

APPLICATION OF THE EXTENDED HAMMETT RELATIONSHIP TO THE IONIZATION CONSTANTS OF SUBSTITUTED ANTHRANILIC ACIDS¹

P. LEGGATE² AND G. E. DUNN

Department of Chemistry, University of Manitoba, Winnipeg, Manitoba

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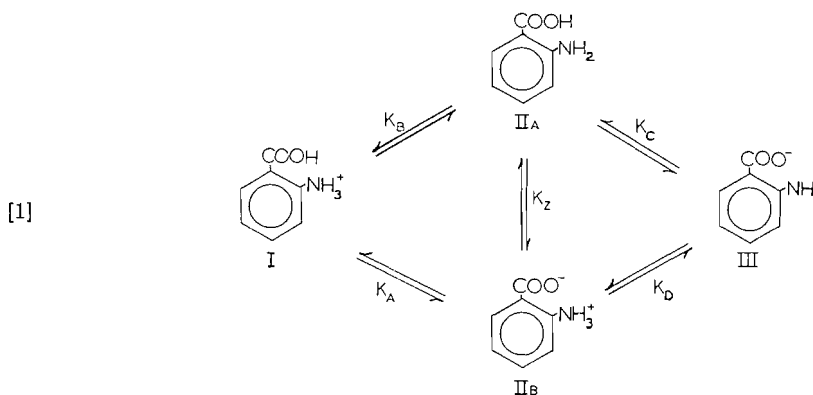
ABSTRACT

The overlapping ionization constants of the carboxyl and amino groups in 14 substituted anthranilic acids have been determined by a spectrophotometric method. The results have been fitted to the extended Hammett relationship $\log K_1K_2/K_1^0K_2^0 = \rho_1\sigma_A + \rho_2\sigma_B$, where A and B refer to ionization of the carboxyl and amino group, respectively. The values of ρ_1 and ρ_2 so obtained have been used to estimate K_2^0 , the equilibrium constant for ionization of neutral anthranilic acid to zwitterion.

An earlier paper (1) described an investigation of the rates of decarboxylation of 4- and 5-substituted anthranilic acids in nitrobenzene. Recently a parallel study of the decarboxylation of substituted salicylic acids in nonaqueous solvents has been performed (2). The extension of this work to the decarboxylation of anthranilic acids in water requires, as a first step, the determination of the two overlapping ionization constants of the acids. The complex character of the ionization equilibria of such acids in aqueous solution provides the opportunity for a somewhat unusual application of a linear free energy relationship.

THE HAMMETT EQUATIONS

In aqueous solutions of anthranilic acids there are assumed to exist four ionic and molecular species in equilibria (3, 4). These are shown in the diagram below, with the accompanying hydronium ions omitted.



The ionization constants K_1 and K_2 , which are obtained experimentally, define the equilibria:



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²N.R.C. Postdoctorate Fellow, 1960-1962.

RH_2^+ and R^- are the species I and III, respectively, of eq. [1], RH is a mixture of zwitterion, RH^\pm (IIB), and 'non-zwitterion', RH^0 (IIA). However, in the equilibria of eqs. [2] and [3], RH can be treated as a single species since the ratio of RH^\pm to RH^0 is independent of pH.

The experimental ionization constants K_1 and K_2 are related to the 'true' constants K_A , K_B , K_C , and K_D by the equations:

$$[4] \quad K_1 = K_A + K_B,$$

$$[5] \quad 1/K_2 = 1/K_C + 1/K_D,$$

$$[6] \quad K_1 K_2 = K_A K_D = K_B K_C.$$

Furthermore,

$$[7] \quad K_z = \frac{K_A}{K_B} = \frac{K_C}{K_D},$$

where

$$K_z = \frac{[\text{RH}^\pm]}{[\text{RH}^0]}.$$

For a series of substituted anthranilic acids, each of the ionization constants K_A , K_B , K_C , and K_D should obey a Hammett relationship. If, however, there is strong hydrogen bonding between the amino and carboxyl groups, then two electronic pathways are available for transmitting the substituent effect. The extension of the Hammett equation to reaction series of this type has been discussed by Jaffe (5) who proposes the use of an equation of the form:

$$[8] \quad \log \frac{K}{K^0} = \rho_1 \sigma_1 + \rho_2 \sigma_2.$$

This equation provides the means of estimating the relative importance of the two possible electronic paths in reactions in which, either two side chains react with one another, or the site of reaction is linked to the benzene ring at two points. The ionization of ortho-substituted benzoic acids represents a special case of the latter type. In this special case a hydrogen bond provides one of the two electronic pathways and a distinction can be made between a 'direct' substituent effect and an 'indirect' (and presumably less potent) effect exerted through the hydrogen bond. Jaffe showed (5) that, among the acids so far investigated, only the *o*-(hydroxymethyl)-benzoic acids provide evidence of a significant 'indirect' effect. However, as there is almost certainly a strong interaction between the amino and carboxyl groups of anthranilic acids, the possibility of indirect effects must be taken into account.

If we consider as an example the ionization constant K_A , a substituent in, say, the 4-position will behave as if para to the reaction site in exerting a direct effect on the ionization of the $-\text{COOH}$ group and as if meta in exerting an indirect effect via the $-\text{NH}_3^+$ group. The Hammett equation* is:

$$[9a] \quad \log \frac{K_A}{K_A^0} = \rho_A \sigma_A + \rho_B \sigma_B.$$

*In this and subsequent equations ρ_A and ρ_B are the Hammett constants for a given substituent considered in relation to the $-\text{COOH}$ (or $-\text{COO}^-$) and the $-\text{NH}_3^+$ (or $-\text{NH}_2$) groups, respectively. Reaction constants are defined by a suffix (A, B, C, or D) referring to the constants K_A , K_B , K_C , and K_D of eq. [1], and a prefix (I or D) indicating whether a direct or indirect effect is involved. In other cases where it is necessary to distinguish between two or more ρ or σ values, numerical suffixes are used.

The corresponding equations for K_B , K_C , and K_D are:

$$[9b] \quad \log \frac{K_B}{K_B^0} = {}_I\rho_B\sigma_A + {}_D\rho_B\sigma_B$$

$$[9c] \quad \log \frac{K_C}{K_C^0} = {}_D\rho_C\sigma_A + {}_I\rho_C\sigma_B$$

$$[9d] \quad \log \frac{K_D}{K_D^0} = {}_I\rho_D\sigma_A + {}_D\rho_D\sigma_B$$

Equation [9a] can be rewritten as:

$$[10] \quad K_A = K_A^0 10^{(D\rho_A\sigma_A + I\rho_A\sigma_B)},$$

and K_B , K_C , and K_D can be redefined in a similar manner. Substitution of these expressions for K_A , K_B , K_C , and K_D in eqs. [4] and [5] enables K_1 and K_2 to be expressed in terms of Hammett parameters:

$$[11a] \quad K_1 = K_A^0 10^{(D\rho_A\sigma_A + I\rho_A\sigma_B)} + K_B^0 10^{(I\rho_B\sigma_A + D\rho_B\sigma_B)},$$

$$[11b] \quad \frac{1}{K_2} = \frac{1}{K_C^0} 10^{-(D\rho_C\sigma_A + I\rho_C\sigma_B)} + \frac{1}{K_D^0} 10^{-(I\rho_D\sigma_A + D\rho_D\sigma_B)}.$$

