Linear Free Energy Relationships and the Reactivity–Selectivity Principle[1,2]

C. D. JOHNSON

School of Chemical Sciences, University of East Anglia, Norwich, England

Received August 13, 1974 (Revised Manuscript Received October 31, 1974)

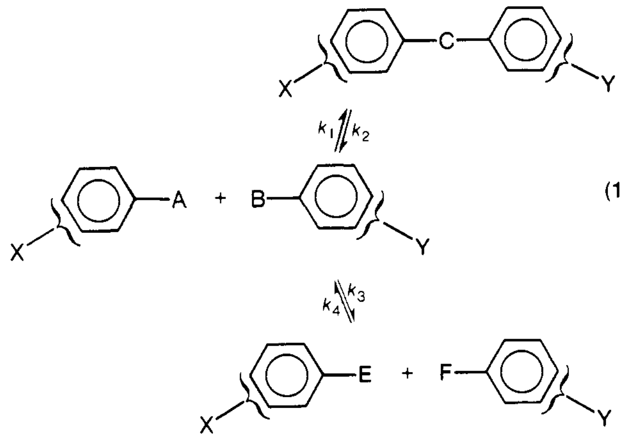
Contents

I. Introduction

That the slopes of linear free energy relationships (LFER's) of Hammett or Bronsted form are in some way measures of gross transition state (TS) structure is well established, in that the observation of curvature in such free energy correlations is widely accepted as indicative of mechanistic changeover. This concept has proved useful in so many mechanistic investigations as to defy enumeration. The problem under discussion here is a somewhat more subtle one, namely the question of the extent to which such FER's yield information on the change of TS structure which results from change in rate of a given chemical process of constant mechanism. A number of theoretical deductions[3–16] have been made of which that of Hammond[3] is most widely quoted, but in general all are taken to manifest themselves by the observation that: (a) an FER for a given reaction series is not linear over large rate and therefore large free energy changes; (b) the greater the rate at which a series of reactions proceed, the more the TS for that series resembles reactants giving rise to decreased selectivity, i.e., smaller Hammett ρ values or Bronsted α or β values. Such deductions comprise the reactivity–selectivity principle (RSP) or the Hammond–Leffler postulate (HLP). In one treatment[7] the possibility of the reverse effect, "anti-Hammond" behavior, is considered.

To investigate the validity of such concepts experimentally, it is first essential to define the type of system which can be legitimately employed for such an enterprise. It would seem that *variations of rate and selectivity induced by solvent change or by a structural change at or adjacent to the reacting center* (for example, substitution of tosylate for bromide as a leaving group, of semicarbazide for phenylhydrazine in additions to carbonyl groups, of phenyl acetate for 1-acetoxy-4-methoxypyridinium in the study of their reactivity with amines, or comparison of aromatic chlorination in acetic acid with nitration in sulfuric acid, etc.) *are not legitimate for such an investigation.* Here one has introduced transition state structural modifications of large magnitude quite independent of those which might be produced according to the operation of the HLP.

Ideal data for such a purpose are provided by observations of k_1, k_2, k_3, or k_4 in schemes as those in eq 1, for which the correspondence produced may be termed a multiple structure–reactivity correlation.[17,18] The effort of substituents X and Y should be large, so that Δ log k and therefore $\Delta\Delta G^{\dagger}$ values encompass as wide a range as possible. This substitution effect on k may be expressed in the form of σ_X values



(1)

(the Hammett equation) or pK_a values (the Bronsted equation). Both treatments are, of course, essentially equivalent in that Bronsted α or β values are ratios of ρ values (the ρ value for the rate correlation divided by the ρ values for the pK_a correlation), but the two relationships are usually discussed as being distinct. One manifestation of this artificial separation has been that generally more stringent and methodical regulations have been placed on steric effects in the formulation of Hammett than of Bronsted correlations. Thus in the plot of Figure 4 given later, a wide variation of base types is displayed; presumably the resultant variations of the steric and proximity effects in this and other reactions which yield Bronsted style correlations parallel that for protonation equilibration in the medium employed for definition of pK_a. A method for overcoming any breakdown in this compensation effect is the Pfluger analysis discussed subsequently.

Applications of the RSP to systems such as eq 1 should, according to (a) and (b), lead to the type of free energy relationship shown in Figure 1. We can find, however, *absolutely no evidence* for this pattern of behavior; the pertinent results are now discussed.

II. How Linear Are "Linear" FER's?

Information for the clarification of proposition (a) of section I is readily available; an ever increasing number of such correlations show good linearity with no indication of any curvature. The only reason for small departures from linearity are that the experimental observation of the wide reactivity ranges involved may introduce differential errors.

Several examples have been cited in this context pre-

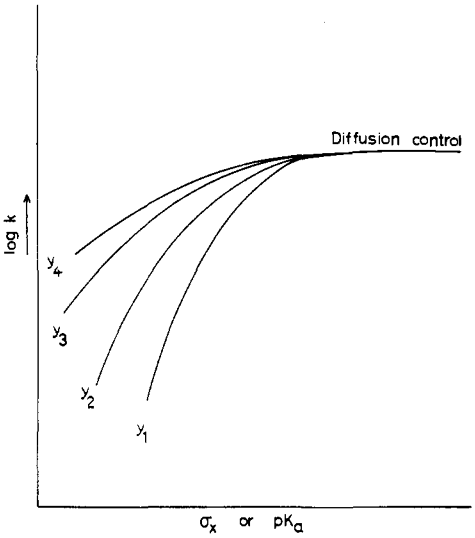


Figure 1. Multiple structure–reactivity relationship for eq 1, incorporating the RSP.

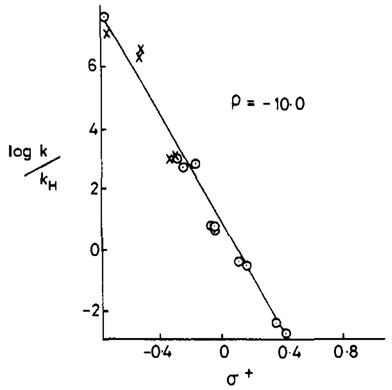


Figure 2. LFER for chlorination of 2-substituted thiophenes X and benzenes ⊙ (CH_3COOH, 25°). $\Delta\Delta G^\dagger$ for this correlation is 14 kcal/mol!

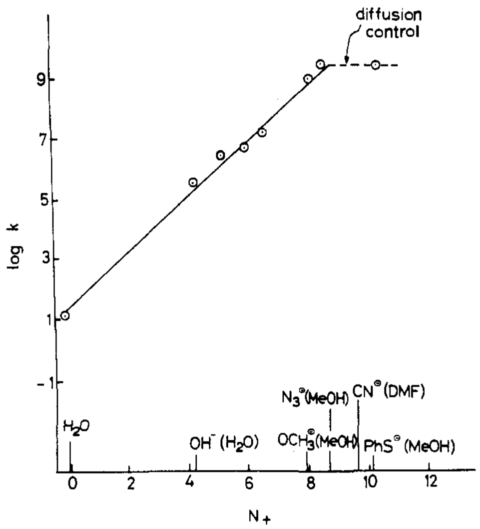


Figure 3. LFER for combination of *p*-nitrobenzenediazonium ion with anions, 23°. N_+ = (log k_N^{PNMG} − log $k_{H_2O}^{PNMG}$) where PNMG is *p*-nitro(Malachite Green).

