SEPARATION OF INDUCTIVE AND RESONANCE EFFECTS

by

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STATEMENT BY AUTHOR

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FOREWORD

The author wishes to thank Dr. John P. Schaefer for his understanding guidance of this research, and, above all, for his patience. The author wishes to acknowledge the California Research Corporation for supporting this investigation in part.

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ABSTRACT

A series of 3,5-dimethyl-4-substituted benzoic acids has been prepared and a study made of their ionization constants. A satisfactory Hammett correlation was obtained with the compounds containing small 4-substituents. For the compounds with bulky 4-substituents a degree of steric inhibition of resonance of the order of 70% was calculated. Evidence was obtained supporting the additivity of σ values in the Hammett Equation and for a low steric requirement of the proton.

INTRODUCTION

The free energy change for a reaction depends on both a potential energy term and a kinetic energy term.[1] The kinetic energy is constant in a reaction series properly planned and run, and the change in log (k/k_o), which is a measure of the free energy change, is dependent on the change in the potential energy term. Any or all of four factors, not separable by thermodynamic methods, may contribute to the potential energy term: (1) polar interactions, (2) resonance interactions, (3) steric interactions, and (4) potential energies of solvation. These four factors are basically electrical interactions, either of attraction or repulsion.

Polar interactions are associated with coulombic forces which result from charge separation within the substituent and the functional center. They require a σ bond or space for their transmission. The separation of charges can result from differences in electronegativities of the atoms involved, resonance interactions, or poles (unit electrical charges) within the substituent or the functional center.

Resonance interactions require a quantum-mechanical description. A resonance interaction is an interaction that requires at least two valence bond structures for the adequate description of a bond.

Steric interactions result from van der Waal's type forces. The interaction may be one either of attraction or repulsion, but the latter is generally involved in considerations of reactivity. Angle strain energies are usually classified as steric interactions.

Potential energies of solvation make up the fourth factor in the potential energy term. These energies may be directly related to any or all of the other three factors, or may be more specific solvation interactions.

Resonance within the substituent may lead to a resonance contribution to the polar effect of the substituent. That is, in aromatic systems the resonance of the substituent with the benzene ring contributes indirectly (by induction) to determining the net electron density at the functional center. Hence the polar effect may be regarded as being made up of a resonance contribution and an inductive contribution, the latter being considered to arise from a polar interaction referred to a given site in the substituent.

The present work, which concerns the preparation of a series of 3,5-dimethyl-4-substituted benzoic acids and a study of their ionization constants, was undertaken as an attempt to provide a critical test of the quantitative values ascribed in the literature to resonance and inductive contributions to the polar effect. In addition, the ionization constants of these compounds with their para-substituent and two meta-substituents provide a check on the validity of the additivity of σ values in the Hammett Equation. The ionization constants of some compounds, notably the hydroxy- and amino-compounds, also provide valuable information relating to the steric requirement of the proton.

HISTORY

The most general relationship known for the effect of substituents on rates and equilibria in aromatic systems is the Hammett Equation[2]

$$\log (k/k_o) = \rho\sigma$$

where σ is a parameter characteristic of the substituent and ρ is a constant dependent on the nature of the reaction. Sigma is a quantitative measure of the polar effect that a given substituent has on a meta or para reaction site in a benzene ring. Hammett originally defined σ as equal to $\log (K/K_o)$ for the ionization of substituted benzoic acids in water at 25°, where the subscript zero refers to the unsubstituted benzene derivative. Rho is a quantitative measure of the susceptibility of a given reaction series to polar substituents.

The fundamental principle upon which the Hammett Equation rests is the postulate that the effect of structure on rates and equilibria is usually determined only by the polar effect of the substituent.[3] That is, in a given reaction series the free energy change caused by varying the substituent depends only on the differences in the polar effects of the substituents, and that the resonance, steric, and solvation contributions to the potential energy term are constant.

This postulate holds only in reaction series which meet the following conditions: (1) there is no steric interaction between the substituent and the reaction center, (2) there is no unusual resonance interaction between the substituent and the reaction center, (3) there is no neighboring group participation, and (4) there is no change of reaction mechanism. Any failure of the Hammett Equation can usually be traced to a reaction series in which one or more of these conditions have not been met.

Jaffe's comprehensive review[4] showed that experimentally measured rate and equilibrium constants for 3180 reactions followed the Hammett Equation with a median precision of $\pm 15\%$. This widespread applicability of the Hammett Equation supports the fundamental postulate upon which it is based.

Any method designed to achieve the separation of resonance and inductive polar effects must take into account all factors which contribute to the potential energy term (the kinetic energy change is constant in a reaction series). The success of the Hammett Equation indicates that the only variable in a properly-run reaction series is the polar effect and the problem becomes one of devising reaction series where either the resonance polar effect or the inductive polar effect will be eliminated. Then the σ values obtained for the substituent in the reaction series will be a measure only of the other effect, and comparison with the normal σ value will give a quantitative measure of the relative importance of each effect.

