

Measurement of Effective Charge in an Organic Reaction in Solution

By Sergio Thea

ISTITUTO DI CHIMICA ORGANICA DELL'UNIVERSITA', CORSO EUROPA,
GENOVA, ITALY

Andrew Williams

UNIVERSITY CHEMICAL LABORATORY, UNIVERSITY OF KENT AT
CANTERBURY, CANTERBURY, KENT, CT2 7NH

1 Introduction

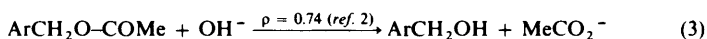
Charge-change is one of the most fundamental consequences of mechanism. Estimation of the variation of charge at an atom is thus a worthwhile goal in the study of the mechanism of a reaction. The result of charge-change is manifested most simply in the effect of change of polar substituents on the equilibrium constant or rate constant for a reaction. The magnitude of the polar effect is predicated by the magnitude of the charge-change at a centre linked with the substituent; it is the tenet of this review that the reverse of this holds and that the value of the charge-change can be estimated from the value of the polar effect. It is implicit in our discussion that the substituents should be able to 'see' or 'report' the charge at a reaction centre and should therefore be coupled to the centre directly, by a conjugating system, by a short run of sigma bonds, or by a short distance 'through' space.

Free energy correlations such as those of Hammett and Brønsted are an essential part of the training of organic chemists.¹ These correlations (equations 1 and 2) are important in the prediction of equilibrium constants, rate constants, the demonstration of the plurality or otherwise of steps or mechanisms, and the determination of charge-change at a reaction centre. The selectivity of a rate or equilibrium constant to change in polar substituent (for example ρ or β) is usually a relative quantity obtained by comparison with the substituent effect on a standard equilibrium.

$$\log k_x = \rho \sigma_x + C_1 \quad (1)$$

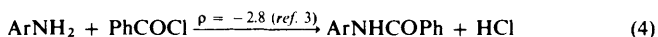
$$\log k_x = \beta \rho K_x + C_2 \quad (2)$$

The physical significance of the selectivity parameter is often not clear because the standard reaction may not be related to the reaction under investigation. For example equations 3 and 4 illustrate reactions where the standard equilibrium is the

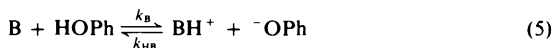


¹ H. Maskill, 'The Physical Basis of Organic Chemistry', Oxford University Press, Oxford, 1985.

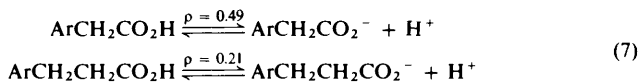
² E. Tommila, *Ann. Acad. Sci. Fennicae*, 1942, **A59**, 4.



ionization of benzoic acids rather than the more appropriate ionization of aryl alcohols or anilines. The Brønsted selectivity of a proton-transfer reaction (equation 5) is significant because the standard equilibrium (equation 6) is directly



related to the reaction in hand. The magnitude of a normal selectivity parameter is not useful as it does not correspond directly to the magnitude of the change in charge. The sign of the parameter indicates whether charge is accumulating or dispersing in a reaction but such data come more readily from a knowledge of the stoichiometry. Attack of anilines on benzoyl chloride has a negative ρ value suggesting a decrease in charge on the nitrogen on passage to the transition-state. Inspection of the rate law (rate = $k[\text{ArNH}_2][\text{PhCOCl}]$) and knowledge of the identity of the products (ArNHCOPh) indicates that charge must be donated by the nitrogen; the inverse could only happen if the amino-nitrogen were acting as an electrophile. Different ρ values are observed for the ionization of ω -arylalkanoic acids (equation 7) where the change in charge on ionization should be independent



of chain length; this provides a further example where selectivity is not a direct measure of charge-change.