These equations are obviously too complex to be fitted to the ionization constants, but fortunately a very much simpler Hammett equation is available. Thus, from eq. [6] there may be obtained the logarithmic relationships:

$$[12] \quad \log \frac{K_1 K_2}{K_1^0 K_2^0} = \log \frac{K_A K_D}{K_A^0 K_D^0} = \log \frac{K_B K_C}{K_B^0 K_C^0}.$$

Combining eqs. [12], [9a], and [9d] gives:

$$[13] \quad \log \frac{K_1 K_2}{K_1^0 K_2^0} = \sigma_A (D\rho_A + I\rho_D) + \sigma_B (I\rho_A + D\rho_D).$$

Similarly, from eqs. [12], [9b], and [9c]:

$$[14] \quad \log \frac{K_1 K_2}{K_1^0 K_2^0} = \sigma_A (I\rho_B + D\rho_C) + \sigma_B (D\rho_B + I\rho_C).$$

However, if two or more sets of experimental data are available, a linear equation of general form:

$$\log \frac{K_1 K_2}{K_1^0 K_2^0} = A\sigma_A + B\sigma_B,$$

in which A and B are constants, must have a unique solution providing σ_A and σ_B are not themselves linearly related. Equations [13] and [14] can therefore be rewritten as a single equation.

$$[15] \quad \log \frac{K_1 K_2}{K_1^0 K_2^0} = \rho_1\sigma_A + \rho_2\sigma_B,$$

where

$$[16a] \quad \rho_1 = D\rho_A + I\rho_D = I\rho_B + D\rho_C,$$

$$[16b] \quad \rho_2 = I\rho_A + D\rho_D = D\rho_B + I\rho_C.$$

Equation [15] defines a simple relationship between the experimental ionization constants and the Hammett parameters and it is, therefore, of importance that the chemical significance of this equation be defined. For this purpose it is convenient to consider the 'specific' case in which the postulated indirect substituent effects are assumed to be negligible. (Henceforth the 'general' case is that in which the indirect effects are taken into account and the 'specific' case is that in which indirect effects are assumed to be negligible.)

In the specific case the identities [16*a*] and [16*b*] simplify to:

$$[17a] \quad \rho_1 = {}_D\rho_A = {}_D\rho_C,$$

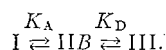
$$[17b] \quad \rho_2 = {}_D\rho_B = {}_D\rho_D.$$

(For the remainder of this paper only ρ_A and ρ_B are referred to; the argument could equally well be pursued in terms of ρ_C and ρ_D .)

The identity [17*a*] implies that the effect of a substituent on the ionization of the $-\text{COOH}$ is the same whether an NH_2 or NH_3^+ group occupies the ortho position and the identity [17*b*] carries the same implication for the ionization of the $-\text{NH}_3^+$ group. These conclusions are related to the principle, proposed by Jaffe (6), that the effect of a substituent is independent of a second substituent in an ortho position relative to the reacting side chain, provided that this ortho substituent does not participate in the reaction. The independence of the reaction constant on the nature of an ortho substituent should include the case where there is no ortho substituent. It follows, therefore, that within the limits of experimental error, ${}_D\rho_A$ should have the value 1.00 which is by definition the ρ -value for benzoic acid. Similarly, the value of ${}_D\rho_B$ should show reasonable agreement with the experimentally determined value (7) of 2.889 for the Hammett reaction constant of the anilinium ion. From the identities [17*a*] and [17*b*] it follows that in the specific case eq. [15] becomes:

$$[18] \quad \log \frac{K_1 K_2}{K_1^0 K_2^0} = {}_D\rho_A \sigma_A + {}_D\rho_B \sigma_B.$$

This equation is mathematically identical to the eq. [8], proposed by Jaffe (5), for reactions in which the substituent effect can be transmitted by two electronic pathways. Equation [18], however, possesses a very different chemical significance. As implied by eq. [12], this equation provides a Hammett relationship for both the experimental constants K_1 and K_2 and the true constants K_A and K_D (or K_B and K_C). When expressed in the latter terms it is seen as an application of the Hammett equation to two successive equilibria which are not readily distinguished by experimental means. The two equilibria may be represented (for example) by the lower half of eq. [1] which may be rewritten in an abbreviated form:



The character of the system requires that a substituent para (or meta) to the reaction center (the carboxyl group) in I is meta (or para) to the reaction center (the anilinium group) in IIB. The above interpretation can be extended to the general case represented by eq. [15]; this is an abbreviated form of eq. [13] which contains four Hammett reaction constants and represents the application of the Hammett relationship to a system of two successive equilibria, in each of which both indirect and direct substituent effects are assumed to operate. Whether or not the indirect effects are significant, eq. [15] enables

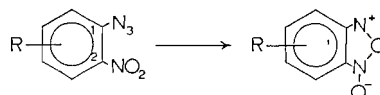
the product of the two experimental ionization constants to be fitted to a Hammett equation which can be solved for ρ_1 and ρ_2 . Relationships between the individual constants (K_1 or K_2) and the Hammett parameters are provided by eqs. [11] in the general case or in the specific case, by the equations

$$[19a] \quad K_1 = K_A^0 10^{\rho_A \sigma_A} + K_B^0 10^{\rho_B \sigma_B},$$

$$[19b] \quad \frac{1}{K_2} = \frac{1}{K_C^0} 10^{-\rho_A \sigma_A} + \frac{1}{K_D^0} 10^{-\rho_B \sigma_B}.$$

Thus, if a significant fit of the experimental data to eq. [15] is obtained, then the values of ρ_1 and ρ_2 required by this equation can be used to solve eqs. [11] or [19] for the true ionization constants K_A^0 , K_B^0 , K_C^0 , and K_D^0 of anthranilic acid. Finally, by use of eq. [7] the zwitterion constant K_Z^0 and therefore the zwitterion content can be obtained. Providing that there is a statistically significant agreement between experimental data and the theoretical equations then we have a most unusual method for determining the zwitterion content of an aromatic amino acid. Furthermore, the fit of the experimental data to eqs. [11] or [19] could provide a criterion as to whether or not the indirect substituent effects are significant. However, this criterion must be used with caution as the extended computational sequence will greatly magnify errors in both the experimental data and the Hammett substituent constants. Lack of agreement between experiment and theory may well be due to these errors rather than indicative of indirect substituent effects.

In the above discussion the possible application of the Hammett equation to the zwitterion constant K_Z has been ignored. Actual K_Z values are difficult to determine and any such relationship could not be easily verified experimentally. Nevertheless, this equilibrium is of interest in that it involves the interaction of two side chains and is therefore subject to two 'direct' substituent effects. In this respect it is closely analogous to the intramolecular reaction of the *o*-nitroazides.