Roberts and Moreland[5] prepared a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and their esters and measured k/k_o for three reactions. The reaction rates of each of the different compounds were found to parallel one another throughout the series. Since the compounds contained no unsaturation, the only effect the substituents could exert was an inductive polar effect.

The results obtained by Roberts and Moreland show that there is a definite contribution of the resonance polar effect to the total polar effect. In every case the σ' is closer to the Hammett σ_m than to the σ_p, as would be predicted from π-bond resonance theory.

In 1930 Ingold[6] proposed that the ratio of rate constants (k_B/k_A) of alkaline to acidic hydrolysis of an ester is a function only of the polar effect, although each taken by itself might be affected by other effects.

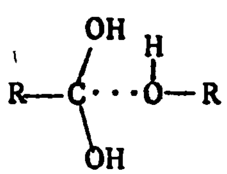
Following along the lines of Ingold's proposal, Taft[7] formulated the following equation for the normal hydrolysis of esters.

$$\sigma^* = (1/2.48)[\log (k/k_o)_B - \log (k/k_o)_A]$$

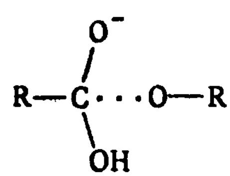
σ^* is analogous to the Hammett substituent constant but expressed with an asterisk to denote its different nature and origin [i.e., $\sigma^* \neq \log (K/K_o)$ for the ionization of carboxylic acids]. To adjust the σ^* values onto approximately the same scale as the Hammett σ values, Taft introduced the factor 2.48.

The Taft Equation involves three basic assumptions. (1) The relative free energy of activation ($\therefore \log k/k_o$) for these reactions may be treated as the sum of independent contributions from polar, resonance, and steric effects. (2) In corresponding acidic and alkaline reactions, the steric and resonance effects are the same. (3) The polar effects of substituents are markedly greater in the alkaline than in the acidic series.

The accepted mechanism of ester hydrolysis[8] supports assumption (2) regarding steric effects.



Acidic Transition State



Basic Transition State

The two transition states differ only in the presence of two small protons, so the substituent steric effects must be very nearly equal.

The mechanism also supports assumption (2) regarding resonance effects. A resonance effect would arise from conjugation between the substituent and the ester function in the transition state. However, both transition states are saturated with respect to such conjugation.

The Hammett reaction constants ρ supports assumption (3). For the reaction of meta- and para-substituted benzoates, $\rho_B = +2.2 - +2.8$, $\rho_A = -0.2 - +0.5$.[9]

Perhaps the most striking confirmation of both Taft's σ^* values and Roberts and Moreland's σ' values comes from a comparison of the two. Because of the availability of the data, Taft gave his σ^* values for $-CH_2X$ whereas Roberts and Moreland's data are for simply -X. The average value for the ratio σ'/σ^* was found to be 0.450,[10] and no significant deviation from this value was observed.

DISCUSSION

I. Preparation of Compounds

All of the compounds used in this study were synthesized from mesitylene (1). Nitration of 1 gave nitromesitylene (2) which on oxidation with chromic acid gave 3,5-dimethyl-4-nitrobenzoic acid (3). Reduction of 3 with hydrogen in the presence of rhodium-carbon catalyst gave 3,5-dimethyl-4-aminobenzoic acid (4) which was acetylated to the N-acetyl derivative (5) and alkylated with a formic acid-formaldehyde solution to produce 3,5-dimethyl-4-dimethylaminobenzoic acid (6).

Diazotization of 4 followed by decomposition of the diazonium salt gave the 4-chloro- (7), 4-bromo (8), 4-cyano- (9), and 4-hydroxy- (10) derivatives of 3,5-dimethylbenzoic acid. Alkylation of 10 with ethyl iodide resulted in formation of 3,5-dimethyl-4-ethoxybenzoic acid (11) after hydrolysis of the ethyl ester.

Acetylation of mesitylene with acetic anhydride and aluminum chloride followed by vigorous oxidation gave a low yield of 3,6-dimethylterephthalic acid (12) which was converted to the dimethyl ester and partially saponified by 3,5-dimethyl-4-carbomethoxybenzoic acid (13). Oxidation of mesitylene with nitric acid gave 3,5-dimethylbenzoic acid.

Ionization constants of the carboxylic acids were measured potentiometrically in 50% by volume aqueous ethanol and are tabulated in the first column in Table 1.

II. Results

In Figure 1, the observed pK_a's have been plotted as a function of $\Sigma\sigma$. The Hammett Equation predicts that the points obtained in such a plot will lie on a straight line with ρ, for this reaction,[11] equal to 1.522. It is apparent from Figure 1 that, with the exception of 3,5-dimethylbenzoic acid, the compounds with small, symmetrical, 4-substituents do follow the predicted Hammett correlation. However, definite deviations are noted for those compounds with bulky 4-substituents. The presence of the two methyl groups ortho to the larger substituents has caused them to twist out of the plane of the ring thereby diminishing the resonance contribution to their total polar effect. For those compounds containing large 4-substituents, $\Sigma\sigma$ is not an accurate measure of the total polar effect, and deviations from a Hammett correlation should be expected.

