[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Electrostatic Influence of Substituents on Reaction Rates. II[1]

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In a recent paper, Shookhoff and the author[2] showed that the effect of a polar substituent on the rate of saponification of some aliphatic esters and amides can quantitatively be ascribed to the electrostatic influence of the substituent. The necessary computations involved the use of some equations previously derived by Kirkwood and the author[3]; these equations have proved their worth in considerations of ionization equilibria.[4] The present paper is devoted to a discussion of the effect of substitution on the rate of reaction of aromatic compounds.

Kirkwood and the author assumed that the molecule containing the substituent constituted a cavity from which the solvent is excluded. The material in the cavity was assigned a low "internal" dielectric constant to take account, as a first approximation, of the polarization of the molecule. In this way, both the effect transmitted through the molecule and that transmitted through the solvent can be taken into account. The method recently put forward by Ri and Eyring[5] provides a means of making computations similar to those involved here. Their model is such that most of the electrostatic effect is transmitted through the molecule. In this way, it is in marked contrast with Bjerrum's[6] original suggestion (approximately valid for the effect of charged substituents at large distances) that the entire electrostatic effect is transmitted through the solvent.

The present discussion of reaction velocity can be based on the assumption that the reaction proceeds by way of an activated complex.[2,7] The following equation takes into account the effect of a dipolar substituent on reaction velocity.

$$\log k - \log k^0 = \Delta \log k = \frac{eM \cos \zeta}{2.303kTR^2D_E} \quad (1)$$

Here k is the velocity constant for the substituted compound, k^0 the corresponding constant for the unsubstituted compound. M is the dipole moment of the substituent,[8] e the electronic charge, k the Boltzmann constant and T the absolute temperature. R is the distance between the substituent and the charge which the reacting ion contributes to the activated complex, ζ the angle between the dipole and the line joining its center with this charge. D_E, the "effective" dielectric constant, has been tabulated for cavities which are ellipsoidal in shape. Because of mathematical limitations, the calculations can be applied only to para substituted compounds.

The volumes of the substituted esters were estimated for the solvent and temperature of the experiment, using the data given by Traube.[9]

The first table shows the results, given to the nearest 0.05 logarithmic unit, of the computations of the effect of substituents on the rate of saponification of the substituted phenylacetic esters.

The ester is designated in the first column. The second column lists the value of Δ log k, determined experimentally in 88% alcohol by Kindler.[10] The third and fourth columns contain the values of Δ log k computed by the equations of Kirkwood and the author, using distances, (R), between the dipole and the negative charge of the activated complex of 6.1 and 6.6 Å., respectively. The final column contains the values obtained using a distance of 6.1 Å. and the equations based on Bjerrum's model.

The values computed for the methoxyl and amino substituents have been placed in parentheses, not only because of the uncertainty in the angle of the moments of these groups, but also because the negative sign of the moment indicates an unusually large interaction between these groups and the benzene ring.[11] For the purposes of the computation, it was assumed that the carbethoxy group can rotate freely with respect to the methoxyl or amino substituent.

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[1] Presented on April 11, 1940, at the Cincinnati meeting of the American Chemical Society.

[2] Westheimer and Shookhoff, THIS JOURNAL, **62**, 269 (1940).

[3] Kirkwood and Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); **7**, 437 (1939); Westheimer and Kirkwood, *ibid.*, **6**, 513 (1938).

[4] Westheimer and Shookhoff, THIS JOURNAL, **61**, 555 (1939); Westheimer, *ibid.*, **61**, 1977 (1939).

[5] Ri and Eyring, *J. Chem. Phys.*, **8**, 433 (1940).

[6] Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923); Eucken, *Z. angew. Chem.*, **45**, 203 (1932).

[7] Brönsted, *Chem. Rev.*, **5**, 231 (1928); Eyring, *J. Chem. Phys.*, **3**, 107 (1935).

[8] Smyth, *J. Phys. Chem.*, **41**, 209 (1937).

[9] Traube, *Samml. chem. chem.-tech. Vortr.*, **4**, 255 (1890). The "co-volume" in all solvents other than water was assumed equal to 20.

[10] Kindler, *Ann.*, **452**, 90 (1927).

[11] Marsden and Sutton, *J. Chem. Soc.*, 599 (1936).

