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Substituent Effects. I. Introduction

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Substituents can exert two primary effects on an adjacent molecule, due to polarity of the intervening σ-bond and to mutual resonance interactions. Previous attempts to devise a quantitative theory of substituent effects are criticized. The mode of transmission of the primary effects to the reaction center is discussed. The need for further experimental work on systems other than benzene is emphasized.

There is still no satisfactory quantitative theory of the way in which substituents alter the physical and chemical properties of organic molecules. The purpose of the present paper is to analyze the possible modes of action of substituents, to criticize previous approaches to the problem and to outline the steps that must be taken to reach a solution. Subsequent papers of the series will describe progress toward this goal.

It is not yet possible to estimate the effects of substituents by *a priori* quantum mechanical calculation; one must admit empirical parameters to describe the effects of substituents and the corresponding response of a reaction center. One approach of this kind has been based on the existence of free energy relationships of the type implied by the Brönsted catalysis law and embodied in the case of benzene derivatives in the Hammett equation.[2] Here the over-all effect is expressed as a product of two factors, one (σ) characteristic of the substituent and the other (ρ) characteristic of the reaction center. The effect of a given substituent on a given reaction center will also depend on their mutual orientation in a molecule; in the Hammett treatment this factor is absorbed into the substituent constants σ, a given substituent having a different σ-constant for each possible orientation. The Hammett equation was originally applied only to reactions of benzene derivatives, but it can be extended easily to other systems. However in addition to being purely empirical, it suffers from an excess of parameters; for the number of possible orientations of a given substituent in different molecules is exceedingly large and a different empirically determined σ-constant must be used in each case.

The form of the Hammett equation clearly requires there be no direct interaction (*i.e.*, mutual conjugation[3]) between the reaction center and the substituent; such interactions, if they occur, will produce variable effects in different substituents so that their relative efficacy can no longer be expressed in terms of single fixed σ-constants.[4] A possible solution is to add a second term to the Hammett equation, *i.e.*

$$\log k/k_0 = \rho\sigma + \rho'\sigma' \qquad (1)$$

where ρ' is a new constant measuring the sensitivity of the reaction center to mutual conjugation and σ' is a corresponding measure of the conjugative power of the substituent. Relations of this type have been proposed[5] but they suffer from the disadvantage of requiring even more parameters than the original Hammett approach.

The basic interactions between a substituent and an adjacent substrate are of two kinds, inductive and mesomeric. Since these effects cannot be calculated theoretically, we must accept two empirical parameters for each substituent. We must also accept two parameters for each reaction center, to allow for its general response to polarization of the substrate by the substituent and for its special response to mutual conjugation. This already commits us to a large number of empirical parameters; we cannot accept any more if our treatment of substituents is to be meaningful. We must therefore be able to estimate the efficiency of transmission of the primary substituent effect to the reaction center without involving ourselves in any additional empirical parameters.

Taft and his collaborators[6] have tried to subdivide the effects of substituents in benzene into inductive and mesomeric parts. They did this by making arbitrary assumptions concerning the relative efficiency of transmission to the positions *meta* and *para* to the substituent. Although these assumptions were justified to some extent by the correspondence between the inductive substituent constants calculated for benzene and the corresponding constants found for certain saturated systems where no resonance interactions could be involved, their treatment is unsatisfactory for two reasons. First, they could draw no valid conclusions concerning the manner in which substituent effects are transmitted across a molecule; secondly, their treatment could not be extended to other molecules (*e.g.*, naphthalene) without introducing numerous additional parameters.

Jaffé[7] has calculated the effects of substituents in various aromatic systems on the assumption that they act only by polarizing the π-electrons. This assumption is certainly incorrect; for substituents can exert effects of comparable magnitude in saturated systems where there are no π-electrons to polarize. A very good example is provided by the effect of "*para*" substituents X in the bicyclooctane-4-carboxylic acids (I), the changes in pK_A with substitution being comparable with

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[1] Department of Chemistry, University of Chicago, Chicago 37, Ill.

[2] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 186.

[3] M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3351 (1952), theorems 47–49.

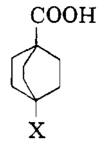
[4] *Cf.* H. van Bekkum, P. E. Verkade and B. M. Wepster, *Rev. trav. chim.*, **78**, 815 (1959).

[5] Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, **32**, 971 (1959).

[6] *Cf.* R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959); R. W. Taft, S. Ehrenson, I. C. Lewis and R. E. Glick, *ibid.*, **81**, 5352 (1959).