The departures from the linear relationship are in the direction that classical theory would predict. The $-NO_2$, $-COOCH_3$, and $-COO^-$ substituents are electron withdrawing groups and inhibition of resonance should make the corresponding acids weaker than the linear plot would suggest.

TABLE 1.--Ionization Constants and Sigma Values for 3,5-Dimethyl-4-substituted Benzoic Acids.

4-Substituent	pK_a [a]	σ [b]	$\Sigma\sigma$ [c]	σ_c [d]	$\Delta\sigma$ [e]	σ_r [f]
CN	4.90 ± .01	+0.66	+0.52	+0.53	-0.01	+0.08
NO_2	4.91 ± .01	+0.78	+0.64	+0.53	+0.11	+0.15
$COOCH_3$	5.44 ± .01	+0.45	+0.31	+0.18	+0.13	+0.15
Br	5.56 ± .01	+0.23	+0.09	+0.10	-0.01	-0.22
Cl	5.59 ± .01	+0.23	+0.09	+0.08	+0.01	-0.24
$NHCOCH_3$	5.68 ± .01	0.00	-0.14	+0.02	-0.16	-0.28
Benzoic Acid	5.71 ± .03					
H	6.00 ± .01	0.00	-0.14	-0.19	+0.05	(0.00)
OC_2H_5	6.02 ± .01	-0.24	-0.38	-0.20	-0.18	-0.49
COO^-	6.21 ± .02	0.00	-0.14	-0.33	+0.19	
$N(CH_3)_2$	6.23 ± .01	-0.83	-0.97	-0.34	-0.63	-0.93
OH	6.46 ± .01	-0.37	-0.51	-0.49	-0.02	-0.62
NH_2	6.86 ± .02	-0.66	-0.80	-0.76	-0.04	-0.76

[a] All measurements are in 50% by volume ethanol-water and are uncorrected for liquid junction potentials.

[b] Sigma values are taken from the compilations of McDaniel and Brown[11] based on the ionization of benzoic acids.

[c] To obtain $\Sigma\sigma$, -0.14 [$= 2 \times (\sigma_p)_{CH_3}$] was added to the sigma value of the substituent.

[d] The experimentally determined pK_a's and a ρ value of 1.522[11] were substituted into the Hammett Equation to obtain σ_c.

[e] To obtain $\Delta\sigma$, σ_c was subtracted from $\Sigma\sigma$.

[f] To obtain σ_r, σ_I, as given by Taft and Lewis,[12] was subtracted from σ.

