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THE REACTIVITY-SELECTIVITY PRINCIPLE: FACT OR FICTION?

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The idea that there is a relationship between the rate of a chemical reaction and the selectivity of the reagents involved, and that this in some way stems from transition state change with reaction rate variation, has been widely held for many decades. A popular undergraduate text-book[1] sets out the concept thus: "In a set of similar reactions, the higher the E_{act}, the later the transition state is reached in the reaction process.... Thus, in the attack by a reagent of high reactivity, the transition state tends to resemble the reactant: in the attack by a reagent of low reactivity, the transition state tends to resemble the products.

Practically, this postulate has been found extremely useful in the interpretation of experimental results: among other things as we shall see, it enables us to account for the relationship between reactivity and selectivity." Most chemists have accepted these concepts as axiomatic. Other representations have been given, from vaguely worded generalisations to precise mathematical definitions, with echoes over the whole range of organic reactivity, through to inorganic oxidation-reduction systems,[3] and electrode reactions.[4] Some of the latest discussions of this principle are set out,[5-21] but these must be taken as illustrative rather than comprehensive.

Thus, in general, if two reagents R_1 and R_2, where R_1 is more reactive than R_2, are allowed to react with substrates A and B, it is considered that not only will R_1 react faster with A (and B) than will R_2, but the ratio of rate constants k_A/k_B will be greater for R_2 than R_1. Qualitatively, the principle means therefore that log k/log K relationships such as embodied in the Hammett or Bronsted treatments of data will be curved, approaching a zero slope as k becomes larger; in the limit, zero selectivity as denoted by zero slopes (ρ, α or β) of such plots is produced by reagents of infinite reactivity, coincident with diffusion control. Quantitative treatments of this approach have been made, of which the Marcus treatment is the best known, and this has been applied to electron,[3] proton (see later), and methyl[21] transfers. For a family of free energy relationships, substrates $X_1, X_2 \ldots X_n$ reacting with reagents $Y_1Y_2 \ldots Y_m$ (multiple structure-reactivity relationships), the selectivity denoted by ρ, α or β will decrease as the rate gets faster, if the reactivity-selectivity principle (RSP) is in operation.

Jencks has recently summarised[7] a systematic way of treating such potential reactivity-selectivity effects by defining direct and cross correlations as shown in Fig. 1. Here the curvature of free energy correlations, of which the slope represents a change in the selectivity factor $\Delta G^{\neq}/\Delta G^{\circ}$, is described by

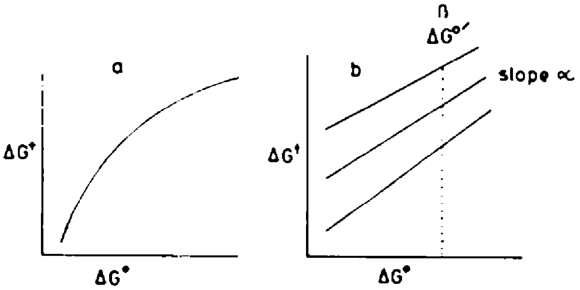


Fig. 1. Definition of Hammond and Cordes coefficients from FERs. [a]Direct correlation, Hammond coefficient $p = \delta(d\Delta G^{\neq}/d\Delta G^{0})/\delta\Delta G^{0} = \delta\alpha/\delta\Delta G^{0}$. [b]Cross correlation, Cordes coefficients $1/C = \delta\alpha/\delta\Delta G^{0\prime} = \delta\beta/\delta G^{0}$. For a specific example (see Table 1). For an unambiguous demonstration of the RSP, these plots should also be curved ($p \neq 0$). If $p = 0$, as shown here, a "crossover" or isokinetic point is predicted where selectivity becomes reversed. Such a situation frequently occurs in practise (there are several examples within the discussion). This is not really accommodated by the RSP, which predicts a limiting value of zero for selectivity with a highly reactive reagent.

Hammond coefficients p, and variations in slope (selectivity) of a family of linear free energy relationships (LFERs) by Cordes coefficients $1/c$. The question under discussion hinges on the degree of divergence of these parameters from zero, and to what extent such divergence is due solely to change in rate; the experimental demonstration of an LFER thus appears generally incompatible with the RSP.[22]

The view-point that there is no validity in the RSP is undoubtedly considered extreme. Nevertheless, taking extreme to mean difficult to justify, then some chemists who have considered this concept may admit that the alternative position is now somewhat tenuous; advocates of the RSP are faced with explaining the rapidly increasing body of experimental data where it fails to appear. Indeed, it may be doubted if such a widely held concept ever rested on slimmer or more dubious evidence. Is it really possible, however, seriously to suggest that *all* claims to its observation in the form of non-zero Hammond or Cordes coefficients arise in fact from alternative causes through consideration of reaction series

(i) in which there is a change in mechanism or rate determining step, a category which includes the onset of diffusion control

(ii) or in which variation in rate accompanies selectivity variation arising entirely from changes in steric or solvent effects or proximity interactions due to discontinuous or non-systematic changes in structure or reaction conditions along members of the reaction series

(iii) or in which the rate change investigated is not sufficient to permit the separation of what might be genuine RSP effects from experimental noise

(iv) or, finally, in which substituent-substituent interactions occur, a particularly complex and intriguing effect discussed in some detail later?

Consideration of this situation falls into two parts which must be emphasised as quite distinct: first of all, discussion of experimental evidence for and against observation of changes in selectivity induced entirely by rate variation, and secondly, what such observations may or may not tell us about the theoretical connection between transition state variation and reaction rate.

The experimental area to be discussed first is one in which we have been particularly involved – that of proton exchange reactions from acid to unsaturated carbon nucleophiles.[23–26] The basic experiment is the observation of acid-catalysed hydrogen exchange at the 2- and 6-positions of 4-nitro-N,N-dimethylaniline in deuteriosulphuric acid, which can be followed by nmr. Here, reaction proceeds on minority species free base, and the observed rate constants k_{obs} do not vary greatly with acidity, the effect of increasing rate with increasing acidity being offset by decreasing free base concentration. Variation in rate over a wide acid concentration (20–100%) can therefore be followed. The k_{obs} values must thus be converted to k_{fb} using eqn (1).

$$\log k_{fb} = \log k_{obs} + pK_a + H_0''' . \qquad (1)$$

We have carefully checked the H_0''' acidity function,[27] and find that it is defined by indicators whose logarithmic ionisation ratio acidity plots are accurately parallel to one another in the overlapping regions, that 4-nitro-N,N-dimethylaniline is a well behaved member of the series, and that the anchoring of the scale is correct. The $\log k_{fb}$ values give an accurately linear plot against H_c,[28] the acidity function defining the corresponding equilibrium carbon protonation process, over a rate range of 10^9 (number of points 27, slope 0.65 ± 0.01, correlation coeff. 0.996).

The zero Hammond coefficient of this Bronsted plot has no accord with Marcus theory, a quantification of the RSP.[29] Calculations show[25] that even making the pre-exchange term[29] zero which produces minimal curvature in the appropriate Bronsted plot, because in the model evoked by Marcus the primitive parabolas now overlap in their regions most nearly approximating linearity, there should still be a variation in slope of about 0.2 over the rate range considered.

In addition, parallelism is found between this plot, and those for proton exchange from aqueous sulphuric acid to other aromatics, as well as to olefins and acetylenes (Table 1 for examples), and the generalised result[25] for all such molecules considered is that zero Hammond and Cordes coefficients are maintained. (The slope for benzene represents the only clear-cut anomaly, 1.81 instead of unity, implying a product-like "late" transition state. If this is indeed the case, the difficulty of correlating this with a low reactivity is well illustrated by the figure in Ref. 24, where the steep slope for benzene can be seen to involve it in "crossovers" with other molecules of more normal slopes.)