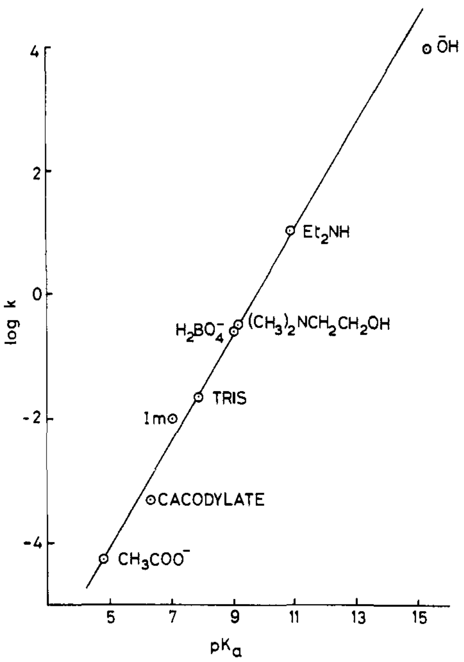


Figure 4. Bronsted plot for the base-catalyzed cyclization of ethyl 2-hydroxymethylbenzoate to phthalide (H_2O, 25°).

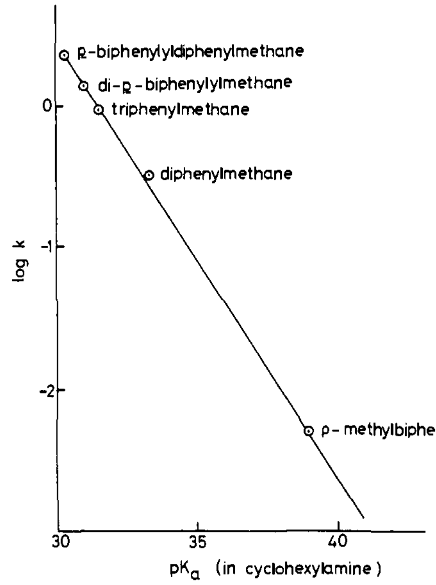


Figure 5. Bronsted plot for the tritium exchange rates of hydrocarbons with lithium cyclohexylamide in cyclohexylamine (25°).

viously;[19] further recent examples of some importance are given in Figures 2,[2,20] 3,[21] 4,[22] and 5.[23] It is impossible to believe that TS structure remains constant over such wide free energy changes, and yet in no case can curvature be described. Indeed it is hard to see how the Hammett equation could have come to occupy such a central position in mechanistic deductions if workers had constantly been faced with the problem of arbitrary separation of curvature produced on the one hand by mechanistic changes and on the other by operation of the RSP. Although the observation of diffusion control (see Figures 1 and 3) formally fits the predictions of the RSP (zero selectivity and maximum rate), it is, in fact, an example of a mechanistic changeover to a process on which substituents have no effect but other factors, such as temperature, viscosity of the medium, do.

Nevertheless, positional selectivity may be retained in these latter circumstances; thus in the nitration of pseudocumene which occurs at diffusion rate,[24] 5- and 6-nitropseudocumenes are produced by direct reaction without intervention of *ipso*-attack in a 9:1 ratio.[25] This is explicable in terms of rate-determining (diffusion rate) formation of an intermediate which precedes the Wheland intermediate.

Recently, carbene selectivity has been shown to respond to appropriate LFER's.[26]

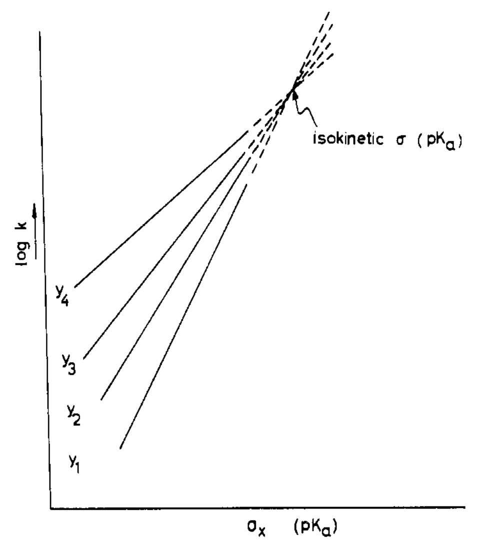


Figure 6. Modified multiple structure-reactivity relationship.

III. Multiple Structure-Reactivity Relationships

Accepting the assumption that FER's are linear over wide free energy changes still leaves point (b) in the first section to be considered. Figure 6 represents the modification of Figure 1 to demonstrate the situation.

A number of very interesting points arise from consideration of such multiple structure-reactivity correlations. A similar situation is encountered in the dependence of ρ values on temperature. If for a given series, for which the Hammett equation holds, $\Delta H^{\dagger}$ is accurately proportional to $\Delta S^{\dagger}$, then there exists an isokinetic temperature at which substituents have no effect on reaction rate and beyond which substituent effects are reversed. This situation has intrigued chemists for obvious reasons, and it has received lengthy and extensive discussion,[27,28] but rigorous evaluation of such issues is consistently obstructed by the experimental difficulties involved in establishment of accurate rate measurements so that, for example, the magnitude of $\partial \Delta H / \partial T$ (ΔC_p) values is uncertain.

Figure 6 represents an analogous situation much more readily susceptible to experimental verification or denial. If the variation of Y for a constant X (eq 1) also produces rate changes conforming to the Hammett or Bronsted equation, then there exists an isokinetic σ value for X and Y at which substituent effects on rate are zero, and beyond which their effects are reversed.

For correlations Y_2 and Y_1 we have respectively:

$$\log k_{Y_2} - (\log k_{Y_2})_{X=H} = \sigma_X \rho_{Y_2} \qquad (2)$$

$$\log k_{Y_1} - (\log k_{Y_1})_{X=H} = \sigma_X \rho_{Y_1} \qquad (3)$$

When $\log k_{Y_2} = \log k_{Y_1}$, i.e., at the isokinetic value of σ_X

$$(\sigma_X)_{\text{isok}} = \frac{(\log k_{Y_2})_{X=H} - (\log k_{Y_1})_{X=H}}{\rho_{Y_1} - \rho_{Y_2}} = C \qquad (4)$$

Expressions such as eq 4 have been widely quoted as quantitative formulations of the HLP.[11-13,29,30] It may be noticed that even if the opposite type of reactivity-selectivity relationship is observed, i.e., "anti-Hammond" behavior, an isokinetic σ value will still arise. When there is no dependence of selectivity on reactivity, *C* becomes infinitely large, and the correlation lines are parallel.

We now consider two practical examples of the operation of eq 4 which have been recently quoted. The first is the reaction of arylsulfonyl chlorides and anilines. Extensive measurements have been provided, and these show strict adherence to Hammett and Bronsted equations (Figure 7).[31] The appropriate form of eq 4 in this case is

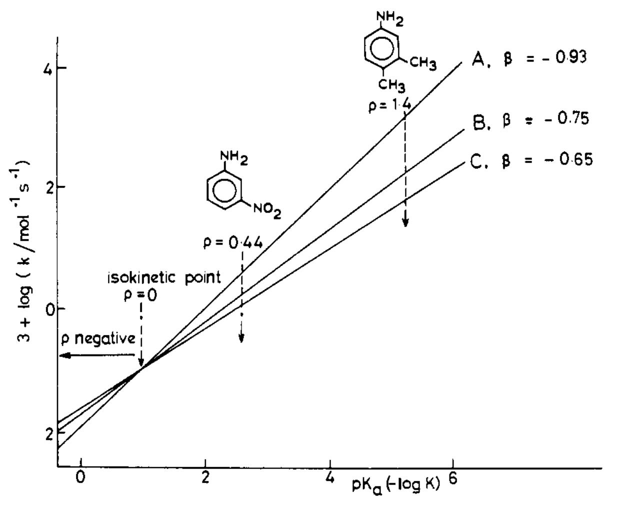


Figure 7. Bronsted plot for arylsulfonyl chloride-aniline reaction (MeOH, 25°). A = $p\text{-}NO_2C_6H_4SO_2Cl$; B = $C_6H_5SO_2Cl$; C = $CH_3OC_6H_4SO_2Cl$.