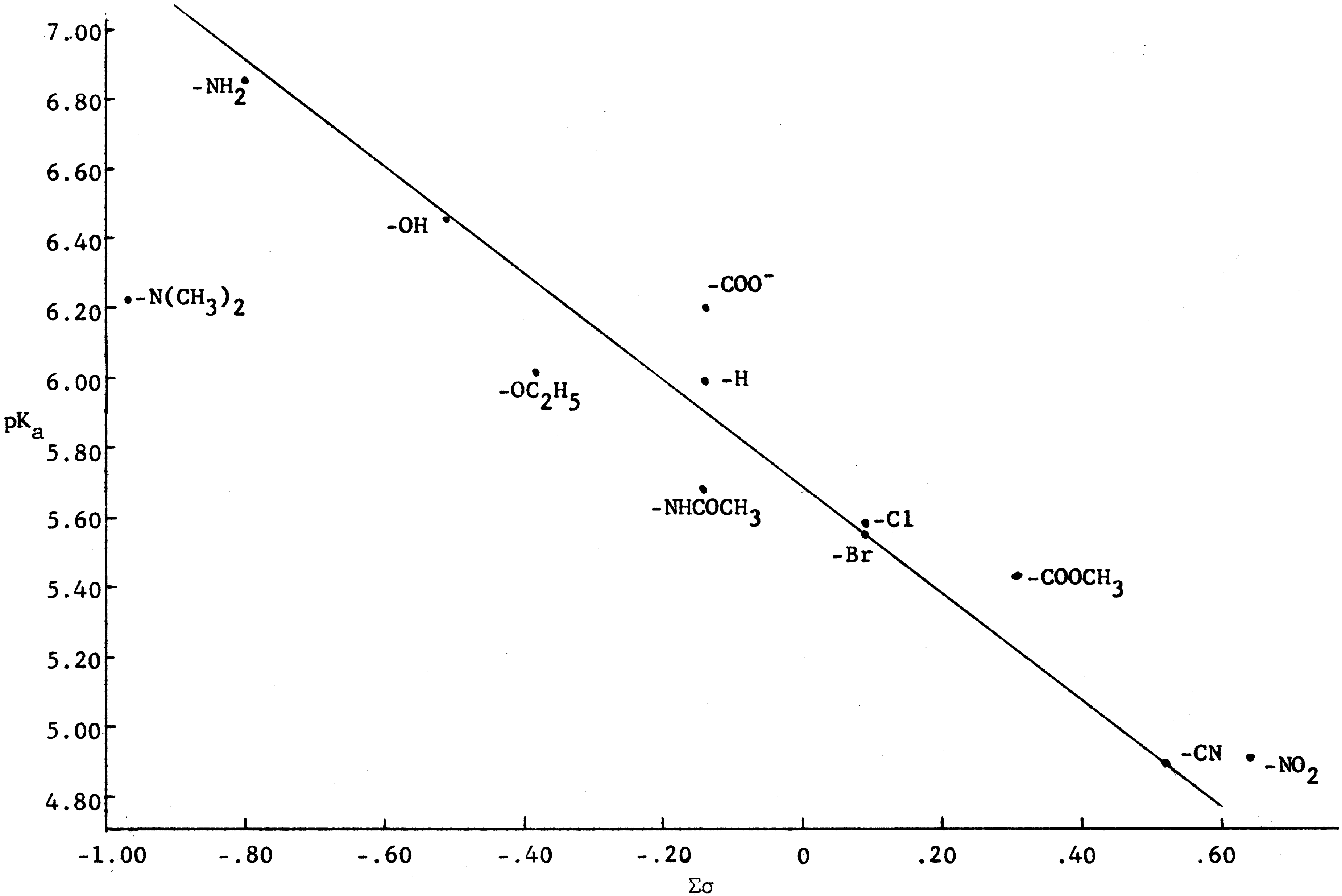


Figure 1.--Plot of pK_a vs. $\Sigma\sigma$.

Conversely, the $-N(CH_3)_2$, $-OC_2H_5$, and $-NHCOCH_3$ groups are electron donating groups and resonance inhibition should make the corresponding acids stronger. It is evident from Figure 1 that these effects are actually observed.

The last two columns of Table 1 list values for $\Delta\sigma$ and σ_r. As calculated, $\Delta\sigma$ is the change in the polar effect due to steric inhibition of resonance in the 4-substituent. That is, it is the resonance contribution to the polar effect that has been eliminated by the resonance inhibition caused by the ortho methyl groups. The σ_r values are the resonance contributions to the total polar effect as calculated from Taft and Lewis σ_I values.[12] Although the $\Delta\sigma$ and σ_r values show good agreement for the $-NO_2$ and $-COOCH_3$ groups, serious deviations are observed for the $-NHCOCH_3$, $-OC_2H_5$, and $-N(CH_3)_2$ groups. (No σ_I values are available for the COO^- ion so comparison is not possible at this time.)

Taft's σ_r values have been plotted against the experimentally-determined $\Delta\sigma$ values in Figure 2. An excellent correlation is observed; four of the five points of interest--and the origin--lie within 0.02 σ units of a straight line.

The resonance contribution to the polar effect observed in the present study is not the same as that observed by Taft and by Roberts, as evidenced by the differences between $\Delta\sigma$ and σ_r, but the linear correlation of Figure 2 suggests that the observed $\Delta\sigma$ values are proportional to