Table 1 Rate-limiting carbon protonations in aqueous sulphuric acid

Reaction[a]	dlogk dlogk$_0$[b]	acidity range[c]	logk (60% acid)
4-nitro-N,N-dimethylaniline (2,6-positions)	1.00	23-100	0.62
4-methylacetophenone (3,5-positions)	0.92	68-96	-[illegible].59
thiophene (2-position)	0.95	17-47	-1.77
phenylacetylene	1.16	6-49	-0.98
styrene	1.04	25-53	-1.43

[a] Temperature 25°, except for amine and acetophenone (60°).

[b] log k_0 refers to 4-nitro-N,N-dimethylaniline.

[c] Acid per cent.

The same picture emerges from consideration of the data in aqueous perchloric acid.[26] Accurate linearity of log k H_c plots for protonation of azulenes, benzenes, and olefins imply zero Hammond coefficients. These slopes are essentially constant (Fig. 2) with an averaged value within experimental error of that in sulphuric acid; thus the Cordes coefficient is zero. These slope parameters march in a steady horizontal course undeterred by the predicted slopes for reactant-like or product-like transition states over a rate change of 10^{11}.

The parallelism of the log k H_c plots has implications for the applicability of Hammett correlations, and their variation with acidity. Table 2 shows the Cordes cross correlation expressing this. The fact that the profiles for the hydration of styrenes proceeding by rate-determining proton uptake are parallel, together with the observation of an accurate σ^+ plot at one acidity, means that an accurate σ^+ plot will be produced at *any* acidity with a constant ρ value.

Table 2 Cordes cross correlation[a] for styrene hydration[b,c,d,e] (for hydration of styrenes $XC_6H_4CH{=}CH_2$, X = p-OCH_3, p-CH_3, H, p-Cl, p-NO_2, in $HClO_4$–H_2O)

H_c	ρ
0	-3.71 ± 0.17 (0.997)
-5	-3.81 ± 0.17 (0.997)
-10	-3.91 ± 0.16 (0.997)

[a] $\delta\sigma^{+}\ \delta(-d\log k\ dH_c) = \delta H_c\ \delta\rho = c$

[b] Ref. 26.

[c] Reactivity range of each correlation: 10^4.

[d] Overall reactivity range: 10^{11}.

[e] Corresponding relationships arising from essentially zero Hammond and Cordes coefficients obtain for styrene and acetylene hydrolyses in aqueous sulphuric acid.[25]

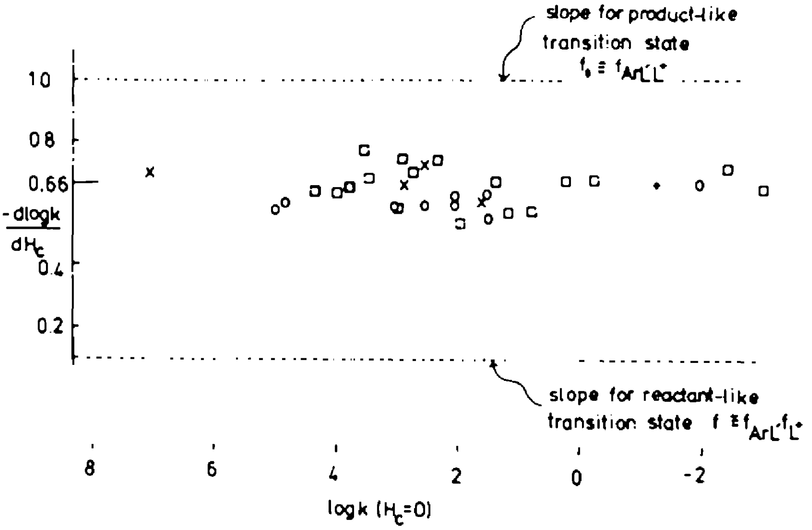


Fig. 2. Constant selectivity displayed by H_3O^+ in $HClO_4$–H_2O for carbon bases. Limiting slopes are defined and calculated in Ref. 5. ×, azulenes; □, olefins; ○, benzenes; •, 2-position of thiophene. L,L' = hydrogen isotopes.

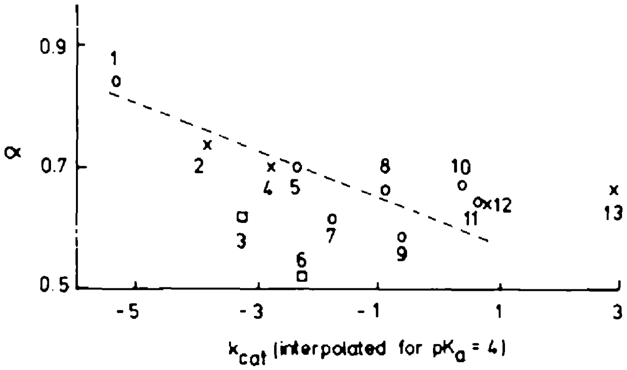


Fig. 3. Relationship between Bronsted coefficients and relative reactivity for hydrolysis (rate limiting protonation) of carbon bases. ○ original points,[32] the dotted line is defined by these; ×, points more recently added;[33–35] □, azulenes.[34] 1, phenylvinyl ether; 2, methylvinyl sulfide; 3, azulene-1-*t*; 4, *β*-methoxy-*trans*-*β*-methylstyrene; 5, ethylvinyl ether; 6, guaiazulene-3-*t* (based on three points); 7, phenylisopropenyl ether; 8, methylcyclohexenyl ether; 9, ethylcyclohexenyl ether; 10, ethylcyclopentenyl ether; 11, ethylisopropenyl ether; 12, 3-methoxyindene; 13, methyl *α*-cyclopropylvinyl ether.

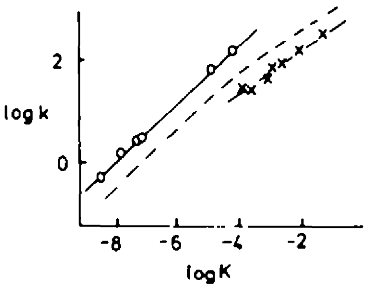
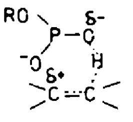


Fig. 4. Separate linear Bronsted plots for the hydrolysis of methyl *α*-cyclopropylvinyl ether, and composite curve. ○, RPO_3H^-, *β* = 0.74; ×, RCOOH, *β* = 0.67.

These arguments may be taken to the extreme by Tidwell's results,[30,31] which demonstrate a very respectable linear correlation between σ^+ and rates of protonation of α-substituted olefins in sulphuric acid, which in the most recent work is shown to cover a rate change of 10^{22}, the original plot[30] now having been extended in the upper region by data on enamine protonation and in the lower region by use of trifluoromethyl substituents.[31] The acidity arbitrarily chosen for correlation is H_0 0; however, the assumption that the correlation is a real one and not just fortuitous for this acidity alone, together with the observed parallelism of rate acidity profiles for the less reactive of these molecules (about the lower two-thirds) has the implication that the ρ value (10.5) is again invariant with acidity, and the Hammond and Cordes coefficients are constant over this extraordinarily large rate range. This fascinating correlation will be referred to later.

In the area of proton additions to unsaturated carbon atoms where general acid catalysis can be observed, Kresge has reported evidence for non-zero Cordes and Hammond coefficients. Figure 3 shows the initial data[32] for the variation of α values with reactivity for vinyl ethers, the results being derived from a structurally consistent set of acids, aliphatic carboxylic. Even at this stage, the correlation was stated to be poor, and the conclusion drawn that α was not very sensitive to rate change. However, recent results[33 35] do not confirm even the slight trend previously considered to exist. They suggest the Cordes coefficient over this wide reactivity range (10^8) is zero.