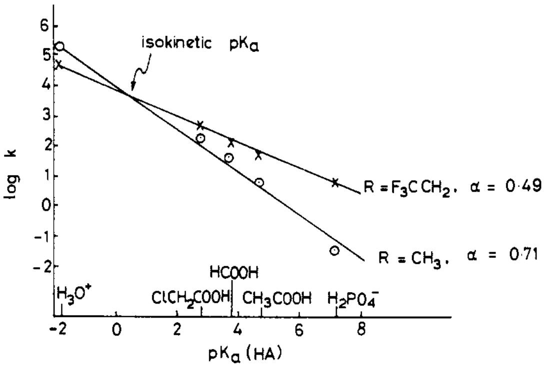
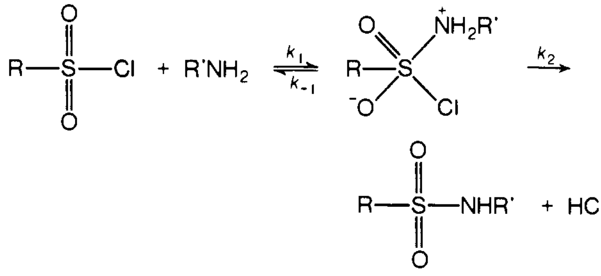


Figure 8. Bronsted plot for the elimination of alcohols from *N,O*-trimethylenephthalimidium-alcohol addition compounds (aqueous buffers, 25°).

$$\frac{\sigma_X}{\beta_X - \beta_H} = \frac{\log K_1 - \log K_2}{\rho_1 - \rho_2} = C \qquad (5)$$

from whence $\log K_2 = -0.75$ when $\rho_2 = 0$, i.e., at the isokinetic point, beyond which a complete reversal of amine reactivity occurs. (This system appears to comprise an example of "anti-Hammond" behavior, in that the more reactive chlorides are more selective). However, there has been controversy over the mechanism of this reaction.[32] Rogne favors a concerted SN2 process, but it could be a two-step process involving a quinquecovalent intermediate with k_{obsd} varying from k_1 to k_1k_2/k_{-1},[33] eq 6, or involve a transition from an SN2 to an SN1 mechanism.

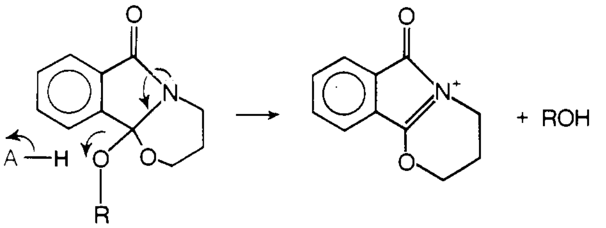


$$RSO_2Cl + R'NH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\overset{+}{S}(O)(O^-)(NH_2R')Cl \xrightarrow{k_2} RSO_2NHR' + HCl \qquad (6)$$

The second example (eq 7 and Figure 8) deals with an elimination of alcohols (R = CH_3, CH_3CH_2, $ClCH_2CH_2$, Cl_2CHCH_2, $CH{\equiv}CCH_2$, and F_3CCH_2) to yield phthalimidium

TABLE I. Brønsted β Values for Benzisoxazole Eliminations

Substituent X	β	$\beta/\beta_{5\text{-OMe}}$	$\beta/\beta_{5\text{-NO}_2}$
5-OMe	0.66	1.00	1.00
H	0.74	1.08	1.09
6-OMe	0.72	1.04	1.02
5-Cl	0.69	1.05	1.05
5-Cl	0.72	1.10	1.08
6-NO_2	0.71	1.09	1.01
5-NO_2	0.74	1.00	1.00
5,7-(NO_2)	0.65		0.91



(7)

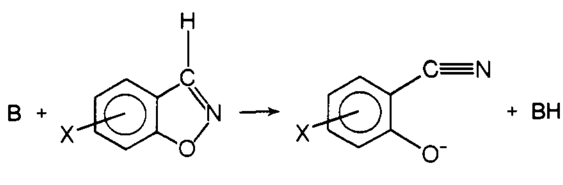
cations.[34] The rates do not show much variation with structure, and an isokinetic pK_a value of ~1 is found. Again, however, this case is ambiguous; doubt arises that this represents a consequence of the HLP since there is drastic variation of structure in R adjacent to the reaction site, which would lead in certain instances to acceleration by relief of steric strain or in others to interactions with the annular oxygen.

A third example recently described involves addition of styrenes to 9-substituted acridizinium cations.[35]

In the next section are examined further reaction series which are mechanistically unambiguous, satisfy to a large extent the steric requirements of eq 1, and cover as wide a free energy change as possible. Considering the very large amount of repetitive experimental work which must go into the collection of accurate data for construction of diagrams of the form of Figures 1 and 6, coupled with the necessity that the mechanism stays constant over a wide energy range, it is perhaps not surprising that only a few appropriate correlations have been reported. Nevertheless, a sufficient number do exist to permit critical evaluation; these demonstrate quite clearly that selectivity in such cases is completely independent of reactivity.

IV. Multiple Structure-Reactivity Relationships—the Absence of Dependence of Selectivity on Reactivity

An important paper containing a multiplicity of significant data deals with the base-catalyzed eliminations of benzisoxazoles. Using a series of tertiary bases, together with H_2O and



(8)

OH^-, β values for the reaction are found to be constant, within experimental error.[36] The β values (see Table I) were treated using Pfluger's analysis, which involves plotting the logarithmic rates against those for one substrate which are considered proportional to the "kinetic pK_a values" of the base catalysts. This increases the precision of the correlation, which comprises a rate change of 10^{11}, and thus a total free energy change of 15 kcal/mol.

This paper also considers β values obtained by Bell[37] for base-catalyzed abstraction of acidic hydrogens from carbonyl compounds, the rates of which cover a range of ca. 10^{15}.

TABLE II. Brønsted β Values for Proton Abstraction from Carbon Acids

Carbon acid	pK_a	k_{H_2O}, sec^{-1}	β^a	β^b
Acetone	20.0	4.7×10^{-10}	0.88	0.88
Hexane-2,5-dione	18.7		0.89	0.89
Chloroacetone	16.5	5.5×10^{-8}	0.82	0.90
Bromoacetone	16.1		0.82	0.89
Dichloroacetone	14.9	7.3×10^{-7}	0.82	0.87
2-Carbethoxycyclopentanone	13.1	2.3×10^{-3}	0.64	0.38
Ethyl acetoacetate	10.5	1.2×10^{-3}	0.59	0.59
2-Carboethoxycyclohexanone	10.0	9.7×10^{-6}	0.58	0.73
Benzoylacetone	9.7	1.1×10^{-2}	0.52	0.60
Acetylacetone	9.3	1.7×10^{-2}	0.48	0.50
3-Bromoacetylacetone	8.3	2.3×10^{-2}	0.42	0.57

[a] From plot of log k vs. pK_a value of catalyzing base. [b] Using Pfluger analysis.