TABLE I

SAPONIFICATION OF THE ETHYL ESTERS OF SUBSTITUTED PHENYLACETIC ACIDS

$V = 265\ \text{Å}.^3$ $T = 30°$ $\cos \zeta = 0.92$ $D = 28$

Ester, ethyl	$\Delta \log k$ (obsd.)	K.-W. $\Delta \log k$ $R = 6.1$ Å.	K.-W. $\Delta \log k$ $R = 6.6$ Å.	B.-E. $\Delta \log k$ $R = 6.1$ Å.
p-Nitrophenylacetate	0.86	0.90	0.60	0.20
p-Chlorophenylacetate	.41	.35	.25	.10
p-Methylphenylacetate	− .04	− .05	− .05	.00
p-Methoxyphenylacetate	− .04	(− .05)	(− .05)	(.00)
p-Aminophenylacetate	− .20	(− .25)	(− .15)	(− .05)

It is at once clear that Bjerrum's equation yields results far too small in absolute magnitude. Using the equations of Kirkwood and the author, the calculated values of $\Delta \log k$ are in good agreement with the experimental when the value of 6.1 Å. is chosen for R. The value of 6.6 Å., however, is that which best fits the data for the ionization constants of the substituted phenylacetic acids in water.

The few pertinent data of Harman[12] suggest that the difference may largely be due to solvent effect. It can be stated, as an approximation, that, while the present equations adequately account for the effect of change in solvent on the relative ionization constants of aliphatic acids, they underestimate the effect of solvent on the relative ionization constants of aromatic acids. This situation can, at least qualitatively, be explained. The benzene ring is actually a flat plate.[13] The equations, based on a prolate ellipsoidal model, somewhat underestimate the amount of solvent close to the substituent, and therefore underestimate the effect of change in solvent.

In the remaining tables, the computations are given, whenever posssible, for two values of R: first the value which best fits the experimental data, then that previously used in the computations of acid strength.

Table II contains the data for the saponification of esters of substituted hydrocinnamic acids[9] in 88% alcohol, Table III the data for the reaction between substituted benzyl chlorides and sodium iodide to yield substituted benzyl iodides and sodium chloride in acetone solution at 20°.[14]

It is seen that the computed values agree quite well with the experimental for the data summarized in Tables II and III.

The agreement in the latter case could not have been anticipated with certainty, since the sodium iodide is probably not completely ionized in acetone solution.

TABLE II

SAPONIFICATION OF HYDROCINNAMIC ESTERS

$V = 295\ \text{Å}.^3$ $T = 30°$ $D = 28$ $\cos \zeta = 0.99$

Ester, ethyl	$\Delta \log k$ (obsd.)	$\Delta \log k$ $R = 7.2$ Å.	$\Delta \log k$ $R = 7.7$ Å.
p-Chlorohydrocinnamate	0.18	0.20	0.15
p-Methoxyhydrocinnamate	− .08	− .05	− .05

TABLE III

REACTION OF SUBSTITUTED BENZYL CHLORIDES WITH SODIUM IODIDE IN ACETONE

$V = 210\ \text{Å}.^3$ $T = 20°$ $D = 20$ $R = 6.2$ Å.

Halide	$\Delta \log k$ (obsd.)	$\Delta \log k$ (calcd.)
p-Nitrobenzyl chloride	0.79	0.80
p-Fluorobenzyl chloride	.16	.30
p-Chlorobenzyl chloride	.33	.30
p-Bromobenzyl chloride	.37	.30
p-Iodobenzyl chloride	.35	.25

Tables IV, V and VI deal with the alkaline hydrolysis of substituted benzoic[15] and cinnamic

TABLE IV

SAPONIFICATION OF BENZOIC ESTERS IN 88% ALCOHOL

$V = 240\ \text{Å}.^3$ $T = 30°$ $D = 28$

Ester, ethyl	$\Delta \log k$ (obsd.)	$\Delta \log k$ $R = 5.2$ Å.	$\Delta \log k$ $R = 5.9$ Å.
p-Nitrobenzoate	2.02	1.75	1.05
p-Fluorobenzoate	0.28	0.65	0.40
p-Chlorobenzoate	.64	.70	.45
p-Bromobenzoate	.70	.70	.40
p-Iodobenzoate	.70	.60	.35
p-Methylbenzoate	− .33	− .15	− .10
p-Methoxybenzoate	(− .67)	(− .15)	(− .10)
p-Aminobenzoate	(−1.63)	(− .50)	(− .30)

TABLE V

SAPONIFICATION OF CINNAMIC ESTERS IN 88% ALCOHOL

$V = 285\ \text{Å}.^3$ $T = 30°$ $D = 28$ $R = 6.1^a$ $\cos \zeta = 0.99$

Ester, ethyl	$\Delta \log k$ (obsd.)	$\Delta \log k$ (calcd.)
p-Nitrocinnamate	0.99	0.85
p-Fluorocinnamate	.14	.30
p-Chlorocinnamate	.32	.35
p-Bromocinnamate	.35	.35
p-Iodocinnamate	.35	.25
p-Methylcinnamate	− .15	− .05

[a] No value of R for the cinnamic acids will yield results of a high degree of internal consistency.

