

Effective Charge and Leffler's Index as Mechanistic Tools for Reactions in Solution

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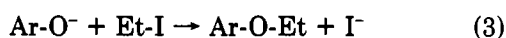
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Knowledge of the change in electrical charge on particular atoms is essential to understanding the mechanism of a reaction. Linear free-energy relationships, notably the "Hammett" and "Brønsted" types (eq 1 and 2, respectively)¹ have been used extensively to estimate charge change at reaction centers.

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

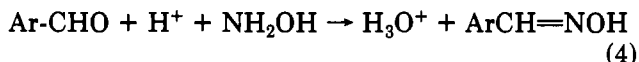
$$\log k_x = \beta\rho K_x + C_2 \quad (2)$$

The use of these equations to determine even a qualitative charge description is often either erroneous or unnecessary. In an undergraduate example, it can be deduced from a negative ρ value that the attack of aryl oxide ions on ethyl iodide involves depletion of charge on the oxygen and gain of charge on the ethyl iodide atoms (eq 3). The observation of a second-order



rate law and aryl ether product gives the same answer. The Hammett equation is irrelevant with regard to exact measurement of charge in this case because of the different modes of transmission of the substituent effect in benzoic acid ionization and in the reaction in hand. The correlation of sign of the Hammett coefficient and the sign of the charge change may even be ambiguous if the standard equilibrium is markedly different from a reaction under study; this problem could be particularly important for low values of the Hammett coefficient.

Not all qualitative charge distributions can be solved by simple reference to rate law or product. The acid-catalyzed condensation of hydroxylamine and benzaldehydes (eq 4) could involve charge build up or depletion on the carbonyl carbon depending on the relative timing of the addition of the electrophile and nucleophile.



Although charge changes in a reaction are directly connected to the substituent effect in, say, a Brønsted or Hammett relationship, the connection is usually complex because the standard reaction is often completely divorced from the reaction in question. I shall demonstrate in this Account that it is possible to determine charge change by the use of substituent effects measured against standard equilibria *directly related* to the reaction. This approach is not novel but has been neglected because of the lack of suitable data on sub-

stituent effects on appropriate equilibria.

Leffler² first advanced the hypothesis that kinetics should give a description of the transition state in terms of the known structures of reactant and product states if the effects of *modifiers* on the rate constant were compared with their effects on the overall equilibrium constant of the reaction. If the progression from A to B (eq 5) involves a smooth change, as might occur if the modifier affects only one bond, then the structure of that bond in the transition state would be somewhere between that of A and B. Leffler's equation is a general



$$d \ln k/d \ln K = \alpha \quad (6)$$

one where modifiers can be variation in temperature,^{2b} solvent,³ secondary isotope effect,⁴ and pressure.^{2b} By far the most popular modifier is a polar substituent that causes variation in rate or equilibrium by electrostatic interaction with charge or dipole at the reaction center.⁵ Thus, the value of α when determined from polar substituent effects is a measure of the change in *charge* distribution at the reaction site during formation of the transition state from the reactants.

It is often convenient in practice to express changes in rate and equilibrium constant with respect to a property of the substituent such as σ or the pK of an acid containing the substituent. Equation 6 then transforms into eq 7 and 8, where β_F and ρ_F are the

$$\alpha = (d \ln k/d \text{p}K_a)/(d \ln K/d \text{p}K_a) = \beta_F/\beta_{EQ} \quad (7)$$

$$\alpha = (d \ln k/d \sigma)/(d \ln K/d \sigma) = \rho_F/\rho_{EQ} \quad (8)$$

Brønsted and Hammett coefficients for the forward reaction rate constant and β_{EQ} and ρ_{EQ} are those for the overall reaction which is termed a *calibrating* equilibrium. The equilibrium representing the property of the substituent is termed a *standardizing* equilibrium and is best chosen to resemble the reaction in question. For example, reactions of esters with varied leaving groups are usually best correlated with the ionization of the leaving alcohol (eq 9 and 10).

In order to be useful in describing the structure of the transition state, the substituent variation must be remote from the reaction center to obviate gross mecha-

(1) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper and Row: New York, 1981.