Andersen *et al.* (8) have recently correlated the rate constants for a series of substituted *o*-nitroazides by the use of a two-parameter Hammett equation of the type proposed by Jaffe (5):

$$[8] \quad \log \frac{K}{K^0} = \rho_1 \sigma_1 + \rho_2 \sigma_2.$$

The σ_1 and σ_2 terms are the substituent constants of R relative to positions 1 and 2, the points of attachment of the nitro and azido groups. Anderson found that ρ_1 is positive and ρ_2 negative in agreement with the rule that ρ -values are negative when a high electron density favors the reaction. Similarly, the tautomeric equilibrium defined by K_Z involves simultaneously the release of a proton from the $-\text{COOH}$ group (favored by low electron density) and the acceptance of a proton by the $-\text{NH}_2$ group (favored by high electron density). The expected Hammett equation would be:

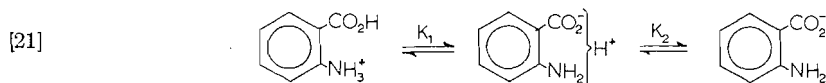
$$\log \frac{K_Z}{K_Z^0} = \rho_1 \sigma_A + \rho_2 \sigma_B,$$

where ρ_1 is positive and ρ_2 negative. In the specific case in which the indirect substituent effects on the other equilibrium constants are ignored, ρ_1 and ρ_2 can be identified with the reaction constants ρ_A and ρ_B . Thus

$$[20] \quad \log \frac{K_z}{K_z^0} = \rho_A \sigma_A - \rho_B \sigma_B.$$

Both ρ_A and ρ_B are assumed to be positive as they are defined for reactions which are favored by a low electron density—the ionizations of the $-\text{COOH}$ and $-\text{NH}_3^+$ groups respectively. Equation [20] can also be deduced directly from eq. [7] on the assumption that K_A , K_B , K_C , and K_D each obey a simple Hammett relationship.

Equation [15] is crucial to the present work in that it provides the simplest experimentally verifiable Hammett relationship for the system. However, in deducing this and other relationships, it has been assumed that eq. [1] is a valid representation of the equilibria existing in aqueous solutions of an anthranilic acid. The possibility must be considered that there are alternatives to this hypothesis. The only chemically reasonable alternative assumption is that the interactions between $-\text{COOH}$ (or $-\text{COO}^-$) and $-\text{NH}_2$ (or NH_3^+) groups are so strong that it is impossible either to consider the zwitterion (IIB) and non-zwitterion (IIA) as separate species or to distinguish between ionizations from the $-\text{COOH}$ and $-\text{NH}_3^+$ groups. In such circumstances the ionic equilibria could be represented as:



Experimental and true ionization constants are now identical. The substituent effects will be somewhat similar to those found in reactions of the nitroazides, two 'direct' effects at a single reaction center. The Hammett equations would be:

$$[22] \quad \log \frac{K_1}{K_1^0} = \rho_1 \sigma_A + \rho_2 \sigma_B,$$

$$[23] \quad \log \frac{K_2}{K_2^0} = \rho_3 \sigma_A + \rho_4 \sigma_B.$$

A combination of eqs. [22] and [23] gives an equation which is mathematically identical to eq. [15]. This equation is therefore still valid even if the existing equilibria are represented by eq. [21]. However, if eq. [21] rather than eq. [1] represents the equilibria existing in aqueous solutions of anthranilic acids, then the data should fit eqs. [22] and [23] individually as well as eq. [15].

DETERMINATION OF IONIZATION CONSTANTS

A spectrophotometric method for the determination of the overlapping ionization constants of dibasic acids was first described by Thamer and Voigt (9). This method was modified by Kok-Peng Ang (10) and, in this latter form, has been applied to aromatic amino acids by Bryson and Matthews (11). In the present work some further modifications were made, particularly as regards the method of computation.

The extinction coefficient, ϵ , of an aqueous solution of a dibasic acid at any given wavelength is related to the hydrogen ion activity, α , by the equation:

$$\alpha^2(\epsilon - \epsilon_1) + \alpha K_1(\epsilon - \epsilon_2) + K_1 K_2(\epsilon - \epsilon_3) = 0.$$

In the present case ϵ_1 , ϵ_2 , and ϵ_3 are the extinction coefficients of RH_2^+ , RH , and R^- respectively, and K_1 and K_2 are the first and second ionization constants as defined in eqs. [2] and [3]. ϵ_1 and ϵ_3 can be determined directly by measurements in acid or alkaline solutions, but ϵ_2 is not directly available. In the present work all the solutions used in the determination of K_1 and K_2 for any particular acid were of the same concentration and it is therefore convenient to use D , the optical density, in place of ϵ in describing the method and carrying out the calculations. The above equation can therefore be rewritten:

$$[24] \quad \alpha^2(D - D_1) + \alpha K_1(D - D_2) + K_1 K_2(D - D_3) = 0.$$

Kok-Peng Ang's solution of this equation for K_1 and K_2 requires that some wavelength be found for which the variation of D with pH exhibits a maximum or minimum (Fig. 1). Any value of D corresponding to the 'steep' portion of the curve will then define two values (α_1, α_2) of α and thus provide two simultaneous equations of the form of eq. [24]. Combining these equations gives

$$[25] \quad D = D_2 + K_2 P,$$

where

$$P = \frac{(D_3 - D)(\alpha_1 + \alpha_2)}{\alpha_1 \alpha_2}$$

and

$$[26] \quad D = D_1 + K_1 Q,$$

where

$$Q = \frac{D_2 - D}{\alpha_1 + \alpha_2}.$$

A plot of D against P is linear with slope K_2 and intercept D_2 . The value of D_2 is inserted into eq. [26] and D is plotted against Q to give K_1 .

In the present work an IBM 1620 computer was available and computational labor

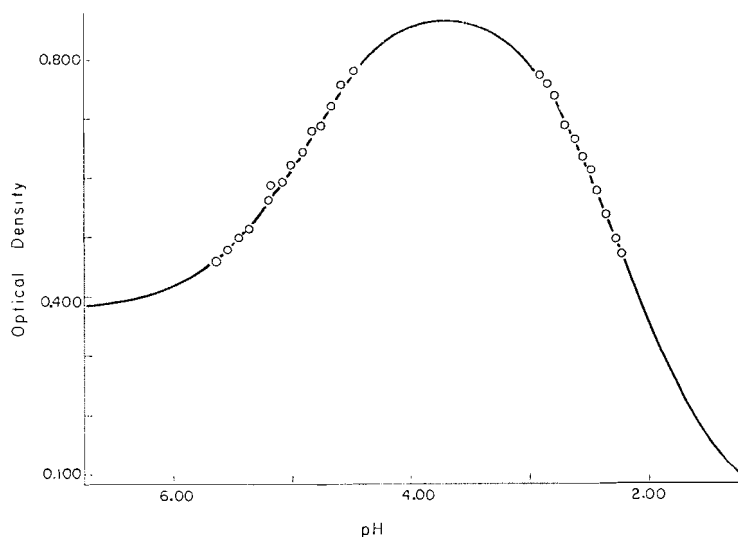


FIG. 1. Variation of optical density with pH at $\lambda = 345 \text{ m}\mu$ for anthranilic acid. Circles represent the experimental points of Table I and the line is calculated from eq. [24] using the parameters of Table II.

was not an important consideration. It was therefore possible to eliminate the following, otherwise unavoidable, weaknesses in the method of computation.