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[12] Harman, *Trans. Faraday Soc.*, **35**, 1336 (1939).

[13] Lonsdale, *Proc. Roy. Soc.* (London), **A123**, 494 (1929).

[14] Bennett and Jones, *J. Chem. Soc.*, 1815 (1935).

[15] Kindler, *Ann.*, **450**, 1 (1926).

TABLE VI

ALKALINE HYDROLYSIS OF AMIDES IN WATER

$V = 195$ Å.^{3} $T = 100°$ $D = 55$

Amide	$\Delta \log k$ (obsd.)	$\Delta \log k$ $R = 5.6$ Å.	$\Delta \log k$ $R = 5.9$ Å.
p-Nitrobenzamide	0.82	0.80	0.60
p-Chlorobenzamide	.28	.30	.25
p-Bromobenzamide	.28	.30	.25
p-Iodobenzamide	.23	.25	.20
p-Methylbenzamide	− .18	− .05	− .05
p-Methoxybenzamide	(− .31)	(− .05)	(− .05)
p-Aminobenzamide	(− .72)	(− .25)	(− .15)

esters[16] in aqueous alcohol at 30° and of substituted benzamides[17] in water at 100°.

The agreement in the cases considered in Tables IV, V and VI is moderately good. Large discrepancies are found only for the compounds with methoxyl and amino substituents in the para positions. These substituents caused no difficulties in the case of the esters of the phenylacetic acids. It is then clear that the deviations may be connected with the fact that there is a completely conjugated system between the substituent and the reacting group. It was pointed out previously[4] that the resonance interaction of a carbethoxy group with these particular substituents will be large. Such resonance will stabilize the ester as compared with the activated complex, and will result in a rate of saponification slower than that predicted on the basis of electrostatic considerations alone. This is at least qualitatively in accord with the actual experimental facts.

It is also interesting to note that the value of R which best fits the data for the cinnamic esters is 6.3 Å., while the value which best fits the data for the hydrocinnamic esters is 7.2 Å. This is not likely to be a true difference in length; it might be expected rather that the average length of the hydrocinnamic esters would be equal to or less than that of the *trans* cinnamic esters. The apparent difference in distance is probably connected with the completely conjugated chain in the cinnamic esters. The approximation introduced by regarding a substituent as a point dipole is more nearly justifiable for the hydrocinnamic than for the cinnamic esters. The actual charge distribution in the cinnamic esters will result in a greater effect of the dipole than could be anticipated on the basis of the dipole moment alone, and will be reflected in the computation by an unusually small value of R.

Another case of interest is one in which none of the reactants is a charged particle. The effect of a dipolar substituent on such a reaction will be large only if a substantial moment is created in the formation of the activated complex. For example, in the reaction between an alkylating agent and an amine, the activated complex can be considered a resonance hybrid of the uncharged reactants and the ionic reaction products. Such an activated complex will have a high dipole moment. When the moment of the substituent and the moment created in the activated complex are co-linear, the following approximate equation applies to a reaction between uncharged particles

$$\Delta \log k = \frac{2M_1M_2}{2.303kTR^3D_i} \qquad (2)$$

M_1 is the moment of the substituent, M_2 is the moment formed during the reaction in the activated complex and D_i the "internal" dielectric constant. This equation will be justified by the treatment in the appendix.

A case in which equation (2) can be tested is the reaction, investigated by Hammett and Pfluger,[18] between trimethylamine and the methyl esters of substituted benzoic acids. It seems reasonable that the new dipole of the activated complex is co-linear with the dipole in the para position in the benzene ring, and the negative end of the new moment is toward the center of the molecule. The data are summarized in Table VII.

TABLE VII

REACTION BETWEEN TRIMETHYLAMINE AND BENZOIC ESTERS

$R = 6.5$ Å. $T = 100°$.

Substituted methyl ester	Log k (obsd.)	Log k (calcd.)
p-Methylbenzoate	−0.10	−0.10
p-Nitrobenzoate	− .85	− .90

The calculations are made on the basis of the assumption that the new moment in the activated complex is 7 Debye units, the moment anticipated if the reactants and products make equal contributions to the structure of the activated complex. Stearn and Eyring[19] estimated, from the effect of change of solvent on the rate, that a moment of about 6 D is produced in the reaction between an amine and an alkyl halide.

Appendix

The general expression for the net electrostatic work done can be obtained from the equations of Kirkwood.[20]

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[16] Kindler, *Ann.*, **464**, 278 (1928).