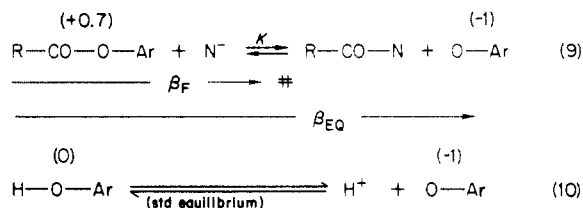
(2) (a) Leffler, J. E. *Science* 1953, 117, 340. (b) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; pp 156-161.

(3) Cox, B. G.; Gibson, A. *Symp. Faraday Soc.* 1975, 10, 107.

(4) Gajewski, J. J. *Acc. Chem. Res.* 1980, 13, 142.

(5) (a) Hine, J. J. *Am. Chem. Soc.* 1959, 81, 1126. (b) Hine, J.; Bailey, W. C. *Ibid.* 1959, 81, 2075. (c) Hine, J. *Ibid.* 1960, 82, 4877. (d) Reimann, J. E.; Jencks, W. P. *Ibid.* 1966, 88, 3973. (e) Fersht, A. R. *Ibid.* 1971, 93, 3504.

Andrew Williams obtained his D. Phil. under Gordon Lowe at Oxford in 1964 and spent the next year with Myron Bender at Northwestern before joining the University of Kent in 1966. He has been studying fundamental mechanisms of reactions in solution, including enzyme- and polymer-catalyzed reactions, largely of the acyl-transfer type.



nism changes caused by, for example, steric effects. The total electronic change in the modifier must also not be large enough to cause a gross variation in transition-state structure.

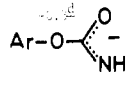
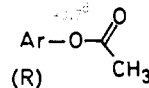
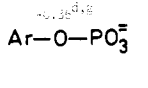
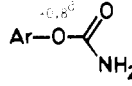
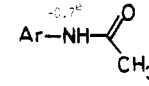
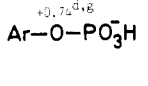
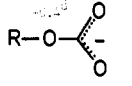
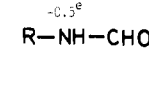
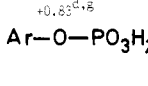
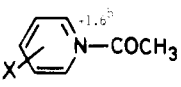
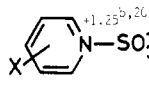
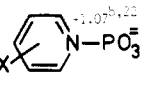
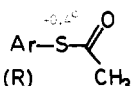

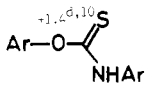
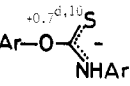
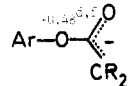

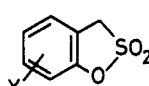
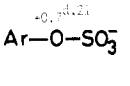
We can express the Leffler α value using a physically more familiar quantity, namely, the "effective" charge⁶ on an atom in the transition state relative to that in a standard equilibrium such as the ionization of an acid. "Effective" charge has been defined by McGowan^{7,8a} as the hypothetical charge that would give the same electronic effect in a rate or physical property as the group in question. We use a slightly different definition—the "effective" charge is the hypothetical charge required to give the observed substituent effect compared to that in the standard equilibrium where the charge is defined; effective charge is noted in parentheses throughout this Account.

The Brønsted β_{EQ} value for the calibrating equilibrium in eq 9 is 1.7 times that for the standard equilibrium which is unity. If we define the charge *change* on the phenolic oxygen in eq 10 as -1 , the effective charge change on the oxygen giving rise to the enhanced selectivity to substituent change in the calibrating equilibrium is -1.7 . The *change* in effective charge to the transition state for eq 9 is β_F measured against the ionization of phenols. We can compute the effective charge for the atoms in product, reactant, and transition states to be -1 , $+0.7$, and $0.7 - \beta_F$. If we had used Hammett ρ values, the effective charges would be the same but would equal respectively -1 , $(\rho_{EQ}/\rho_{std} - 1)$, and $0.7 - \rho_F/\rho_{std}$.