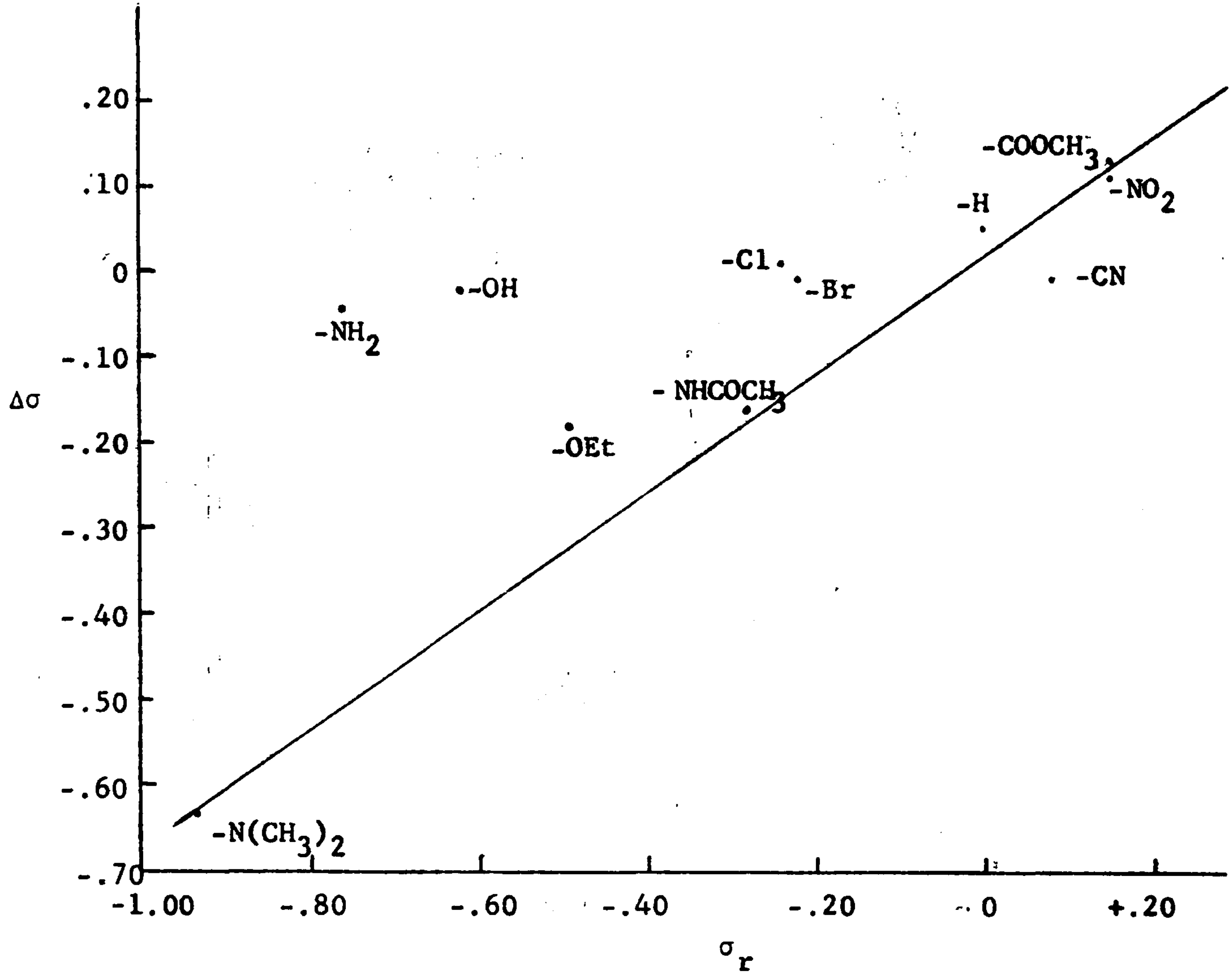


Figure 2.--Plot of σ_r vs. $\Delta\sigma$.

the σ_r values of Taft. This must mean that the proportion of σ_r actually eliminated by forcing the 4-substituent out of the plane of the ring is constant in these four compounds. The proportion of resonance inhibition in these compounds is about 70%.

The observed data, as plotted in Figure 1, provide a favorable check on the validity of the additivity of σ values in the Hammett Equation. The reaction center is influenced by the polar effects of three substituents and yet five out of the six expected points give, within experimental error, a linear plot with the right slope. This indicates that, in proper reaction series, $\log (k/k_o) = \rho\Sigma\sigma$ is a valid form of the Hammett Equation.

That the amino and hydroxy compounds lie on the line lends specific information relating to the steric requirement of the proton. It is apparent from the σ_I values obtained by Taft and Lewis[13] that the resonance contribution is the major factor in the polar effect of both the hydroxy and amino groups. Both Hammond[14] and Wepster[15] have criticized Brown for assigning a significant effect to the steric requirements of the proton in Brown and coworkers'[16] studies of aniline and anilinium compounds. No steric inhibition of resonance has been observed for the hydroxy and amino compounds in the present study, thus supporting the criticism. Although the free amine, and not an anilinium ion or compound, was examined, the same conclusion should apply, for the change in bonding from sp^2 to sp^3 should result in the $-NH_3^+$ being of smaller effective size than the free $-NH_2$ group.[17]

EXPERIMENTAL

I. Preparation of Compounds

A. Nitromesitylene

Mesitylene was nitrated according to the procedure given in "Organic Syntheses."[18] The quantities given were quadrupled, and the air-dried product obtained from the steam distillation was used without further purification.

B. 3,5-Dimethyl-4-nitrobenzoic Acid

In a 1-l., 3-neck flask fitted with a stirrer, dropping funnel and condenser was added a mixture of 64 g. of nitromesitylene, 300 ml. of glacial acetic acid, and 80 ml. of concentrated sulfuric acid, the mixture heated to reflux and the dropwise addition of a solution of 120 g. of chromium trioxide in about 400 ml. of water begun. The dropping rate was continually adjusted to maintain a moderate reflux and the stirring was continued for 30 minutes after the addition of the chromium trioxide solution had been completed. The reaction mixture was poured onto about 750 cc. of ice and cooled in an ice bath with intermittent stirring. The cold mixture was filtered by suction and the solid washed well with 500-1000 ml. of water until the filtrate was clear. The solid was placed in 100 ml. of 10% sodium hydroxide solution, stirred well, and the mixture was filtered by suction. The residue, after thorough washings with water and 10% sodium hydroxide solution, was steam distilled from basic solution to recover more starting material. The filtrate was acidified with 100 ml. of 6 N hydrochloric acid solution, cooled in an ice bath, and the cold mixture was filtered by suction to collect the precipitate. Repeated recrystallizations of the crude product from 95% ethanol solution yielded 8-15 g. of very faintly yellow crystals, m.p. 225.5-227° (lit.[19] 212-217°). <u>Anal.</u> Calcd. for $C_9H_9O_4N$: eq. wt., 195. Found: 197 ± 4.

