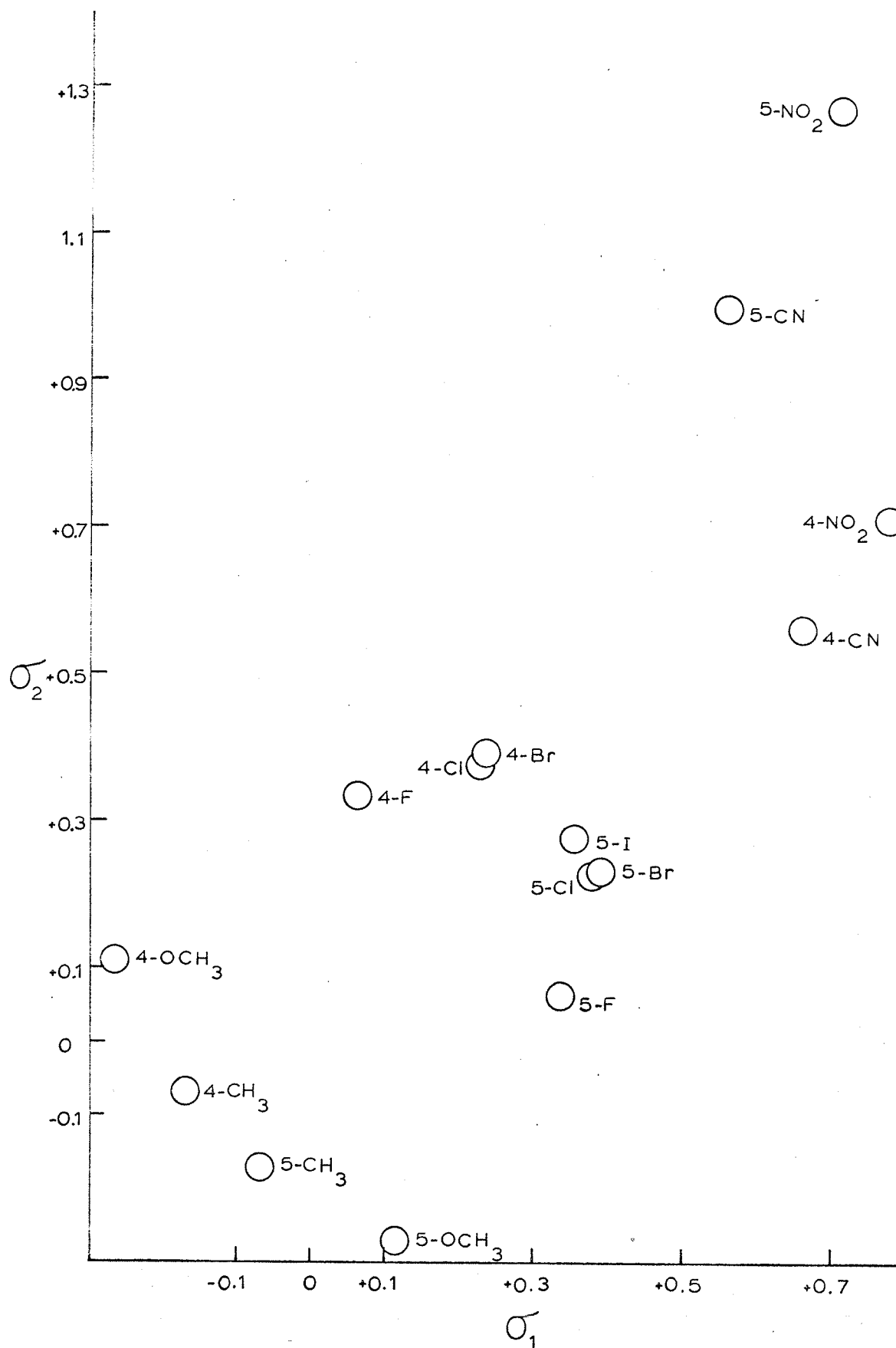
FIGURE 7. A plot of ΔHNP (experimental) versus σ_1
using the data in Table 8.



where n is the number of sets of values of σ_1 and σ_2 . (104).
Using the substituent constants in Table 8, it was found
that $r_{\sigma_1\sigma_2} = 0.756$.

Figure 8 is a graph of σ_1 versus σ_2 for the values
used in the present study.

