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On the Analysis of Substituent Effects. Part 2.[1] Brönsted and Related Plots

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Conclusions reached in Part 1 concerning rate–structure relationships are used in the construction of a theoretical model for the mechanism of covalent bond formation and/or cleavage. In this model the changes in the structure of the reaction complex as it proceeds along the reaction co-ordinate are controlled by a requirement to make charge-transfer between the species joined by the covalent bond as facile as possible. The changes in the electronic structure do not smoothly follow the changes in the geometry of the atomic nuclei, and as a consequence the global pattern of rate–equilibrium and rate–rate relationships is not expected to be very simple. However, the permissible changes in electronic structure suggest that this pattern should exhibit certain simple local features, notably straight lines with slopes close to particular values. Reports of experimental observations which are in accord with the predicted features are cited.

The overall pattern of variation in reactivity for reactions involving covalent-bond formation and/or cleavage is not clear,[2,3] and the way in which motions of electrons and atomic nuclei determine this pattern is not well understood.[4] Some data sets, but not others, conform closely to quantitative linear relationships (see below) such as the Brönsted relationship[5] between log k_i and log K_i, and the Ritchie relationship[6] between log k_j and log k_i. Some exhibit an inverse relationship between selectivity and absolute reactivity, while others exhibit either independence or even a direct relationship between these quantities.[2,3] Explanations of the inverse selectivity–reactivity behaviour in terms of the well known Leffler–Hammond Principle[7] appear to be inconsistent with the existence of linear rate–structure and rate–equilibrium relationships.[3] In Part 1[1] we were concerned with the electronic basis of linearity, and of deviations from linearity, in quantitative rate–structure plots. Here we use our findings from that work to construct a non-rigorous theoretical model for the mechanism of the transformation of a reaction complex from the reactant state to the product state along the reaction co-ordinate. The model is then used to generate expectations concerning rate–equilibrium and rate–rate plots, and hence the overall relationship between selectivity and reactivity. We shall see that some of these expectations are novel and that there is experimental evidence for these novel expectations.

Theory

Brönsted and Analogous Relationships.—The Brönsted relationship[5] for substituent effects is given by equation (1) in which k_i and K_i refer to the rate constant and the equilibrium constant of the same reaction: originally the relationship was concerned with proton transfers but it is followed in many types of nucleophile–electrophile reaction. Also in common use are quasi-Brönsted relationships in which the equilibrium constant refers to protonation of a species but the rate constant refers to some other reaction, *e.g.* alkylation or acylation, of the same species. Finally, there are relationships [equation (2)] in which the rate constants for different reactions of the same species are compared. The Ritchie relationship, equation (3), is a specific example, in which $\delta \log k_i = N_+$ and γ is unity. There is no general simple relationship between the values of β or γ and the absolute rates of reaction.

$$\delta \log k_i = \beta \delta \log K_i \qquad (1)$$

$$\delta \log k_j = \gamma \delta \log k_i \qquad (2)$$

$$\log k_j - \log k_o = N_+ \qquad (3)$$

For substituents which obey the Hammett-like relationship of Part 1 [equation (4)] the values of β and γ are well expressed by equations (5), unless the values of λ are significantly different for the processes compared.

$$\delta P = \rho[\sigma_{ST} - \lambda(\sigma_{ST} - \sigma_I)] \qquad (4)$$

$$\beta = \rho_{Forward}/(\rho_{Forward} - \rho_{Reverse})$$
$$\gamma = \rho_j/\rho_i \qquad (5)$$

The Theoretical Model for a Reaction Mechanism.—During the course of a transformation of a reaction complex from the reactant state to the product state there is a marked change in the geometry of the set of atomic nuclei (nuclear structure) and a marked change in the distribution of the electron population (electronic structure). In Part 1 we concluded from the results of analyses of substituent effects on reaction rates that there is only a small change in the electronic structure of a reaction complex in the immediate neighbourhood of the substituent group in proceeding from the reactant state to the activated state. Also, in certain reactions there is a marked difference in the effect on log k of this small change according to whether or not the strength of the substituent field exceeds a critical value. The small change may be associated with a first-order perturbation of a zeroth-order electronic wavefunction. The marked difference may be associated with a change in the zeroth-order wavefunction that is perturbed.