The evidence for non-zero Hammond coefficients may also be viewed critically. Figure 4 shows the raw data for methyl α-cyclopropylvinyl ether,[35] which is converted into a curve by sliding the two straight lines together, and considering them as part of an overall curve. However, this curvature may not be produced in reality by conversion of the transition state through a continuum induced by change in reactivity, but rather by an abrupt change in transition state structure from **1** to **2**, produced by use of two completely different acid catalysts, to the extent that the actual charge on the transition state is different. It is possible that many examples of such non-zero Hammond coefficients for proton exchange reactions to carbon bases may come about as artefacts induced by the use of non-systematic acid or base series,[34 36] and indeed Kresge has emphasised the necessity for a structurally homogeneous set of acid-base catalysts covering a wide pK_a range to determine the shape of Bronsted plots.[37]



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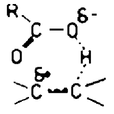

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The initial reaction discussed, that of proton exchange on 4-nitro-N,N-dimethylaniline, and the incorporation of nuclear exchange for other aromatic molecules within Fig. 2, also implies zero Hammond and Cordes coefficients for aromatic electrophilic substitution in general. A very interesting example has recently been given for nitration in aqueous sulphuric acid.[38] The relevant equations are set out below, eqn (5) showing that a constant selectivity involves constancy of the final transition state term; Table 3 shows that selectivity remains around unity for a whole variety of aromatic substrates over a rate range of 10[illegible].

$$HNO_3 + H^+ \overset{K}{\rightleftharpoons} NO_2^+ + H_2O \tag{2}$$

$$Ar + NO_2^+ \xrightarrow{k^{Ar}} \text{Wheland intermediate} \tag{3}$$

Thus:

$$k_2^{Ar}(\text{obs}) = k^{Ar}Kf_{Ar}f_{HNO_3}a_{H^+} \cdot \ a_{H_2O}f_{\neq} \tag{4}$$

and so:

$$\log k_2^{Ar}(\text{obs}) \quad \log k_2^{Bz}(\text{obs}) + \log(k^{Ar}\ k^{Bz}) + \log(f_{Ar}f_{\neq}^{Bz}\ f_{\neq}^{Ar}f_{Bz}) \tag{5}$$

where f is an activity coefficient and a an activity, Ar stands for any aromatic compound except benzene, which is Bz.

Table 3. Nitration of aromatics in aqueous sulphuric acid

Compound[a]	$\frac{d \log k_2 (\text{obs. benzene})}{d \log k_2 (\text{obs. aromatic})}$[b]	Intercept (log reactivity relative to benzene)
2-Bromo-1, 3-xylene	1.00 (0.999)	0.6
Chlorobenzene	1.03 (0.999)	-1.2
p-Chlorotoluene	0.94 (0.998)	0.1
p-Dibromobenzene	0.95 (0.996)	-2.9
m-Nitrotoluene	0.91 (1.000)	-4.8
p-Nitrotoluene	0.95 (0.996)	-3.1
2-Phenylethanesulphonic acid	0.97 (0.997)	0
Phenylmethanesulphonic acid	0.85 (0.998)	-1.2
$C_6H_5(CH_2)_2N^+Me_3$	1.04 (1.000)	-0.8
2-Methoxy-4-methylthiazole	1.02 (0.999)	0.5
2-Methylisoquinolinium	0.84 (0.996)	-6.0
1-Phenylimidazole	0.88 (0.999)	-4.5
Methylphenethyl ether	0.94 (0.995)	0.1
Methyl 3-phenylpropyl ether	0.93 (0.999)	0.6
Acetanilide	1.02 (0.999)	0.5

[a] Examples have been chosen from the original extensive compilation which fulfil the criteria (i) unambiguity of reacting species (ii) acid range covered more than 10% (iii) more than two points defining rate-acidity profile.

[b] Correlation coefficient in brackets.

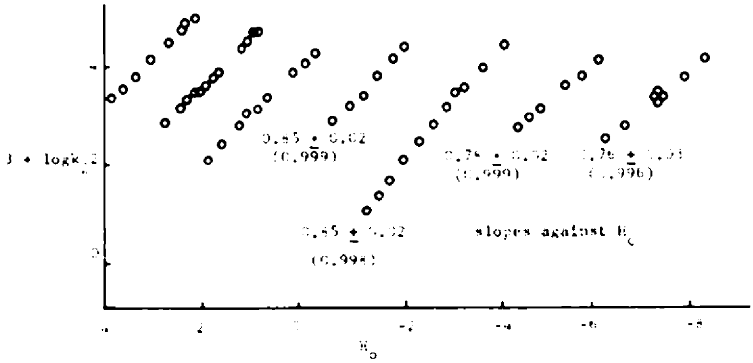
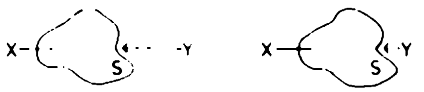


Fig. 5. Aromatic bromination, HOBr, H_2O, $HClO_4$ (25) Compounds in order of increasing reactivity 3,5-$Me_2C_6H_3(CH_2)_2N^+Me_2$, 3-$MeC_6H_4(CH_2)_2N^+Me_3$, $C_6H_5(CH_2)_2N^+Me_3$, 4-$MeOC_6H_4N^+Me_3$, 4-$MeC_6H_4N^+Me_3$, $C_6H_5N^+Me_3$, 2,4,6-$Me_3C_5H_2N^+H$, 2,6-$Me_2C_5H_3N^+H$.

Similar data exist for bromination of substituted aromatic amines in sulphuric acid (Fig. 5). Here the results for different molecules do not always overlap in acidity, but the slopes against H_X are essentially constant; Hammond and Cordes coefficients are zero for a reactivity range of 10.[13] The area of aromatic electrophilic substitution is one in which evidence against the operation of the RSP is thus particularly clear-cut, a conclusion recently given additional support.[26,40,41]

To add to these results demonstrating constant selectivity for proton exchange and aromatic electrophilic substitution reactions, recent studies have revealed constant selectivity for the reaction of nucleophiles with carbonium ions[42,43] and carbonyl compounds,[42,44] for S_N2 reactivity for pyridine displacement of various leaving groups from alkylating agents,[45-48] for hydrolysis of oxocarbonium ions in aqueous sulphuric acid,[49] for acetolysis of l-azulylethyl tosylates,[51] and for reactions of methylating agents (CH_3X) with substituted thiophenoxides.[52] In all these cases, the reactivity range is very large, and this fact and the wide variety of reaction types considered make it hard to see how they could all be exceptions to an otherwise general rule.

Metzger has put forward[53] the interesting idea that steric effects should vary with transition state structure, steric interactions at the reaction site being less pronounced for a fast exothermic reaction with a reactant-like "loose" transition state 3 (for a bimolecular reaction) than for a slow endothermic reaction with a product-like "tight" transition state 4; this again should produce a change in selectivity with a change in rate. Thus, for reaction at a sterically congested centre, the Hammett equation would become modified to eqn (6), where dS varies with rate, and the correlation between log k and the appropriate form of σ thus becomes curved.