FIGURE 8. A plot indicating the extent of linear correlation between σ_1 and σ_2 .



DISCUSSION AND CONCLUSIONS

In comparing the applicability of the one and two-parameter Hammett equations to the relative acidities of the series of substituted salicylic acid determined in this investigation, it should be noted that the former equation will always correlate the data at least as well as the latter. This can readily be seen since, mathematically, the one-parameter equation is only a special case of the two-parameter form, with ρ_2 equal to zero.

The criterion that must be examined in determining whether the two-parameter, modified Hammett equation is necessary, is the extent to which its use improves on the fit to the data provided by the simple Hammett equation.

A quantitative indication of this is obtained by a comparison of the deviations of the observed values of Δ_{HNP} from the values calculated on the basis of the two Hammett equations. In obtaining the calculated values, the statistically derived values of ρ are used in their respective Hammett equations as has been done in the preceding section on Results. A mean value of these deviations between experimental and calculated Δ_{HNP} values,

S_{ext} , is given by equation (11). As derived in the preceding section, this value is 7.9 for the two-parameter equation and 18.4 for the one-parameter equation.

Therefore, the two-parameter Hammett equation (2)

actually fits the data much better than the one-parameter equation (1). If the latter were a sufficient relationship, the two equations should have similar values of S_{ext} .

Another quantitative estimation of the validity of the two-parameter Hammett equation is the value and reliability of ρ_2 . As has been mentioned, if the two-parameter equation is used to correlate data that could actually be equally well represented by a fit to a one-parameter equation, ρ_2 should be very close to zero. The further ρ_2 is from zero, the more important the second term in equation (2) becomes. It has been proposed (56) that in order to be considered a valid representation of the data, a two-parameter equation must have a value which is different from zero at a confidence level greater than 95% as determined by a Student's t-test. In the present case such a test, which measures the probability that a number with a given deviation is greater than a designated value, indicates that 59.3 ± 7.8 which has been derived as the value of ρ_2 in the present investigation is different from zero at a confidence level considerably greater than 99.5%. As a matter of interest, the value of ρ_2 at the 95% confidence level is 59.3 ± 17.1 ; that is at the 95% confidence level $42.2 \leq \rho_2 \leq 76.4$.

Therefore, on the basis of the fit of the experimental

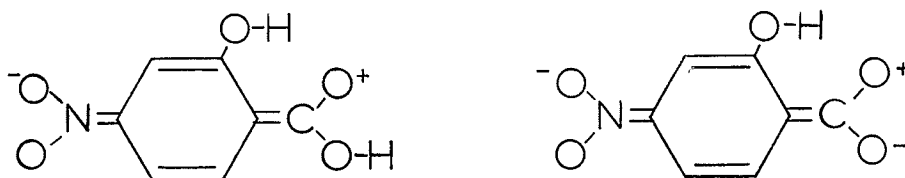
data to the two-parameter equation compared with the one-parameter equation, as measured by $\rho_2 S_{\text{ext}}$, and on the basis of the extent to which ρ_2 differs from zero, it can be concluded that the acidities of a series of substituted salicylic acids in benzene relative to salicylic acid obey a two-parameter Hammett equation rather than the simple one-parameter form. This is in agreement with the prediction (56) that substituted benzene derivatives in which the reaction center is hydrogen bonded to a vicinal group should obey such a two-parameter equation in their reactions.

That such a fit to the two-parameter equation is a result of the introduction of the ortho hydroxy group and not just due to changes in sigma values on changing solvent, some other solvent effect, or the method of measurement can be seen from the fact that the relative acidities of benzoic acids determined by potentiometric titration in solvents of low dielectric constant such as bromo- and chlorobenzene obey a simple Hammett equation (77).

Although the salicylic acids do in general obey the two-parameter Hammett equation, there are some deviations, as can be seen from Figure 6. The most notable of these is the 4-nitrosalicylic acid for which the calculated value of ΔHNP is approximately 20 millivolts higher than the experimental value.