2 Estimation of Charge from Polar Substituent Effects

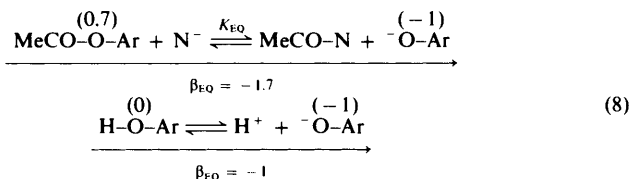
Polar substituent effects are due to interaction with dipole- or charge-change at a reaction centre;⁴⁻⁶ given an experimental selectivity, it should, in principle, be possible to estimate a value for the charge-change giving rise to it. The change in charge at the reaction centre in an equilibrium is the change in hypothetical charge required to give the observed substituent effect compared with that in a standard equilibrium where the charge-change is defined. Typical standard equilibria would be the ionization of phenols, pyridinium ions, carboxylic acids, or any ionization directly related to the reaction in hand. The transfer of the acetyl group from a phenol donor to an acceptor nucleophile (equation 8) has a β_{EQ} of -1.7 . The product phenolate ion has a unit negative charge and the standard equilibrium has a defined charge-change of -1 for ionization of the phenol (corresponding to a β_{EQ}

³ E. G. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1934, 1079.

⁴ L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 96.

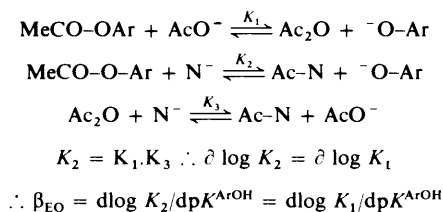
⁵ H. H. Jaffe, *Chem. Rev.*, 1953, **53**, 191.

⁶ J. Hine, *J. Am. Chem. Soc.*, 1960, **82**, 4877.



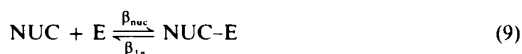
of -1); the ether oxygen in the starting phenyl ester therefore has a charge of $+0.7$ units relative to the charge-change in the ionization of phenol.⁷

The value of β_{EQ} is independent of the non-variant nucleophile and will depend only on the nature of the acyl function and the leaving group as shown in Scheme 1. Equilibrium constants need not be measured explicitly to determine β_{EQ} .



Scheme 1

The value of β_{EQ} may be obtained for the reaction (equation 9) from equation 10



$$\beta_{\text{EQ}} = \beta_{\text{nuc}} + \beta_{\text{lg}} \quad (10)$$

provided the rate limiting step for the measurement of β_{nuc} is the same as that for β_{lg} .

3 Application to Equilibria

Figure 1 and Scheme 2 illustrate charges induced on some donor atoms (the leaving group) by a variety of acyl and other groups. Absolute charge on atoms in molecules is not integral⁸ and is a function of adjacent atoms and solvating species. The defined charge-change on an atom in the standard equilibrium is thus not a true representation even if the overall charge-change may be integral. We refer to the 'measured' charge as 'EFFECTIVE' charge to distinguish it from the absolute charge.

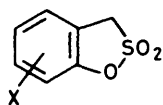
Figure 1 and Scheme 2 illustrate some interesting charge-data which may be related to knowledge from other sources. The carbonyl function induces considerable effective positive charge on the donor nucleophile consistent with a simple resonance explanation; the carbonyl and sulphonyl groups are more electropositive than hydrogen as would be expected from their Hammett sigma

⁷ J. Gerstein and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 4655.

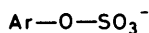
⁸ J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory', McGraw-Hill, New York, 1970.

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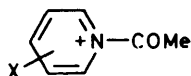
| | | |
|--|---|---|
| $\text{Ar}-\text{O}-\text{CO}-\text{Me}$ (+0.7) | $\text{Ar}-\text{O}-\text{PO}_3^{2-}$ (+0.35) | $\text{Ar}-\text{O}-\text{CO}-\text{CR}_2^-$ (+0.48) |
| $\text{Ar}-\text{NH}-\text{CO}-\text{Me}$ (+0.7) | $\text{Ar}-\text{O}-\text{PO}_3\text{H}^-$ (+0.74) | $\text{Ar}-\text{O}-\text{CO}-\text{NH}_2$ (+0.8) |
| $\text{R}-\text{NH}-\text{CO}_2^-$ (+0.3) | $\text{Ar}-\text{O}-\text{PO}_3\text{H}_2$ (+0.83) | $\text{Ar}-\text{O}-\text{CO}-\text{NH}^-$ (+0.3) |
| $\text{R}-\text{O}-\text{CO}_2^-$ (+0.4) | $\text{Ar}-\text{S}-\text{CO}-\text{Me}$ (+0.4) | $\text{R}-\text{NH}-\text{CHO}$ (+0.5) |
| $\text{Ar}-\text{O}-\text{CS}-\text{NH}-\text{Ar}$ (+1.4) | $\text{Ar}-\text{O}-\text{CS}^--\text{NAr}$ (+0.7) | $\text{Ar}-\text{O}-\text{SO}_2\text{R}$ (+0.8) |