3 4

"Steric" centre S Reagent Y Substituent X

3 Fast reaction, early TS, small steric effect of S

4 Slow reaction, late TS, large steric effect of S

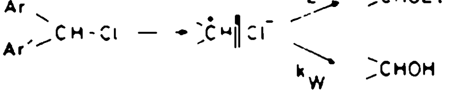
$$\log k/k_0 = dS + \rho\sigma. \qquad (6)$$

Again, however, selectivity and thus the influence of steric effects appear to be constant. For example, the reaction of methoxide ions with 1-chloro-4-X-2,6-dinitrobenzene in methanol at 50° to form the Meisenheimer complex yields an excellent straight line plot for log k vs σ^- over a 10^6 change in rate ($\Delta G^{\neq}$ 37 kJ mol^{-1}).[54] A linear plot for a similar rate change is also observed for the log rates of hydrolysis of 2,6-dimethyl-4-X-benzoyl chlorides proceeding by an acylium ion mechanism, against σ^+.[55] In both cases, steric crowding at the reaction centre would be expected to be large. It is also relevant that Taft's scale of E_s values for assessment of the size of steric interactions,[56] which have been widely used, appear to require no adjustment with change in reaction rate when used in kinetic correlations.

In the field of S_N1 reactivity, it has been suggested[57] that the stability-selectivity relationship becomes more comprehensive and comprehensible if viewed as an example of an LFER rather than, as often recently suggested,[48b,58-61] a manifestation of the RSP.

The corollary[57] is that variations in Grunwald-Winstein m values and Hammett ρ values cannot be interpreted in terms of transition state variation as rate is varied. These conclusions have been queried,[62] but nevertheless we do not wish to withdraw our original arguments,[57] and suggest they are still worth consideration.

For example, Pross[58] has recently provided data for the selectivity S ($= k_E/k_W$) of ethanol and water attack on substituted diphenylmethyl chlorides, and demonstrates that log S plots linearly against σ^+. Thus, in 70% ethanol water the following selectivities S are found: unsubstituted, 3.25; *p*-chloro, 2.84; *p*-methyl, 4.66, *p,p*-dichloro, 2.75.



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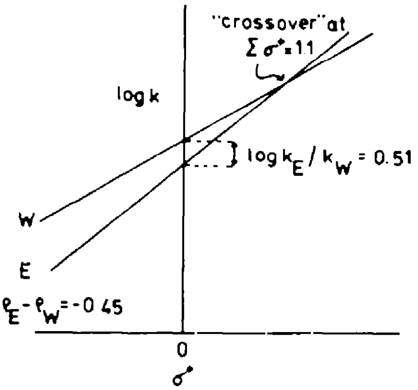


Fig. 6. LFERs for ethanol and water attack on diphenylmethyl chlorides

Innumerable precedents would indicate that the reactivity of a side chain attached to an aromatic nucleus, in which *m*- and *p*-substituents are systematically altered, would follow, at least approximately, a Hammett type LFER, and further, whether the reaction was an equilibrium, or, as in this case, irreversible, that the ρ value would alter as the reagent solvent was changed. We may thus write:

$$\log k_E = \rho_E \Sigma\sigma^{+} + \log(k_E)_0 \tag{8}$$

$$\log k_W = \rho_W \Sigma\sigma^{+} + \log(k_W)_0 \tag{9}$$

so that

$$\log k_E/k_W = S = (\rho_E - \rho_W)\Sigma\sigma^{+} + \log(k_E/k_W)_0. \tag{10}$$

The data do indeed yield a linear plot of log S $\Sigma\sigma^{+}$, of slope −0.45, so that from eqn (10) the diagram shown in Fig. 6 can be constructed, showing the individual log k vs σ^{+} plots. Such a treatment shows

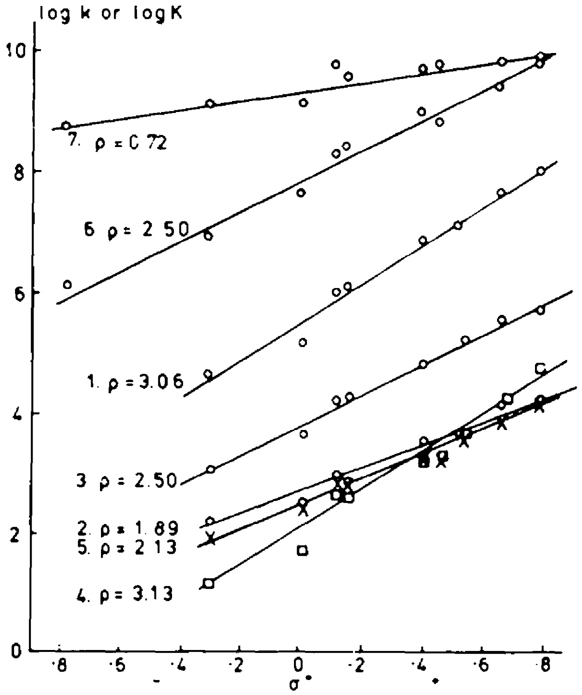


Fig. 7 Reactions of substituted diazonium ions with nucleophiles correlated with σ^{+} values (see Ref. 66a). 1, $C_6H_5SO_2^-$, MeOH, 25° (log K). 2, $C_6H_5SO_2^-$, MeOH, 25° (log k). 3, OH^-, H_2O, 23° (log k). 4, CN^-, H_2O, 23° (log K). 5, CN^-, H_2O, 23° (log k). 6, N_3^-, MeOH, 23° (log k). 7, $C_6H_5S^-$, MeOH, 23° (log k diffusion controlled. As Rappoport[61] has suggested, this complicates comparisons of selectivity). Slopes of Bronsted plots: ρ_2/ρ_1 = 0.62 (Ritchie gives 0.64); ρ_5/ρ_4 = 0.68 (Ritchie gives 0.65).

that "cross-overs" can occur, that a substrate for which log S is zero does not have to be "infinitely" reactive, and avoids the necessity of postulating a rather vague reactivity region in which log S approaches the σ^+ axis asymptotically to avoid becoming negative, as demanded by the RSP[59] (Fig. 1b).

It is also revealing to apply these arguments to Ritchie's experiments[42] on cation reactivity. These have shown that for a wide range of nucleophiles and nucleophilic solvents with various types of organic cations

$$\log k = N_+ + \log k_0 \tag{11}$$

where k is the observed second order rate constant for the reaction of a given nucleophilic system with a given cation, k_0 is dependent solely on the identity of the cation, and N_+ is dependent solely on the nucleophilic system in which the rate is measured. This clearly shows an absence of any dependence of reactivity on selectivity, and in accepting this, it has been widely supposed that therefore these results are anomalous, and need some special explanation.[61] This is not necessarily so, however, and in fact these conclusions may well be compatible with other results in this area of reactivity, considered to support the RSP.[48b,58-63]

Suppose that a series of cations differing one from another by systematic substituent change obey eqn (11). Suppose further that their logarithmic rates of reaction with a certain nucleophile system plot linearly against, say, an appropriate series of equilibrium constants or logarithmic rates, possibly defined in terms of some σ scale. Then it inevitably follows, provided eqn (11) is followed *exactly*, that the slopes of all such plots of this cationic series with other nucleophilic systems must be the same; i.e. selectivity remains the same, and m and ρ values are constant.

Figure 7 shows the data for a series of *m*- and *p*-substituted diazonium compounds plotted against σ^+, and Fig. 8 for substituted phenyltropylium ions plotted against the $pK_{R}+$ values in water. Where available, relevant equilibria data are plotted as well.