The deviation of the 4-nitrosalicylic acid could be

due to resonance effects. In benzene solution the hydrogen bond between hydroxy and carboxyl groups will hold the latter in the plane of the benzene ring and, as a result, will allow an increase in resonance interactions between a substituent such as 4-nitro and the carboxyl group over that which could occur if no hydrogen bond were present. The 4-nitrosalicylic acid is weaker than the equation predicts, a condition which could be attributed to structures which are more important in the acid, such as:



Here, the anionic structure already has a charge on the hydroxy oxygen and the introduction of another charge on the carboxyl oxygen will be energetically unfavourable. As a result this structure will be less important than in the undissociated acid and therefore this resonance weakens the acid.

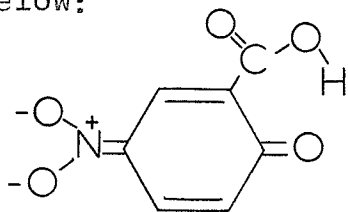
It is found that 5-nitrosalicylic acid does not deviate from the two-parameter Hammett plot, thus lending support to the hypothesis that the deviation of the 4-nitro acid is due to resonance effects since a 5-substituted acid cannot take part in such resonance interaction to an appreciable extent. It is also found that 4-nitrobenzoic acid does not deviate from the simple Hammett plot for 4-substi-

tuted benzoic acids in benzene (23). This indicates that, as suggested, the effect in 4-nitrosalicylic acid is a result of increased coplanarity of the carboxyl group and the benzene ring as a result of hydrogen bonding. It is significant that 4-nitrosalicylic acid does not deviate from the simple Hammett equation in aqueous solution. Since deviation does occur in benzene for both the simple and modified Hammett equations, this suggests that hydrogen bonding in salicylic acid is not strong enough in water to cause the necessary carboxyl group - benzene ring coplanarity.

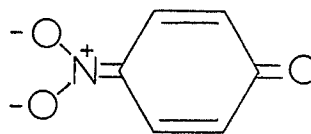
A drawback to the resonance explanation for the deviation of 4-nitrosalicylic acid from the two-parameter Hammett equation is the fact that 4-cyanosalicylic acid does not deviate although resonance interactions should also be possible with this group.

From Figure 7 it can be seen that, omitting the abnormal 4-nitro acid, 5-nitro and 5-cyanosalicylic acids deviate more from the simple Hammett equation than the other acids. This is the result that would be expected if a fairly large fraction of the effect of a substituent on acidity were through the hydrogen bond, since these strongly electron-withdrawing substituents para to the hydroxy group would be expected to have the largest effect on such hydrogen bonding through the phenolic group. In correlating the acidities of the salicylic acids measured in this investigation with the two-parameter Hammett equation,

it was found that sigma minus values for σ_2 gave a better fit to the equation than ordinary sigma values for these substituents and the former were therefore used. This is also the case in a Hammett plot of the acidities of phenols in water and suggests that resonance structures similar to those that increase the acidity of 4-nitrophenol (50) stabilize the anion. Such a structure for 4-nitrophenol anion and by analogy for 5-nitrosalicylate are indicated below:



5-nitrosalicylate



4-nitrophenolate

Although most other electron-withdrawing groups will not be able to form structures such as that indicated for 5-nitrosalicylate, and therefore sigma minus values will not generally be required for σ_2 for 5-substituted acids, the tendency will be in the same direction. That is, an increase in the acidity of the phenolic hydrogen will occur, strengthening its hydrogen bond to the carboxylate oxygen and increasing anion stability.

In connection with the 5-cyanosalicylic acid it should be mentioned that its neutralization equivalent was lower than was to be expected on the basis of the titration of the other acids. The titration indicated that the acid

was only 91% pure (see set 25, Table 5). Efforts at purification did not have an appreciable effect. It was also found that a sample of this acid prepared independently from that synthesized in the present investigation (28) gave a titration equivalent to 89% purity (see set 23, Table 5) which is very similar to that obtained from the acid prepared in this work. The two samples also gave essentially the same ΔHNP value. The fact that purification efforts resulted in no noticeable change in the titration and that two independent preparations gave the same per cent purity casts some doubt on the explanation of this result on the basis of lack of purity. The alternative explanation, that neither of these samples, which were prepared by the same method, is 5-cyanosalicylic acid is also doubtful since an infrared spectral study on the sample in reference (28) indicated the presence of a cyano group and an elemental analysis indicated the correct per centage of nitrogen for 5-cyanosalicylic acid. Although the acid prepared in this investigation was not examined in this manner, the fact that its ΔHNP value is the same as for the other sample indicates that the two are the same acid. No satisfactory explanation for this low titration of the 5-cyanosalicylic acid is available.