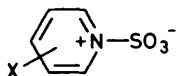
(+0.7)



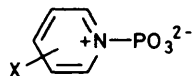
(+0.7)



(+1.6)



(+1.25)

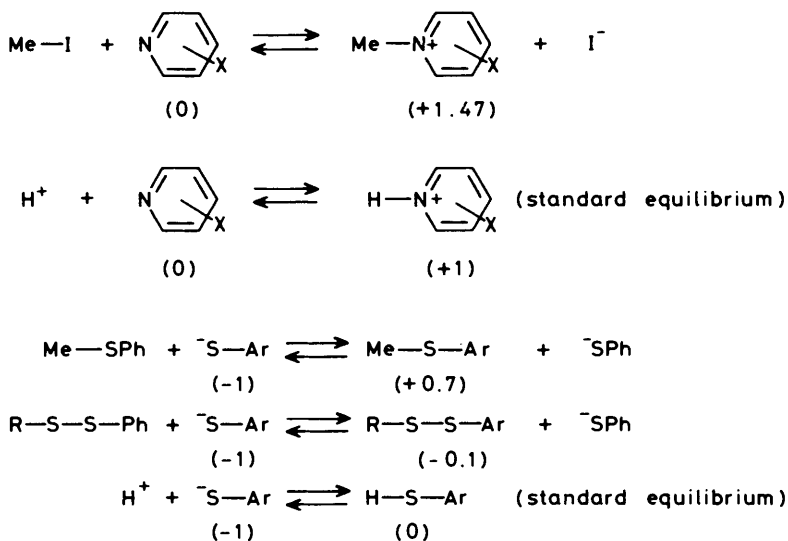


(+1.07)

Figure 1 Effective charges on atoms adjacent to acyl functions. Standard ionizations are related to the leaving group in question; throughout the article effective charges are given in parentheses and changes in effective charge are shown by a Greek delta

values. The sulphuryl and acetyl groups are equally electron withdrawing from oxygen but the sulphuryl group induces a smaller positive charge on pyridine nitrogen than does acetyl; this difference is thought to be due to the electrostatic interaction between formal positive and negative charges in the pyridine-*N*-sulphonates. The rather large charge induced on oxygen by the thionamido-group deserves note and could result from the very high dipolar nature of the C=S bond.⁹ The effective charge on the ether oxygen in esters is relatively insensitive to substituents (in the acyl group itself) except when the formal charge is changed. The acyl substituents (RN-CO- and R₂C-CO-) induce less positive charge on oxygen than do their uncharged analogues. A similar variation in induced charge is seen in the phosphoryl group in its various stages of protonation. It may be that the effect is

⁹ S. V. Hill, S. Thea, and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1983, 437.



Scheme 2

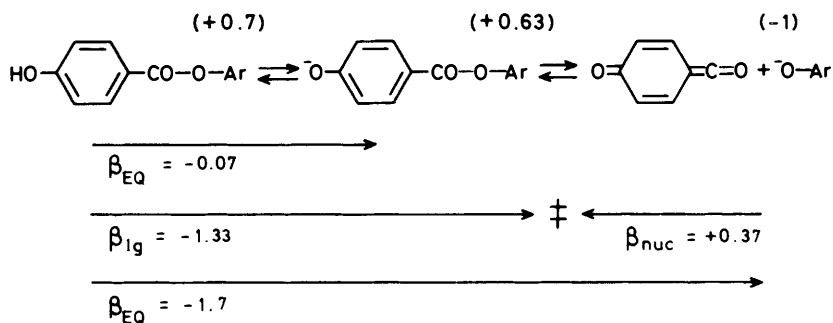
due to electrostatic interaction. The benzoylglycyl group (PhCONHCH₂CO-) induces 0.7 units of positive effective charge on oxygen,¹⁰ identical with that induced by the acetyl group; attack of hydroxide on the methyl esters of the corresponding acids shows an almost two orders of magnitude difference in reactivity. Owing to the relative insensitivity of the effective charge to acyl substituent we can estimate the β_{EQ} for other acyl group transfers with some degree of accuracy; the assumption of a β_{EQ} enables us to calculate β_{nuc} in the example shown in Scheme 3.¹¹