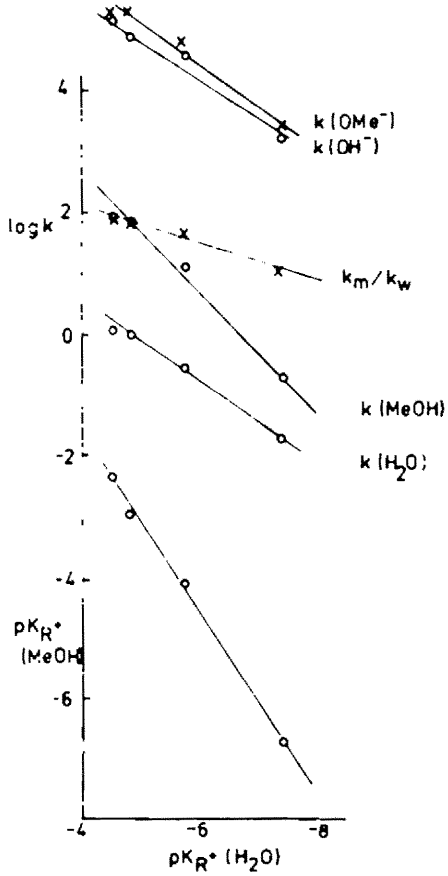


Fig. 8. Reactions of substituted phenyltropylium ions with nucleophiles (see Table 4).

Table 4. Reactions and equilibria of substituted phenyltropylium ions in aqueous and methanol solution[a]

Substituent	logk(MeOH, s^{-1})[b]	logk(H_2O, s^{-1})[c]	log(k_{MeOH} k_{H_2O})[d]	pK_R+(MeOH)	pK_R+(H_2O)	logk(OMe^-, Ms^{-1})	logk(OH^-, Ms
p-Cl	1.96	0.08	1.89	2.30	4.55	8.28	5.15
H	1.85	0.00	1.85	2.92	4.84	8.26	4.90
p-OMe	1.11	-0.57	1.68	4.09	5.75	7.83	4.60
p-NMe_2	-0.66	-1.70	1.04	6.68	7.35	6.36	3.23

[a] Refs. 42, 66b.

[b] Slope against pK_R+(MeOH) 0.66.

[c] Slope against pK_R+(H_2O) 0.72.

[d] Not strictly comparable with selectivities obtained by competition in a common solvent.

The slopes of the LFERs thus obtained are by no means constant, but show the degree of variation expected from the wide range of different solvents and reagents used. These changes are amply large enough to produce the magnitude of variation in selectivities and m values found for other cation systems. The direction of the variation is such as to produce both apparent RSP and anti-RSP effects, and crossovers occur, indicating a change from positive to negative logarithmic selectivity ratios. Data from Fig. 8 is analysed in Table 4. These show an apparent anti-RSP effect, but the slopes of the kinetic data against the corresponding equilibria produce good straight lines of similar slope (Bronsted plots for the diazo-compounds also have similar slopes as shown in Fig. 7). Results for a 3-member series of triphenylmethylcarbonium ions (Crystal Violet, Malachite Green, and *p*-nitro-Malachite Green) have also been obtained.[42] Here ρ values are generally smaller than for the diazo or tropylium ion reactions (see later discussion), but again their variation with nucleophile is appreciable.

Calculations shown in Table 5 illustrate the general point that within the "noise" of the extensive Ritchie plots there is enough deviation to allow for slope variations of appropriate LFERs amply sufficient to account for the range of selectivity ratios and m values observed in carbonium and cation reactivity.

It is stressed that the above arguments are not intended to imply that the detailed reaction mechanism for all cations with nucleophiles is the same necessarily; according to Winstein and others[64] there are distinctly different degrees of solvation of cations involved in rate-determining reaction, and the species involved in the reactions of stable cations studied by Ritchie might well be different to those for less stable cations generated *in situ* as unstable intermediates.

Table 5. Deviations from the constant selectivity relationship eqn (1) for diazonium compounds $XC_6H_4N_2^+$[42,66a]

		2.[a] $C_6H_5SO_2^-$, MeOH, 25°, N^+=3.67, ρ=1.89,			3.[a] OH^-, H_2O, 23°, N^+=4.75, ρ=2.50,		
X	log k_c	logk (exptal.)	logk[b]	logk[c]	logk(exptal.)	logk[b]	logk[c]
p-NO_2	0.68	4.28	4.35	4.21	5.73	5.43	5.78
H	-1.20	2.51	2.47	2.72	3.65	3.55	3.80
p-CH_3	-1.54	2.20	2.13	2.13	3.08	3.21	3.03

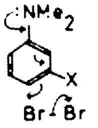
[a] For graph, see corresponding number in Figure 7.

[b] Calculated from eqn (11).

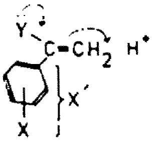
[c] Calculated from log k = $\sigma^+\rho$ + intercept.

We do not believe, however, that Ritchie's results represent anything extraordinary: the same lack of selectivity change will be found if any reaction series of constant mechanism can be examined over a sufficiently large rate range. This does emphasise the possible dangers, previously pointed out[5,57] and recently reemphasised,[65] in interpreting results, where different ρ values arise for change of solvent or reagent, in terms of variable transition state structures giving rise to RSP effects, and in basing deductions on data covering only a limited range of reactivity. Precisely the same points have been made in connection with work on CO reactivity.[44]

It is relevant to the next section of the discussion to refer back to Tidwell's results[30,31] on the protonation of α-substituted carbon-carbon double bonds, together with a further two correlations which also cover very wide rate changes (about 10^{17} in both cases), namely acid-catalysed hydrogen exchange for aromatic and heteroaromatic molecules,[67] and bromination of substituted benzenes.[68] Within the range of molecules studied and the scatter they produce in the LFERs, there exist "subpopulations" for which ρ-values do change, apparently in the direction expected from operation of the RSP, although the overall spread of results suggests that in fact this principle cannot be operative. Figure 1 of Dubois' paper[68] demonstrates this particularly clearly. This effect may rather be ascribed to substituent-substituent or "coupled" interactions and accounted for by "cross-product" terms in the log rate σ^+ correlation as originally defined by Miller.[69] Dubois has shown[68] by MO calculations that this does not appear to involve any change in transition state characteristics which involve it becoming more reactant or product-like, as reaction rate is varied, although it manifests itself as a non-zero Cordes coefficient. Putting it in an alternative form, the phenomenon appears to arise when substituent variation occurs at a position where both bond-breaking and bond-making can be observed on the route to the transition state; i.e. the substituents act as good witnesses of the overall reaction, as illustrated in **5** and **6**, for the bromination[68] and protonation reactions[30,31] respectively.



5. $\rho = -2.2$
cf -11.6 for monosubstituted benzenes



6

Y	$d\log k/d\sigma^+ = (\rho)$
NH_2	-1.1
MeO	-1.7
H	-2.9
CF_3	-4.0

cf $\rho = 1.09$ for pK_{BH^+}/σ^+ benzoic acids
1.85 benzaldehydes

A number of very interesting examples involving general acid or base catalysis are to be found in Jencks' work, and these, and others closely related, are collected in Table 6. It has become popular to express bond changes during the course of a given reaction in the form of three-dimensional reaction coordinate diagrams[84] (Albery–More O'Ferrall–Jencks diagrams); whatever the degree of legitimacy of such representations, it appears that these non-zero Cordes coefficients occur when the relevant substituent variation has an influence on both coordinates of such a diagram (central atom effect[7]), but become very small or zero when the substituent variation influences only one such coordinate (end atom effect[7]). This effect is clearly shown in Table 6. It may be noted that the free energy changes involved are generally very large, and that there is no evidence within this compilation for curved Bronsted plots, i.e. Hammond coefficients are zero.

A corollary of the difference in influence of end and central atoms is that there must be an imbalance between the relative rate changes induced by substituent change at a central atom and those induced at an end atom. The cause of this imbalance may be through-conjugation, as in the results of Dubois,[68] Tidwell,[30,31] and Katritzky,[67] or electrostatic interactions (the Hine effect) as noted particularly for central atom effects in general acid catalysis mechanisms,[7] i.e. substituent-substituent interactions of one form or another occurring either in the ground or transition state.