C. <u>3,5-Dimethyl-4-aminobenzoic Acid</u>

A mixture of 20 g. of 3,5-dimethyl-4-nitrobenzoic acid, 0.5 g. of 5% rhodium on carbon catalyst, and about 300 ml. of 95% ethanol solution was heated until all of the acid had dissolved. The black suspension was placed in a Paar Pressure Reaction Apparatus and shaken with hydrogen until the stoichiometric amount had been taken up (three moles of hydrogen per mole of starting material). When reaction was complete, the reaction mixture was poured into 500 ml. of 95% ethanol solution, the mixture heated to dissolve the white solid, and the resulting suspension filtered by gravity. Concentration of the filtrate and repeated recrystallizations yielded 6-8 g. of long white needles, m.p. 257-257.5° dec. (lit.[20] 242°). <u>Anal.</u> Calcd. for $C_9H_{11}O_2N$: eq. wt., 165. Found: 166 ± 1.

D. <u>3,5-Dimethyl-4-N-acetylaminobenzoic Acid</u>

A solution of 5 g. of 3,5-dimethyl-4-aminobenzoic acid, 20 ml. of acetic anhydride, and 300 ml. of benzene was refluxed for 24 hours. The reaction mixture was cooled in an ice bath and the mixture filtered by suction to collect the precipitate. Recrystallizations from 95% ethanol solution yielded about 1.5 g. of long white needles, m.p. 270-272.5°. <u>Anal.</u> Calcd. for $C_{11}H_{13}O_3N$: eq. wt. 207. Found: 209 ± 1.

E. <u>3,5-Dimethyl-4-dimethylaminobenzoic Acid</u>

A mixture of 5 g. of 3,5-dimethyl-4-aminobenzoic acid, 15 ml. of 40% aqueous formaldehyde, and 300 ml. of formic acid was refluxed for 12 hours. The solution was cooled to room temperature and 10 ml. of concentrated hydrochloric acid added. The excess solvent was removed by distillation under reduced pressure. The residue was neutralized with 10% sodium hydroxide solution and the mixture was filtered by suction to collect the precipitate. The crude product was recrystallized from 95% ethanol solution yielding about 1.5 g. of colorless, clear crystals, m.p. 186.5-190.5° dec. <u>Anal.</u> Calcd. for $C_{11}H_{15}O_2N$: eq. wt., 193. Found: 195 ± 1.

F. <u>3,5-Dimethyl-4-bromobenzoic Acid</u>

1. <u>Preparation of Cuprous Bromide Solution</u>.--Twelve grams of anhydrous copper sulfate was hydrated and pulverized

in about 35 ml. of water. To this solution was added 10.5 g. of sodium bromide and the mixture was warmed. Six grams of sodium bisulfite was dissolved in about 45 ml. of 10% sodium hydroxide solution and this alkaline solution was added dropwise to the warm copper sulfate-sodium bromide solution until the green color had been discharged. The white precipitate was filtered by gravity from the mixture and immediately dissolved in 35 ml. of 48% hydrobromic acid solution.

2. Diazotization and Bromination of 3,5-Dimethyl-4-aminobenzoic Acid.--A suspension of 5 g. of the amine in 50 ml. of 48% hydrobromic acid solution was heated until the solution became clear, and cooled by addition of ice and immersion in an ice bath. A solution of 2.1 g. of sodium nitrite in 35 ml. of water was added dropwise with stirring to the cold amine solution. The cuprous bromide-hydrobromic acid solution was added rapidly and with stirring to the diazotized solution. The reaction mixture was left in the ice bath for about 15 min., with intermittent stirring, and allowed to stand at room temperature for 3 hrs. The reaction mixture was boiled for 3 min., cooled overnight, and poured into 300 ml. of water. The mixture was filtered by suction and the crude product washed well on the filter. Repeated recrystallizations from 95% ethanol solution yielded about 1.5 g. of white crystals, m.p. 219.5-220.5°

(lit.[21] 214-215°). Anal. Calcd. for $C_9H_9O_2Br$: eq. wt., 229. Found: 229 ± 1.