In the two-parameter Hammett equation the values of $\rho_1\sigma_1$ and $\rho_2\sigma_2$ refer to the effect of a substituent on the acidity of salicylic acid through two different paths.

These are the direct effect on the carboxyl group and the effect through the phenolic group. The former stabilizes the carboxylate ion through electron-withdrawal by a substituent and the latter occurs as the result of changes in the strength of the intramolecular hydrogen bond caused by the electronic influence of substituents. Therefore, the values of ρ_1 and ρ_2 should give a quantitative measure of the relative importance the two paths will have in transmitting the effect of a substituent on the strength of the salicylic acid. The value of ρ_2/ρ_1 was found to be 0.40. This indicates that the effect of a substituent on acidity by the phenolic path is 2/5 the effect by the carboxyl path. Thus the effect via the phenolic path, which is due to hydrogen bonding, is quite important and represents a fairly large fraction of the effect of a substituent on the acidity of salicylic acids in benzene.

In order to arrive at more general conclusions it is necessary to compare the results in benzene solution with those in water.

In a recent study of the thermodynamic ionization constants of sixteen substituted salicylic acids in water (67) it was found that a simple one-parameter Hammett equation was sufficient to give a good correlation with the data. A statistical fit to a two-parameter equation gave values of $.820 \pm .038$ and $.101 \pm .046$ for ρ_1 and ρ_2 respectively (28). The value of ρ_2 did not differ from zero at a

confidence level greater than 95% on the basis of the Student's t-test. It was therefore concluded that the fit of the data to the two-parameter equation did not constitute a significant improvement over the one-parameter equation and that the effect of a substituent through the phenolic group was very small or nonexistent (28).

Obviously, then, the situation is different in the solvents benzene and water. In the former an intramolecular hydrogen bond between the phenolic and carboxyl groups is known to exist, while in water very limited evidence is available on the hydrogen bonding situation. The only reasonable explanation for the experimental observation that two different Hammett equations are obeyed by salicylic acids in the two solvents, and that the equation obeyed in benzene where hydrogen bonding is known to exist is the one predicted for such hydrogen bonding (56), is that any intramolecular hydrogen bonding in aqueous solution is too weak for a substituent to have an effect on the acidity of a compound by that path.

In relation to the discussion of the experimental results of this investigation and the conclusions derived from them, a somewhat more detailed discussion of some of the literature evidence on the subject of intramolecular hydrogen bonding as it pertains to these conclusions is given.

The only important evidence, other than acid strengths,

in favor of intramolecular hydrogen bonding in aqueous solution of salicylic acid is based on an infrared study in deuterium oxide (13). The basis of the investigation is that the C = O stretching frequency of a carboxyl group is 140 cm^{-1} higher than the asymmetric stretching frequency of the carboxylate ion. Therefore, any tendency for the carboxylate group to protonate, including hydrogen bonding, would shift its frequency toward that of the carboxyl group. It was found that the asymmetric frequency of the carboxylate ion was 68 cm^{-1} higher and the C=O carboxyl stretching frequency was 25 cm^{-1} lower in salicylic acid than in benzoic acid. Since the latter cannot form intramolecular hydrogen bonds, it was concluded that these spectral differences, which indicate more protonation in salicylic than benzoic acid, were due to strong intramolecular hydrogen bonding in the salicylic acid and salicylate ion. These conclusions are based on the implicit assumption that solvation is similar for the two types of acids.

The conclusion that a strong hydrogen bond exists in aqueous solutions of salicylic acid and salicylate ion is very difficult to correlate with the results of the present investigation. Such a situation would mean that salicylic acid is very similar in benzene and water, except for solvation which does not have an appreciable

effect on the type of Hammett equation that applies (since benzoic acids obey a simple Hammett equation in benzene (23)), and that salicylic acid should therefore obey the two-parameter Hammett equation in water as well as in benzene.