While the effective charge is an experimental quantity, its interpretation is subject to stricture. Values of β or ρ or of the other selectivity parameters such as ρ^* , ρ_1 when taken alone can sometimes be used to determine mechanism because it is now known that certain mechanisms have these selectivities within certain ranges. The isolated β or ρ value for a rate is of no use with regard to charge measurement unless it is compared with a calibrating equilibrium. For example, the attack of phenolate ions on isocyanic acid has a β_N value of 0.66:^{8b} taken alone this value could indicate either a large or small change in charge on the oxygen. The β_N must be compared with the β_{EQ} in the calibrating equilibrium before it is of any use.

In general, the effective charge for a transition state may only be interpreted in a straightforward way when the substituent interacts with *only one bond undergoing a major electronic change*. The index will only therefore apply to the electronic state of that bond in the transition state interacting with the substituent. The effective charge at an atom in a transition state cannot be simply related to bond order because it could be the net result of more than one bond or hybridization

Table I
Effective Charges on Atoms Adjacent to Acyl Functions^a

^a Most of the effective charges recorded here are from ref 17. ^b Relative to the ionization of pyridinium ions. ^c Relative to the ionization of thiols. ^d Relative to the ionization of the hydroxyl group Ar-OH or R-OH. ^e Relative to the ionization of ammonium ions. ^f From Alborz, M.; Douglas, K. T. *J. Chem. Soc., Perkin Trans. 2* 1982, 331. ^g From Bourne, N.; Williams, A. *J. Org. Chem.* 1984, 49, 1200.

change and solvent interaction. We believe that in most cases effective charge is the safer parameter to employ, rather than the Leffler index, because there is the danger with the latter that it could be assumed to be a direct measure of bond order.

Effective charges refer to the *solvated* state of reactant and product in the standard and calibrating equilibrium. We conform in this Account to the convention of omitting solvent from written structures and point out that it is safer, but not always possible, to use the same solvent system for both calibrating and standard equilibria.

The essence of the present approach to estimation of an unknown charge is to compare the properties of the unknown with those of a related *known* structure. Such an approach is a standard tool throughout science.

As well as providing us with detailed charge in the transition state relative to that in a known structure, knowledge of effective charge is of use in distinguishing between grossly different mechanistic paths.

Effective Charge on Reactant and Product Atoms


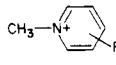

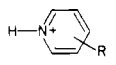
Acyl Group Transfer. The effective charge on the oxygen in the donor ester (eq 9) is independent of the nature of the acceptor group (N) and we may express this value with reference only to the acyl function and

(6) Jencks, W. P. *Brookhaven Symp. Quant. Biol.* 1971, 36, 1.

(7) McGowan, J. C. *J. Appl. Chem.* 1960, 10, 312.

(8) (a) McGowan, J. C. *Chem. Ind.* 1948, 632. (b) Al Rawi, H.; Williams, A. *J. Am. Chem. Soc.* 1977, 99, 2671.

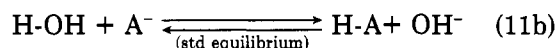
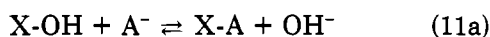
Table II
Comparison of β Values for Transfer of a Variety of Groups between Basic Donors and Acceptors^a

formal electrophile being transferred		base donor	adduct	β_{EQ}^b
CH_3^+ ²⁴	+			1.47 ^c
		(0)	(+1.47)	
H^+	+			1.0
		(0)	(+1.0)	
CH_3^+ ²⁵	+	S-Ar	$\text{CH}_3\text{-S-Ar}$	1.7
		(-1)	(+0.7)	
H^+	+	S-Ar	H-S-Ar	1.0
		(-1)	(0)	
R-S^+ ²⁶	+	S-Ar	R-S-S-Ar	0.9
		(-1)	(-0.1)	

^a Effective charge, defined and measured, is given in parentheses. ^b For the formation of adduct. ^c This refers to acetonitrile solvent and the standard is in water. The effective charge will reflect the difference in solvation as well as bonding differences.