Effective charge is relative to that in a standard equilibrium where the location of the charge is also defined. For example all the charge is defined to be concentrated on the oxygen in the ionization of phenols (equation 8). Although there must be (real) charge changes elsewhere in a molecule the determined effective charge is that which would give the required Brønsted or Hammett selectivity if it were located on the atom defined in the standard equilibrium.

Solvent has a profound effect on the Hammett parameters for the ionization of many acids.⁵ A solvent which solvates ions more weakly than does water might be expected to enable a greater charge build-up on an atom with a consequently larger effective charge or β value. Solvation can be discussed in terms of effective charge change in an ionization in a standard solvent. Throughout this review (with one exception) the solvent in both standard and calibrating equilibria is water.

¹⁰ E. Chrystiuk, A. Jusoh, D. Santafianos, and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1986, 163.

¹¹ G. Cevasco, G. Guanti, A. R. Hopkins, S. Thea, and A. Williams, *J. Org. Chem.*, 1985, **50**, 479.

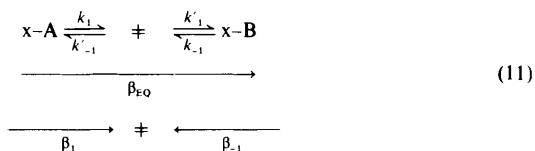


Scheme 3

Scheme 2 illustrates some substituent effects on equilibria for non-acyl group transfer; the methyl group is more electropositive than hydrogen inducing excess positive charge on both pyridine nitrogen and thiol sulphur donor atoms. In the examples given the equilibrium transfer of methyl from iodide to pyridine is measured in acetonitrile whereas the ionization of the pyridine is measured in water. The effective charge induced by the methyl cation will therefore include a solvation effect. The sulphenyl group (derived from sulphenic acid R-S-OH) appears to have an electropositivity towards thiol sulphur similar to that of hydrogen.

4 Application to Transition-states

A transition-state may be regarded formally as a species in equilibrium with ground- and product-states. Theory indicates that given the above assumption, the decomposition of the transition-state forward to products or back to reactants is structure independent with 'rate constants' (k'_1 and k'_{-1}) proportional to kT/h . The values β_1 and β_{-1} (equation 11) are therefore hypothetical β_{EQ} values for reaction from reactant and product respectively to transition-state and are thus measures of effective charge-change on the appropriate atom.



Both Brønsted¹² and Hammett¹³ recognized that the substituent effect on the reaction rate constant should be compared with the equilibrium in hand; for expediency, since substituent effects on equilibria are difficult to obtain (excepting redox or proton transfer) other standards, namely ionizations were chosen.

¹² J. N. Brønsted and K. Pedersen, *Z. Phys. Chem. (Leipzig)*, 1924, **108**, 185.

¹³ L. P. Hammett, *Chem. Rev.*, 1935, **17**, 125.

Leffler¹⁴ defined the parameter α (equation 12) which expresses the transition-state

$$\alpha = d \ln k_1 / d \ln K_{EQ} \quad (12)$$

structure as a linear function of ground- and product-state structures. The equation is general and modifiers of k and K can be temperature,¹⁵ solvent,¹⁶ secondary isotope,¹⁷ and pressure.¹⁵ Variation of polar substituents will yield a value of α which measures the change in charge in the transition-state compared with the change from reactant (x-A) to product (x-B) in equation 11. In order to be able to compare charge between reactions it is usually more useful to employ a standard ionization equilibrium. The reaction under investigation is called the 'calibration equilibrium' because it calibrates the effective charge-change to the transition-state in terms of the overall charge-change.

