Effect of intramolecular hydrogen bonding on the relative acidities of substituted salicylic acids in benzene solution[1]

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The relative acidities of fifteen 4- and 5-substituted salicylic acids were determined in benzene solution by potentiometric titration. The potentials at half neutralization (h.n.p.) relative to that of salicylic acid were considered to measure the acidities of the substituted acids relative to the parent acid. These potentials, designated by Δ_{hnp}, gave a significantly better correlation with Hammett's sigma constants in an equation of the form proposed by Jaffe, $\Delta_{hnp} = \rho_1\sigma_1 + \rho_2\sigma_2$, than in a simple Hammett equation, $\Delta_{hnp} = \rho_1\sigma_1$. In these equations the subscripts 1 and 2 refer to the position of a substituent relative to the carboxyl group and to the phenolic group respectively. 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 almost half as large as the direct effect through the carboxyl group. 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 in water.

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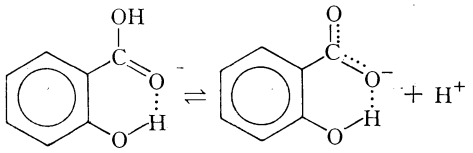
Salicylic acid is a much stronger acid than the other monohydroxybenzoic acids because an intramolecular hydrogen bond stabilizes the salicylate anion more than it does the un-ionized acid. In *m*- and *p*-



hydroxybenzoic acids the phenolic group is not in a position to chelate with the carboxyl group, so the acidities of these acids are not "abnormal". This interpretation was first clearly expressed in modern terms by Baker (1) and has become so widely accepted that it is a common feature in all textbooks which deal with the strengths of organic acids.

Jaffe (2) pointed out that, according to the above interpretation, substituents in the 4- and 5-positions of salicylic acids should influence the acidity of the carboxyl group by two paths: a "direct" one through the carboxyl group, and an "indirect" one through the phenolic group via the intramolecular hydrogen bond. These should be expressed quantitatively by the Hammett relationship (3) in the form of eq. [1] for the direct effect and eq. [2] for the indirect one.

$$[1] \qquad \text{Log } (K/K_0) = \rho_1\sigma_1$$

$$[2] \qquad \text{Log } (K/K_0) = \rho_2\sigma_2^-$$

In these equations K and K_0 are the ionization constants of substituted and unsubstituted salicylic acids respectively, σ_1 is Hammett's sigma constant for the substituent with reference to the carboxyl group, σ_2^- is the sigma constant for the same substituent with reference to the phenolic group, and ρ_1, ρ_2 measure the susceptibility of the ionization constants to electronic influences via the direct and indirect routes respectively. Jaffe proposed (2) that the direct and indirect effects should be additive so that the overall effect of a substituent in the 4- or 5-position would be given by eq. [3].

$$[3] \qquad \text{Log } (K/K_0) = \rho_1\sigma_1 + \rho_2\sigma_2^-$$

However, in a recent paper Dunn and Kung (4) showed that the ionization constants of sixteen 4- and 5-substituted salicylic acids in water at 25° are not correlated significantly better by eq. [3] than by eq. [1] (taking the 95% confidence level as the lower limit of significance).

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The two most obvious explanations for the failure of salicylic acids to obey eq. [3] are, first, that chelation is not a sufficiently strong interaction to appear as a second term in the Hammett equation and, second, that in aqueous solution intramolecular hydrogen bonds are replaced by intermolecular hydrogen bonds to the solvent. The object of our investigation was to test these two explanations by comparing the fit of eq. [1] and eq. [3] to the relative acidities of substituted salicylic acids in a solvent of low polarity, where intermolecular hydrogen bonding with the solvent is less likely and where spectrophotometric studies have shown chelation to exist (5, 6).

EXPERIMENTAL

Method

Relative strengths of the substituted acids were determined by titrating benzene solutions of the acids with tetrabutylammonium hydroxide in benzene containing 10% methanol by volume. The method is essentially that of Cundiff and Markunas (7). It has the disadvantage that the titrant must contain methanol to keep the base in solution, so that at the end point the solution being titrated is about 0.1 *M* in methanol. Obviously the alcohol can preferentially solvate the acids and their anions so that this method does not reduce the possibility of intermolecular hydrogen bonding to a minimum. However, it has the advantages that it is rapid, gives normal titration curves, and has been widely used. Most important of all, linear correlations have been found between the ionization constant in water and the potential at half neutralization for a large number of acids and bases in solvents with a wide range of dielectric constants, both protonic and aprotic (8–14).