These values, given in Table II, may be taken to indicate a decreasing selectivity with increasing rate of reaction, but application of the Pfluger analysis using acetone and ethyl acetoacetate as standards indicates that β values are essentially constant provided the acids are divided into the two structural classes, mono- and β-diketones (see the right-hand side of Table II). If plotted together, the higher acidity of the latter and the resultant higher reaction velocity, together with the smaller β value (average 0.55; cf. 0.88 for the monoketones), would indeed produce the *appearance* of curvature in a Bronsted plot including both groups of acids.

The use of the Pfluger procedure in this case, as well as having the effect of cancelling out any steric inconsistencies in the series of bases employed, would appear to be in line with the reasoning of Kresge,[38] that interactions may be present in the TS that are not reflected on either side of the acid-base equilibrium, and that indeed such circumstances can lead to β values less than zero or more than unity. Bordwell has substantiated this experimentally,[39] while his work also demonstrates essentially constant β values for kinetic acidities of carbon acids over wide reactivity ranges,[40] as does Kresge's for vinyl ether hydrolyses involving rate-determining protonation.[41]

Kemp and Casey's conclusion to these considerations[36]—"that proton transfer reactions have transition states characterized by a sensitivity to substituent change which is invariant over appreciable changes in transition state energy"—seems completely appropriate. That it can be extended to a wide variety of reactions other than that of proton transfer is shown by Figures 9–13. These display constant selectivity over very wide free energy changes for Michael additions,[42] aromatic nucleophilic substitutions,[43] cation-anion combination reactions[21] (see also Figure 3), base-catalyzed ester hydrolyses,[18] and SN1 reactions,[44] respectively.

The RSP has been much quoted and employed in the complex region of nucleophilic substitution (where four possible rate-determining steps have been described[45]), usually under the synonym (since relative rate of reaction is taken as a measure of stability) of a "stability-selectivity relationship". Ritchie considers that the origin of apparent RSP's for solvolysis reactions reported by other workers[46,47] involving competition between H_2O and other nucleophiles may be in the ability of the added nucleophile to act as a general base catalyst.[21,48] However, Ritchie's assertion that desolvation of the nucleophile is the rate-limiting step in the reactions studied by him[21] does not explain the different cation reactivities (see Figure 11), as Harris et al. have pointed out.[49] These latter workers demonstrate the apparent applicability of the RSP to

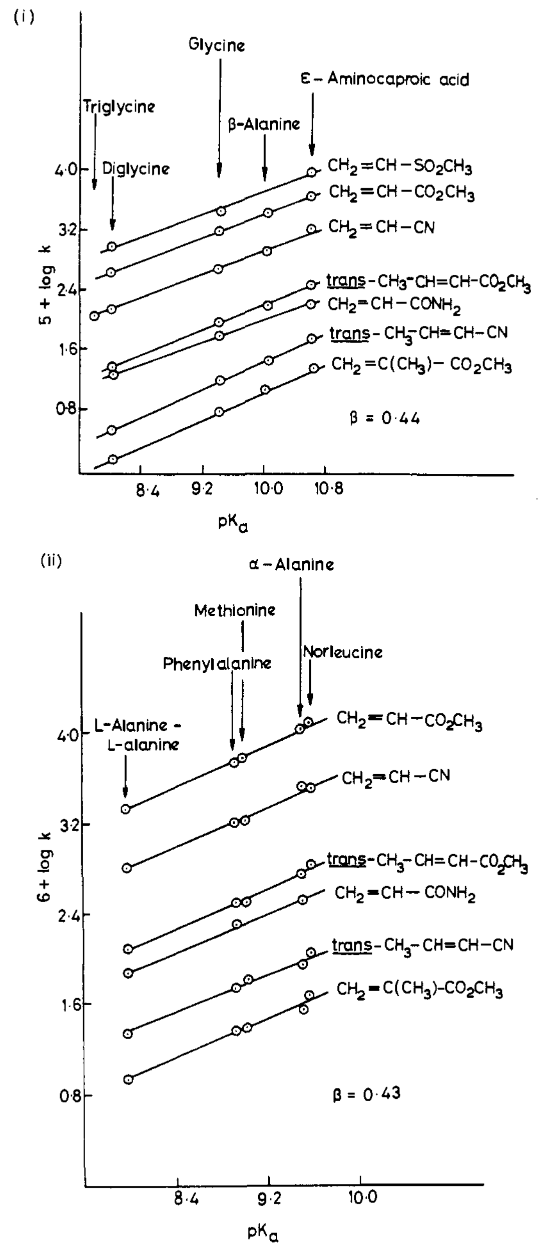


Figure 9. Bronsted plot for the Michael addition of amino acids to α,β-unsaturated compounds (aqueous buffers, 30°): (i) amino acids of type $NH_2CHRCOOH$; (ii) $NH_2CR^1R^2COOH$.

the proportion of ethanolysis/hydrolysis products from 2-adamantyl *p*-X-benzenesulfonates in 70% ethanol.[50] The isoparametric value $(\sigma_X)_{isok}$ in eq 4 for this reaction is −0.84, for greater negative σ values ethanol becoming more nucleophilic than water as usually expected. ρ_W is 1.76 ± 0.04 and ρ_E is 1.40 ± 0.10 for 76°. The error is quite large in the latter value, and other workers show constant selectivity for attack of nucleophiles in methyl sulfonate esters over a much wider range of reactivity.[51] It seems that in this highly interesting and complex area, where certainly there is still much work to be done, again the automatic equation of reactivity with selectivity can be a misleading one.

Data for aromatic electrophilic substitution, coupling reactions,[52] are shown in Table III. Rate variations here are large both for substituent variation in the diazo compound and in the aromatic component. Nevertheless, for sites of reaction with constant steric effects selectivity appears almost constant, and such variations as there are present are randomly distributed independently of rate. The Stock-Brown relationship,[53] applying to a wide range of aromatic electrophilic sub-

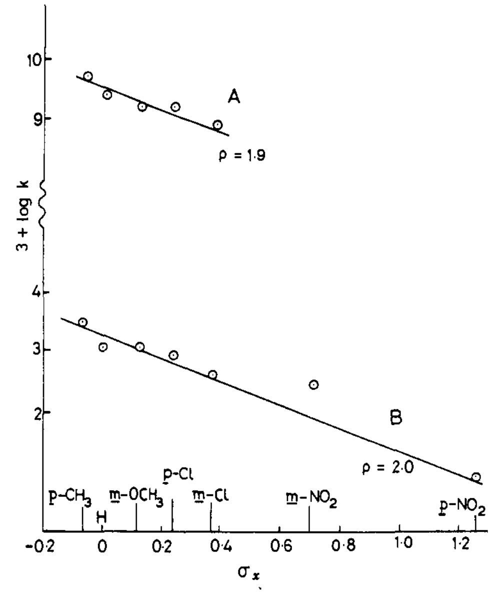


Figure 10. Reaction of substituted phenoxides with (A) 1-chloro-2,4-dinitrobenzene and (B) 1,4-dichloro-2-nitrobenzene (H_2O/dioxane, 65°).