[7] H. H. Jaffé, *J. Chem. Phys.*, **20**, 279, 778 (1952); *J. Am. Chem. Soc.*, **76**, 4261, 5843 (1954); **77**, 274 (1955).

those in the corresponding *m*-substituted benzoic acids (II).[8] A further difficulty lies in the calculation of the π-electron polarizations. The simple Hückel method, which Jaffé used, is very unsuitable for calculations of this kind since it greatly overestimates the differential charges in conjugated systems. No calculations of this kind have been reported using more accurate methods. Another complication is the choice of suitable MO parameters for the numerous heteroatoms that appear in typical substituents.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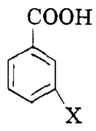
II

There are at least five distinct processes by which substituents can affect a distant reaction center. Three of these are initiated by the polarity of the bond linking the substituent to the substrate (*i.e.*, the primary inductive effect) and two by resonance interactions between them (*i.e.*, the mesomeric and electromeric effects); *i.e.:* (a) The electric dipole field of the polar substituent-substrate bond can influence the reaction center across space (field effect). (b) The primary inductive effect can be transmitted to the reaction center by successive polarization of intervening σ-bonds (σ-inductive effect). (c) The electrostatic charge set up at a conjugated atom adjacent to the substituent may polarize the corresponding π-electron system (inductoelectromeric[9] or π-inductive[7] effect). The resulting charges set up in the π-electron system can influence the reaction center either by a field effect or by secondary polarization of intervening σ-bonds. (d) The π-electron system can also be polarized by resonance interactions with the substituent (mesomeric effect). (e) There may be mutual conjugation[3] between the substituent and reaction center through an intervening conjugated system (electromeric effect).

All these effects can be demonstrated experimentally. The importance of the field effect is shown by the difference between the first and second dissociation constants of saturated dicarboxylic acids.[10] The σ-inductive effect is necessary to explain the increase in dipole moment along a homologous series. Thus the difference between the dipole moments of methyl chloride (1.86 D.) and ethyl chloride (2.05 D.) must be ascribed to inductive polarization of the carbon–carbon bond in the latter. The π-inductive effect is necessary to explain the low reactivity of pyridine to electrophilic substitution and the enhanced acidity of the methyl group in β-picoline.[9] The mesomeric and electromeric effects are of course familiar from many examples. The problem of the transmission of substituent effects across a molecule is thus complex since there are so many possible mechanisms involved. Although the variation of each effect with distance can be estimated theoretically without too much uncertainty, the absolute magnitude of the various effects must be found from experiment.

(a) The field effect probably presents the most difficult problem. Most authors have treated the field of polar bonds as being due to a point dipole located at the center of the bond, the resulting potential varying as the inverse square of the distance. This, however, must be a poor approximation for two reasons. First, the field is set up by a dipole of length comparable to the distance between the substituent and the reaction center. The field in this case varies less rapidly with distance, the variation being intermediate between the first and second power. Secondly, in the case of reactions carried out in solution, the substituent will be solvated and its electric charge effectively dispersed over a shell of solvent molecules. This polarization of surrounding solvent molecules will reduce the field produced by the substituent at the reaction center. On the other hand, the field due to the charge on the atom adjacent to the substituent will be propagated through the middle of the molecule, a region of low dielectric constant. The net effect will therefore approximate that of a point charge at the atom adjacent to the substituent, the potential of which will vary as the inverse first power of the distance. For these reasons it is probably a better approximation to take the field at the reaction center as inversely proportional to the first power of the distance between it and the substituent, rather than the second power. In this preliminary work we have assumed this to be the case since any precise calculation would be very difficult.

(b) The inductive effect must die away exponentially along a series of bonds, the charge on the *n*th atom in the chain being some constant fraction (ϵ) of the charge on the $(n - 1)$th. This relation has been generally accepted. If the whole effect of substituents in saturated systems is inductive. than ϵ must lie in the range 0.35–0.50.[11] The fall-off factor may be different in unsaturated systems where the σ-bonds are formed by sp^2-carbon atoms, but there is no reason to suppose this would be the case.

(c) It can be shown that the π-inductive effect of a $\pm$I substituent runs parallel to that of a $\pm$E substituent.[12] The π-inductive effect therefore varies with distance in approximately the same way as the mesomeric or electromeric effects (see below).

(d) The charge δq_{ij} produced at atom j through mesomeric polarization of a conjugated system by a substituent at atom i can be written to a first approximation as

$$\delta q_{\mathrm{ij}} = M_{\mathrm{i}}\,\tau_{\mathrm{ij}} \qquad (2)$$

where M_i is a constant characteristic of the substituent and τ_{ij} is the transmission coefficient for the

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[8] J. D. Roberts and W. T. Moreland, *J. Am. Chem. Soc.*, **75**, 2167 (1953).

[9] D. A. Brown and M. J. S. Dewar, *J. Chem. Soc.*, 2406 (1953).

[10] *Cf.* J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).

[11] G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941; J. C. McGowan, *Nature*, **159**, 644 (1947); *Chemistry & Industry*, 632 (1948).