Potential was followed during the titration with a Radiometer model 4C pH meter using a Radiometer G202B glass electrode and a K-100 calomel electrode containing KCl-saturated methanol in the salt bridge. About 1 mmole of the acid to be titrated was dissolved in 50 ml of benzene in a tall-form beaker and thermostatted at 25.0 ± 0.1°. The high electrical resistance of this solution was minimized by making the solution about 0.006 *M* in tetrabutylammonium iodide and by bringing the tips of the electrodes to within 1–2 mm of each other in the solution. The electrodes were shielded from stray electrical fields by a grounded steel cylinder which surrounded the titration beaker. The titrant, tetrabutylammonium hydroxide in benzene–methanol, was delivered from a 10 ml automatic buret protected from atmospheric moisture and carbon dioxide by Drierite- and Ascarite-filled tubes. Potentials were recorded after each addition of titrant and the results from a typical titration are shown in Fig. 1.

Materials

The 5-methyl-, 5-chloro-, 5-bromo-, 5-iodo-, 5-nitro-, and 4-nitro-salicylic acids, as well as salicylic acid itself, were commercial products, and the preparation of 4-methyl-, 4-cyano-, and 5-cyanosalicylic acids have been previously described (4). The 4-methoxy and 5-methoxy acids were prepared by methylating the corresponding hydroxy acids (15). All these acids were purified to constant melting point by recrystallization from water or aqueous ethanol. All melting points were determined with a Hershberg melting-point apparatus (16) using calibrated Anschütz thermometers.

4-Bromosalicylic Acid

This acid was prepared from 4-aminosalicylic acid by the Sandmeyer reaction. A solution of 18 g of sodium nitrite in 50 ml of water was added over a period of 1.5 h to 38.5 g of 4-aminosalicylic acid in 40 ml of water and 120 ml of 48% hydrobromic acid at 0°. The diazonium salt solution was poured into a cold solution of cuprous bromide prepared from 78 g of copper sulfate pentahydrate in 120 ml of 48% hydrobromic acid. The resulting mixture was stirred for 10 min and then warmed to 50° for 15 min. The solid product was filtered, dried, and extracted with ether. The ether extract was treated twice with charcoal and then evaporated, and the residue was recrystallized twice from water–ethanol. The yield of 4-bromosalicylic acid was 8 g (21%), melting at 212.6–214.0° (lit. (17) m.p. 212°).

4-Chlorosalicylic Acid

This acid was prepared by treating 4-chloroanthranilic acid with nitrous acid. Concentrated sulfuric acid was added slowly to a suspension of 10 g of 4-chloroanthranilic acid in 100 ml of water until the acid had completely dissolved. This solution was cooled to 0°, whereupon the sulfate salt partly precipitated, and 5.0 g of sodium nitrite in 15 ml of water was added dropwise over a period of 1 h. The resulting clear solution was poured into 200 ml of boiling water, cooled, and filtered. The residue was dissolved in ether, treated with charcoal, and extracted with aqueous sodium hydroxide. On acidification of the extract there was obtained, after recrystallization from water–ethanol, 1.5 g (15%) of 4-chlorosalicylic acid melting at 217.1–217.5° (lit. (18) 211°).

4-Fluorosalicylic Acid

This acid was prepared by oxidizing 4-fluorotoluene to 4-fluorobenzoic acid and then to 4-fluorosalicylic acid by the method of Kaeding and Collins (19). A suspension of 10 g of 4-fluorotoluene in a solution containing 10 g of magnesium sulfate and 45 g of potassium permanganate in 1.5 l of water was stirred at 75–80° for 2 days. The solution was treated with sodium bisulfite, filtered, and acidified. The yield was 6.5 g (51%) of 4-fluorobenzoic acid melting at 184–186° (unrecrystallized) (lit. (20) 186°).