It is felt that although such infrared spectral studies in D_2O may well become the most important method of investigation of hydrogen bonding effects in water, further study of factors which might influence the spectra and their interpretation is necessary. For example, it appears to be highly desirable to compare the spectrum of benzoic acid with an ortho-substituted benzoic acid, such as o-bromobenzoic acid, which cannot hydrogen bond with the carboxyl group to an important extent but which affects the acidity through steric factors. It could then be seen whether the spectral shifts in salicylic acid attributed to hydrogen bonding could be due to steric effects.

It was mentioned in the Literature Review that an ultraviolet spectrophotometric study of the hydroxybenzoic acids had been interpreted as indicating that salicylic acid has an intramolecular hydrogen bond in ethanol which persists in the monosodium salt (98). The results do not seem to warrant this conclusion and a discussion is given here in support of this opinion.

The experiments measure the ultraviolet spectra of salicylic acid and sodium salicylate in ethanol in the region of $3000\overset{\circ}{\text{A}}$, where phenol shows a peak. On the basis of these spectra it is concluded that on going from the acid to the monosodium salt, the meta and para hydroxybenzoic acids undergo a significantly larger spectral shift than the salicylic acid. From this it is deduced that in salicylic acid an intramolecular hydrogen bond, which appears to be assumed to exist in the acidic form, is retained in the monoanion. Hydrogen bonding in the other hydroxybenzoic acids, which is considered to be intermolecular, is broken in the monoanion. The spectral shifts for the hydroxybenzoic acids, estimated from the spectral diagrams in this study (98) are given in Table 11. Although these estimations are not highly accurate, it can be seen that the shifts of the maxima in the spectra on going from acid to monoanion are not very different for the three hydroxybenzoic acids. Such small spectral shifts, together with the initial requirement of assuming an intramolecular hydrogen bond in the acid form in ethanol, make any conclusions concerning changes in the state of hydrogen bonding in salicylic acid rather unreliable.

Of more interest in this particular study is an examination of the spectra of the hydroxybenzoic acids in various solvents which the authors have obtained, but not

TABLE 11. The ultraviolet spectrophotometric wavelength shifts on changing conditions for the hydroxybenzoic acids.*

Acid	λ (A)	Solvent Changed	
		From	To
Salicylic	-110	C ₂ H ₅ OH	C ₂ H ₅ OH+ 2 moles C ₂ H ₅ ONa
4-hydroxybenzoic	-140	C ₂ H ₅ OH	C ₂ H ₅ OH + 2 moles C ₂ H ₅ ONa
3-hydroxybenzoic	-100	C ₂ H ₅ OH	C ₂ H ₅ OH + 2 moles C ₂ H ₅ ONa
Salicylic	-200	CCl ₄	water
Salicylic	-140	dioxane	water
4-hydroxybenzoic	- 20	dioxane	water
3-hydroxybenzoic	- 50	CCl ₄	water
3-hydroxybenzoic	- 90	dioxane	water

* Data taken from reference (98)

discussed. The wavelength shifts of the spectral maxima have been estimated for a change in solvent from carbon tetrachloride or dioxane to water and are given in Table 11. It can be seen that salicylic acid exhibits a significantly larger spectral shift as the result of such a solvent change than do the other hydroxybenzoic acids. As mentioned in the Literature Review, other investigations have shown the presence of an intramolecular hydrogen bond in solutions of salicylic acid in solvents of low dielectric constant. Thus the spectral results can reasonably be interpreted as indicating a loss in hydrogen bonding in salicylic acid on going to water while meta and para hydroxybenzoic acids which have no such chelate hydrogen bond do not exhibit such a spectral shift.

An investigation into the NMR proton shifts of the OH group in a series of substituted 2-hydroxyacetophenones has been carried out in carbon tetrachloride solution (103). The results, together with infrared spectral frequency data obtained at the same time, have been interpreted in terms of substituent effects on the strength of the intramolecular hydrogen bond between the carbonyl oxygen and the phenolic hydrogen. The observations are interpreted as indicating that electron-withdrawing substituents in the 5-position relative to the carbonyl group decrease the electron density on the phenolic oxygen and thus increase hydrogen bonding. Such substituents in the

4-position decrease the electron density on the carbonyl oxygen and therefore reduce hydrogen bond strength.

It is of interest to compare these conclusions with the results obtained in the present investigation in order to obtain insight into the method whereby a substituent increases or decreases hydrogen bond strength, and therefore acid strength, in salicylic acids. It must be remembered that in salicylic acids there is the additional direct effect on acidity, similar to that in benzoic acid.