We now describe a model general mechanism for covalent bond formation and/or cleavage within a reaction complex. The mechanism has the following features.

(i) The change in the electronic structure of the reaction complex as the nuclear structure progresses from the reactant state to the product state is described by first-order perturbations of two or more zeroth-order wavefunctions. The particular zeroth-order wave function appropriate to the reactant state is called the ground-state wavefunction and the others are described in terms of charge-transfer (including charge-resonance) between conveniently chosen molecular sub-units of the reaction complex and local excitations within such sub-units.

(ii) The heterolytic formation or cleavage of a covalent bond between two molecular sub-units is associated with charge-transfer between them. Two or more charge-transfers may occur simultaneously in the same reaction complex, as, for example, in an S_N2 or an $E2$ reaction. Charge-transfer between the two sub-units occurs spontaneously at particular separations and orientations of the sub-units. In reaching these nuclear structures there are, in principle, contributions to the change in potential energy not only from changes in the interactions between the sub-units directly involved in the charge-transfer but also from other structural changes within the solvated reaction complex. The particular nuclear structure with the lowest overall potential energy characterises the activated state. In covalent-bond formation it is possible that large potential energy increases arising out of steric interactions between the reaction partners or out of solvent displacements could be avoided by the occurrence of structural changes within the solvated reaction partners that would assist spontaneous charge-transfer at large separations of the reaction partners. Of course these latter structural changes would in themselves cost energy, and would occur only to the extent that there was a net energy advantage. If the limit of these structural changes was reached the reaction partners would have to move closer before spontaneous charge-transfer could occur.

(iii) Beyond a certain point, electronic structural changes in any molecular species are better described by perturbations of a locally excited zeroth-order wavefunction than by perturbations of the ground-state zeroth-order wavefunction. It is possible that perturbations of a locally excited zeroth-order wavefunction of a particular reactant would result in a net energy advantage with respect to some reaction partners but not with respect to others, even though perturbations of the ground-state zeroth-order wavefunction resulted in a net energy advantage with respect to all these reaction partners. The structures at the points of changeover of zeroth-order wavefunction will be called stationary configurations.

(iv) In concert with the charge-transfer the changes in electronic structure that assist the charge-transfer relax, and changes that would assist charge-transfer in the opposite direction are activated. In proceeding from the activated state to the product state these latter changes relax gradually as the nuclear structure changes. Since the activated state is associated with an abrupt major rearrangement of the electronic structure of the reaction complex as a whole, it is not meaningful to assign one particular electronic structure to that state.

(v) The changes in electronic structure occuring within each of the sub-units of the reaction complex could be monitored by varying the nature of substituent groups which do not themselves change electronic structure throughout the transformation of the reaction complex. Each such substituent group exerts a constant field in which the changes in electronic structure in the remainder of the reaction complex occur, and thus it affects the energy required to make these changes. The magnitude of a substituent field falls off rapidly with distance from its source (see Part 1), and hence substituents monitor directly changes that occur only in those sub-units that are physically close to them.

(vi) The changes in interaction between sub-units as the nuclear structure of the reaction complex progresses are described by variable sub-unit fields. These changes affect the absolute reaction rate.

(vii) Solvent effects are formally divided into constant field and variable field components. The former component arises out of solvent molecules that behave like substituent groups which do not change their electronic structure during the transformation of the complex. The latter component arises out of solvent molecules which are either physically displaced relative to the reaction complex or else change their electronic structure.

In brief, during the course of covalent-bond formation and/or cleavage in a reaction complex, the change in the electronic structure of the complex does not smoothly follow the change in the nuclear structure. Instead there is an abrupt major rearrangement of the electronic structure at a critical nuclear structure which characterises the activated state. The electronic structures before and after the rearrangement are determined by a requirement for charge-transfer between the molecular sub-units directly involved in the covalent bond to be as facile as possible. There are constraints on the extent of the perturbations of the electronic structures that can occur within any particular sub-unit or the complex, and hence the structures of some sub-units may remain fixed in one of perhaps two or more stationary configurations along at least part of the reaction co-ordinate. The change in potential energy of the reaction complex as it moves along the reaction co-ordinate is determined by: the changes in the structures of the individual sub-units; the effects on these changes of constant fields generated by substituent groups and the constant component of the field generated by the solvent; the effects of variable fields of certain sub-units on their neighbouring sub-units; and the effects of the variable component of the field generated by the solvent.