A solution of 5.0 g of 4-fluorobenzoic acid in 100 ml of diphenyl ether was heated to 180° and 5.0 g of basic cupric carbonate (21) was added with

stirring. Stirring was continued at this temperature for 1.5 h, and then the mixture was cooled, diluted with ether, and filtered. The brown copper complex that remained was decomposed by treatment with HCl-saturated ether. The ether solution was filtered, washed with sodium bicarbonate solution and then with water, dried, and evaporated. The residue was a mixture of 4-fluorobenzoic and 4-fluorosalicylic acids. It was dissolved in 50 ml of chloroform and extracted with 200 ml of 0.3 *M* aqueous ferric chloride. The aqueous extract was re-extracted with three 30 ml portions of chloroform, acidified with HCl gas, and extracted twice more with 25 ml portions of chloroform. The two 25 ml extracts were combined and evaporated to dryness. The remaining chloroform solutions were combined and concentrated to 50 ml, and the whole extraction process was repeated. The two residues were combined and recrystallized from ethanol–water, in the presence of charcoal, to give 0.4 g (7%) of 4-fluorosalicylic acid melting at 188.2–189.8° (lit. (22) 185°). A mixture melting point with the 4-fluorobenzoic acid showed a 15° depression.

Tetrabutylammonium Hydroxide

The titrant was prepared using the method of Cundiff and Markunas (23) by treating 40 g of tetrabutylammonium iodide in 100 ml of absolute methanol with 21 g of silver oxide at 0° under nitrogen. The mixture was stirred for 2 h and filtered under nitrogen, and the filtrate made up to 1 l with dry benzene.

Benzene

Benzene was washed repeatedly with sulfuric acid and then with water till neutral, dried over sodium sulfate, and distilled, the low-boiling water azeotrope being discarded.

RESULTS

Titration curves of all the substituted acids resembled very closely the one shown for salicylic acid in Fig. 1. There is a small break near the middle of the vertical portion of the curve at the end point of the titration. It corresponds to a displacement in the lower half of the vertical portion of about 0.1 ml toward higher volume. This small break was found in the titrations of all substituted salicylic acids in benzene, but not in the titration of benzoic acid in benzene or of salicylic acids in water. No satisfactory explanation has been found for this behavior. The volume at the end point was taken from the vertical portion of the curve after the break and the half-neutralization potential (h.n.p.) was read from the curve at half this volume.

All previous workers in media of low dielectric constant have found that h.n.p.

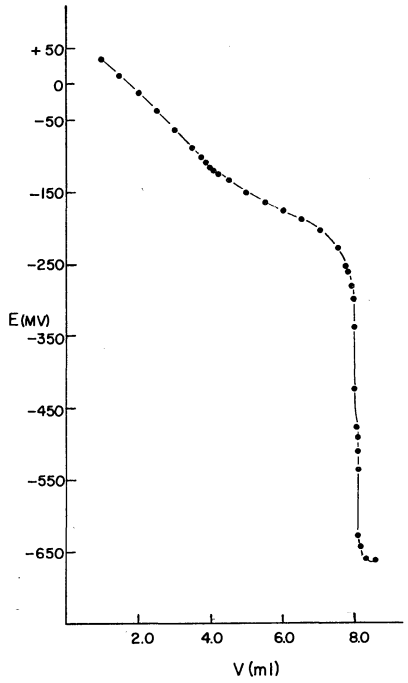

FIG. 1. Titration curve for salicylic acid in benzene–methanol.

varies from day to day with changes in liquid junction potentials and asymmetry potentials of the glass electrode. It is therefore common practice to designate one particular acid as a reference compound and to determine the h.n.p.'s of this acid and the one under investigation in immediate succession. The difference in half-neutralization potential (Δ_{hnp}) between the two acids is very nearly constant from day to day. In the present investigation, salicylic acid was taken as the reference acid and its h.n.p. was taken immediately before and immediately after that of each substituted salicylic acid. The maximum difference in h.n.p. for determinations on the same day was 6.2 mV and the average difference for 29 days was 2.4 mV. The standard deviation of h.n.p. from the mean is ± 1.5 mV, which is taken as the experimental uncertainty in h.n.p. This leads to an uncertainty of ± 3.0 mV in Δ_{hnp}. It was observed that, although h.n.p. for a given acid measured under the same conditions on different days could vary by as much as 12 mV, the maximum difference between

TABLE I

Effect of conditions on h.n.p. and Δ_{hnp} for substituted salicylic acids

Substituent	Acid ($M \times 10^3$)	Tetrabutylammonium iodide ($M \times 10^3$)	Methanol*	h.n.p.	Δ_{hnp}
5-Chloro	5.80	5.42	4.11	−80.9	+70.7
	14.48	5.42	6.41	−38.4	+72.6
	14.55	5.46	6.49	−50.1	+70.1
4-Methoxy	5.83	5.47	4.16	−192.8	−41.2
	7.31	2.72	3.83	−172.0	−43.2
	7.18	2.73	3.71	−179.3	−48.7
	14.56	5.47	6.43	−163.3	−43.1
5-Cyano	5.79	5.42	3.75	−8.0	+145.2
	5.82	5.45	3.78	−10.7	+141.6
	14.49	5.48	8.75	+40.5	+147.3

*$10^3 \times$ ml methanol/ml solution at the half-neutralization point.