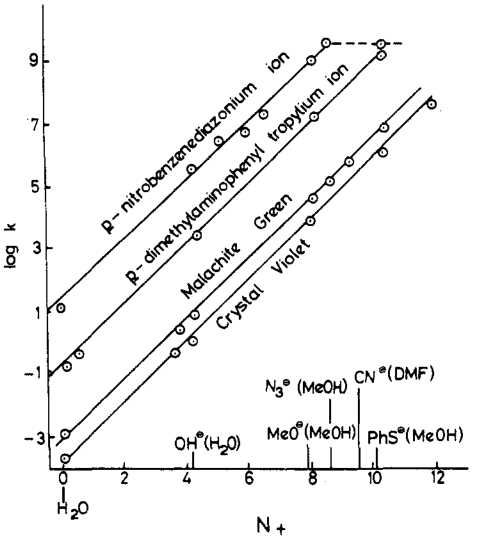


Figure 11. Cation-anion combination reactions (see also Figure 3).

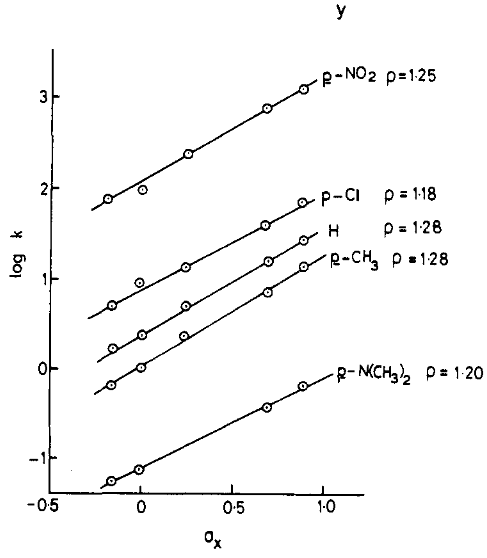


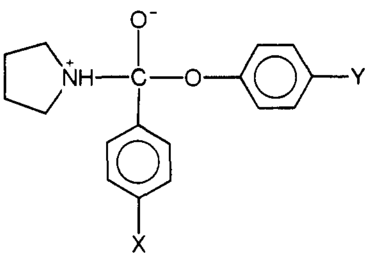
Figure 12. Alkaline hydrolysis of $YC_6H_4CO_2C_6H_4X$ (CH_3CN/H_2O, 25°).

TABLE III. Selectivities of Substituted Benzenediazonium Cations $XC_6H_4N_2^+$ with Benzene and Naphthalene Substrates at 25°

Aromatic substrate	Position of reaction	ρ	Log k (X = H)
1. Resorcinol	4	3.46	−1.87
2. 4-Methylphenol	2	4.27	3.02
3. 4-Methoxyphenol	2	4.09	4.50
4. 1-Hydroxynaphthalene-4-sulfonic acid	2	3.94	4.56
5. 3-Hydroxyphenolate anion	4	3.75	5.68
6. 1-Naphthol	4	4.80	−1.90
7. 1-Naphtholate anion	4	4.15	7.50

stitutions, has been quoted as reactivity–selectivity relationship;[54,55] however, it represents a connection between intramolecular and intermolecular selectivity only.[56] Although attempts have been made to correlate such factors with reactivity,[57,58] the above results on diazo coupling which fit clearly into the pattern of eq 1, show no such connection exists. This conclusion has been substantiated in a consideration of the applicability of the Bronsted equation to base-catalyzed diazo couplings where proton loss becomes rate limiting,[59] as well as in hydrogen exchange in substituted benzenes.[60]

The points made in this section are summarized nicely by results[61] for the reactions of esters with pyrrolidine (CH_3CN, 25°) for which the rate-determining step is collapse of the tetrahedral intermediate **1**; ρ values for the reaction are given in Table IV. Series 1 and 2 show the same selectivity toward pyrrolidine despite a rate difference of 10^4. However, series 3 shows a different selectivity due to the *o*-nitro group which can participate in TS interactions by proximity effects. The ρ values for series 4, 5, and 6 are also all similar (they cannot be very accurate as readings for only two points, X = NO_2, Cl, are available), but again alteration of steric effects (series 7) or solvent (series 8 and 9) introduce large selectivity changes.



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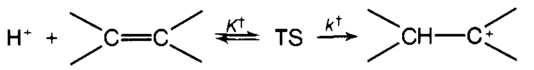
V. Evidence from Rate–Acidity Profiles

Variation of the rates of acid- or base-catalyzed reactions with the acidity of the medium has long been utilized as a key to reaction mechanism.[62] The slopes of plots of logarithmic rates vs. acidity functions or related quantities for such reactions afford an index of TS structure.[62,63] Let us consider this concept in relation to reactions whose rate-determining step is carbon protonation (eq 9), a relatively slow process, cf. oxygen and nitrogen protonation, whose rate can often be readily measured.



(9)

Application of TS theory leads to the expression

$$\log k_{obsd} = -H_C \text{ (or } -H_{R'}) + \log f_{C^+}/f_\ddagger + \text{constant} \qquad (10)$$

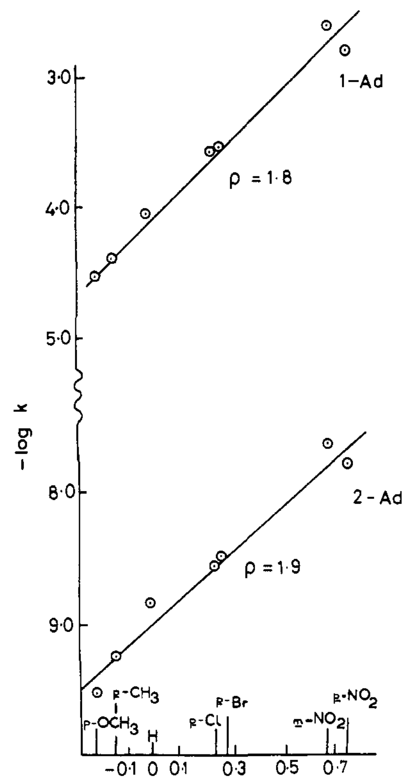


Figure 13. Hammett plot of specific ethanolysis rates of 1- and 2-adamantyl arenesulfonates at 25°.

where H_C or $H_{R'}$ defines the thermodynamic equilibrium for C-protonation.[62] If the TS is product-like, i.e., $f_\ddagger = f_{C^+}$, then eq 10 becomes

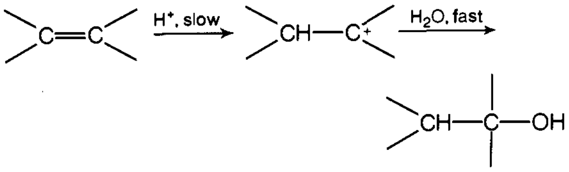
$$\log k_{obsd} = -H_C + \text{constant} \qquad (11)$$

If the TS is reactant-like, i.e., $f_\ddagger = f_C \cdot f_{H^+}$

$$\log k_{obsd} = -\log [H^+] + \text{constant} \qquad (12)$$

A reaction of this A1 type involving a TS intermediate between the two extremes would thus yield a log $k_{obsd} - H_0$ profile in H_2SO_4/H_2O with a slope between −1.6 (the slope of H_C vs. H_0 in this medium) and the shallow dependence of $-\log [H^+]$ (see Figure 14). The equivalent maximum slope in $HClO_4/H_2O$ would be −1.7. Parameters directly indicative of TS structure, α_A values, have indeed been defined for such reactions.[63] The limits of these values are defined by eq 11 and 12, and a close analogy with the Bronsted equation has been demonstrated.[64]