(i) The value of K_2 is highly dependent upon D_3 , the optical density of an alkaline solution, which must therefore be determined with extreme accuracy to avoid undetectable, systematic error in K_2 .

(ii) Similarly, and as previously pointed out by Bryson and Matthews (11), an error in the computed value of D_2 introduces a systematic error into the calculation of K_1 .

(iii) The usual 'least squares' procedure for determining the slope and intercept of a line assumes that only $y(=D)$ is in error and that $x(=P \text{ or } Q)$ is inerrant; this is clearly not true in the present case.

For the computation used in the present work eqs. [25] and [26] are rearranged;

$$[27] \quad D = \frac{D_2 + K_2 D_3 A}{1 + K_2 A} \quad \text{from [25],}$$

$$\text{where} \quad A = 1/\alpha_1 + 1/\alpha_2;$$

$$[28] \quad D = \frac{D_1 + K_1 D_2 A^1}{1 + K_1 A^1} \quad \text{from [26],}$$

$$\text{where} \quad A^1 = 1/(\alpha_1 + \alpha_2).$$

Equations [27] and [28] were solved on the computer by Dolittle's least squares method (12, 13) which takes into account errors in both D and α and thus provides more reliable estimates of the standard errors of the parameters. By this method independent values for K_1 and K_2 are obtained without the necessity of determining either D_1 or D_3 . Furthermore two independent estimates of D_2 are available as a test of the consistency of the calculations.

The method of obtaining the values of D , α_1 , and α_2 for use in the computation of $K_1 K_2$ was also modified. Kok-Peng Ang's procedure required that a continuous curve be constructed through the experimental points (pH, D). The values of α_1 and α_2 are then read from the curve. However, the responsibility of drawing a 'true' curve can be avoided. Thus, in the present work, using the determination of K_2 as the example, the values of D and α_2 which are used in the calculation are the actual experimental points. To obtain the corresponding values of α_1 it is still necessary to draw a curve through the experimental points on the low pH side of the maximum. However, in eq. [27] the terms α_1 and α_2 appear only in the function $A = 1/\alpha_1 + 1/\alpha_2$. For most values $1/\alpha_2 \gg 1/\alpha_1$, and errors in α_1 due to inaccurate curve construction have a negligible effect on the accuracy of the overall calculation.

Similarly for K_1 , D and α_1 are experimental points and α_2 is obtained from a constructed curve.

EXPERIMENTAL

(A) Preparation of the Substituted Anthranilic Acids

The 5-chloro, 5-hydroxy, and 5-methyl anthranilic acids, and anthranilic acid itself, were commercial products. The 5-bromo, 4-chloro, 4-nitro, and 5-nitro acids were prepared as described by Dunn and Prysiazniuk (1). The compound described in that paper as the 4-bromoanthranilic acid was found to be the 5-bromo isomer; an unambiguous synthesis of the 4-bromo acid is described in the present paper.

All the anthranilic acids were purified by one or more recrystallizations from aqueous ethanol in the presence of animal charcoal. The melting points given are for the recrystallized acids. All melting points were determined with a Hershberg melting point apparatus (14) using Anschütz thermometers and are expressed in °C.

'Analar' acetone was purified for use in the permanganate oxidations by distillation from solid potassium permanganate.

4-Methylantranilic Acid

4-Methyl-2-nitrobenzoic acid was prepared by the procedure described by Grob (15). 4-Methyl-2-nitroaniline was diazotized and the diazonium solution treated with cuprous cyanide to yield the 4-methyl-2-nitrobenzotrile, which was hydrolyzed to the 4-methyl-2-nitrobenzoic acid. The crude nitro acid (10 g) in ethanol (75 ml) was hydrogenated during 20 min at 3 atm pressure in the presence of 10% palladium-on-charcoal (1.0 g). 4-Methylantranilic acid (6.0 g, 65%) was recovered from the reaction mixture and, after recrystallization from aqueous ethanol, had m.p. 181–182° (lit. (15) 178–180°).

4-Methoxyantranilic Acid

4-Methoxy-2-nitrobenzoic acid, m.p. 192–193°, was prepared from 4-methoxy-2-nitroaniline by the procedure of Steven *et al.* (16) who give m.p. 195–196°. The nitro acid was hydrogenated under conditions already described (for the 4-methyl-2-nitro acid) to give a 73% yield of 4-methoxyantranilic acid, m.p. 180–181° (lit. (16) 180–181°).

5-Methoxyantranilic Acid

4-Methoxy-2-methylaniline (93 g) was dissolved in 0.4 *N* hydrochloric acid (1.7 l) to give a dark-brown solution which was stirred with animal charcoal and filtered. To this filtrate at 50° were added acetic anhydride (82 ml) and then sodium acetate trihydrate (109 g). The solution was cooled to 15° to precipitate the 4-methoxy-2-methylacetanilide (100 g, 82%) which had m.p. 135–136° (lit. (17) 132–134°). The anilide (10.00 g) in acetone (500 ml) was treated with potassium permanganate (27.0 g) and magnesium sulfate during 48 h at room temperature. Sodium sulfite was then added to destroy excess permanganate and the reaction mixture was filtered. The filtrate was evaporated to 100 ml, diluted with water, and extracted with chloroform to remove unreacted starting material. Acidification yielded *N*-acetyl-5-methoxyantranilic acid (3.9 g, 85% of reacted material), m.p. 165–166° (lit. (18) 165–166°). Hydrolysis of the acetylantranilic acid (7.6 g) was accomplished by warming for 30 min with 6 *N* sodium hydroxide solution. Acidification of the alkaline solution precipitated 5-methoxyantranilic acid (2.5 g, 42%), m.p. 151–152° (lit. (19) 151°).

4-Fluoroantranilic Acid

The preparation of this acid from 5-fluoro-2-methylaniline followed the published procedure of Steck and Fletcher (20). The 4-fluoroantranilic acid so prepared had m.p. 198–199° (lit. (20) 192.5–193.0°).

5-Fluoroantranilic Acid

The 5-fluoro acid was obtained from 4-fluoro-2-methylaniline by the successive acetylation, oxidation, and hydrolysis steps which are described in detail for the preparation of 5-methoxyantranilic acid. Acetylation of the aniline gave an 87% yield of 4-fluoro-2-methylacetanilide, m.p. 110–112° (lit. (21) 113°), which was oxidized in 43% yield to 5-fluoro-*N*-acetylantranilic acid, m.p. 178°. Hydrolysis of this compound gave a 91% yield of the 4-fluoroantranilic acid, m.p. 183–184° (lit. (22) 180°).

5-Phenoxyantranilic Acid

2-Nitro-5-chlorobenzoic acid (25 g) was reacted with potassium phenoxide in nitrobenzene solution as described by Süss and Möller (23) to give 5-phenoxy-2-nitrobenzoic acid (14 g, 65%), m.p. 154–155° (lit. (23) 157°). Hydrogenation of the crude nitro acid (14 g) under conditions already described in the present paper gave 5-phenoxyantranilic acid (9 g, 70%), m.p. 148–149° (lit. (23) 148°). Attempts to apply the same method to the preparation of the 4-phenoxyantranilic acid were unsuccessful, even though the more reactive 2-nitro-4-bromobenzoic acid was used in place of the 4-chloro compound. This failure is to be expected in the absence of an activating nitro group para to the halogen atom.