Δ_{hnp}'s measured on different days was 6.2 mV, which is just outside the combined uncertainties in the two measurements.

The value of h.n.p. for a given acid has been reported to depend upon the concentration of the acid solution being titrated (24), and this was found to be the case in the present investigation. A few acids were not sufficiently soluble to dissolve in the 50 ml of benzene specified in the Experimental section, and for these 100 ml of benzene was used. This meant that the concentration of methanol at the half-neutralization point and the ratio of tetrabutylammonium iodide to acid were significantly different for these acids than for the others, so in each case h.n.p. for the reference acid was determined under the same conditions as those used for the substituted acid. Table I shows the effects of the maximum variation of these factors encountered in this investigation.

TABLE II

Mean values of Δ_{hnp} for substituted salicylic acids

Substituent	Number of determinations	Δ_{hnp} (mV)	Standard deviation
4-Methoxy	6	−43.2	2.7
4-Methyl	5	−34.6	1.8
5-Methyl	4	−21.6	2.8
5-Methoxy	4	+0.6	2.5
4-Fluoro	3	+37.6	1.5
5-Fluoro	6	+57.5	2.9
4-Chloro	6	+60.4	3.0
4-Bromo	4	+70.3	1.7
5-Iodo	5	+71.1	3.0
5-Chloro	6	+72.8	2.1
5-Bromo	4	+76.8	2.1
4-Cyano	2	+133.6	0.8
4-Nitro	4	+138.5	1.3
5-Cyano	6	+145.4	2.1
5-Nitro	5	+179.8	2.7

Since the h.n.p. values were determined on different days, they may be expected to differ by as much as 12 mV even under the same conditions. However, Table I shows that changes in titration conditions produce much larger changes in h.n.p. than this. On the other hand, only one Δ_{hnp} value (−48.7 mV for 4-methoxy) differs from the others by more than their combined uncertainties of 6.0 mV. Since this value was not obtained under extreme conditions, and since another determination under the same conditions gave a value (−43.2 mV) much nearer the average, it is very unlikely that the former value represents a significant result of changes in conditions. It should, therefore, be safe to assume that the final values of Δ_{hnp} reported in Table II are not affected by the much smaller range of conditions used in their determination.

DISCUSSION

In the present work no attempt has been made to interpret h.n.p. as a function of ionization or dissociation of an acid. Figure 1 shows that the titration curves for salicylic acids in benzene–methanol are very similar to those observed for other carboxylic acids in other organic solvents (7, 46) and not very different from those of weak acids in water. Whether the species affecting the glass electrode are solvated protons, ion pairs, undissociated acid molecules, or

all three of these is not of prime importance for our purpose. What is of importance is that Δ_{hnp} should be a measure of electronic influences on the carboxyl group produced by the 4- and 5-substituents of aromatic acids. In aqueous solution this, of course, is the case, since h.n.p. is then proportional to pK of the acid. That it is also the case in nonaqueous solvents is shown by the many instances where Δ_{hnp}'s obtained in such solvents have been shown to be linearly related to pK's of the acids in water (8–14) and, in particular, by those instances where Δ_{hnp}'s of 4- and 5-substituted benzoic acids in solvents such as chloro- and bromobenzene have been shown to obey the Hammett relationship (11).

The presence of a constant 2-substituent, such as alkyl or halogen, in a series of 4- and 5-substituted benzoic acids has been shown (25) not to produce significant deviations of ionization constant from the simple Hammett relationship (eq. [1]). It would therefore be expected that Δ_{hnp}'s of such ortho-substituted acids in nonaqueous solvents should also obey eq. [1], and this has been shown for certain mixed aqueous–organic solvents (26). However, in salicylic acid, where a large part of the acid strength is caused by chelation, it would be expected that the electronic influences of 4- and 5-substituents would be exerted on the carboxyl group not only directly through the aromatic ring but also through an increase or decrease in the strength of the intramolecular hydrogen bond. It would therefore be expected that Δ_{hnp} for substituted salicylic acids should fit eq. [3] rather than eq. [1].