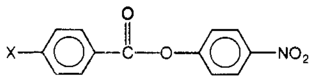
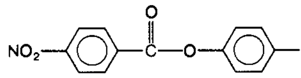
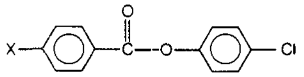
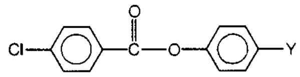
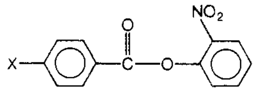
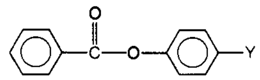
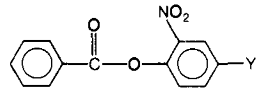
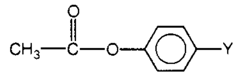
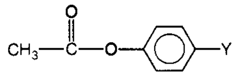
Operation of the HLP for a series of such reactions with differing rates but constant steric effects should therefore produce a diagram of the form of Figure 1, but with H_0 rather than σ_X or pK_a as the x coordinate. Again, however, the practical observations reveal a completely different pattern. Figure 15 shows the results for styrene hydration in D_2SO_4/D_2O mixture,[65] for which the mechanism is



(13)

The linearity of each plot together with the close parallelism, such deviations as do exist being completely random, show the now familiar lack of relationship between selectivity and

Table IV. ρ Values for Ester–Pyrrolidine Reactions at 25°[a]

	Ester	ρ		Ester	ρ
1.		1.02	4.		6.9
2.		1.01	5.		7.6
3.		1.40	6.		7.6
			7.		2.7
			8.		6.2
			9.		4.0

[a] Solvent acetonitrile except for No. 8, where it is chlorobenzene.

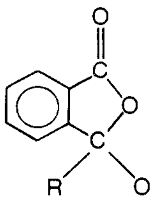
TABLE V. Hydrolysis of 3-Methoxyphthalides in H_2SO_4/H_2O, 25°

Compound 2	$-d \log k/dH_0$	Compound 3	$-d \log k/dH_0$
R = H	0.96	X = Y = H	0.67
CH_3	0.80	X = OCH_3, Y = H	0.69
C_2H_5	0.71	X = CH_3; Y = H	0.68
α-naphthyl	0.77	X = Cl; Y = H	0.67
phenyl	0.67	X = H; Y = OCH_3	0.67
		X = H; Y = NO_2	

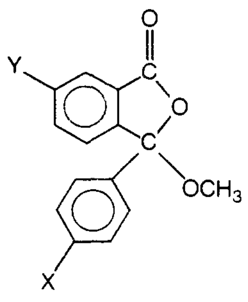
reactivity, and argue for an apparently constant TS. The ρ value for the reaction is −3.0, and the obvious implication of the parallelism of the plots is that this selectivity factor is invariant with acidity.

This pattern of behavior is generally found for investigations of this type, with essentially linear parallel plots over wide free energy ranges. Recent examples include kinetic protonation of alkoxybenzenes in $HClO_4/H_2O$,[63] of acetophenones in D_2SO_4/D_2O,[64] further results on styrene hydration[66] and on α-methylstyrene hydration[65] in $HClO_4/H_2O$ and D_2SO_4/D_2O, respectively, and, all in H_2SO_4/H_2O, the isomerization of *cis*-stilbenes,[67] the dehydration of 1,2-diarylethanols,[68] and the hydration of phenylbenzoylacetylenes.[69] The profiles for this last reaction are given in Figure 16.

Some interesting results have also been provided on the A1 hydrolysis of 3-methoxyphthalides **2** and **3**.[70] Table V shows that change in R, adjacent to the reaction site, in **2** gives variations in the slopes of the rate-acidity profile well outside experimental error, but variations in X and Y in **3**, although producing the same magnitude of rate variations, leave the slopes constant.



2



3

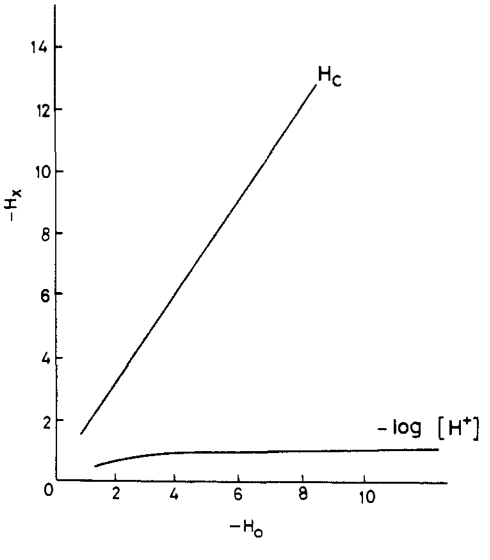


Figure 14. Acidity function variation—the limits of eq 10.

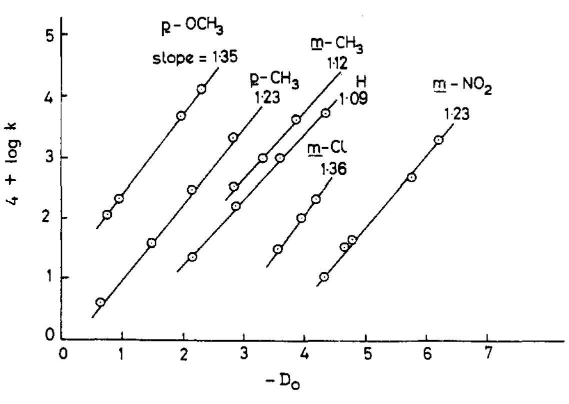


Figure 15. Hydration of styrene derivatives $XC_6H_4CH{=}CH_2$ in D_2SO_4/D_2O, 25°.

Other acid-catalyzed reactions, of the form

$$S + H^+ = SH^+ \tag{14}$$

$$SH^+ + rH_2O \longrightarrow \text{products} \tag{15}$$

are also numerous, and there are many different methods of appraisal.[62] All must, however, in the final analysis, constitute approaches of the form of eq 17, derived from TS theory:

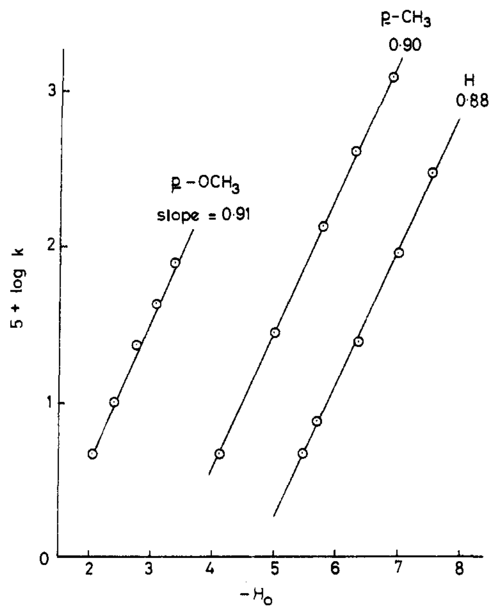


Figure 16. Hydration of phenylbenzoylacetylenes, p-XC_6H_4-$C{\equiv}CCOC_6H_5$ in H_2SO_4/H_2O, 25°.