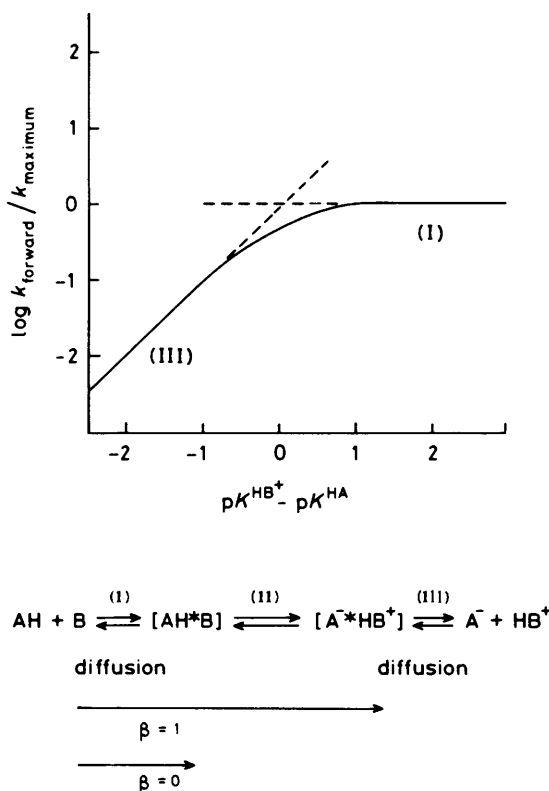


Figure 2 Brønsted plot of the reaction between the varying base (B) and the acid (HA)

¹⁴ J. E. Leffler, *Science*, 1953, **117**, 340.

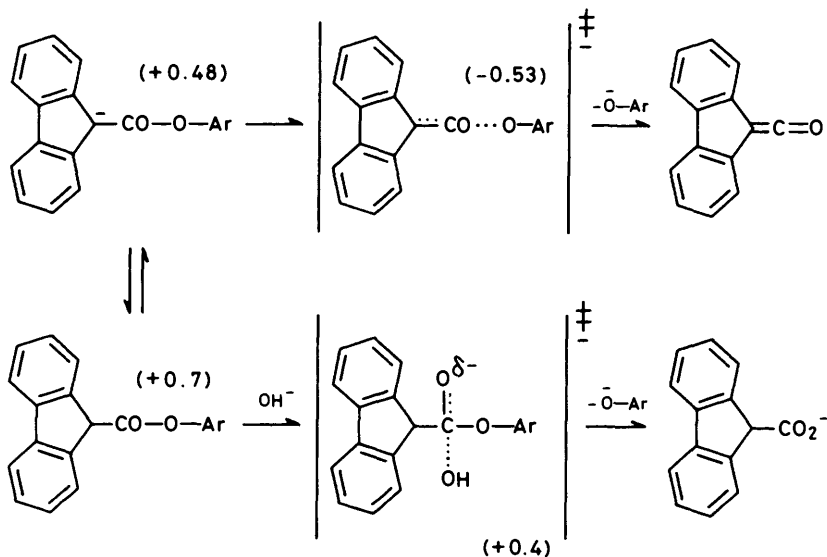
¹⁵ J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', Wiley, New York, 1963, p. 156.

¹⁶ B. G. Cox and A. Gibson, *Symp. Faraday Soc.*, 1975, **10**, 107.

¹⁷ J. J. Gajewski, *Acc. Chem. Res.*, 1980, **13**, 142.

Eigen¹⁸ and Brønsted¹² indicated that variation of the base in a proton-transfer reaction gives a sigmoid plot for the variation of rate constant with base p*K* (Figure 2). The reaction undergoes a change in rate limiting step from (III) to (I) (see Figure 2) as the p*K* of BH⁺ exceeds that of AH. Since the rate limiting steps (I) and (III) are diffusion processes the transition-states will have complete 'B' and 'BH⁺' character respectively, with respect to charge. These structures are in agreement with those predicted from the Leffler α values of zero and unity respectively.

Effective charge-changes can be used diagnostically to distinguish mechanistic paths which give rise to different charge distributions. Aryl esters of 9-fluorenylcarboxylic acid hydrolyse in alkali with a β_{ig} , for the k_{OH} term, of -1.23 .¹⁹ The alkaline hydrolysis of aryl acetates has a β_{ig} of -0.3 ; the charge-change on the ether oxygen is thus -1.23 and -0.3 in an overall change of -1.7 units, indicating a considerable mechanistic difference (Scheme 4). The β_{nuc} for attack of phenolate ions on the ketene may be calculated ($+0.47$) and this agrees with the value for a similar ketene addition reaction ($+0.37$, Scheme 3).