For example, for compounds of type **6**, the effective σ_X^+ value for the $C_6H_4X(X')$ group should be given by $\rho\sigma_X^+/-10.5$, where ρ is the reaction constant obtained by varying X, and -10.5 is the ρ value obtained by Tidwell[30,31] using overall σ^+ values for X′ and Y. However, the varying ρ values obtained for different Y groups indicate apparent variable σ_X^+ values for a given group X, since the electronic

Table 6 Variation of α and β Brønsted coefficient values induced by central atom and end atom substituent effects in general acid and base catalysed reactions

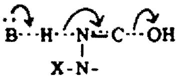
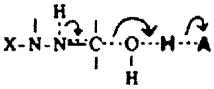
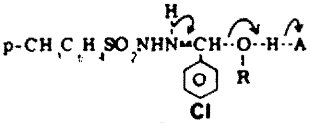
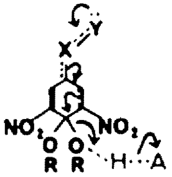
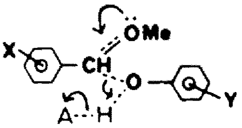
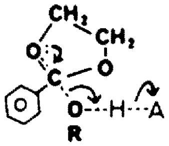
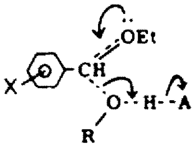
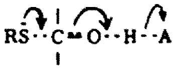
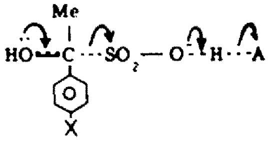
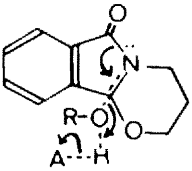
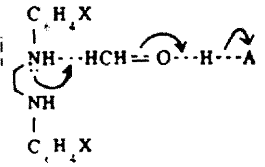
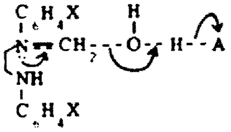
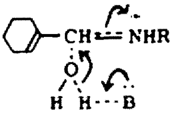
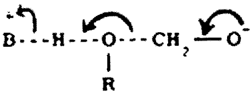
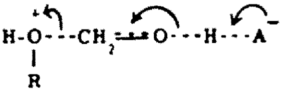
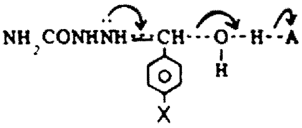
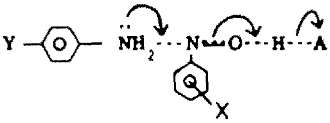
Reaction (H_2O, 25° unless indicated otherwise)		Central atom[a] effect	End atom[a] effect
General base catalysis of carbinolamine dehydration[b]			$\frac{d\beta}{dpK_a^N}=0.00^c$
General acid catalysis of carbinolamine dehydration[b]			$-\frac{d\alpha}{dpK_a^N}=0.02^c$
General acid catalysis of carbinolamine ether dehydration[d]		$\frac{d\alpha}{dpK_{ROH}}=0.05$	
General acid catalysis of Meisenheimer complex breakdown[e]		$\frac{d\alpha}{dpK_{ROH}}=0.12$	$\frac{1}{\rho_{eq}}\frac{d\alpha}{d\sigma_{xy}}=0.01^f$
General acid catalysis of benzaldehyde aryl methyl acetal hydrolysis[g]		$\frac{d\alpha}{dpK_{ArOH}}=0.20$	$\frac{1}{\rho_{eq}}\frac{d\alpha}{d\sigma_x}=0.11^{h,i}$
General acid catalysis of 2-alkoxy-2-phenyl-1,3-dioxolane hydrolysis[j]		$\frac{d\alpha}{dpK_{ROH}}=0.07$	
General acid catalysis of benzaldehyde dialkyl acetals[k]		$\frac{d\alpha}{dpK_{ROH}}=0.05$	$\frac{1}{\rho_{eq}}\frac{d\alpha}{d\sigma}=0.02^{h,i}$
General acid catalysis of thiol anion addition to acetaldehyde[l]			$\frac{d\alpha}{dpK_{RSH}}=0.03$
General acid catalysis of ketone bisulfite breakdown[m]			$\frac{d\alpha}{d\sigma_x}=-0.18^{h,n}$
General acid catalysis of breakdown of alcohol adducts with N,O-trimethylene-phthalimidium cation[o]		$\frac{d\alpha}{dpK_{ROH}}=0.07$	

Table 6 (Contd)

General acid catalysis of N, N'-diphenylethylenediamines attack with formaldehyde[p] (dioxane-H_2O, 25°)			$\frac{d\alpha}{d\sigma_x} = 0.00$
General acid catalysis of carbinolamine dehydration[p] (dioxane-H_2O, 25°)			$\frac{d\alpha}{d\sigma_x} = 0.00$
General base catalysis of Schiff base hydrolysis[q]			$\frac{d\alpha}{dpK_a^N} = 0.03$[r]
General base catalysis of formaldehyde hemiacetal cleavage[s]		$\frac{d\beta}{dpK_{ROH}} = -0.10$	
General acid catalysis of formaldehyde hemiacetal cleavage[s]			$\frac{d\alpha}{dpK_{ROH}} = 0.02$
General acid catalysis of semicarbazone dehydration[t]			$\frac{d\alpha}{d\sigma_x} = 0.00$[h]
General acid catalysis of azobenzene formation[u]		$\frac{d\alpha}{d\sigma_x} = 0.15$	$\frac{d\alpha}{dpK_a^N} = 0.00$

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[a] All coefficients in the last two columns are corrected to two decimal places.

[b] Ref. 70. Carbinolamines derived from $C_6H_5\overset{+}{N}NH_2Cl^-$, $CH_3C_6H_4SO_2NHNH_2$, $CH_3CONHNH_2$, $NH_2CONHNH_2$, $C_2H_5OCONHNH_2$, $HOSO_2C_6H_4NHNH_2$, NH_2NH_2.

[c] pK_a^N refers to the free amine.

[d] Ref. 71. R = C_2H_5, $ClCH_2CH_2$, CF_3CH_2.

[e] Ref. 72. XY = CF_3, CN, SO_2CH_3, NO_2, SO_2CF_3. R = C_2H_5, CH_3, $CH_3OCH_2CH_2$, $ClCH_2CH_2$, $HC \cdot CCH_2$.

[f] ρ_{eq}(= 6.2) refers to the equilibrium addition of OMe^- to 1-methoxy-2,6-dinitro-4-X-benzene: the Cordes coefficient is thus normalised and may be compared directly with that for the central atom.

[g] Ref. 73. X = m-NO_2, m-OMe, H, p-Me, p-OMe, Y=H. X=H, Y = m-NO_2, m-Br, m-F, m-OMe, p-Me, p-OMe.

[h] Classified as an end atom (see Jencks and Jencks), but both bond making and breaking occur on the atom to which C_6H_4X is attached.

[i] ρ_{eq}(= 3.6) refers to the equilibrium formation of oxocarbonium ions from acetophenone acetals: see footnote f.

[j] Ref. 74. R = $ClCH_2CH_2$, $CH = CHCH_2$, $ClCH_2CH_2$, $CH_3OCH_2CH_2$, CH_3.

[k] Ref. 75. R – CH_3CH_2, CH_3, $CH_3OCH_2CH_2$, $ClCH_2CH_2$, CH - $ClCH_2$, CF_3CH_2.
X = Me_2N, CH_3O, CH_3, H.