$$SH^+ + rH_2O \underset{}{\overset{K^\ddagger}{\rightleftharpoons}} TS \xrightarrow{k^\ddagger} \text{primary products} \quad (16)$$

$$k_{SH^+} = k^\ddagger K^\ddagger (f_{SH^+}/f_\ddagger) a_w^{\,r} \quad (17)$$

The unavoidable assumption in any subsequent treatment is that the ratio $f_{SH^+}/f_\ddagger$ is independent of variation in acid strength; i.e.,

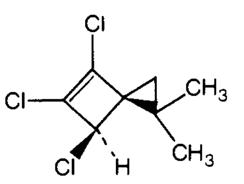
$$\log k_{SH^+} = r \log a_w + \text{constant} \quad (18)$$

The significance of r is thus that it represents a measure of the difference between solvation of SH^+ and TS and is therefore indicative of the difference in structure between the two species. A value of about 2 has been reported for acid-catalyzed ester hydrolysis,[62] but no systematic study has yet been made of the variation (if any) of this parameter on changing the reactivity of SH^+ in line with eq 1; this appears to the author to be a particularly interesting area for investigation of reactivity and TS structure.

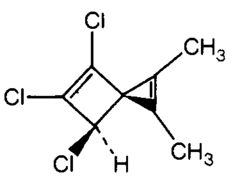
Correlations of reaction rates in alkaline media with H_- or J_- scales can likewise lead to deductions of TS structure. The association with the Bronsted equation has also been pointed out here.[71,72] Bronsted values may be defined by changing the basicity of the medium by systematic substitution of dimethyl sulfoxide for water,[71] so that ρ values are

$$\Delta pK_a = \text{constant} - (H_- + \log[H_2O]/[OH^-]) \quad (19)$$

thus given by the slope of the log k − (H_- + log $[H_2O]/[OH^-]$) plot, and, for example, are revealed by this procedure to be constant for the kinetic acidities of spirocycles **4** and **5** (Figure 17).[73]



4



5

VI. Kinetic Isotope Effects

Evidence independent of that from LFER's concerning the nature of the TS in proton transfer reactions may be derived from the kinetic hydrogen isotope effect. The value is predicted to be a maximum for proton transfers between two acid–base systems of approximately equal pK_a, i.e., when ΔpK_a = 0, and to decrease as ΔpK_a becomes larger in either a positive or negative sense, becoming very much smaller when the TS is "reactant-like" or "product-like".[74-77] This contention has been apparently supported experimentally for the base-catalyzed ionization of carbon acids,[78] and this gives great hope that information on TS structure which LFER's consistently fail to supply may be forthcoming from this alternative source.

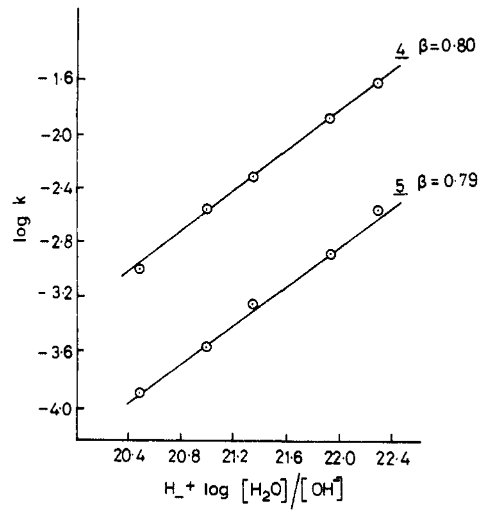


Figure 17. Bronsted plots for the kinetic acidity of spirocycles ($DMSO/H_2O$, 25°).

TABLE VI. Primary Deuterium Kinetic Isotope Effects in Elimination Reactions

	$(p\text{-}ClC_6H_4)CLCCl_3$ (L = H, D; pK_a = 17.1; 45°)				
Base	PhS^-	$p\text{-}NO_2C_6H_4O^-$	PhO^-	OMe^-	OEt^-
$10^5 k_H$/l. mol^{-1} sec^{-1}	2.61	0.145	17.4	5230	
k_H/k_D	3.13	4.83	6.21	4.75	3.40
pK_a (EtOH)	9.3	13.3	15.8	18.3	20.3

	$(XC_6H_4)_2CLCCl_3$ (L = H, D; 30°)			
	NaOMe/MeOH		Bu^tOK/Bu^tOH	
Base	$10^5 k_H$	k_H/k_D	$10^5 k_H$	k_H/k_D
X = p-OMe	8.71	5.21	94.8	3.55
H	47.6	5.08	262	3.97
p-Cl	1130	5.16	22200	3.38
p-NO_2	605,000	4.95	5,730,000	3.82

However, these hopes have subsequently been frustrated. It has been demonstrated that the k_H/k_D vs. ΔpK_a graph for the proton abstraction from carbon acids has a much more poorly defined maximum than originally postulated,[79] and indeed theoretical reinterpretation of the results by the initial workers[80] reveal that the variations in k_H/k_D arise from tunneling and steric effects rather than differences in TS structure.

The contention that steric effects must be kept constant as in eq 1 to allow legitimate investigation of reactivity-selectivity changes is echoed in this area of isotope effects with elimination studies.[82] Primary deuterium isotope effects for elimination from $(p\text{-}ClC_6H_4)_2CHCCl_3$ apparently pass through a maximum at ΔpK_a = 0 (Table VI); this appears fortuitous, however, for examination of data for eliminations from $PhCH_2CH_2S^+Me_2$ in aqueous sulfoxide mixtures reveals a maximum for k_H/k_D for which ΔpK_a is approximately 20. Moreover, when steric effects are kept constant, no signifi-

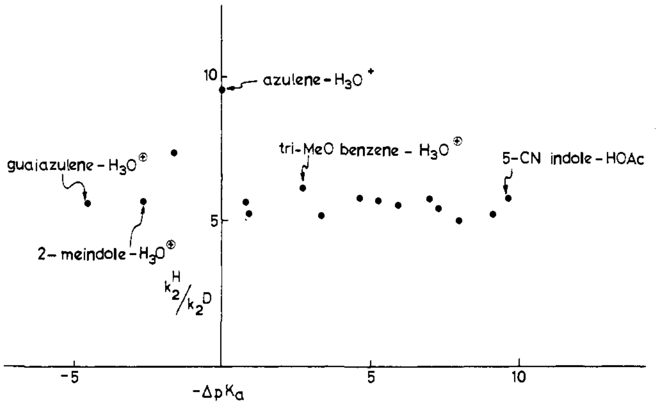


Figure 18. Primary kinetic isotope effects for hydrogen exchange in aromatic nuclei.

cant change in isotope effect occurs even for a very wide reactivity range (Table VI).

Random and fairly small variations have also been reported for k_H/k_D in the benzisoxazole decompositions discussed previously,[36] while a constant deuterium kinetic isotope effect has been demonstrated[81] in eliminations from phenylethyl bromides $XC_6H_4CH_2CH_2Br$ with potassium *tert*-butoxide in *tert*-butyl alcohol, encompassing a rate change of 10^5.