the donor (OAr in eq 9); Table I illustrates effective charges induced on some donor atoms (the "leaving" group) by a variety of acyl groups. Absolute charge on atoms in molecules is not integral⁹ and is a function of adjacent atoms and the solvating species. The absolute charge "seen" by the substituents can only be expressed relative to the charge defined by the standardizing equilibrium. The effective charge induced on oxygen roughly parallels the polarity of the acyl group as judged from σ_p values. All acid functions are more electron withdrawing than hydrogen and gross changes such as ionization of the acyl group alter the effective charge in the predicted direction. Although the SO_3^- and CH_3CO groups induce equally large effective charges on oxygen, the acetyl is much more electron withdrawing than the sulfonato toward pyridine. The cause of this may be an electrostatic effect between the formal positive and negative charges in the pyridine-*N*-sulfonate. An interesting result is the large effective charge induced on oxygen by the $\text{C}=\text{SNHAr}$ group probably due to the highly dipolar character of the $\text{C}=\text{S}$ bond.¹⁰

Transfer of Other Groups. Equations 11a and 11b are general representations of the transfer of a group -X from donor to acceptor. Variation of substituents



in the base A^- will reveal, through their effect on process 11a, an effective charge induced by the X group on the base atom, compared with that induced by the H group in standard reaction 11b. In the previous section X is an acyl function, but it could be any transferable group; for example, an alkyl.¹¹ Few studies have been reported of substituent effects on nonacyl group transfer. The results of some of these are given in Table II.

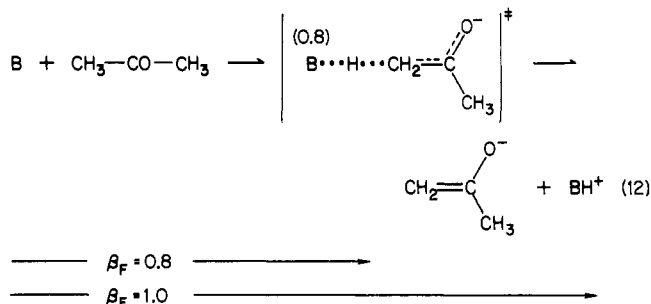
(9) Pople, J. A.; Beveridge, D. L. "Approximate Molecular Orbital Theory"; McGraw-Hill: New York, 1970.

(10) Hill, S. V.; Thea, S.; Williams, A. *J. Chem. Soc., Perkin Trans. 2*, 1983, 437.

(11) (a) Hine, J.; Weimar, R. D. *J. Am. Chem. Soc.* 1965, 87, 3387. (b) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley-Interscience: New York, 1975; Chapter 7. (c) Hine, J. *J. Am. Chem. Soc.* 1971, 93, 3701.

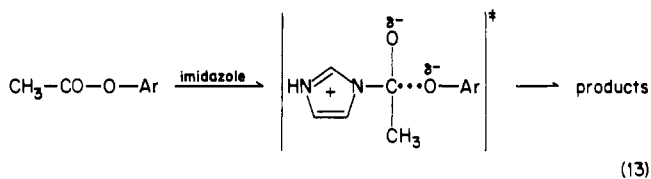
Mechanism

Proton Transfer. The classical Brønsted relationship gives effective charge on the basic atom because the selectivity for the equilibrium (β_{EQ}) is unity. The enolization of acetone, catalyzed by bases with electronegative atoms (eq 12),¹² has a Brønsted coefficient

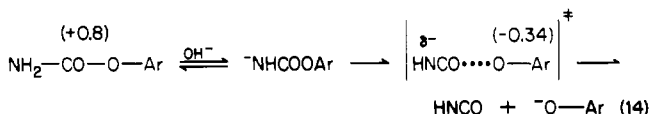


of 0.8 equivalent to an increase of +0.8 unit of effective charge on the basic atom in the transition state. We can deduce from this that the B-H bonding is some 0.8 of that in the product, but we cannot deduce anything about bonding in the rest of the transition state from this experiment.