The description of potential-energy profiles for reaction complexes in terms of mixtures of electronic-state wavefunctions, including charge-transfer wavefunctions, is not new. Pross[4] has recently reviewed work by himself and others on this topic. The distinctive feature in our description concerns the permitted mode of behaviour of electronic structure before and after the charge-transfer. It is this mode of behaviour that has a major effect on the overall pattern of variation in reactivity.

Results and Discussion

Applications of the Theoretical Model.—The existence of stationary configurations implies that the extent of the electronic structure change within a particular nucleophile or electrophile, in reaching the activated state, may be the same for a whole set of reaction partners. Hence for a change of substituent, $\delta \log k$ may be the same for each reaction partner provided there is no significant direct interaction between the nucleophile or electrophile and its reaction partner in the activated state. The absolute value of $\log k$ will depend on the nature of the reaction partner because of the effects of perturbations within the reaction partner. The kinetic behaviour we have just described matches that in the many systems which obey the Ritchie relationship[6] (see above). Our rationalisation of this behaviour is supported by observations of Fukuzumi and Kochi[8] on electrophilic aromatic substitution reactions. The effects of substituents in benzene on $\log k$ are energetically equal to their effects on $h\nu$ for transient charge-transfer bands in mixtures of the reactants, for a set of quite different electrophiles in quite different solvents. Furthermore, the values of $\delta \log k$ usually vary little with the nature of the electrophile or the solvent. These observations imply that there are no significant changes in the structures of the substituted benzenes as the nuclear structure of the solvated reaction complex goes from that of the transient charge-transfer complex to that of the activated state for the substitution reaction, and that these arene structures do not depend on the nature of the electrophile or the solvent; the structures are determined solely by the requirement to assist charge-transfer to the maximum extent. The energy difference between the transient charge-transfer complex and the activated-state species must come mainly from partial desolvation of the reaction complex.

When the molecular sub-unit to which the substituent is attached is non-polar, the maximum extent of the electronic structure change in that sub-unit should be equal and opposite for the assistance of bond cleavage compared with the assistance of bond formation, provided the appropriate zeroth-order wavefunction for that sub-unit is the same in both processes. This means that in equations (5) $\rho_{\text{Forward}} = -\rho_{\text{Reverse}}$, and hence the value of β should be one-half in all systems that involve maximum perturbation of the sub-unit and no significant interaction between the reaction partners in the activated state. When the molecular sub-unit is polar, the value of β should be somewhat different but still constant. Johnson[3] has collected many examples of constancy of ρ and β values within reaction series, and has remarked on the lack of examples of smooth curvature in Brönsted plots.

The Leffler–Hammond Principle implies that smooth curvature should be the norm in Brönsted plots. However, our model suggests that smooth curvature should be observable only in special circumstances, namely, where, in the activated state, the variable reactant is not perturbed to the maximum extent, the variation in the extent of this perturbation within the set of reaction complexes is pronounced, and the variable reaction partner and solvent fields are identical throughout the set of reaction complexes. Klingler and Kochi[9] have demonstrated very marked smooth curvature in a plot of log *k* for the electrochemical oxidation of an organocobalt compound against the values of a continuously varying applied potential, an experimental situation that meets the very stringent requirements of our model. Other experimental observations which have been cited as evidence for an inverse reactivity–selectivity relationship will be discussed below.