[17] Reid, *Am. Chem. J.*, **24**, 397 (1900).

[18] Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933).

[19] Stearn and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).

[20] Kirkwood, *ibid.*, **2**, 351 (1934).

$$\Delta w = \frac{1}{2}\sum_{j=1}^{s}\sum_{k=1}^{s}\frac{e_j e_k}{R_{jk}} + \frac{1}{2}\left(\frac{1}{D} - \frac{1}{D_i}\right)\sum_{n=0}^{\infty}\frac{(n+1)\Delta G_n}{[(n+1) + nD_i/D]b^{n2+1}} \quad (3)$$

$$\Delta G_n = \sum_{j=1}^{s}\sum_{k=1}^{s} e_j e_k r_j^n r_k^n P_n(\cos \vartheta_{jk})$$

The charge e_k is at a distance r_k from the center of the sphere, at a distance R_{jk} from the charge e_j, and the lines between e_k and the center, and e_j and the center meet at an angle of ϑ_{jk}. The P_n are the usual Legendre functions. b is the radius of the sphere, and $(r/b)^2 = x$.

In order to determine the effect of dipole–dipole interaction, it is necessary to evaluate ΔG_n. For the case in which dipoles are equidistant from the center on a diameter, ΔG_n becomes

$$\Delta G_n = 2a^{2n-2}(-1)^n M_1 M_2 \left\{ n^2 \cos \zeta_1 \cos \zeta_2 - \frac{n(n+1)}{2} \sin \zeta_1 \sin \zeta_2 \cos \varphi \right\} \quad (4)$$

Here ζ_1 is the angle between the first dipole and the diameter, ζ_2 the angle between the second dipole and the diameter, and φ the angle between the planes defined by the two dipoles and the diameter. Substituting in equation (3), expanding in a power series in D_i/D and retaining only the first term, equation (5) is obtained

$$\Delta w = \frac{M_1 M_2}{R^3}\left\{ \cos \zeta_1 \cos \zeta_2 \left[\frac{2}{D_i} + 4\sqrt{x}\left(\frac{1}{D} - \frac{1}{D_i}\right) S_1\right] - \sin \zeta_1 \sin \zeta_2 \left[\frac{1}{D_i} + 4\sqrt{x}\left(\frac{1}{D} - \frac{1}{D_i}\right)\right] S_2 \right\}$$

$$S_1 = \sum_{n=0}^{\infty}\left[[n^2 x^n (-1)^n - \frac{n_3}{n+1}\frac{D_i}{D} x^n (-1)^n \right] \quad (5)$$

$$S_2 = \sum_{n=0}^{\infty}\left[n(n+1)(-1)^n x^n - \frac{D_i}{D} n^2 (-1)^n x^n \right]$$

The expression obtained after evaluating the indicated sums is rather complex. However, for the case in which the two dipoles are co-linear, actual numerical computations show that the expression may be replaced, as a first approximation, by equation (2).

The author wishes to thank Professor J. G. Kirkwood for his generous assistance in connection with the derivation given above.

Summary

The electrostatic equations derived by Kirkwood and Westheimer have been applied successfully to calculation of the effect of para substituents on the rate of saponification of the esters of phenylacetic, hydrocinnamic, benzoic and cinnamic esters, to the rate of alkaline hydrolysis of benzamides and the rate of reaction of benzyl chlorides with sodium iodide.

An approximate equation has been derived which applies to dipole–dipole interaction, and has been shown satisfactorily to account for the effect of substituents on the rate of alkylation of trimethylamine by substituted methyl benzoates.

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Heats of Organic Reactions. IX. A New Calorimeter and the Denaturation of Methemoglobin by Alkali

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So many organic reactions cannot be studied calorimetrically in the vapor phase with convenience that we were compelled some time ago to construct a new calorimeter designed specifically to study liquid phase reactions. We have attempted to build a rather flexible unit suitable for work under greatly varying conditions, and thus, of course, had to sacrifice certain valuable characteristics. The calorimeter herein described is neither as sensitive as some nor as accurate as others, but if one is justified in evaluating a "utility coefficient," made up of sensitivity, accuracy, speed of operation, and a few other factors, the comparison will not be very unfavorable to the present instrument.

With this calorimeter we have measured the heats of hydrolysis of several acid anhydrides, the results of which work will be published shortly, and have now studied the irreversible denaturation of methemoglobin in solutions of high *p*H at 25°. We have chosen methemoglobin as the first object of study because of the ease of its preparation in the pure crystalline state, and because this protein is known to be soluble when denatured, except