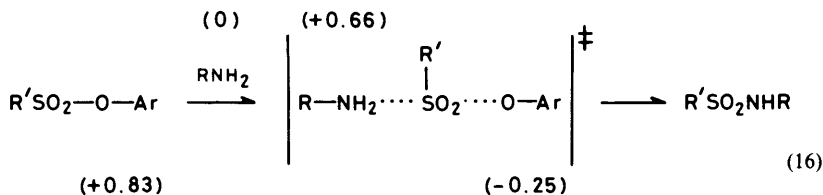
Scheme 4

The effective charge may still be used diagnostically even if the overall β_{EQ} is not known provided it is the same or similar for the comparative reaction. The alkaline hydrolysis of aryl esters of *NN'*-diphenylphosphoramidic acid has a β_{ig} of

¹⁸ M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 1964, 3, 1.

¹⁹ M. Alborz and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1982, 331.

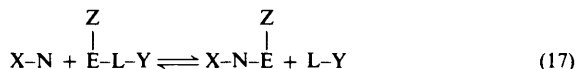
Where it is not possible to obtain a β_{EQ} for the calibrating equilibrium it is often the practice to include simple uncalibrated β values in the charge distribution. This practice is qualitatively valuable but the dangers must be appreciated. For example the aminolysis of aryl sulphonate esters (equation 16)²⁶ includes an uncalibrated



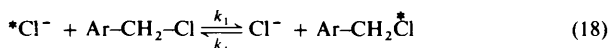
β_{nuc} for attack of the amine. Although one can say that the Ar-O-S bond has a Leffler α of 0.59 for its fission it is not possible to make an estimate of α for the N-S bond formation.

6 Substituents Interacting with Two Bonds

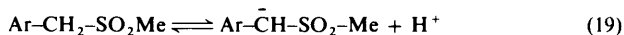
The general reaction (equation 17) illustrates that there are three major substituent



interactions; the substituents on entering (X) and leaving (Y) groups have a first-order interaction with the forming and breaking bonds respectively. The substituents (Z) can interact with both forming and breaking bonds. If equation 17 is used as a calibrating equilibrium for the effect of the (Z) substituent on the transition-state the resultant effective charges or Leffler α value must be discussed carefully. A dramatic example of the problem is given by Pross for the isotope exchange of chloride ion with aryl methyl chlorides (equation 18).²⁷ Since there is



zero substituent effect on the calibrating equilibrium the α value is infinity! The reason for this curious result is that there is exactly zero charge-change on the central carbon in the calibrating equilibrium whereas there is a charge-change in the transition-state. In order to evaluate a reasonable effective charge a different calibration equilibrium must be chosen such as one where a benzylic methylene undergoes ionization as in equation 19.

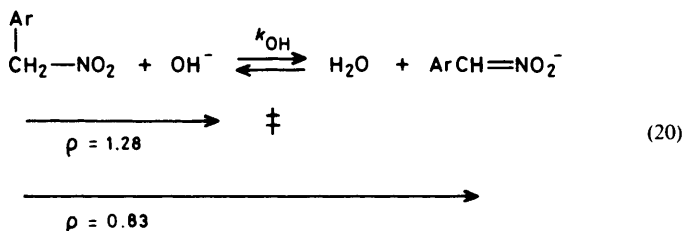


Bordwell first showed that care has to be taken in interpreting Brønsted

²⁶ N. A. Suttle and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1563.

²⁷ A. Pross and S. S. Shaik, *Acc. Chem. Res.*, 1983, **16**, 363.