If, as is indicated by the 2-hydroxyacetophenones, a substituent affects the strength of a hydrogen bond only by changing the electron density on the hydrogen bonded group para to it, a substituent in the 4-position will affect hydrogen bonding only through the carboxyl group. In addition, an electron withdrawing substituent will decrease the hydrogen bond strength. A 5-substituted salicylic acid, on the other hand, will have a hydrogen bond effect via the phenolic group and in this case an electron withdrawing group will increase the strength of this bond.

The results of such a situation would be as follows. The 5-substituted acids would obey a 2-parameter Hammett equation with a positive value of ρ_2 , since the substituent effect would take place via two groups. The 4-substituted acids would obey a one-parameter equation with a value of ρ less than ρ_1 obtained for the two-parameter equation

followed by the 5-substituted acids. This is so because here there is only one path through which both the normal substituent effect and the hydrogen bonding effect occur. Also, in this case the hydrogen bonding effect will be acid weakening if the normal effect is acid strengthening; that is, the substituent is electron-withdrawing. However, Figure 7 shows that the 4-substituted acids do not obey their own simple Hammett equation any better than they obey the one for all substituents. Also, this value of ρ is larger than ρ_1 for the two-parameter equation (220.2 versus 148.1). With the exception of the 4-nitro acid, the salicylic acid with substituents in the 4 position obey the same two-parameter Hammett equation as the 5-substituted acids (Figure 6).

It therefore appears that in the case of the salicylic acids in benzene, the hypothesis that the strength of a hydrogen bond between two ortho groups is only influenced by a change in electron density on the group para to the substituent is not valid. Alternative possibilities are that the substituent only influences the hydrogen bond strength through the phenolic group, or that the electron densities of both phenolic and carboxylic oxygens are affected. The first of these possibilities is very unlikely since it is difficult to see how a 5-substituent can change the acidity of the carboxyl group by changing the

electron density without this also changing the hydrogen bonding ability of this group. Thus it appears probable that a substituent affects hydrogen bond strength by changing the electron density on both carboxyl and phenolic groups. It should be noted that these are opposing effects for any given substituent.

Since a substituent has two opposing electronic effects on the strength of a hydrogen bond, it is possible that under some circumstances or in certain compounds the effects might cancel each other and no net change in hydrogen bond strength would occur on changing substituents. As a result a system could have a strong hydrogen bond without a substituent causing a change in it. It might therefore be argued that in a system such as salicylic acid in water this is the reason for the fit to a one-parameter equation, rather than the two-parameter equation, which takes into account changes in hydrogen bonding brought about by a substituent, and that a strong hydrogen bond could still exist in this system without it obeying the 2-parameter equation.

That this is not so can be seen from the following considerations. The term $\rho_2\sigma_2$ that is considered to be the term due to hydrogen bonding in the two-parameter equation for salicylic acids actually represents that portion of the effect of a substituent on the hydrogen bond strength that occurs through the phenolic group. That is, since σ_2

refers to the position of the substituent relative to the phenolic group, $\rho_2\sigma_2$ takes into account only changes in acid strength that result from the influence of a substituent on this group and the only such effects are due to hydrogen bonding. The change in hydrogen bond strength due to changes in carboxyl group electron density are incorporated into $\rho_1\sigma_1$. Therefore $\rho_2\sigma_2$ is actually a term describing the hydrogen bond effect on acidity via the phenolic group rather than the complete hydrogen bonding effect.

Thus it is not only possible but required that, for the two opposing influences on hydrogen bonding to cancel and as a result no net change in hydrogen bonding to occur, the effect via the phenolic group and therefore ρ_2 should not be zero. If ρ_2 is zero, this means that the effect of any substituent on the strength of the hydrogen bond by way of the OH group is zero. This will occur only if there is no hydrogen bond.

The fact that the value of ρ_2 is quite small in salicylic acid in water means that the hydrogen bond is very weak, or absent, not that it is of almost constant strength as the result of opposing effects. Thus the conclusions previously derived for the hydrogen bonding in water on the basis of a very small ρ_2 in that solvent are still valid.