[12] M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3350 (1952); *cf* theorems 34, 39.

mesomeric effect. (Here M_i will include a contribution from the π-inductive effect; see above.) The transmission coefficient τ_{ij} can be estimated in two ways. First, it can be shown[13] that where π_{ij} is the atom-atom polarizability[14] of atoms i, j

$$\tau_{ij} \sim \pi_{ij} \qquad (3)$$

Secondly, since τ_{ij} is independent of the substituent, it can be estimated by taking one particular case. If the substituent is $-CH_2^-$, the formal negative charge (δq_{ij}) at atom j will be proportional to τ_{ij}. In the case of alternant hydrocarbons

$$\delta q_{ij} = a^2_{oj} \qquad (4)$$

where a_{oj} is the coefficient in the non-bonding molecular orbital of the ion $ArCH_2^-$ at atom j,[15] the methylene group being attached at atom i. These coefficients can be determined very simply.[15]

(e) The transmission of the electromeric effect can be shown to be proportional in a first approximation to that of the mesomeric effect,[16] *i.e.*, proportional to π_{ij} or a^2_{oj}.

The variation of each effect with distance can thus be estimated, at least to a first approximation. However, the absolute importance of the various effects in any given case cannot be estimated theoretically. It is therefore essential to have extensive data for the effects of substituents in a variety of ring systems, the substituents being at varying distances from a reaction center. Data of this kind have been lacking.

Although several hundred series of benzene derivatives have been studied, involving a great variety of substituents and reactions, no systematic investigation has been reported for any other system. Without data of this kind it is impossible to make further progress, given the inadequacy of present chemical theory. Almost the only studies of this kind reported have been those of Berliner and Blommers on the effects of 3′- and 4′-substituents on biphenyl-4-carboxylic acid,[17] of Berliner and Liu[18] on the rates of hydrolysis of the corresponding ethyl esters, of Berliner and Winicov[19] on the dissociation constants of the nitronaphthoic acids, of Fischer, Mitchell, Ogilvie, Packer, Packer and Vaughan[20] on the rates of hydrolysis of substituted ethyl 1-naphthoates, and of Bryson[21] on the effects of substituents on the basicities of 1- and 2-naphthylamines. None of these investigations covered a sufficient range of substituents to be useful.

We have accordingly synthesized a large variety of substituted 1-naphthoic acids, carrying substituents in all five unhindered positions, and have studied the effects of the substituents on the acid strength and on the infrared carbonyl frequencies of the corresponding methyl esters. This work, and the conclusions drawn from it, are described in the following papers.

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[13] M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3350, 3356 (1952); *cf.* theorems 34, 35, 36, 71, 72.

[14] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (*London*), **A191**, 39 (1947); **A192**, 16 (1947).

[15] H. C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 265 (1950).

[16] M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3350 (1950); *cf.* theorems.

[17] E. Berliner and E. A. Blommers, *J. Am. Chem. Soc.*, **73**, 2479 (1951).

[18] E. Berliner and L. H. Liu, *ibid.*, **75**, 2417 (1953).

[19] E. Berliner and E. H. Winicov, *ibid.*, **81**, 1639 (1959).

[20] A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer and J. Vaughan, *J. Chem. Soc.*, 1426 (1958).

[21] A. Bryson, *J. Am. Chem. Soc.*, **82**, 4862 (1960).

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Substituent Effects. II.[1a] The Preparation of a Series of Substituted 1-Naphthoic Acids

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The physical properties of thirty-three 1-naphthoic acids and their methyl esters are reviewed. The preparations of several new disubstituted naphthalenes and of known disubstituted naphthalenes by new routes are described.

This paper describes the syntheses and physical properties of thirty-three 1-naphthoic acids and their derivatives which were prepared for the reasons indicated in Part I. Seven of the acids have not been described previously, while a number of the others have been prepared by improved routes. The methods of synthesis are indicated below; new reactions and new compounds are indicated by asterisks. References (in parentheses) are given to reactions previously described. The melting points of the acids are listed in Table I together with literature values where available.

The syntheses followed conventional routes and only a few points need comment. (a) The replacement of Br by CN by the action of cuprous cyanide in dimethylformamide gave excellent yields.[2a] (b) Hydrolysis of the cyanonaphthoic esters to cyanonaphthoic acids required carefully controlled conditions when the cyano group occupied a β-position. (c) Repeated attempts to reduce the formyl group to methyl in methyl 3-formyl-1-naphthoate failed, using the Huang-Minlon method or catalytic reduction.[2b] We had

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[1a] Part I, *J. Am. Chem. Soc.*, **84**, 3539 (1962).

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[2a] L. Friedman and H. Schechter, *J. Org. Chem.* **26**, 2522 (1961).

[2b] N. P. Buu-Hoi and D. Lavit, *ibid.*, **22**, 912 (1957); R. Robinson and F. Weygand, *J. Chem. Soc.*, 386 (1941).