[l] Ref. 76. R = CH_3CO, $X_nC_6H_{(5-n)}$ where X – p-OCH_3, 3,4-diCl, p-NO_2, penta-F.

[m] Ref. 77. X = NO_2, OMe.

[n] Difference in α is solely due to point for specific acid-catalysis: neglecting this point, the Cordes coefficient becomes zero.

[o] Ref. 78. R = CF_3CH_2, $CHCl_2CH_2$, $CH \equiv CCH_2$, CH_2ClCH_2, CH_3, C_2H_5.

[p] Ref. 79. X = p-OCH_3, H, m-F, p-NO_2.

[q] Ref. 80. R – $CH_3CH_2CH_2$, $HOCH_2CH_2$, CF_3CH_2, NH_2COCH_2, $CO_2^-CH_2$, $CO_2^-CH_2CH_2$.

[r] pK_a of Schiff base.

[s] Ref. 81. R = C_2H_5, H, CH_3, $CH_3OCH_2CH_2$, $ClCH_2CH_2$, Cl_2CHCH_2, F_3CCH_2.

[t] Ref. 82. X = NO_2, Cl, H, CH_3, OCH_3.

[u] Ref. 83. Y = Cl, H, CH_3. X = p-NO_2, m-NO_2, p-Cl, p-CH_3.

interactions between the C=C double bond and the Y group, which influences rate of attack by H_3O^+, in turn influences the response of X.

Detailed discussion of such effects for a specific example has been provided by Bernasconi[72] in the general acid catalysis of Meisenheimer complex breakdown (fourth entry in Table 6). Here $(1/\rho_{eq} \times d\log k/d\sigma^-_{XY} + d\log k/dpK_{HA})$, i.e. $\rho_n + \alpha$, should be equal to $d\log k/dpK_{ROH}$, i.e. β_{lg}, since both measure extent of bond cleavage/formation at the O atom, and thus the apparent extent of change buildup thereon; however large discrepancies exist between numerical values of the two expressions, so that the information provided on transition state structure by the end atom effect is not directly compatible with that provided by the central atom effect.

Originally, Miller,[69] and more recently McClennan[5] and O'Brien and More O'Ferrall[15] have concentrated attention on this phenomenon; in the latter treatment the influence of resonance saturation, and steric effects (e.g. twisting of substituent-bearing aryl groups), as well as substituent-substituent cross interactions and reactivity-selectivity effects are discussed. As the authors point out, the influence of the last cannot be solely responsible for the non-zero Cordes coefficients, because the effect is also found in equilibria series[85] (thus for the pK_{R^+} values of triphenylcarbinols, ρ is found to be 5.1 and 1.4 for monosubstituted and Malachite Green derivatives respectively); they are also observed in measurements on non-reacting molecules involving spectral techniques.[86] It may therefore be pointed out that once again there seems no compelling reason here for postulation of RSP effects, and indeed it seems generally accepted that substituent-substituent interactions, either in the ground state molecule or in the transition state, play an important part; nevertheless this specific area is particularly predicted as one for increased investigation, speculation, and controversy in the future. Thus workers have stated[10,87] that it is in complex mechanistic types, with "coupled" interactions, that the RSP is least likely to apply, and that examples of its operation must be sought in simple reaction modes of "push/pull" type. The alternative opinion may however be advanced, that it is in the latter that reactivity-selectivity effects are most conspicuously absent (with the proviso that, certainly in solution, it is a very moot point if there is such a thing as a simple reaction: the question is really how many effects it is possible to put an experimental figure to), while more debate may be directed at complex reactions, where a relatively large number of variables may be experimentally defined, for here the difficult question arises as to whether apparent manifestations of the RSP can legitimately and uniquely be interpreted in terms of variable transition state structure, or by means of other factors such as substituent-substituent interactions (as well as the discussion here, see also ref. 14).

We now turn from discussion of the validity or otherwise of the RSP, a purported connection between two *experimental* quantities, to the quite distinct question of what all this has to do with transition state structural variations arising exclusively from rate change. The two issues must not be confused: the non-observance of an experimental connection between reactivity and selectivity in any instance means that experimental parameters commonly associated with transition state structure[88] remain constant, and no more. (We have always been careful to make this distinction, as revealed, for example, by reference to the sentence in a recent review[5] immediately following one quoted[14] to suggest otherwise.) All models or pictures constructed to explain the interactions within and between molecules, whether in the ground or transition state, are in the final analysis artefacts. The only realistic way to treat the macroscopic phenomena observed in the laboratory is by definition of mathematical equations which are designed to reproduce as accurately as possible the observed phenomena in terms of other practical observations and which allow predictions about the behaviour of related systems. All pictures or models expressed in molecular terms which fit the equations thus defined can be considered valid, since there is no way in which pictorial concepts based on such a level of subdivision can have any physical reality for us. The principle of Occam's razor informs us that the simpler the mathematical treatment the better: there is no point in including extra parameters for their own sake. Therefore the problem of the validty of the RSP reduces to the question of whether it is ever necessary to include in such mathematical treatments a proportionality between the two experimental quantities reactivity and selectivity, or whether in all cases incorporation of parameters defining interactions (i), (ii), (iii) and (iv) given in the opening section will suffice. A closely related question would be the number of parameters necessary to express accurately substituent effects on reactivity; here it is possible rather less terms are needed than one might have thought if one is guided too literally by the physical pictures of such effects,[91] although in other areas such as solvent or steric effects the picture is one arising from much greater mathematical complexity. For these reasons, it may often be more illuminating to plot one set of experimental data against another set, rather than against some empirical parameter whose experimental definition is imprecise or has become obscured, and to which some theoretical model at the sub-molecular level may have become tenaciously fixed.[92]

Thus, it is necessary to note that to the extent that the RSP cannot be observed in practice and there is much evidence to indicate that the picture of mechanisms characterised by constant selectivity factors certainly cannot be ruled out then to exactly that extent the question of transition state variation with rate change becomes a philosophical rather than a scientific one, since no experimental evidence can be brought to bear on it. Such considerations will for example affect the status accorded to Albery-More O'Ferrall-Jencks contour reaction diagrams which are dependent for their definition on RSP effects, contrasting with mechanistic pictures characterised by constant selectivity factors and in which mechanistic changeover occurs in a region where two separate and discrete pathways both become kinetically significant. The rather depressing corollary to this is that every mechanistic changeover observed becomes potentially a source of argument closely akin to the classical-nonclassical carbonium ion controversy.[93]

The simplest possible model for reconciling LFERs and variable transition state structures has been put forward by Canadian workers.[94]

Figure 9 gives the basic details and equations. The essential device is to extend the Marcus approximation,[29] of Morse curves to parabolas, through to V-shaped potential energy wells, so that

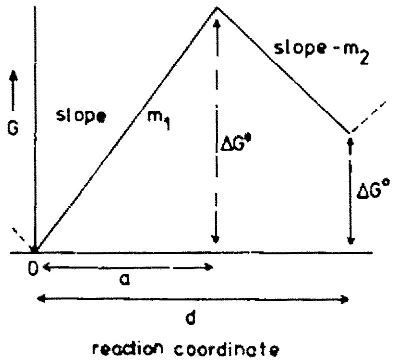
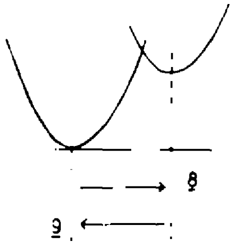


