Some Extensions of Hammett's Equation

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The effect of substituents in the *meta* and *para* position on the rate and equilibrium constants of reactions occurring in side chains of aromatic compounds can be expressed by means of Hammett's equation (*1*):

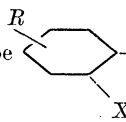
$$\log (k/k^0) = \sigma\rho \qquad (1)$$

In Eq. 1, k and k^0 are the rate or equilibrium constants for the substituted and unsubstituted compounds respectively, σ is the substituent constant that depends only on the nature and position of the substituent, and ρ, the reaction constant, depends only on the reaction, the conditions under which it occurs, and the nature of the side chain. In the form given, Eq. 1 applies to reactions of compounds having a single substituent in a benzene ring attached to the reacting side chain. Extensions to certain more complicated types of compounds will now be proposed.

In a few reactions (*2*) the effects of several substituents in the 3, 4, and 5 positions relative to the reacting side chain have been observed to be additive. Since these reaction series obey Eq. 1, the effect of multiple substituents can obviously be expressed through the sum of their substituent constants:

$$\log (k/k^0) = \rho\Sigma\sigma \qquad (2)$$

Although the evaluation of the literature is not complete at this time, it appears that Eq. 2 generally is a good approximation to the effect of multiple substituents. However, substituents which interact strongly with each other probably must be excepted from this generalization.

Measurements have been made on a few reaction series of compounds of the type 

, where R is a substituent in the 4 or 5 position relative to the reacting side chain Y, and where X, a substituent in the 2 position, is the same throughout the series. Where comparison is possible for several groups X (*3–4*), (which may include X = H), the reaction constants (ρ) are almost always equal within experimental error. Accordingly, such sets of reaction series for several X can be expressed by the single equation

$$\log (k/k^0) = \sigma\rho + X \qquad (3)$$

Here X is the effect the substituent X in the *ortho* position exerts on the reactivity of unsubstituted compound C_6H_5Y; i.e., $X = \log (k_X/k^0)$. The applicability of this equation is naturally subject to the limitation that the substituent X does not affect the mechanism of the reaction.

Equation 3 applies also to the extensive series of nuclear chlorinations of benzyl phenyl ethers (*5*). In this case X represents the cumulative effect of the several substituents in the phenyl group, and σ refers to the substituent in the benzyl group. It might have been anticipated that the effect X could have been correlated with substituent constants, but no such correlation was observed, probably because the substituents in the phenyl group affect the number and steric accessibility of the reaction sites.

Many reactions of compounds having 2 or more aromatic rings in equivalent positions relative to the reaction site have been investigated. In series in which all rings are equally substituted, or which involve different substituents on one ring only, no special problems arise, and Eq. 1 applies. In series which involve a combination of these two situations and also further unsymmetrical substitution, Hammett's equation has occasionally been applied in the form of Eq. 2 (*6*), where the summation extends over the substituents in the different rings. A search of the literature revealed 10 reaction series on which this application of Eq. 2 can be tested. Although more data are expressed by Eq. 2 than by the application of Eq. 1 to either the series of symmetrical compounds or the series involving variation of substituents in one ring only, it was found that the precision in the representation of the data was only moderately reduced by the use of Eq. 2. This fact shows that a substituent in one ring does not greatly affect the susceptibility of the reaction to the influence of a substituent in another ring.

There is no reason to believe that this conclusion should not apply equally to compounds in which several aromatic rings are in nonequivalent positions relative to the reaction site. Hence, for reactions of such compounds the following equation is proposed:

$$\log (k/k^0) = \sigma_1\rho_1 + \sigma_2\rho_2 + \cdots \qquad (4)$$

where ρ_1, $\rho_2 \cdots$ measure the susceptibility of the reaction to the effect of substituents in rings 1, $2 \cdots$, and σ_1, $\sigma_2 \cdots$ refer to the substituents in the respective rings. Only two reaction series could be found in the literature on which Eq. 4 could be tested (*7*), and it was found to apply satisfactorily to both.

It might have been anticipated that Eq. 4 would also apply to reactions of the type $A + B \rightarrow$ products, if both A and B contain a substituted aromatic ring. However, examination of the literature revealed several reaction series of this type (*4, 8*), which did not obey Eq. 4 even approximately.

The four extensions of Hammett's equation proposed in this note obviously cannot express the experimental data with greater precision than Eq. 1, but rather can be expected to have somewhat lower precision. Since Hammett's equation itself is not highly precise these extensions can give only crude estimates of reactivities. However, it is believed that Eq. 2–4 should be useful since they permit representation of a much larger body of data by a single expression.