The example in Part 1 of the σ^+ *versus* σ_{ST} plot indicates that the effect of changing to a new zeroth-order wavefunction for the benzene ring is very marked. The change must, in itself, cost energy. However, the resulting reduction in the sensitivity to electron-attracting ring substituents of charge-transfer to the electrophile or to the side-chain permits a net reduction in the activation energy. Another way of bringing the new zeroth-order wavefunction of the ring into the reaction mechanism would be to increase the magnitude of the combined variable reaction partner and solvent field effects above the level at which the energy gain from increasing the separation of the reactants in the activated state equals the energy loss from the additional perturbation of the ring. Then all ring substituents would exhibit the reduced effects on the ease of charge-transfer to the electrophile or the side-chain. The reverse charge-transfer would not benefit from this enhanced ring perturbation. Consequently, enhanced ring perturbation would not occur in the reverse reaction and ring substituents would exert their full effects. When comparing δ log *k* for attack of a set of substituted nucleophiles on an electrophile which induces the enhanced ring perturbation, with attack of the same set of nucleophiles on an electrophile which does not, the slope should be markedly less than unity, even where the perturbations are at their respective limits. Furthermore, the value of β should be markedly less with the former electrophile than with the latter. Using the observation from the σ^+ *versus* σ_{ST} plot that the reduced substituent effect is one-third of the full substituent effect, the slope of the Ritchie plot should fall from unity to one-third, and the slope of the Brönsted plot should fall from one-half to one-quarter [when $\rho_{\text{Forward}} = -1/3\ \rho_{\text{Reverse}}$, $\beta = 1/4$ by equations (5)]. For the reverse reactions the slope of the Ritchie plot should remain at unity and the slope of the Brönsted plot should rise to three-quarters.

We have found several items of experimental support for the remarkable behaviour described in the previous paragraph.

(i) Arnett and Reich[10] have found the value of β in Brönsted plots for Menschutkin reactions of 3- and 4-substituted pyridines to be very close to one-quarter irrespective of the nature of the alkylating agent. Pyridine and other heteroaromatic bases also have β-values close to one-quarter for base-catalysed diazo-coupling reactions, whereas alicyclic amines have values above one-half.[11]

(ii) Bordwell and his co-workers[12] have found slopes very close to one-third in substituent effect plots of log $k(\text{Nu}^-)$ against $\text{p}K_a(\text{NuH})$ for S_N2 reactions, on benzyl chloride, of sets of anionic aromatic nucleophiles with different atoms (C, N, O, S) at the attacking site. The intercept varied markedly with the nature of the set of nucleophiles. These results would be explained if (a) the enhanced perturbation of the ring structure of each anion occurred in the S_N2 reaction but not in the deprotonation, (b) the reprotonation of each anion required little or no structural change in the anion during the activation stage, but the other processes required the maximum permitted perturbations, and (c) the effects of direct interaction between the substituents and the electrophile were negligible. In electron-transfer reactions of the same anions, the slopes of δ log *k* against $\text{p}K_a(\text{NuH})$ were somewhat greater than unity,[13] indicating that the enhanced perturbation of the ring structure did not occur and that effects of direct interactions between the anions and the electron acceptor were significant.

(iii) Protonation of carbanions can be made more difficult than usual by introducing electron-accepting substituents at the central carbon atom. Enhanced perturbation of the ring structure is indicated by a β-value of three-quarters measured by Bell[14] for the deprotonation of $\text{ArCH}_2\text{CH(COMe)CO}_2\text{Et}$ by RCO_2^- in aqueous solution. With the even stronger electron-accepting substituent NO_2 at the central carbon atom, the excess of electronic charge in the carbanion resides mainly on the α-substituent. The expected value of β is then three-halves instead of three-quarters because in equations (5) $\rho_{\text{Reverse}} = +1/3\ \rho_{\text{Forward}}$. Bordwell and his co-workers[15] have found several examples of β-values close to three-halves for deprotonation of aryl α-nitroalkanes in aqueous solution.

(iv) Alkylation of pyridine can be made easier by introducing very good leaving groups. The enhanced perturbation of the pyridine ring structure that seems to occur in many alkylations appears to be lost when the leaving group is trifluoroacetate. Kurz and El-Nasr[16] have found a marked nitrogen kinetic isotope effect with trifluoroacetate, but no significant effect with poorer leaving groups. This suggests to us that with trifluoroacetate, reducing the N, C separation in the activated state costs less energy than the enhanced perturbation of the pyridine ring.

(v) Hupe and Jencks[17] have reported values of β very close to one-quarter for certain acylations of nucleophiles in which bond formation is rate-determining. This contrasts with very much larger values for other acylations.