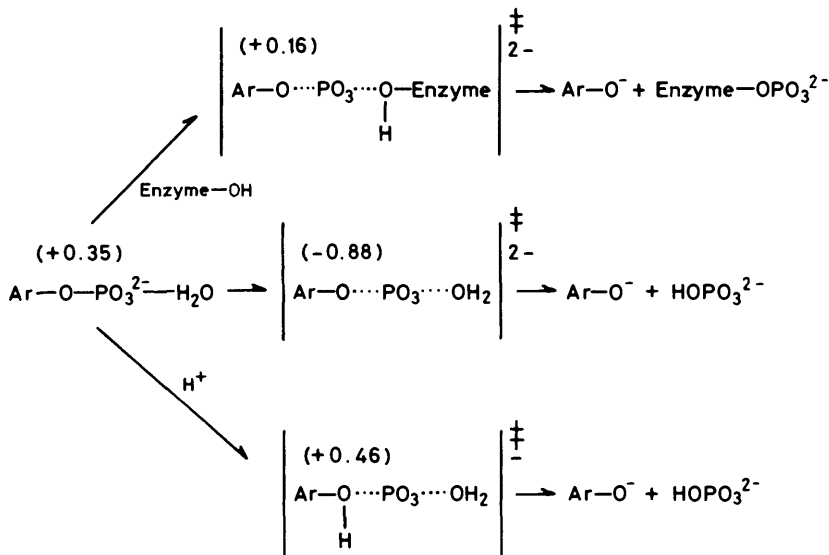
parameters and Leffler α values for reactions with substituents interacting with both forming and breaking bonds. Bordwell found an α value in excess of unity for the slow ionization of nitroalkanes (equation 20).²⁸ A more suitable calibrating equilibrium would be that of equation 19 to estimate the charge-change on the carbon in the transition-state; a difficulty with such a reaction as a calibrating equilibrium for both reactions (equations 18 and 20) is that the charge tends to delocalize onto the activating group, the sulphone.



| Equilibrium | Selectivity (ρ) |
|---|------------------------|
| $\text{ArCHO} + \text{H}_2\text{O} \rightleftharpoons \text{ArCH(OH)}_2$ (+1) (0) | 1.71 ^b |
| $\text{ArCHO} + \text{OH}^- \rightleftharpoons \text{ArCH(OH)O}^-$ (+1) (-0.6) | 2.76 |
| $\text{ArCOMe} + \text{HSO}_3^- \rightleftharpoons \text{ArCMe(SO}_3^-)\text{OH}$ (+1) (+0.3) | 1.2 |
| $\text{ArCOMe} + 2\text{MeOH} \rightleftharpoons \text{ArCMe(OMe)}_2$ (+1) (0) | 1.72 ^b |
| $\text{ArC(Me)=CH}_2 + \text{MeOH} \rightleftharpoons \text{ArCMe(OMe)}_2$ (+0.16) (0) | 0.28 |
| $\text{ArCN} + \text{EtO}^- \rightleftharpoons \text{ArCN}^-(\text{OEt})$ (+1) (-0.58) | 2.7 |
| $\text{ArCN} + \text{EtOH} \rightleftharpoons \text{ArC(NH)(OEt)}$ (+1) (0) | 1.7 ^b |
| $\text{ArCH=NO}_2^- + \text{H}_2\text{O} \rightleftharpoons \text{ArCH}_2\text{NO}_2 + \text{OH}^-$ | -0.83 |
| $\text{ArCH=NNHCONH}_2 + \text{H}_2\text{O} \rightleftharpoons \text{ArCH(OH)NHNHCONH}_2$ (+0.5) (-0.06) | 0.17 |
| $\text{ArCHO} + \text{NH}_2\text{NHCONH}_2 \rightleftharpoons \text{ArCH(OH)NHNHCONH}_2$ (+1) (-0.06) | 1.81 |
| $\text{RCHO} + \text{HSR} \rightleftharpoons \text{RCH(OH)SR}$ (+1) (+0.02) | 1.65 ^a |
| $\text{RCHO} + ^-\text{SR} \rightleftharpoons \text{RCH(O}^-\text{)SR}$ (+1) (-0.77) | 2.97 ^a |

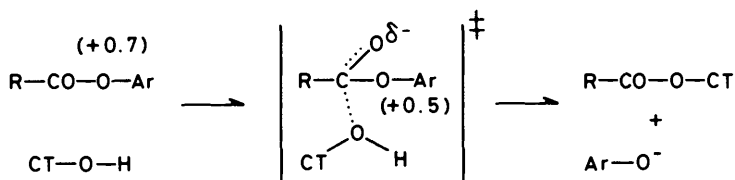
²⁸ F. G. Bordwell and W. J. Boyle, *J. Am. Chem. Soc.*, 1972, **94**, 3907.