4-Bromoantranilic Acid

4-Bromo-2-nitrobenzoic acid was prepared from *o*-nitroaniline by the three stage procedure of Erickson *et al.* (24). Bromination of the *o*-nitroaniline gave an 84% yield of 4-bromo-2-nitroaniline, m.p. 105–106° (lit. (24) 111–112°), which was then diazotized and the diazonium solution treated with cuprous cyanide to give 4-bromo-2-nitrobenzotrile in 67% yield. The nitrile was hydrolyzed to 4-bromo-2-nitrobenzoic acid, m.p. 161–162° (lit. (24) 164–165°). The nitroacid (10.8 g) was dissolved in ammonium hydroxide solution and treated with ferrous ammonium sulfate hexahydrate (100 g) in water (200 ml). The reaction mixture was boiled briefly, cooled, and filtered. Acidification of the filtrate gave 4-bromoantranilic acid (7.0 g, 83%), m.p. 225° (lit. (25) 222°). A melting point depression was observed on mixing with 5-bromoantranilic acid (m.p. 215–216°).

A small quantity of the 4-bromo compound was converted by a diazotization procedure to 4-bromo-salicylic acid, m.p. 203–204° (lit. (26) 214°). This compound was readily distinguished both by melting point and mixed melting point from the 5-bromo isomer which has m.p. 169°. It is of interest that in one recent paper (27) a melting point of 164–165° is quoted for 4-bromosalicylic acid; it is almost certain that this was in fact the 5-isomer.

(B) pK_a Determinations

All measurements were made on solutions of ionic strength $\mu = 0.10$ since for the stronger acids it was necessary to measure optical densities at pH's as low as 1. Consequently, only apparent pK values are reported. These are adequate for the present purpose since the Hammett relationships always concern differences between the pK 's of substituted and unsubstituted aromatic acids where the activity coefficients will be very similar and cancel.

Experimental Procedure

Stock solutions of each acid were prepared by dissolving the appropriate weight of the acid in a slight excess of sodium hydroxide (0.1 *N*) and then diluting to 1 l with distilled water containing sufficient potassium chloride to give an ionic strength of 0.10. Aliquots (10 ml) of this stock solution, delivered from an automatic burette, were diluted to 50 ml with the appropriate buffer to give the solutions on which pH and optical density (*D*) determinations were made. Preliminary experiments were performed on solutions of each acid in 10 to 12 buffers spanning the range 1.0–5.5. The absorption spectra of these solutions in the range 2 750–4 500 Å were recorded. These spectra indicated the optimum wavelength for a pK_a determination, the required concentration of the stock solution, and the approximate pH ranges of the 'steep' portions of pH/*D* curve at the chosen wavelength. In the actual pK_a determinations the buffers were chosen so as to concentrate the experimental points in these steep portions.

Solutions of all the acids eventually became colored on standing, but in the case of the 5-methoxy, 5-hydroxy, and 5-bromo acids and in particular the 5-phenoxy acid, discoloration was observed within a few hours and anomalous optical density readings resulted. Stock solutions of these acids were therefore prepared in oxygen-free water and stored in opaque bottles under nitrogen. Under these conditions no significant variations in optical density were observed during the course of the pK_a determination.

Buffer Solutions

Hydrochloric acid (pH 1.0–1.8), chloroacetate (1.9–3.6), acetate (3.7–5.4), and phosphate (5.7, 6.0, 6.8) buffers were used. All buffers were adjusted to ionic strength 0.10 by addition of potassium chloride. In some initial experiments citrate buffers were used. It was found, however, that the optical density of an acid in a citrate buffer was significantly higher than that in hydrochloric acid or acetate buffers of the same pH and it was assumed that some degree of complex formation was occurring.

pH Measurements

These were made with a Radiometer Model 4C pH meter with shielded glass and silver chloride electrodes in a water bath thermostatically controlled at $25.0 \pm 0.1^\circ$. The instrument was standardized at pH's 1.68, 4.01, and 6.80 with potassium tetroxalate (0.1 *N*), potassium hydrogen phthalate (0.1 *N*), and sodium hydrogen phosphate–potassium hydrogen phosphate (0.25 *N*) buffers prepared from the corresponding National Bureau of Standards pH standards.

Optical Density Measurements

A Beckman DK1 spectrophotometer was used with matched cells contained in a thermostated cell holder at $25.0 \pm 1.0^\circ$. The appropriate buffer solution was used as a standard in the reference cell. In making a pK_a determination the instrument was set at the predetermined optimum wavelength throughout the determination. For each solution a record was made of the optical density over a period of several minutes during which the temperature of the cell oscillated between 24° and 26° several times. This temperature variation produced changes in the optical density of not more than 0.001 absorbance units, except in the case of strongly acid solutions of the nitro acids, in which slightly larger variations were observed.

RESULTS

Table I details the experimental data for anthranilic acid itself. Solutions Nos. 1–11 define the steep portion of the curve on the low pH side of the maximum and solutions Nos. 12–25 the steep portion on the high pH side. These data were used to solve eqs. [27] and [28] by the methods already described.

The values of pK_1 and pK_2 (and K_1 and K_2) calculated from these data are given in Table II, row 1, which also shows the excellent agreement between the two values obtained for D_2 , and between the computed value for D_3 and an experimental value. The values of K_1 and K_2 from a second, independent experiment using a different concentration of anthranilic acid are also given in Table II. The mean values of K_1 and K_2 from the two experiments are seen to be in agreement with previously published values.

Figure 1 compares the experimental data of Table I with a pH vs. *D* curve defined by eq. [24], using the computed values for the parameters K_1 , K_2 , D_1 , D_2 , and D_3 . (The mean of the two computed values of D_2 was used.) A test of the degree of coincidence between experimental data and theoretical equation is given by the value of $s(\text{ext.})$, the external estimate of error.* This is 0.005 for both equation [27] which gives K_2 and eq. [28] which

*Throughout this paper, for any set of experimentally derived data, y, x_1, x_2, \dots , which are used to determine the constant parameters a_1, a_2, \dots of an equation $y = f(x_1, x_2, \dots, a_1, a_2, \dots)$, the "external estimate of error" is defined as $s^2(\text{ext.}) = \sum (y - \bar{y})^2 / (\text{degrees of freedom})$, where \bar{y} is the value of y calculated by inserting the computed values of a_1, a_2, \dots into the equation.

TABLE I

Optical densities of $3.34 \times 10^{-4} M$ solutions of anthranilic acid at $\lambda = 345 m\mu$ and $\mu = 0.10$

Soln. No.	pH	Optical density	Soln. No.	pH	Optical density
1	2.879	0.769	12	4.458	0.779
2	2.820	0.753	13	4.557	0.775
3	2.756	0.735	14	4.647	0.718
4	2.667	0.684	15	4.723	0.687
5	2.582	0.666	16	4.813	0.678
6	2.523	0.629	17	4.897	0.643
7	2.458	0.608	18	4.982	0.620
8	2.408	0.573	19	5.074	0.592
9	2.339	0.533	20	5.182	0.562
10	2.268	0.492	21	5.266	0.541
11	2.206	0.467	22	5.350	0.515
			23	5.444	0.499
			24	5.533	0.480
			25	5.634	0.460
			26	0.1 N NaOH	0.390

gives K_1 . The actual experimental uncertainty in the optical density, D , (i.e., the internal estimate of error) is about 0.005.