The preceding discussion could be indicated in a

mathematical form by dividing the expression for the two-parameter Hammett equation into separate terms for each effect. The equation then becomes:

$$\log \frac{K}{K_0} = \rho'_1 \sigma_1 + \rho_H \sigma_1 + \rho_2 \sigma_2 \quad (23)$$

or

$$\log \frac{K}{K_0} = (\rho'_1 + \rho_H) \sigma_1 + \rho_2 \sigma_2 \quad (24)$$

The term $\rho'_1 \sigma_1$ refers to the normal direct effect of a substituent on carboxyl acidity. The term $\rho_H \sigma_1$ is the effect on acidity due to changes in hydrogen bond strength resulting from a change in carboxyl group electron density by a substituent. Similarly $\rho_2 \sigma_2$ is the corresponding hydrogen bond effect due to a change in the electron density on the phenolic oxygen. The values of ρ'_1 and ρ_2 are implicitly positive while ρ_H is negative. It can be seen that the net value of $\rho_1 = (\rho'_1 + \rho_H)$ should be less than ρ'_1 . The term ρ'_1 should have a value very similar to that for a simple Hammett equation of benzoic acids in benzene determined in the same manner. It can be seen that when the net effect on hydrogen bonding is zero, the term $\rho_H \sigma_1$ is equal to $\rho_2 \sigma_2$, rather than the latter being zero.

It should be possible to determine the value of ρ'_1 by constructing a Hammett plot of benzoic acids in benzene determined by potentiometric titration under conditions

similar to those used for the salicylic acids in this investigation. A comparison of ρ_2 and ρ_H , the hydrogen bond effects on acidity resulting from substituent effects on the phenolic and carboxyl groups respectively, could then be made.

Since the conclusions based on the results of the present investigation together with those for aqueous solutions of salicylic acids indicate that in the latter case any intramolecular hydrogen bond appears to be quite weak, an alternative explanation is required to account for the high acidity of salicylic acid in water.

The only reasonable alternative explanation that appears to be available at present is that of the steric effects of ortho-substituted benzoic acids discussed in the Literature Review. As indicated in Table 12 this effect can be quite large in cases where intramolecular hydrogen bonding could not be an important factor. It is the values of K_{ortho}/K_{para} that are of greatest significance since electronic effects are similar in the two isomers, and the greater strength of the ortho isomer is due to its steric interaction with the carboxyl group. As seen in this table, this "ortho effect", measured by K_{ortho}/K_{para} , is largest for the hydroxy group. If steric hindrance of the carboxyl group by the phenol group is the cause of the high acidity of salicylic acid, an increase in the

TABLE 12. Ionization constants of substituted benzoic acids*

Substituent	$K \times 10^5$	K_{ortho}/K_{para} same substituent
2-Hydroxy	101	34.2
4-Hydroxy	2.95	
2-Methyl	12.4	3.0
4-Methyl	4.2	
2-tert.-Butyl	29.1	6.6
4-tert.-Butyl	4.4	
2-Bromo	140	13.1
4-Bromo	10.7	

* Data taken from reference (66).

effective size of the phenolic group through solvation would have to be of major importance since the actual size of the hydroxy group is much smaller than many of the others, such as bromo, in which the ortho effect is less. Such an explanation is supported by suggestions which have been made (23) on the basis of a comparison of relative strengths of a series of benzoic acids in benzene, alcohols, and water, as described in the Literature Review.

SUMMARY

1. The relative acidities of a series of fifteen substituted salicylic acids have been determined in benzene solution by potentiometric titration.
2. These relative acidities, with salicylic acid as a reference compound, have been shown to obey the two-parameter Hammett equation

$$\Delta \text{HNP} = \rho_1 \sigma_1 + \rho_2 \sigma_2$$

significantly better than a simple Hammett equation

$$\Delta \text{HNP} = \rho \sigma_1$$

in such solution, where a strong intramolecular hydrogen bond occurs.

3. These results, together with the experimental observations that the simple equation is an adequate representation of the data in water, lead to the conclusion that in the latter solvent, the intramolecular hydrogen bond is too weak for a change in its strength by a substituent acting through the phenolic group to affect the acidity of salicylic acid appreciably.
4. A possible mechanism whereby a substituent affects the strength of the hydrogen bond, and through it the acid strength, of salicylic acid in benzene is discussed.
5. An alternative explanation to that of hydrogen bonding which might cause the high acidity of salicylic acid in water is suggested.

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