studied. Hall³¹ showed that alkaline phosphatase has a very shallow Brønsted plot (Figure 3) for k_{cat}/K_m for aryl phosphates against the $\text{p}K$ of the corresponding phenol; we compare the β_{lg} (-0.19) with values for other phosphoryl group transfer reactions (Scheme 7). The electronic requirements of the enzymatic phosphorylation are close to those of the monophosphate hydrolysis catalysed by the proton. It is inferred that there is considerable electrophilic participation in the enzymatic reaction. The small change in effective charge in the acylation of chymotrypsin by specific substrates is consistent with electrophilic catalysis feeding positive charge to the ether oxygen (Scheme 8).³²



Scheme 7

CHYMOTRYPSIN (CT) acylation by specific substrates



Scheme 8

³¹ A. D. Hall and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 1680.

³² (a) A. Williams, *Biochemistry*, 1970, 3383; (b) W. P. Jencks, *Cold Spring Harbor Symposia on Quantitative Biology*, 1971, 36, 1.

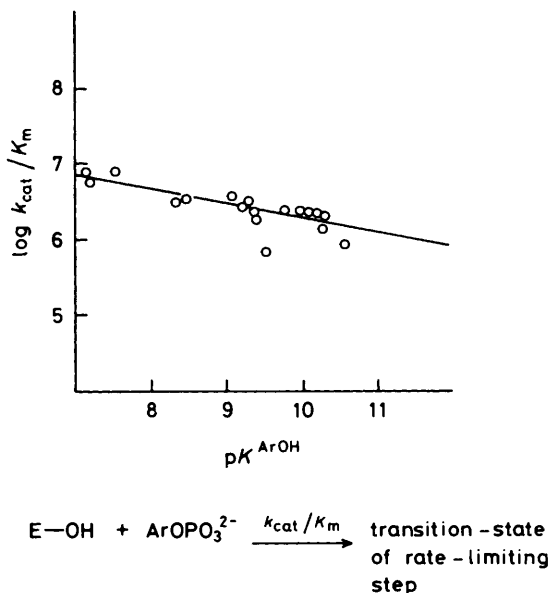


Figure 3 Phosphorylation of alkaline phosphatase with aryl monoposphate esters

8 Concluding Remarks

Neither the Leffler α index nor the effective charge-change relative to the overall charge-change are measures of the isolated bond-order in the transition-state. These parameters are measures of the structure of the transition-state relative to those of reactant- and product-states; this structure includes both solvation, bond-order, and any other factor affecting the charge on the atom 'seen' by a polar substituent. There is a convention that solvation is excluded in pictorial representations of reaction mechanisms in solution; this tends to exaggerate the importance of the isolated bond-order. It is, nevertheless, the overall structure of the transition-state (not the isolated reactant molecules) which is important in explaining reactivity and not simply knowledge of bond-order.

We stress that polar substituent effects do not directly measure bond-order; particularly when the polar substituent interacts with only one bond it is possible to define the charge on an atom relative to a defined charge-change in a standard ionization. Work on the dissection of this effective charge in contributions from 'bond-order', solvation and other effects is in its infancy but is progressing in various laboratories.^{11,21,29,33}

There seems no sure empirical way of dealing with substituent effects on reaction

³³ (a) C. F. Bernasconi, *Tetrahedron*, 1985, **41**, 3219; (b) F. Terrier, J. Lelievre, A. P. Chatrousse, and P. Farrell, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1479; (c) W. P. Jencks, S. R. Brant, J. R. Gandler, G. Fendrich, and C. Nakamura, *J. Am. Chem. Soc.*, 1982, **104**, 7045; (d) E. Grunwald, *J. Am. Chem. Soc.*, 1985, **107**, 125 and 4710.

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rates except by comparison with effects on standard equilibria. In this respect the approach described in this article is quite general; detail of the structure of the transition-state other than charge comes from volumes of activation, secondary isotope effects, and entropy changes calibrated by the magnitude of the same effects on standard equilibria.

In order to obtain information on 'bond-order' and solvation it is going to be very important to define exactly what is meant by these quantities in such a manner that they can be related to the effect in question. At present the available definitions of bond-order are not suitable to compare with charge obtained from polar substituent effects.

This review is based on an invited lecture given at a meeting of the Organic Reaction Mechanisms Group of the Royal Society of Chemistry, Perkin Division, held at University College London in January 1986.