Ionization constants were obtained for 15 substituted anthranilic acids. Values of K_1 , K_2 , and D_2 are given in Table III, including duplicate determinations which were made for four of the acids. For these acids the weighted mean of the duplicate values of K_1 and K_2 were used in the calculations of the Hammett relationships described in the next section. No value of K_1 is given for the 5-nitro acid, which exhibited a very broad maximum at a very low pH. The determination of K_1 would have required the use of very strongly acidic solutions for which sufficiently accurate pH data were unobtainable.

The third ionization constant of 5-hydroxyanthranilic acid, involving ionization of the hydroxyl group, was readily accessible from our data so it was calculated although it was not needed for the purposes of this paper.

$$K_3 = \frac{[A^-][H^+]}{[A^-]}$$

On the assumption that there is no significant overlapping of the second and third ionization constants, K_3 may be determined approximately by use of the relationship:

$$K_3 = \frac{(D - D_3)a}{D_4 - D}$$

where D_3 and D_4 are optical densities of solutions of the same concentration containing only A^- and A^- respectively. D is the optical density at hydrogen ion concentration a . A value of D_3 has already been computed in the calculation of K_2 ; D_4 was obtained by measurement of a solution in 0.10 N sodium hydroxide. Using $D_3 = 0.154$, $D_4 = 0.929$, $D = 0.414$ at pH = 9.069, the values $K_3 = 4.31 \times 10^{-10}$, $pK_3 = 9.36$ were obtained.

DISCUSSION

Equation [15] can be written in the form:

$$[15] \quad \log K_1 K_2 = \rho_1 \sigma_A + \rho_2 \sigma_B + \log K_1^0 K_2^0.$$

TABLE II
Apparent ionization constants of anthranilic acid at 25 °C and $\mu = 0.10$

	$K_1 \times 10^3$	$K_2 \times 10^5$	pK_1	pK_2	D_2		D_3	
					(From K_1)	(From K_2)	(Calcd.)	(Expt.)
Experiment 1*	6.97 ± 1.20	1.46 ± 0.14	2.16 ± 0.07	4.84 ± 0.04	0.935 ± 0.016	0.944 ± 0.018	0.387	0.387
Experiment 2*	6.72 ± 0.37	1.40 ± 0.10	2.17 ± 0.02	4.85 ± 0.03	0.912 ± 0.008	0.919 ± 0.010	0.383	0.381
Weighted Mean*	6.74 ± 0.36	1.42 ± 0.08	2.17 ± 0.02	4.85 ± 0.03				
Liquori and Ripamonti (28)†	7.32	1.60	2.14	4.80				
Kilpe and Harjanne (29)‡	9.34	1.05	2.05	4.95				

*The uncertainties shown are standard deviations.

†Extrapolated to $\mu = 0$.

‡ $\mu = 0.012$ for pK_1 and $\mu = 0.108$ for pK_2 .

TABLE III
 Ionization constants K_1 and K_2

Substituent	λ , $m\mu$	Concn. $\times 10^1 M$	D_2		$K_1 \times 10^3$	$K_2 \times 10^5$
			From K_1	From K_2		
5-OMe	307 (min.)	3.54	0.158 ± 0.008	0.177 ± 0.008	4.25 ± 0.34	0.300 ± 0.032
5-Me	290 (min.)	4.06	0.201 ± 0.013	0.230 ± 0.019	4.35 ± 0.34	0.252 ± 0.057
5-F	288 (min.)	9.02	0.200 ± 0.020	0.225 ± 0.005	9.32 ± 0.49	1.56 ± 0.05
5-Br	360 (max.)	6.12	1.184 ± 0.034	1.038 ± 0.018	19.9 ± 2.7	3.89 ± 0.31
		5.14			27.3 ± 1.7	
5-Cl	355 (max.)	3.84	0.861 ± 0.014	0.852 ± 0.009	20.6 ± 4.1	4.50 ± 0.28
5-OH	308 (max.)	8.54	0.442 ± 0.004	0.454 ± 0.004	1.91 ± 0.11	0.432 ± 0.023
None	345 (max.)	6.68	0.935 ± 0.016	0.944 ± 0.018	6.97 ± 1.20	1.46 ± 0.14
		6.59	0.912 ± 0.008	0.919 ± 0.010	6.72 ± 0.37	1.40 ± 0.10
4-OMe	340 (max.)	3.42	0.572 ± 0.011	0.571 ± 0.007	8.74 ± 0.94	1.33 ± 0.07
4-Me	347 (max.)	7.42	0.951 ± 0.033	0.945 ± 0.014	4.51 ± 1.01	0.845 ± 0.057
4-F	325 (max.)	5.42	1.053 ± 0.020	0.993 ± 0.010	38.4 ± 5.3	2.50 ± 0.14
4-Br	340 (max.)	2.64	1.033 ± 0.008	1.027 ± 0.013	57.5 ± 4.3	4.30 ± 0.25
4-Cl	340 (max.)	2.94	1.015 ± 0.016	0.963 ± 0.057	59.5 ± 9.0	3.29 ± 0.80
		2.94	0.995 ± 0.015	0.994 ± 0.007	66.1 ± 13.6	3.64 ± 0.16
4-NO ₂	408 (max.)	3.92	0.921 ± 0.009	0.931 ± 0.007	$222. \pm 43.$	20.6 ± 2.6
		3.86				18.8 ± 3.1
5-OPh	302 (min.)	5.06	0.345 ± 0.010	0.339 ± 0.018	4.55 ± 0.31	1.65 ± 0.17
5-NO ₂	345 (max.)	0.63				12.3 ± 0.1

This equation was solved for the constant terms ρ_1 , ρ_2 , and $\log K_1^0 K_2^0$ by application of Dolittle's least squares procedure (12, 13) to the experimental data for 13 of the 14 acids for which both K_1 and K_2 had been determined. Data for the 5-phenoxy acid were rejected for reasons given below. The σ -values which were used are listed in Table IV and are those given by McDaniel and Brown (30) with the exception of the σ_B values for the 5-fluoro and 5-nitro acids. The values reported by Biggs and Robinson (7) are used for these two σ_B 's which define the effect of a *p*-fluoro and of a *p*-nitro substituent, respectively, on the amino group. Statistical weights were calculated from an assumed standard deviation (30) of 0.020 for all the σ 's, and from standard deviations of $\log K_1 K_2$ values which were calculated from the standard deviations given in Table III for each of the individual ionization constants.