Carboxyl Group Transfer. Nucleophilic substitution into aryloxy esters (eq 9) is correlated by the ionization of phenols (eq 10) which is employed as the standardizing equilibrium. Attack of imidazole on aryloxy esters exhibits a change of -0.79 unit¹³ of effective charge on the aryl oxygen. In this reaction cleavage of the tetrahedral intermediate initially formed is thought to be rate limiting;¹³ that explains the larger change in effective charge than in the attack of hydroxide on aryl acetates (-0.3)¹⁴ where cleavage of the C-OAr bond appears not to occur in the rate-limiting step.



The above considerations can help diagnose the gross difference in mechanism between hydroxide-catalyzed hydrolysis of aryl carbamates and aryl acetates. The β_{lg} for attack of hydroxide ion on aryl carbamates indicates a change in effective charge of -1.16 (eq 14) on



the oxygen compared with a total change of -1.80 units in the calibrating equilibrium (eq 10). This change is well in excess of the -0.3 unit seen in the alkaline hydrolysis of aryl acetates ($\text{B}_{\text{Ac}2}$ mechanism) and is explained by an E1cB process with rate-limiting cyanate formation.^{8b,15}

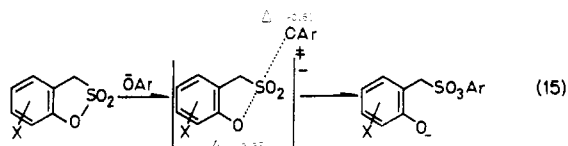
Sulfonyl Group Transfer. The observation that phenolate ions react with sultones to give arenesulfonate esters (eq 15)¹⁶ provided the opportunity to measure

(12) Bender M. L.; Williams, A. *J. Am. Chem. Soc.* 1966, 88, 2502.

(13) Williams, A.; Naylor, R. A. *J. Chem. Soc. B* 1971, 1967.

(14) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* 1964, 86, 837.

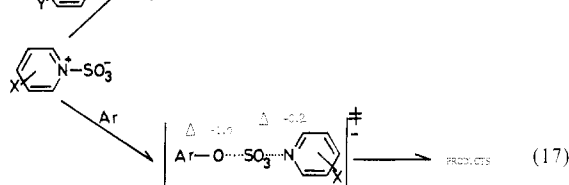
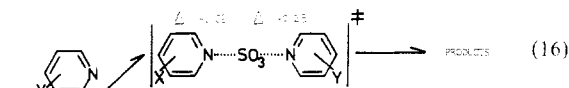
(15) Williams, A. *J. Chem. Soc., Perkin Trans. 2* 1972, 808.



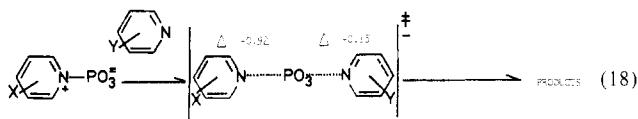
substituent effects on bonds undergoing both formation and fission.¹⁷ In a system where the effective charges on leaving group and nucleophile are defined by the *same* standardizing equilibrium (phenol ionization), it might be expected that conservation of the *change* in charge Δ ($\sum \Delta = 0$) would be consistent with a concerted process.¹⁷ In a stepwise mechanism the central group ($-\text{SO}_2-$) would be expected to take some of the charge; the observation that changes in effective charge are of equal magnitude within the experimental error is evidence for a symmetrical and hence concerted process.

Conservation of effective charge, while apparently a reasonable hypothesis, is subject to many problems,^{18,19} not least its being subject to the sum of the errors in the constituent effective charges. The approach is valid provided the effective charge is defined on the same standard equilibrium and it refers to similar atoms in the reaction, as in the above example. Of course absolute charge is conserved; it is important that in this case the two types of charge not be confused.

Transfer of the SO_3 group between pyridine acceptors is a symmetrical reaction (eq 16);²⁰ the change in effective charge Δ on the entering nitrogen is not of equal magnitude to the change on the leaving nitrogen. The excess must reside in the SO_3 group of atoms in which the negatively charged oxygens must assist in expulsion of the leaving group. The sulfur and three oxygens lose 0.79 of their original charge and will thus approximate to sulfur trioxide in structure in the transition state. A similar charge distribution is deduced for the transfer of the SO_3 group between pyridine and phenolate ions (eq 17).²¹ The interpretation in the latter case is subject to the stated reservations regarding effective charge conservation because the effective charge on oxygen is measured against phenol ionization whereas the other is against pyridine ionization.