It should be noted, however, that eq. [1] is just a special case of eq. [3], so that they will not be distinguishable if σ_1 and σ_2^- are linearly correlated. Jaffe (2) has suggested that the correlation coefficient between σ_1 and σ_2^- can be no larger than 0.9 if the equations are to be distinguished. For the 15 acids used in this investigation the linear correlation coefficient between σ_1 and σ_2^- is 0.756.

Figure 2 shows a plot of Δ_{hnp} against σ_1 as required by eq. [1]. The line was obtained by fitting the data to eq. [1] by the least-squares method (27) and corresponds to $\rho = 220 \pm 16$.[3] The external estimate of error[4] (s_{ext}) in Δ_{hnp} is 18.4. A least-squares fit (27) of the same data to eq. [3] gives $\rho_1 = 148 \pm 10$, $\rho_2 = 59.3 \pm 7.8$, and $s_{ext} = 7.9$. All σ values are from the compilation by Hine (28) and, where σ and σ^- differ, the latter is used for σ_2. Figure 3 shows a plot of the experimental Δ_{hnp}'s against those calculated from eq. [3] using the above values for ρ_1 and ρ_2. It is clear that eq. [3] gives a distinctly better fit to the data than does eq. [1]. This is evidenced by the smaller external estimate of error for eq. [3] and by the fact that Student's t-test (27) shows ρ_2 to be different from zero at better than 99.9% confidence level. The better fit of the data to eq. [3] makes it clear that Jaffe's equation *can* be used to detect transmission of substituent effects through the ortho-hydroxy group of salicylic acids.

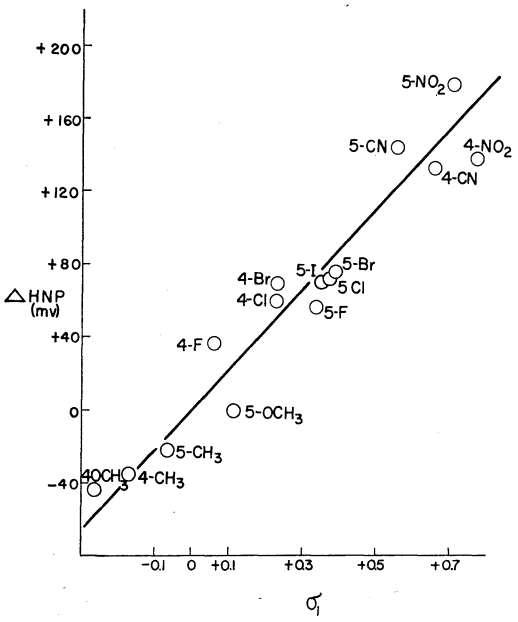

FIG. 2. Data from Table II plotted by eq. [1].

[3]Numbers following ± are standard deviations.

[4]The external estimate of error, s_{ext}, is given by $s_{ext}^2 = \sum(y - \tilde{y})^2/n$, where y is Δ_{hnp} observed, $\tilde{y}$ is Δ_{hnp} calculated from the equation, and n is the degrees of freedom.

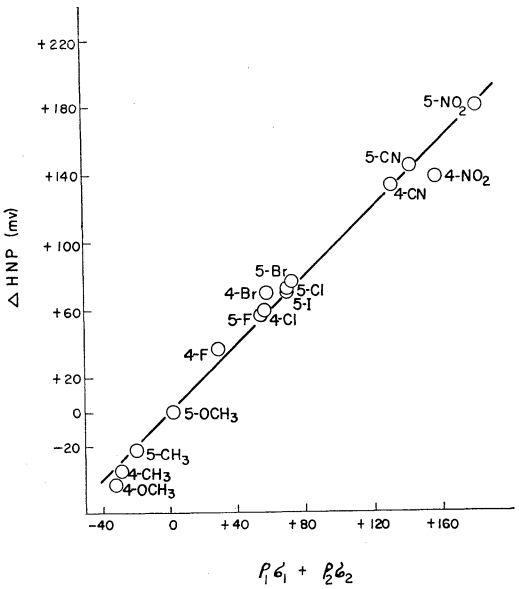

FIG. 3. Data from Table II plotted by eq. [3].