 TABLE IV
 Comparison of experimental and calculated values of $\log K_1 K_2$

Substituent	σ_A	σ_B	Log $K_1 K_2$	
			Experimental	Calculated
5-OMe	0.115	-0.268	7.91 ± 0.05	7.79
5-Me	-0.069	-0.170	7.61 ± 0.04	7.62
5-F	0.337	-0.026	6.84 ± 0.03	6.87
5-Br	0.391	0.232	6.01 ± 0.09	6.02
5-Cl	0.373	0.227	6.03 ± 0.09	6.05
5-OH	0.121	-0.370	8.08 ± 0.03	8.10
None	0.000	0.000	7.02 ± 0.03	7.04
4-OMe	-0.268	0.115	6.93 ± 0.05	6.88
4-Me	-0.170	-0.069	7.42 ± 0.10	7.38
4-F	0.062	0.337	6.02 ± 0.07	5.94
4-Br	0.232	0.391	5.61 ± 0.04	5.65
4-Cl	0.227	0.373	5.65 ± 0.06	5.71
4-NO ₂	0.778	0.710	4.35 ± 0.10	4.25
5-OPh	0.252	-0.320	7.12 ± 0.05	(7.85)

Solution of eq. [15] gave $\rho_1 = 0.751$, $\rho_2 = 3.111$, and $\log K_1^0 K_2^0 = -7.039$. These calculated constants were inserted into eq. [15] to obtain calculated values (\bar{y}) of $\log K_1 K_2$ which are listed, together with the corresponding experimental values (y), in Table IV.

When data for all 14 acids were fitted to eq. [15] the difference, $y - \bar{y}$, between the experimental and the calculated values for the 5-phenoxy acid was several times larger than the corresponding value for any other acid and also its own standard deviation. The K_1 and K_2 constants for this acid were, therefore, not used in subsequent calculations. This large discrepancy between observed and calculated values of $\log K_1 K_2$ for 5-phenoxy-anthranilic acid is shown in Table IV where the Hammett parameters defined by the other 13 acids have been used to calculate $\log K_1 K_2$ for the 5-phenoxy acid.

The data for the same 13 acids were also fitted to the four other equations following.

$$[22] \quad \log K_1 = \rho_1 \sigma_A + \rho_2 \sigma_B + \log K_1^0,$$

$$[23] \quad \log K_2 = \rho_1 \sigma_A + \rho_2 \sigma_B + \log K_2^0,$$

$$[29] \quad \log K_1 K_2 = \rho_1 \sigma_A + \log K_1^0 K_2^0,$$

$$[30] \quad \log K_1 K_2 = \rho_1 \sigma_B + \log K_1^0 K_2^0.$$

Table V gives the calculated parameters for these equations. Equations [22] and [23] are valid only if the existing equilibria can be represented by eq. [21] rather than the generally accepted eq. [1]. Equations [29] and [30] have no obvious physical significance; they are included only for purposes of comparison in estimating the significance of the fit of the data to eq. [15].

TABLE V
Comparison of Hammett equations

Eq.	ρ_1	ρ_2	$s^2(\text{ext.})^*$	$s^2(\text{int.})^\dagger$	R^\ddagger	F^\S	F'^\parallel
[15]	$0.751 \pm .084$	$3.111 \pm .071$	0.0039	0.0057	0.997	1 560	73
[22]	$0.491 \pm .146$	$1.727 \pm .114$	0.0091	0.0024	0.981	255	
[23]	$0.426 \pm .144$	$1.254 \pm .130$	0.0113	0.0009	0.949	93	
[29]	$2.086 \pm .121$		0.640	0.0057	0.481		
[30]	$3.331 \pm .019$		0.0419	0.0057	0.983		

* $s^2(\text{ext.}) = \Sigma (y - \bar{y})^2 / (n - 3)$, where the numerator is the sum of the squares of the deviations from the estimated regression equation and the denominator is the degrees of freedom.

† $s^2(\text{int.}) = \Sigma (\text{observed standard error of } y)^2 / (n - 3)$.

‡ R = multiple correlation coefficient.

§ F is the variance ratio comparing the equation in question with a completely random distribution and tests the hypothesis $\rho_1 = 0, \rho_2 = 0$.

∥ F' is the variance ratio between the three-parameter eq. [15] and the two-parameter eq. [30] and indicates whether the former gives a significantly better fit to the data.

The statistics of Table V, which describe the significance of the fit of the data to each equation, amply demonstrate the superiority of eq. [15] as an accurate interpretation of the experimental results. Only for this equation is $s^2(\text{int.})$, calculated from the known experimental uncertainties, greater than $s^2(\text{ext.})$ which is calculated from the fit of the data to the theoretical equation. The data give a considerably less significant fit to eqs. [22] and [23], indicating that the zwitterion and neutral acid cannot be treated as a single species.

The multiple correlation coefficient and the F -test show eq. [15] to be significant within the 99% confidence limit. Jaffe (5) has pointed out that equations of the same mathematical form as eq. [15] may give an excellent but entirely fallacious fit of the data if σ_A and σ_B are highly correlated. He has proposed that equations of this type should only be considered to give a meaningful interpretation of the data if $r_{AB} < 0.9$, where r_{AB} is

TABLE VI
 Comparison of experimental and calculated values of pK_1 and pK_2

Substituent	pK_1			pK_2		
	Expt.	From eq. [11a]	From eq. [19a]	Expt.	From eq. [11b]	From eq. [19b]
5-OMe	2.37 ± .03	2.38	2.54	5.57 ± .06	5.45	5.38
5-Me	2.48 ± .03	2.43	2.54	5.13 ± .01	5.20	5.16
5-F	2.03 ± .02	2.03	2.17	4.82 ± .01	4.86	4.76
5-Br	1.60 ± .03	1.66	1.61	4.41 ± .03	4.34	4.39
5-Cl	1.69 ± .08	1.68	1.63	4.35 ± .03	4.36	4.40
5-OH	2.72 ± .02	2.42	2.58	5.37 ± .02	5.72	5.67
None	2.17 ± .03	2.18	2.23	4.85 ± .05	4.85	4.83
4-OMe	2.06 ± .05	1.98	1.99	4.88 ± .02	4.85	4.86
4-Me	2.35 ± .10	2.35	2.42	5.07 ± .03	5.02	5.00
4-F	1.42 ± .07	1.45	1.34	4.60 ± .02	4.44	4.55
4-Br	1.24 ± .03	1.33	1.17	4.37 ± .03	4.27	4.42
4-Cl	1.21 ± .07	1.37	1.22	4.44 ± .03	4.29	4.43
4-NO ₂	0.65 ± .08	0.56	0.19	3.70 ± .06	3.63	3.99
5-OPh	2.34 ± .08	(2.28)	(2.48)	4.88 ± .04	(5.58)	(5.53)
s ² (ext.)		0.125	0.282		0.196	0.207

the correlation coefficient between σ_A and σ_B . The value of $r_{AB} = 0.590$ for our substituents amply fulfills this condition and, indeed, is lower than in any of the cases discussed by Jaffe.