Phosphoryl Group Transfer. Transfer of the PO_3^- group between pyridine donors and acceptors (eq 18)



(16) Farrar, C. R.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1912.

(17) Deacon, T.; Farrar, C. R.; Sikkell, B. J.; Williams, A. *J. Am. Chem. Soc.* **1978**, *100*, 2525.

(18) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

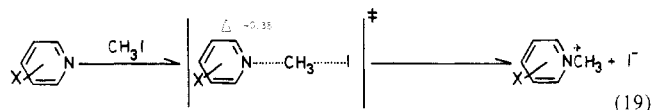
(19) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 464.

(20) Hopkins, A. R.; Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 3358.

(21) Hopkins, A. R.; Day, R. A.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 6062.

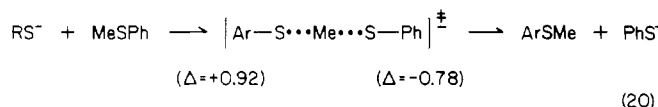
is a symmetrical reaction.^{22,23} The change in charge on the leaving group (-0.9) is not balanced by the loss in effective charge on the entering nitrogen ($+0.15$). The excess charge must come from the PO_3 group of atoms which assists in the expulsion of the leaving group. Since nearly unit charge is removed from these atoms, they will resemble the metaphosphate ion, PO_3^- , in the transition state. In this example the effective charge is measured relative to that in the pyridine ionization.

Transfer of Alkyl and Related Groups. Equilibrium constants and their variation are even more difficult to measure for alkyl group transfer than for acyl groups. Arnett and Reich²⁴ obtained data for the transfer of methyl between pyridines and iodide ion in acetonitrile solvent (eq 19). Relative to the standard



ionization of pyridinium ions in water, the β_{EQ} is 1.47, indicating that the methyl group is more electropositive than hydrogen when attached to pyridine nitrogen. The above authors²⁴ vigorously deny the relevance of their parameters to the "mechanism" of the reaction; the α for pyridine attack on methyl iodide (0.26) is consistent with an effective charge of $+0.38$ on nitrogen in the transition state relative to a calibrating change of 1.47. This low value could arise from weak N-C bonding or a compensation effect which could include solvent. In any case a better description of the charge distribution awaits data for the ionization of pyridinium ions in acetonitrile. It is likely that the $+1.47$ units on the *N*-methylpyridinium nitrogen is an upper limit. The electronic state of the C-I bond in the transition state is *not* monitored by these substituent effects.

Methyl is also more electron withdrawing than hydrogen when compared against sulfur; Lewis and Kukes²⁵ found data for the transfer of methyl from sulfur to sulfur (eq 20), which can be interpreted as



being consistent with a total effective charge change of $+1.7$ when compared with the standard ionization of thiophenols. The change in effective charge on entering and leaving sulfurs is approximately balanced, consistent with a concerted methyl group transfer.

The transfer of the MeS group bears a superficial relationship to the methyl group transfer. Data for the attack of thiol anion on disulfides²⁶ may be translated to indicate a balance in the change of effective charge on entering and leaving groups (eq 21). The data are consistent with a concerted transfer of the RS group. This conclusion is reinforced by the observation of a linear Brønsted relationship²⁶ over a range of pK^{RSH} where curvature would be expected for a stepwise

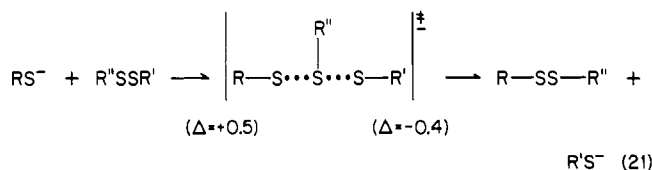
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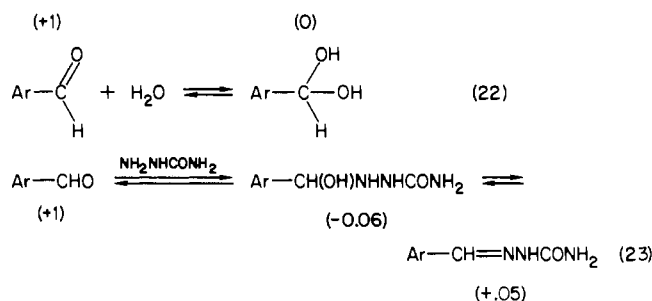
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process. In this example the effective charges refer to the ionization of thiols as the standard equilibrium.