The detailed data on which these considerations are based will be published in the near future in connection with a review of Hammett's equation.

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Electrophoretic Behavior of Acid Phosphatase in Human Prostatic Extracts[1]

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In attempting the electrophoretic isolation of acid phosphatase from partially purified extracts of human prostatic tissue we noted that the electrophoretic patterns consistently showed two major protein components in addition to the enzyme. Since scarcely anything is known regarding the properties of the proteins of the prostate, we thought it advisable to present our findings at this time.

Strips of prostatic tissue were extracted overnight at 7° C with 6 ml of 0.85% NaCl per gram (wet weight) of tissue. The extract was dialyzed against distilled water until free of salt, and the insoluble material that appeared with the removal of salt was spun down and discarded. The supernate was lyophilized. A 1–1.5% aqueous solution of the dried powder was fractionated in two steps with $(NH_4)_2SO_4$ at 0° C as follows: The precipitate salted out at half saturation was discarded. The concentration of $(NH_4)_2SO_4$ was increased to two-thirds saturation, and the resulting precipitate was dissolved in a volume of water about two-thirds that of the original solution of powder and dialyzed against running tap water until free of $(NH_4)_2SO_4$. Additional protein was then removed by adjusting the dialyzed solution to pH 4.9 with *N*/10 acetic acid and storing at 0° C for 6 hr. The resulting precipitate was spun down and discarded. After a final dialysis against running tap water the supernate was dried from the frozen state. A white powder resulted.

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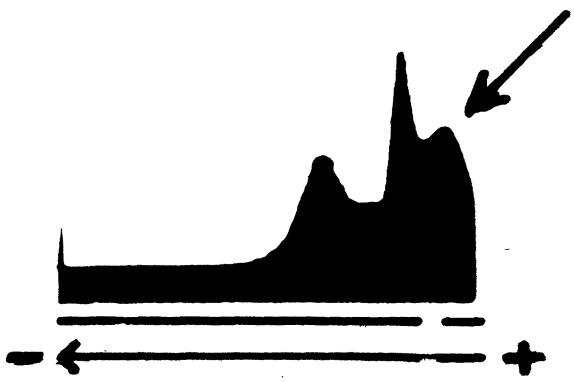
Electrophoretic analysis was carried out in the 2-ml cell of a Perkin-Elmer-Tiselius apparatus, Model 38. Patterns were obtained by both the Philpot-Svensson technique and the schlieren scanning technique, the latter being used for measurements of mobilities.

Mobilities were determined at intervals from pH 4.05 to pH 7.65 at an ionic strength of 0.05 and protein concentrations of approximately 0.75 and 1.5%. Acetate buffers, as reported by Boyd (*1*), were used for the acid range. The Gomori tris(hydroxymethyl)-aminomethane buffer (*2*) was used at pH 7.65, ionic strength 0.05. To make this buffer, 50 ml of 1 *N* HCl were added to 65.4 ml of 0.98 *M* tris(hydroxymethyl)-aminomethane solution, and the mixture made up to 1 liter with distilled water.

At the termination of each electrophoretic run, appropriate fractions were removed from the resolved mixture by means of a needle and syringe and analyzed for phosphatase activity and nitrogen content.

Eight electrophoretic analyses, using five separate extracts, were carried out. Partially purified extracts resolved over a pH range of 4.05–7.65 exhibited three major components. Only one of these seemed to represent prostatic phosphomonoesterase as judged by the activity-nitrogen ratios of the various fractions of the electrophoretically resolved solution withdrawn from the cell. The enzyme was estimated, by measurement of areas under corresponding peaks in the electrophoretic diagrams, to be approximately 10% of the total protein content.

Figure 1 is a representative pattern. The purified extract was obtained from a surgical specimen showing benign hyperplasia. The arrow denotes the component that showed the highest activity-nitrogen ratio; it is therefore assumed to be associated with prostatic phosphomonoesterase. This component has



Acetate buffer; pH 4.60
$\Gamma/2 = 0.1$; conc. = 2.5 mg N/ml; 113 min

FIG. 1. A cylindrical lens pattern (ascending limb) of partially purified prostatic acid phosphomonoesterase after electrophoresis. (Activity/nitrogen solution before electrophoresis = 86 units/mg nitrogen. Activity/nitrogen of component denoted by arrow = 113 units/mg nitrogen.) (A unit is 1 mg of phosphorus hydrolyzed in 30 min at 37° C from *M*/60 sodium β-glycerophosphate [Eastman Kodak Co.] in acetate buffer at pH 5.5, ionic strength 0.2.)