G. 3,5-Dimethyl-4-chlorobenzoic Acid

The procedure given for the preparation of 3,5-dimethyl-4-bromobenzoic acid was used. (Six grams of sodium chloride was used instead of 10.5 g. of sodium bromide, and concentrated hydrochloric acid was used instead of 48% hydrobromic acid solution.) Repeated heating with decolorizing charcoal in 95% ethanol solution and repeated recrystallizations from 95% ethanol solution yielded about 0.8 g. of white crystals, m.p. 217.5-218.5° (lit.[22] 220°d). Anal. Calcd. for $C_9H_9O_2Cl$: eq. wt., 184.5. Found: 185 ± 1.

H. 3,5-Dimethyl-4-cyanobenzoic Acid

1. Preparation of Cuprous Chloride Solution.--A solution of 2.1 g. of sodium bisulfite and 1.4 g. of sodium hydroxide in 20 ml. of water was added slowly and with stirring to a solution of 9.5 g. of copper sulfate hydrate and 2.5 g. of sodium chloride in 31 ml. of hot water. The mixture was cooled to room temperature and the residue washed by decantation and dissolved in 16 ml. of water.

2. Preparation of Cuprous Cyanide Solution.--Five grams of sodium cyanide in 8 ml. of water was added to the cuprous chloride solution slowly and with stirring.

3. Diazotization and Nitrilation of 3,5-Dimethyl-4-aminobenzoic Acid.--A suspension of 5 g. of the amine in 50 ml. of concentrated sulfuric acid was heated until the solution became clear, and cooled by addition of ice and immersion in an ice bath. A solution of 2.2 g. of sodium nitrite in 10 ml. of water was added dropwise with stirring to the cold amine solution. The solution was neutralized to litmus by addition of about 300 g. of anhydrous sodium carbonate. The cooled cuprous cyanide solution was rapidly added with stirring to the diazotized solution. The reaction mixture was allowed to warm to room temperature, with intermittent stirring, and to stand overnight. The reaction mixture was poured into 300 ml. of water and enough 6 N hydrochloric acid solution was added to effect complete precipitation. The crude product was filtered by suction and washed well on the filter. Repeated heating with decolorizing charcoal in glacial acetic acid and repeated recrystallizations from glacial acetic acid yielded about 0.4 g. of white needles, m.p. 216.5-218°. Anal. Calcd. for $C_{10}H_9O_2N$: eq. wt., 175. Found: 175 ± 1.

I. 3,5-Dimethyl-4-hydroxybenzoic Acid

A suspension of 5 g. of 3,5-dimethyl-4-aminobenzoic acid in 50 ml. of concentrated sulfuric acid was heated until the solution became clear, and cooled by addition of ice and immersion in an ice bath. A solution of 2.2 g.

of sodium nitrite in 10 ml. of water was quickly added with stirring to the cold amine solution and the stirring continued for about 5 min. The reaction mixture was removed from the ice bath, heated nearly to boiling, and allowed to cool to room temperature. The mixture was filtered by suction and the crude product washed well on the filter. Repeated heating with decolorizing charcoal in 95% ethanol solution and repeated recrystallizations from an ethanol-water solvent pair yielded about 1 g. of product, m.p. 226.5-227.5° (lit.[23] 218°). Anal. Calcd. for $C_9H_{10}O_3$: eq. wt., 166. Found: 166 ± 1.

J. 3,5-Dimethyl-4-ethoxybenzoic Acid

Anhydrous sodium carbonate was added to a solution of 3 g. of crude 3,5-dimethyl-4-hydroxybenzoic acid in 200 ml. of 50% ethanol solution until the litmus end point was reached. The solvent was removed by warming under reduced pressure. Eight milliliters of ethyl iodide and 200 ml. of absolute ethanol were added to the dry sodium salt-excess sodium carbonate mixture and the resultant mixture refluxed for 36 hours. The reaction mixture was cooled and acidified, but the product was obtained as an oil. The oil was extracted with ether, the ether removed, and the residue dissolved in 10% sodium hydroxide solution. The mixture was filtered and the filtrate acidified with 6 N hydrochloric acid solution.

The resultant mixture was filtered and the crude product washed well on the filter. Repeated recrystallizations from an ethanol-water solvent pair yielded about 1 g. of a white powder, m.p. 186-188°. Anal. Calcd. for $C_{11}H_{14}O_3$: eq. wt., 194. Found: 195 ± 2.

K. 3,5-Dimethyl-4-carboxybenzoic Acid

Mesitylene was acetylated and acetomesitylene oxidized according to the method of Hufford and Noyes.[24] Unfortunately, in the final step of the oxidation, great quantities of an unidentified fluorescent white solid were obtained in addition to the dicarboxylic acid. The dicarboxylic acid was extracted with and initially recrystallized from 95% ethanol solution. Final recrystallizations were made from glacial acetic acid, and fine white crystals, m.p. 302-304° (lit.[25] 297-298°), were obtained. Anal. Calcd. for $C_{10}H_{10}O_4$: eq. wt., 97. Found: 98 ± 1.