Fig. 9. Hypothetical model for reconciling LFERs and variable transition state structure. $\Delta G^* = m_1(\Delta G^0 - m_2 d)/(m_1 - m_2)$, whence $\alpha = d\Delta G^*/d\Delta G^0 = m_1/(m_1 - m_2)$, and $d\alpha/d\Delta G^0 = 0$. As $\alpha \to 0$, $m_1 \to 0$, $a \to 0$; as $\alpha \to 1$, $m_2 \to 0$, $a \to d$

in 2-dimensional representation they are described by straight lines. As in Marcus theory, the internuclear distance stays the same for each reaction of the series; the slopes of the wells (m_1 and m_2) may however change from reactant to product. What physical reality this model might have is impossible to judge; certainly in the Marcus model it is the curvature of the overlapping parabolas which gives rise to the prediction of RSP effects. Nevertheless, essentially linear FERs can arise for quite appreciable free energy changes from the Marcus model for reactions of high intrinsic energy, because for these cases the parabolic curvature in much of the region of overlap is only slight,[95] and the model 7 approaches that of Hopkinson.[94] This is the reason for the postulation of high W' values[29] for proton exchanges considered to give markedly curved Bronsted plots,[34-36] in which consideration of the exchange term alone would predict only slight curvature. Aspects of this argument have been put forward in a perceptive article by Farcasiu;[96] as he points out, the RSP should not be observable for reactions with a high intrinsic free energy, such as elimination reactions, where the initial and final states are much lower in energy than the transition state, and which thus fall into the category of model 7. If any manifestation of the RSP is to be found, the Marcus theoretical model thus suggests that it must be sought in highly exothermic rapid reactions **8** or highly endothermic slow reactions **9**, just the situation, unfortunately, which may be complicated by onset of diffusion control of forward or backward processes.

7



8

9

More complex models can be used to explain not only non-observance of the RSP, but also, where considered appropriate, both RSP and anti-RSP effects (positive and negative Hammond and Cordes coefficients). The basic method in all these cases is to postulate two influences at work on the data in hand, so that RSP effects in one can be cancelled, emphasised, or over-ruled in the other, as occasion appears to demand. Three variations (i), (ii) and (iii), of this fundamental theme may be discerned:

(i) reactions which do not show RSP effects have two steps contributing to the rate-determining process. Scott has set out the generalised scheme for this.[97] A specific example has been provided by Pross[10,98] who explains the lack of RSP effects in Ritchie's results[42] for carbonium ion reactions with nucleophiles as due to a desolvation step followed by reaction, the more "inherently" reactive electrophiles being also the most strongly solvated, and vice versa. Pross[48b] has also suggested that reactivity-selectivity relationships in S_N2 reactions may be masked by the fact that while selectivity is governed solely by the HOMO LUMO gap,[46] reactivity is also influenced by the leaving group bond breaking term. Similarly, linear Bronsted plots for acetal hydrolysis have been interptreted[99] in terms of a pre-equilibrium for formation of hydrogen bridge-bonded complexes between general acid and acetal followed by slow proton transfer. Indeed generalised Marcus theory for exchange combined with an adjustable pre-exchange factor fits this category to a degree, in that variation of curvature in Bronsted plots from very pronounced to hardly perceptible may be accommodated by changing the relative sizes of $\Delta G_0^{\ddagger}$ and W'.[24]

(ii) there are effects both parallel to (Hammond) and perpendicular to (anti-Hammond or Thornton)[100] the reaction coordinate which act in opposition to one another. There are many examples of this approach; one such is the proposal[10] that the zero Hammond and Cordes coefficients observed by Kemp and Casey in the acid-catalysed decomposition of benzisoxazole[36b] are due to precisely balanced Hammond and Thornton effects.

It is hard to comment on the validity of interpretations (i) and (ii); certainly in general they appear perfectly reasonable. However, the following points may be made. Firstly, if it is accepted that unambiguous experimental demonstrations of the RSP are very difficult to find, then it would be rather strange to suggest that Nature has created an effect, and then taken great pains to ensure that it cannot be detected in practice! Secondly, suggestion of the various effects is not in itself sufficient;

experimental verification and quantification is required, otherwise any way an experiment turns out may be claimed to authenticate their use. For example, Pross' interpretation[10] of Kemp and Casey's results[36b] could easily have been modified to accommodate either negative or positive non-zero Hammond and Cordes coefficients, by appropriate adjustment of the weight given to the parallel and perpendicular effects; the fundamental question is whether these effects have been defined sufficiently accurately to give them *predictive* value. If such effects do indeed need to be taken into account, they do not yet seem to have been evaluated and defined experimentally so that prophesies of how they will operate in any given situation can be made.

(iii) there are RSP effects at work on both coordinates of the experimental plot defining the selectivity pattern, so that overall cancellation can occur. For example, σ^+ is implicated many times in correlation of reactivity data. Such plots cover very wide reactivity ranges; they are thus particularly pertinent to the discussion of the RSP. The point has been raised[10,14] that since σ^+ values are derived from a reactivity series which might also contain RSP effects, a cancellation could occur leading to suppression of intrinsic curvature. The validity of this proposition seems doubtful, however. Definition of the σ^+ scale is now only of chronological significance, since this scale (and the σ and σ scales) correlate not only equilibria in solution,[85,101] but also in the gas phase,[102] as well as being verified by calculations in which an isodesmic process in the absence of solvent is assumed.[103] It therefore seems a reasonable assumption that σ^+ values are good indicators of internal electronic effects arising in the stabilisation of a positive charge by a substituent, and independent of RSP influences, solvent interactions, and other external features (the terms internal and external are used in the sense defined by Hepler[104]), and furthermore suggest that specially modified values such as postulated by the Yukawa-Tsuno equation[91] are not in fact required; the variation in ρ values alone accounts for solvent effects and also substituent effects being only fractionally developed in the transition states for S_N1 hydrolyses or aromatic electrophilic substitution compared to those in equilibria series.[105]

As noted previously, an excellent text-book[1] asserts that the RSP has been found extremely useful; in the event, one example of dubious validity is given. No systematic pattern exists for prediction of the mode of action of the principle in any given instance. Alternatively, the number of times consideration of LFERs, together with the corollary that curvature stems only from a change in mechanism or rate-determining step, have led to a coherent picture of reaction pathways defies documentation. There are few examples of mechanistic investigation where LFERs, particularly of Hammett form, have not been gainfully employed; for any mechanistic possibility, the form the equation will take can be predicted with considerable accuracy, and in the absence of mechanistic change, the limit of linearity is habitually the limit of the experimental range covered. The general reaction to this situation seems to be that the RSP is valid, that the concept must be preserved at all costs, and that in consequence FERs are usually curved, while LFERs are exceptional and non-typical, arise under special circumstances only, or contain RSP effects masked by experimental noise. Even for the most whole-hearted proponent of the RSP, the implications of the alternative view-point would possibly be worth examination; at the very least, non-critical use of the principle may be ill-advised.

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$$\Delta G^{\neq} = W^r + \lambda/4(1 + \Delta G^0/\lambda)^2$$

is for the overlap of parabolae $y = mx^2$, $y = m(x - d)^2 + \Delta G^0$, where W^r is the pre-exchange work factor for bringing the reactants together, orienting them in the correct position for reaction, and in some cases desolvating them, $\lambda = md^2$ where d is the (constant) internuclear distance, and $\Delta G^{\neq}$ is the free energy of activation and ΔG^0 is the free energy of equilibrium for the equivalent equilibrium process.

Thus $\alpha = d\Delta G^{\neq}/d\Delta G^0 = \frac{1}{2}(1 + \Delta G^0/\lambda)$ and $d\alpha/d\Delta G^0 = \frac{1}{2}\lambda$. When $\Delta G^0 = 0$, $\Delta G^{\neq}$ is called the intrinsic free energy of the reaction ($\Delta G_0^{\neq}$).

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