It was pointed out earlier that in the specific case, where indirect effects are negligible, $\rho_1 = {}_D\rho_A$ and $\rho_2 = {}_D\rho_B$. Furthermore, ${}_D\rho_A$ and ${}_D\rho_B$ should, in theory, be approximately equal to 1.00 and 2.89, respectively. These theoretical values are outside the standard deviations of $\rho_1 (= 0.751 \pm 0.084)$ and $\rho_2 (= 3.111 \pm 0.071)$ shown in Table V. This might be considered evidence for the existence of an indirect effect, although the differences between theoretical and experimental values are no greater than some reported by Jaffe (6) for ortho-substituted systems where chelation is impossible. However, it may be worthwhile to explore the possibility of indirect effects as an explanation for the discrepancy. In that case eq. [16] would give

$$\rho_1 = {}_D\rho_A + {}_I\rho_D = 0.751,$$

$$\rho_2 = {}_I\rho_A + {}_D\rho_D = 3.111.$$

If ${}_D\rho_A$ and ${}_D\rho_D$ were given their theoretical values of 1.000 and 2.889, respectively, the indirect effects would become ${}_I\rho_D = -0.249$ and ${}_I\rho_A = +0.222$. Since the former of these represents the indirect effect of substituents via chelation upon the ionization of a NH_3^+ group, it would be expected to be positive. It seems unlikely, therefore, that the deviation from the theoretical values is really the result of an indirect effect. This conclusion is reinforced by the fact that no indirect effect is observed in the similar but simpler system of salicylic acids (5, 31).

A further test of the indirect effect would be to compare the fit of the experimental K_1 's and K_2 's to eqs. [11a] and [11b] which include the indirect effect, with the fit of the same data, to [19a] and [19b] which do not. This was attempted using ${}_D\rho_A = 1.000$, ${}_I\rho_A = 0.222$, ${}_D\rho_D = 2.889$, and ${}_I\rho_D = -0.249$ for eqs. [11], or $\rho_A = 0.751$ and $\rho_B = 3.111$ for eqs. [19], and weighting the K 's inversely as the squares of their standard deviations. Table VI compares the observed pK_1 's and pK_2 's with those calculated by the two methods. It is seen that, while the pK_1 's fit eq. [11] somewhat better than eq. [19], there is little to choose between [11] and [19] as methods for calculating pK_2 . Since for both

series $s^2(\text{ext.})$ is at least double $s^2(\text{int.})$, the better fit to eq. [11] can hardly be taken as evidence for an indirect effect.

TABLE VII
Calculated ionization constants for eq. [1]

Eq.	$K_A^0 \times 10^3$	$K_B^0 \times 10^3$	$(K_A^0 + K_B^0) \times 10^3$	Experimental $K_1^0 \times 10^3$	K_z^0
[11a]	$3.2 \pm .3$	$3.4 \pm .6$	$6.6 \pm .8$	$6.7 \pm .4$	$1.0 \pm .3$
[19a]	$1.9 \pm .2$	$3.9 \pm .6$	$5.9 \pm .8$	$6.7 \pm .4$	$0.5 \pm .1$
Eq.	$K_C^0 \times 10^5$	$K_D^0 \times 10^5$	$(1/K_C^0 + 1/K_D^0) \times 10^{-5}$	Experimental $1/K_2^0 \times 10^{-5}$	K_z^0
[11b]	$3.2 \pm .4$	$2.5 \pm .2$	$0.71 \pm .04$	$0.70 \pm .04$	$1.2 \pm .3$
[19b]	$2.7 \pm .1$	$3.2 \pm .3$	$0.68 \pm .04$	$0.70 \pm .04$	$0.9 \pm .1$

In fitting the K_1 's and K_2 's to eqs. [11] and [19] the data for 5-phenoxyanthranilic acid were omitted, as indicated previously, because of their poor fit to eq. [15]. The values of K_A^0 , K_B^0 , K_C^0 , and K_D^0 obtained from the remaining 13 acids were used to calculate pK_1 and pK_2 for the 5-phenoxy acid and these are shown in parentheses in Table VI. It is seen that the calculated pK_1 agrees reasonably well with experiment but that pK_2 is widely out. Examination of eq. [19b] shows that the calculated value of K_2 for this acid is largely determined by the second term of the equation, which depends upon σ for the para-phenoxy group. It appears, therefore, that either the experimental value of K_2 is grossly in error or σ_{para} is incorrect. In order to fit the experimental K_2 into eqs. [15] and [19b] a value of $\sigma = -0.088$ would be required for the *p*-phenoxy group, and it is interesting to note that this is in good agreement with the σ_p reported by Jaffe (6) for reactions other than ionization constants of benzoic acids. However, our data ought, in principle, to correlate with the ionization constants of benzoic acids, and the 5-phenoxy acid is particularly susceptible to oxidative side reactions, so that it is probably not safe to attach any particular significance to our apparent σ -value.

Table VII shows the values for K_A^0 , K_B^0 , K_C^0 , and K_D^0 obtained from eqs. [11] and [19] and for the values of K_z^0 derived from these by means of eq. [7]. The extended series of computations from the original data causes an accumulation of uncertainties in the quantities presented in Table VII but it is seen that they are consistent within their standard deviations. For example, eq. [4], which requires that $K_A^0 + K_B^0 = K_1^0$, and eq. [5], which requires that $1/K_C^0 + 1/K_D^0 = 1/K_2^0$, are both satisfied. The uncertainty in K_z^0 is correspondingly large, but K_z^0 evidently lies in the region 0.4–1.5, with the theoretically preferable eq. [19a] giving a range of 0.4–1.0, equivalent to 30–50% zwitterion.

Previous calculations giving $K_z^0 = 0.2$, or 17% zwitterion, have been based on the assumption that K_A^0 may be equated to the ionization constant of the methyl ester of anthranilic acid, $pK_E = 2.09$ (3). This assumption, as applied to *p*-aminobenzoic acid, has been criticized by Bryson and Matthews (11) on the grounds that the various alkyl esters have different ionization constants and that among these the methyl ester is out of line. The assumption may be particularly questionable when applied to anthranilic acid esters because of the known acid-strengthening effect of bulky ortho substituents in anilinium ions (32). The reported ionization constant of the ester, $K_E = 8.13 \times 10^{-3}$, is indeed larger than our K_A^0 , whether one considers its most probable value of 1.9×10^{-3} or the maximum value of 3.5×10^{-3} obtained by inclusion of indirect substituent effects

via eq. [11a]. In fact, Table II shows that the ionization constant of the ester is larger than most modern estimates of K_1^0 , which, since $K_1^0 = K_A^0 + K_B^0$, makes the assumption that $K_E = K_A^0$ untenable.

Finally, it may be pointed out that, although the equilibrium constant for zwitterion formation by anthranilic acid is still not known with great precision, the relative equilibrium constants for zwitterion formation by substituted anthranilic acids may be calculated from eq. [20] with considerable certainty. If K_z^0 is assumed to be 1.0, then among our acids K_z varies from 17.5 (95% zwitterion) for 5-hydroxy to 0.019 (2% zwitterion) for 4-nitroanthranilic acid.

SUMMARY

The ionization constants of substituted anthranilic acids give an excellent fit to the two-parameter Hammett eq. [15], showing that these acids at the isoelectric point are better represented as a mixture of zwitterion and neutral acid than as a single hybrid species; previous estimates of the % zwitterion are low because of the erroneous assumption that the ionization of the amino group is the same in anthranilic acid as in its methyl ester; and indirect transmission of substituent effects via chelation is very improbable since in some cases it would have to act in the sense opposite to that predicted by theory.

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