Hybridization Changes Monitored by Substituent Effects

Calibration Equilibria. When the polar substituent "sees" the charge change on an atom undergoing only a "hybridization" change, the concept of effective charge is not easily applied. The most convenient substituent parameters to use are Hammett's σ , Taft's σ^* , or Charton's σ_1^1 because ionizations are not explicitly involved. Let us consider addition to the ArCO group. A standardizing equilibrium is necessary for the quantitative evaluation of "charge" and we take the addition of water to benzaldehydes as a standard with arbitrarily defined unit change in effective charge on the central carbon (eq 22). The Hammett ρ value for the equi-



librium between semicarbazone and benzaldehyde²⁷ indicates that there is +0.05 arbitrary unit of effective charge on the trigonal carbon attached to the nitrogen, compared with the standard system. The effective charges for a few representative equilibria presented in Table III have been calculated and the values agree with expectation; for example, trigonal carbon is essentially more electrophilic than is tetrahedral.²⁸

Apparent Anomalies. Bordwell²⁹ has convincingly shown that the Leffler index for the ionization of substituted nitroalkanes exceeds unity. An explanation of the anomalous behavior, summarized by Kresge,³⁰ is that union of reactants creates negative charge on the central atom absent before and after the union. The overall reaction is not suitable as a calibrating equilibrium as the negative charge does not reside on the carbon in the nitronate ion base.

A dramatic example of the breakdown of rate/equilibrium relationships occurs for identity exchange reactions where the substituent changes the rate but not the equilibrium constant, thus giving an infinite α

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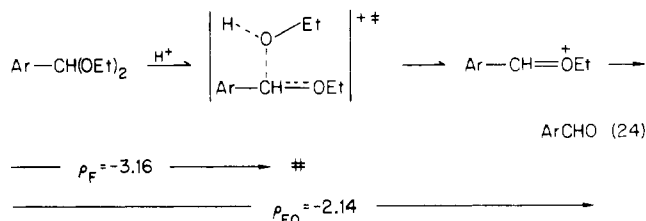
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value.³¹ Proper treatment is required for these relationships to give useful effective charge data.

The acid-catalyzed hydrolysis of diethyl acetals of substituted benzaldehydes has a ρ value well in excess of that for the equilibrium constant (eq 24),³² providing



a further example of an apparent breakdown of the Leffler hypothesis. The transition state proposed from other data has considerable positive character, consistent with an effective charge more positive than that on the aldehyde function. In order to gauge the effective charge on the carbon-oxygen bond in the transition state, we need to know the ρ value for the equilibrium from acetal to oxonium ion, which should be more negative than -3.16.

Anomalous behavior might also arise from differential "solvation" effects on the transition state compared with those on the product.³ This explanation has been invoked for the anomalously negative β_{lg} values sometimes observed in oxyanion release.³³ The oxygen is considered to be less solvated in the transition state than in the product, thus leading to a less dispersed charge which will be more susceptible to substituents than is the more solvated ion.³⁴

Enzyme Mechanisms

The determination of substituent effects for enzyme-catalyzed reactions is only possible with enzymes of wide specificity.^{6,35} Electronic effects can still be hidden under specific interactions of enzyme and substrate; this problem must be countered by the use of a sufficiently large range and number of substituents to obtain a statistical trend.

A number of hydrolytic enzymes have been investigated in this way. There seems to be good evidence that the leaving group of the substrate is more positive than it would otherwise be in a normal chemical hydrolysis. This has been attributed to electrophilic participation, an hypothesis supported also by static evidence from X-ray data.³⁶ For example, the Brønsted β_{lg} against the ionization of phenols for the acylation of chymo-

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