L. 3,5-Dimethyl-4-carbomethoxybenzoic Acid

1. Preparation of the Dimethyl Ester.--The procedure used was a modification of the method of Feist.[26] Anhydrous sodium carbonate was added to a solution of 5 g. of the dicarboxylic acid in about 200 ml. of 50% ethanol solution until the litmus end point was reached. The solvent was removed by warming under reduced pressure. About 10 g. of dimethyl sulfate and 200 ml. of methanol were added to the

dry sodium salt-excess sodium carbonate mixture and the reaction mixture refluxed for 40 hours. The excess methanol was removed by warming under reduced pressure. The residue was extracted with ether, the ether removed, and the new residue vacuum distilled. The dimethyl ester boiled at 120-130°/0.5-1.5 mm. and melted at 70-73°. It was used without purification in the next step.

2. Partial Hydrolysis of the Diester.--A solution of 3 g. of the dimethyl ester, 5 g. of potassium carbonate, and 200 ml. of 50% methanol solution was refluxed for one hour. The clear solution was acidified with 6 N hydrochloric acid solution and the mixture filtered by suction to collect the precipitate. The crude product was recrystallized from water and long white crystals, m.p. 152.5-154° (lit.[27] 154°), were obtained. Anal. Calcd. for $C_{11}H_{12}O_4$: eq. wt., 208. Found: 209 ± 1.

M. 3,5-Dimethylbenzoic Acid

Mesitylene was oxidized according to the procedure of Snyder, Adams and McIntosh, Jr.[28] Repeated recrystallizations from 95% ethanol solution yielded shiny white leaves, m.p. 172-172.5° (lit.[29] 165.5-166.5°). Anal. Calcd. for $C_9H_{10}O_2$: eq. wt., 150. Found: 151 ± 1.

II. Determination of pK_a's

The samples to be run were dried at 50° for 24 hours under 4-7 mm. pressure. Duplicate determinations were made on each compound and good agreement of values was obtained.

In a typical determination, a teflon-covered magnetic stirring bar and 50-125 mg. of sample were placed in the titrating vessel. Exactly 50 ml. of anhydrous ethanol was pipetted into the titrating vessel and the sample was allowed to dissolve. As soon as solution of the sample was complete, 50 ml. of ion-free water was pipetted into the titrating vessel. The potentiometric titrations were followed on a Beckman Model G pH Meter, standardized before each run with Beckman pH 4 buffer. After each addition of base, an equal volume of anhydrous alcohol was added before the pH was recorded. The solutions were constantly stirred and all titrations were carried out at 25°.

Carbonate-free sodium hydroxide was used as titrant. It was standardized by titrating against potassium acid phthalate samples in 50% ethanol solution, as above.

REFERENCES

1. The material on page 1 and all but the last paragraph on page 2 is an abstraction from pp. 559-579 of R. W. Taft in "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956.

2. L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, Chapter VII.

3. Ibid., pp. 194-196.

4. H. H. Jaffé, Chem. Rev., 53, 191 (1953).

5. J. D. Roberts and W. T. Moreland, Jr., J. Am. Chem. Soc., 75, 2167 (1953).

6. C. K. Ingold, J. Chem. Soc., 1930, 1032.

7. Taft, op. cit., pp. 587-597.

8. M. L. Bender, J. Am. Chem. Soc., 73, 1626 (1951).

9. Jaffé, op. cit., pp. 201-202.

10. Taft, op. cit., p. 594.

11. D. H. McDaniel and H. C. Brown, J. Org. Chem., 23, 420 (1958).

12. R. W. Taft and I. C. Lewis, J. Am. Chem. Soc., 80, 2436 (1958).

13. Ibid.

14. G. S. Hammond in "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956, Chapter 9.

15. B. M. Wepster, Rec. trav. chim., 76, 357 (1957).

16. H. C. Brown and A. Cahn, J. Am. Chem. Soc., 72, 2939 (1950).

17. Wepster, loc. cit.

18. A. H. Blatt (ed.), "Organic Syntheses," John Wiley & Sons, Inc., New York, 1943, Col. Vol. 2, p. 449.

19. H. L. Wheeler and C. Hoffman, Am. Chem. J., 44, 118 (1910).

20. Ibid., p. 119.

21. H. J. Schmitz, Ann., 193, 174 (1878).

22. R. Fittig and S. Hoogewerff, Ann., 150, 325 (1869).

23. J. Thiele and H. Eichwede, Ann., 311, 372 (1900).

24. R. W. Hufford and W. A. Noyes, J. Am. Chem. Soc., 43, 928 (1921).

25. P. Jannasch and M. Weiler, Ber., 28, 534 (1898).

26. F. Feist, Ann., 433, 61 (1923).

27. Ibid.

28. H. R. Snyder, R. R. Adams and A. V. McIntosh, Jr., J. Am. Chem. Soc., 63, 3280 (1941).

29. Ibid.