There is also evidence of enhanced perturbation of saturated hydrocarbon sub-units. Bernasconi and his co-workers[18] have reported a β-value of one-quarter for attack of piperidine and morpholine on the α-carbon atom of β-nitrostyrene in water. Bordwell has reported values of approximately three-halves for the deprotonation of several non-aryl nitroalkanes.[19]

The unusual values of β that we have interpreted in terms of enhanced perturbations within one of the reaction partners involved in covalent-bond formation or cleavage, are not in general matched by unusual values measured with respect to the other reaction partner. For example, β-values for the bases involved in the deprotonation reactions mentioned above are close to one-half. Also, Lewis and Hu[20] have obtained a non-zero (+0.6) value of ρ for ring substituent effects on methyl cation exchange between identical aryl sulphonates. The substituent effect on the nucleophile is distinctly smaller than the corresponding substituent effect on the leaving group, in accord with enhanced perturbation of the ring in the nucleophile but not in the leaving group. In our model, there is no general requirement for correlation between electronic structural changes in the two reaction partners.

The existence of appreciable non-charge-transfer interactions between the reaction partners is expected to affect the values of β and γ significantly. As the magnitude of the effects of net repulsive interactions becomes larger within a series of similar reactions, the selectivity should rise and the overall reactivity should fall. However, no simple mathematical relationship between the two is expected because of the effects of the structural changes within the reaction partners during the activation process. In particular, smooth curvature is not expected in Brönsted plots. Nevertheless, a qualitative inverse reactivity–selectivity relationship is conceivable in some reaction series, and there is evidence for this.[2]

Conclusions

The overall pattern of rate–equilibrium and rate–rate relationships for reactions involving covalent-bond formation and/or cleavage is not simple. However, the pattern does exhibit certain simple features such as straight lines with slopes close to a particular value ($\beta = -\frac{1}{2}, 0, \frac{1}{4}, \frac{1}{2}, \frac{3}{4}, 1, \frac{3}{2}; \gamma = \frac{1}{3}, 1$), smooth curves, and approximate curves. The theoretical model for the general mechanism of such reactions described in this paper provides the basis for a quite simple unified explanation of these features.

References

1 Part 1, preceding paper.
2 A. Pross, *Adv. Phys. Org. Chem.*, 1977, **14**, 69.
3 C. D. Johnson, *Tetrahedron*, 1980, **36**, 3641; *Chem. Rev.*, 1975, **75**, 755.
4 A. Pross, *Adv. Phys. Org. Chem.*, 1985, **21**, 99.
5 R. P. Bell in 'Correlation Analysis in Chemistry: Recent Advances,' eds. N. B. Chapman and J. Shorter, Plenum, New York, 1978, ch. 2.
6 C. D. Ritchie, *Acc. Chem. Res.*, 1972, **5**, 348.
7 J. E. Leffler, *Science*, 1953, **117**, 340; J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963.
8 S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, 1981, **103**, 7240.
9 R. J. Klingler and J. K. Kochi, *J. Am. Chem. Soc.*, 1982, **104**, 4186.
10 E. M. Arnett and R. Reich, *J. Am. Chem. Soc.*, 1980, **102**, 5892.
11 S. B. Hanna, C. Jermini, H. Loewenschuss, and H. Zollinger, *J. Am. Chem. Soc.*, 1974, **96**, 7222.
12 F. G. Bordwell and D. L. Hughes, *J. Org. Chem.*, 1982, **47**, 169; *J. Am. Chem. Soc.*, 1984, **106**, 3234.
13 F. G. Bordwell and A. H. Clemens, *J. Org. Chem.*, 1981, **46**, 1035.
14 R. P. Bell and S. Grainger, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1367.
15 F. G. Bordwell, W. J. Boyle, J. A. Hautala, and K. C. Yeo, *J. Am. Chem. Soc.*, 1969, **91**, 4002.
16 J. L. Kurz and M. M. S. El-Nasr, *J. Am. Chem. Soc.*, 1982, **104**, 5823.
17 D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 451.
18 C. F. Bernasconi, R. A. Renfrow, and P. R. Tia, *J. Am. Chem. Soc.*, 1986, **108**, 4541.
19 F. G. Bordwell, *Faraday Symp. Chem. Soc.*, 1975, **10**, 100.
20 E. S. Lewis and D. D. Hu, *J. Am. Chem. Soc.*, 1984, **106**, 3292.

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