With this established, it is interesting to compare the behavior of the Δ_{hnp}'s of salicylic acids in benzene–methanol with that of their ionization constants in water previously reported (4). In the nonaqueous medium $\rho_2/\rho_1 = 0.4$, indicating that nearly a third of the substituent effect is transmitted to the carboxyl group through the phenolic linkage. In water, on the other hand, ρ_2 is hardly outside the experimental uncertainty and $\rho_2/\rho_1 = 0.1$, showing that little or no substituent effect reaches the carboxyl group by the indirect route. This suggests very strongly that intramolecular hydrogen bonding is much less important in aqueous solution than it is in benzene–methanol.

It is entirely reasonable to suppose that hydrogen-bonded chelation should compete less effectively with intermolecular hydrogen bonding as the solvent becomes more capable of forming hydrogen bonds. There is, in fact, considerable evidence that this is so. The change in nuclear magnetic resonance shifts for *o*-nitrophenols as the solvent is changed from chloroform to acetone is attributed to less chelation in the latter solvent (30). Similarly, the anomalously low acidities of 2,4- and 2,5-dinitrophenols in benzene relative to those in water are attributed to chelation in the former solvent (31). Differential vapor pressure studies of *o*-nitrophenol show it to be chelated in ethylene chloride (32), whereas other studies show little or no chelation in water (33). The activation energy for rotation of the phenolic hydroxyl group in salicylaldehyde has been shown by nuclear magnetic resonance to decrease as the solvent is changed from benzene to acetone to dimethylsulfoxide (34). Infrared studies show that both maleic acid (35) and its monoanion (36) have strong intramolecular hydrogen bonds in the solid; in dimethylformamide nuclear magnetic resonance evidence shows chelation of the monoanion but not of the acid (37); in deuterium oxide infrared spectra show chelation of the anion to be weak (38); and in dioxane chelation has disappeared completely (39).

Intramolecular hydrogen bonding in salicylic acid has been demonstrated for the solid acid by X-ray crystallography (40) and for solutions of the acid in cyclohexane, ether, and carbon tetrachloride by ultraviolet and infrared spectra (5, 6, 41, 42) and in benzene by ^{13}C nuclear magnetic resonance shifts (43). The extent of chelation was shown to be measurably less in benzene than in carbon tetrachloride solution (42). The fact that the acidity of salicylic acid decreases less rapidly than that of *p*-hydroxybenzoic acid as the ethanol content of mixed ethanol–water solvents is increased has been interpreted as the result of a solvent-independent chelation in the salicylate ion (44), but it could equally well be the result of increased chelation in the less aqueous solvents. The only evidences that intramolecular hydrogen bonding persists in aqueous solutions of salicylic acid or its anion are the original argument from its large ionization constant (1) and the infrared spectra of the acid and its anion in deuterium oxide solution (39). The latter have been interpreted as showing a strong intramolecular hydrogen bond in both the acid and the anion.

The conclusion that a strong hydrogen bond exists in aqueous solutions of salicylic

acid and (or) salicylate ion is very difficult to reconcile with the results of the present investigation. In particular, it is difficult to account for the 40-fold difference in ionization constant between salicylic and *p*-hydroxybenzoic acids if chelation is weak in aqueous solution. However, the effect of ortho-substituents on the ionization of benzoic acids is complex and not yet completely understood. A deficiency of current theory may be seen in the following example. All ortho-substituted benzoic acids are stronger than their para isomers, and this is currently attributed to destabilization of the un-ionized acid by steric interference with conjugation between the carboxyl group and the aromatic ring (39, 45). However, the ionization constants of 4-substituted 2,6-dimethylbenzoic acids obey the Hammett relationship as well as do those of 4-substituted benzoic acids, even when strongly conjugating substituents such as 4-methoxy and 4-nitro are used (26, 27). To accommodate these observations one must conclude that ortho-methyl groups interfere with conjugation between the carboxyl group and the aromatic ring but not with conjugation between the carboxyl group and a para-substituent. Evidently ortho-substituent effects are the result of several competing and sometimes conflicting factors. Perhaps, then, it is a serious oversimplification to attribute the unusual acid strength of salicylic acid to intramolecular hydrogen bonding alone.

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