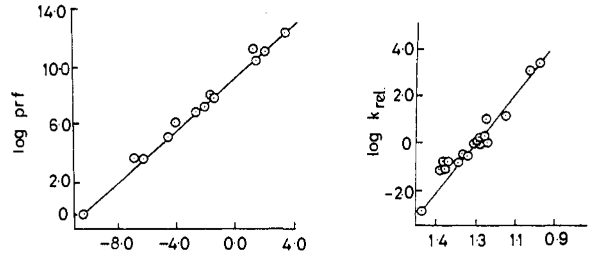
Curiously enough, deuterium kinetic isotope effects in eliminations[83] from $PhCH_2CH_2Br$ are constant with variation of X in *p*-$XC_6H_4O^-$, but the same conditions for elimination from *p*-$XC_6H_4CH_2CH_2Br$ using phenoxide and *p*-nitrophenoxide as base produce ρ values of 2.64 and 1.84, respectively,[84] the latter base reacting 10^6 times faster than the former; whereas for proton transfer reactions discussed previously in diazo coupling,[59] in which β values remain constant, apparent variation of k_H/k_D with a maximum at $\Delta pK_a = 0$ is observed.

Variations in α-isotope effects in the formolysis of 2-arylethylarenesulfonates proceeding by anchimeric assistance were initially explained in terms of the Hammond postulate,[85] but a more recent account suggests that there is no significant difference as the rate is varied.[86] Most remarkable of all is a series of data which reveals effectively constant k_H/k_D values for acid-catalyzed hydrogen exchange in aromatic nuclei covering a reactivity range of ca. 10^9 (Figure 18), a result which clearly demonstrates, as Challis and Millar[87] point out, either that the TS structure is unchanging with reactivity or that primary isotope effects do not indicate TS structure.

VII. Conclusion

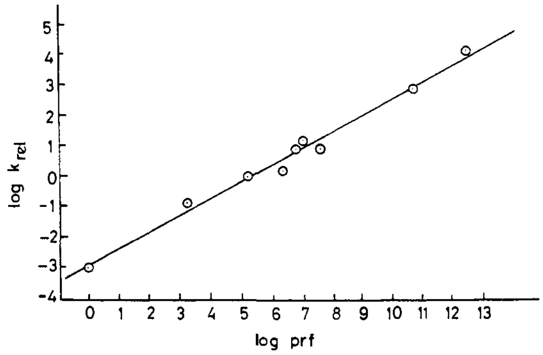
It is quite clear that selectivity is independent of reactivity from which the theoretical deduction may be made that TS structure is independent of reaction rate; the same conclusion may be drawn from isotope studies. The question of whether this interpretation is correct, or that TS structures do vary, but selectivity parameters and isotope effects fail to respond in the predicted manner, is at this stage impossible to answer in any precise fashion.

Arguments based on the construction of free energy-reaction coordinate profiles from which the correlation between the HLP and the RSP arise[3,5,6,8,13] appear on inspection to contain assumptions which are difficult to substantiate. Thus, the arbitrary decision has to be taken that each member of a series starts at the same point on the reaction coordinate and furnishes products similarly aligned in the rate-determining step. This is by no means necessarily correct. For example, in the para-nitration of nitro- and methoxybenzene the latter **6** can be considered to have a contribution in the ground state from a canonical form **7** which effectively "starts it off" further along the reaction coordinate than for the former **8–9**.



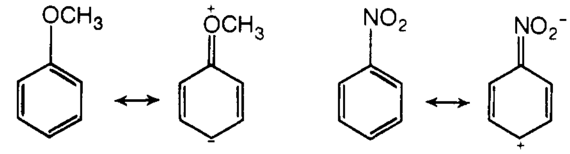
(i) log partial rate factors (bromination in CH_3COOH) vs basicities

(ii) log rel. rates for protodetritiation (CF_3COOH, 70°) vs localisation energies calculated by the w-technique



(iii) bromination vs protodetritiation

Figure 19. Electrophilic substitution in polynuclear aromatic nuclei: (i) log partial rate factors (bromination in CH_3COOH) vs. basicities (HF); (ii) log relative rates for protodetritiation (CF_3COOH, 70°) vs. localization energies calculated by the ω-technique; (iii) bromination vs. protodetritiation.



6 **7** **8** **9**

Difference in solvation between ground states and TS's for one member of a series and another would also be expected to play a part. Similarly, the disposition of the energies of reactants and products as well as the TS's about the energy axis have to be taken into account, and this again introduces assumptions of questionable validity,[36] which make quantitative extrapolation of such diagrams to prediction of experimental results extremely difficult. When a sequence of TS's is termed "reactant-like", consideration should certainly be given to which ground state this is related. A detailed analysis of some of these effects has been presented,[88] while the anomalies and approximations involved in TS theory have been commented on and attempts made to develop alternative theories using perturbation treatment.[90]

However, the essential point of the HLP, that similar structures have similar energies, seems entirely reasonable,[91] and therefore any deductions based on the equation of energies and structures which accord with experimental observation bear it out. Among these may be numbered: the assumption of the Wheland intermediate as a model for TS structure in electrophilic substitution, both in correlation with MO calculations based on localization energies and with HF equilibria[92–97] (Figure 19); the application of the Principle of Least Motion to organic reactions;[98] and the partitioning of reaction pathways arising from a common substrate according to the reaction conditions as in the enolization of α,β-unsaturated ketones in acid or base.[99] Certainly, however, none of these require any dependency of reactivity on selectivity; indeed Figure 19 represents further examples of LFER's over enormous free energy changes.

The contention that, for reaction schemes of the form discussed in the previous sections, selectivity is uninfluenced by reaction rate seems an extreme one, even if vindicated in a large number of unequivocal examples, and necessary to remove the possibility of inversion of reactivity orders as shown in Figure 6. Nevertheless, it is in keeping with the overall pattern of the quantitative laws of physical organic chemistry, which in general are of remarkably simple form, high efficiency, and wide applicability, considered both in terms of the free energy ranges covered and the variety of reaction types correlated. Thus the demonstration of constant slopes of log k vs. H_0 or log a_w for acid-catalyzed reactions discussed in section V recaptures something if not all of the original simplicity of the Hammett–Zucker hypothesis and increases the efficacy of subsequent modified treatments,[62] suggesting that statements such as those of Bell[100] with regard to these reactions are perhaps unduly pessimistic.

Nevertheless, in general the situation presented here would seem to represent an overall set-back to our understanding of the complex systems of organic chemistry; an impasse has been reached for which the manner of circumvention is by no means apparent. One intuitively expects far more frequent and systematic breakdown in the quantitative rules of organic chemistry than is in practice observed, which would provide the *modus operandi* for more refined treatments of genuine theoretical significance. The linearity of FER's, and the ambiguous situation which this poses in respect of understanding of TS structures, is paralleled, for example, by the observation that Hammett σ values are sensibly independent of solvent; this is one factor making the equation such a comprehensive one, but by the same token it thus fails to provide information on differential substituent–solvent interactions which must certainly be present.

An expression of this ingenuous and therefore uninformative situation has been given, with respect to proton transfer reactions, by Bordwell,[79] paraphrasing Hammett:[101] "the hope, which at one time seemed bright, for a simple general correlation of Bronsted coefficients, kinetic isotopic effect, and solvent isotope effects with the extent of proton transfer in the TS has proved vain". The key problem facing theoreticians is the explanation of the efficiency of such simple and straightforward laws in their government of the highly complex systems of organic chemistry.

Acknowledgments. The author would like to thank Professor K. Schofield, Dr. S. Clementi, and Dr. R. B. Moodie for discussion and encouragement, and Professors D. Farcaşiu, D. S. Kemp, E. S. Lewis, R. N. McDonald, and O. Rogne for helpful correspondence.

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