Reactivity–Selectivity Relationships. II.[1] A Simple Model to Explain Nucleophile–Electrophile Combination Reactions and Its Implications for the Reactivity–Selectivity Principle

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Abstract: A model designed to explain the mechanism of nucleophile-electrophile combination reactions based on solvation effects is presented, and the hitherto inexplicable N_+ correlation is rationalized. The model supports the reactivity-selectivity principle but emphasizes that solvation effects may mask its general applicability.

The validity of the reactivity-selectivity principle has recently been cast into doubt as an increasing number of workers have published experimental data in which the expected inverse relationship was not observed.[2,3] The most striking of these recent reports was a series of publications by Ritchie and coworkers[3] in which they found that the nucleophilic activity of a large number of nucleophiles, in their reaction with electrophiles, was correlated by

$$\log k = \log k_0 + N_+ \qquad (1)$$

where k is the rate constant for reaction of an electrophile with a given nucleophilic system (i.e., a given nucleophile in a given solvent), k_0 is dependent solely on the identity of the electrophile, and N_+ is a parameter characteristic of the nucleophilic system.

The correlation expressed in (1) represents a failure of the reactivity-selectivity principle because N_+ values for a given nucleophilic system do not change with different electrophiles. In other words, different electrophiles of widely varying structure and reactivity exhibit constant selectivity. The correlation is particularly striking when one takes into account the following factors.

(a) The nucleophiles used belong to different classes and include both charged and neutral species as well as S-, N-, and O-based nucleophiles.

(b) The group of electrophiles studied originally, which consisted of a large number of organic cations, was extended to include a number of esters.

(c) The correlation holds for different solvents.

(d) In spite of the correlation's fundamental simplicity, many facets of the mechanism of the cation-anion reactions were found to be completely contradictory.

(e) The correlation, particularly in view of its generality, not only contradicts the reactivity-selectivity principle but also questions the validity of the Hammond postulate[4] which today exists as an integral part of theoretical chemistry. This follows since the reactivity-selectivity principle is based on the Hammond postulate. It has been argued that the reactivity-selectivity principle and the Hammond postulate need not be irrevocably tied together since the former represents a theoretical concept while the latter attempts to relate two experimentally defined quantities.[2a] While this may be the case, the justification and validity of any theoretical concept must ultimately depend on experimental confirmation, and therefore the experimental limitations must be clearly defined if the theoretical basis is not to be undermined. For the above stated reasons, a proper understanding of simple combination reactions is useful not only for itself, but also serves to probe some of the fundamental ideas in chemistry.

In order to examine the precise nature of combination reactions, therefore, an analysis of Ritchie's work is required.[3] One of the key conclusions reached by Ritchie was that the nucleophile and electrophile are completely separated in the transition state, and that electrophile desolvation has not begun. This conclusion was arrived at by comparison of rate and equilibrium data. While the rates for nucleophile-electrophile combination reactions were correlated so successfully by eq 1, there was no corresponding correlation of equilibrium constants. Thus the relative rate constants for reaction of a series of cations with hydroxide ion in water and methoxide ion in methanol remained almost constant, while the ratios for the corresponding equilibrium constants[3f] varied by a factor of 10^4. Assuming that in the alcohol and ether products, hydroxide and methoxide ions have essentially the same steric requirements[3f] and that alcohol and ether solvation is cation independent, the variation in the magnitude of equilibrium constant ratios was attributed to differences in cation solvation.[3h] This may be expressed as

$$G_{S_1}(E_1) - G_{S_2}(E_1) \neq G_{S_1}(E_2) - G_{S_2}(E_2) \qquad (2)$$

where $G_{S_1}(E_1)$ represents the free energy of solvation of electrophile 1 in solvent 1, $G_{S_2}(E_1)$ represents the free energy of solvation of electrophile 1 in solvent 2, and $G_{S_1}(E_2)$ and $G_{S_2}(E_2)$ represent the same quantities for electrophile 2, respectively. Now, if electrophile solvation is variable, as concluded by the lack of equilibrium-equilibrium correlation, the question remains as to *why the corresponding rate constants correlate so well.* The solution proposed by Ritchie was that the solvation of the electrophile in both ground and transition states is essentially identical. In this way differential solvation effects would not be reflected in the relative rate constants.[3i] This conclusion, seemingly sound, is difficult to reconcile with other experimental facts. As pointed out by Ritchie, many inconsistencies arise. They are summarized as follows.

(a) If electrophile-nucleophile distances in the transition state are large, and electrophile desolvation has not begun, it is difficult to understand why the absolute rate constants for the combination reaction are so electrophile dependent (rate constants for cation-anion reactions extend over six orders of magnitude).

(b) The Bronsted plot of N_+ values[3b] for amines resulted in a Bronsted slope of approximately 0.5, which is not consistent with a "reactant-like" transition state implied by a solvated electrophile in the transition state.

(c) ρ values for reactions of substituted benzenediazonium ions with a given nucleophile and reactions of arylsulfinates with a given aryldiazonium ion indicated that substituent effects on rates are about half those on equilibria.[5] This result also indicates a transition state which is advanced and possesses "product-like" character.

In view of the conflicting conclusions expressed above, it appeared that a thorough examination was required in order to reconcile the inherent difficulties. Since the major factor leading to the internal contradiction was the conclusion that the electrophile is equally solvated both in the ground and transition states, we decided to base our analysis on the assumption that this conclusion is incorrect, and in the course of such an analysis we hoped to find an alternative explanation for the remarkable rate correlation.

Since it was clear that the activation energy for nucleophile-electrophile reactions was essentially due to solvation factors and the "inherent reactivity" of the electrophile and nucleophile, the following analysis was conducted

$$\Delta G^{\ddagger}{}_{S_1}(N_1)(E_1) = \alpha_1 G_{S_1}(N_1) + \beta_1 G_{S_1}(E_1) \qquad (3)$$

$$\Delta G^{\ddagger}{}_{S_2}(N_2)(E_1) = \alpha_2 G_{S_2}(N_2) + \beta_1' G_{S_2}(E_1) \qquad (4)$$

where $\Delta G^{\ddagger}{}_{S_1}(N_1)(E_1)$ is the free energy of activation for reaction of electrophile 1 with nucleophile 1 in solvent 1, $G_{S_1}(N_1)$ is the free energy of solvation of nucleophile 1 in solvent 1, $G_{S_1}(E_1)$ is the free energy of solvation of electrophile 1 in solvent 1, $\Delta G^{\ddagger}{}_{S_2}(N_2)(E_1)$ is the free energy of activation for reaction of electrophile 1 with nucleophile 2 in solvent 2, $G_{S_2}(N_2)$ is the free energy of solvation of nucleophile 2 in solvent 2, and $G_{S_2}(E_1)$ is the free energy of solvation of electrophile 1 in solvent 2. α_1 and α_2 represent factors whose magnitude indicates the degree of desolvation in the transition state of nucleophile 1 in solvent 1 and nucleophile 2 in solvent 2, respectively. Similarly, β_1 and β_1' represent the degree of desolvation of electrophile 1 in solvents 1 and 2, respectively.

The rationale behind (3) and (4) is that the free energy of activation in such nucleophile-electrophile combination reactions may be attributed to partial desolvation of both nucleophile and electrophile in the transition state and their "inherent reactivity", represented by α and β. Subtracting (3) from (4):

$$\Delta\Delta G^{\ddagger}(E_1) = \alpha_2 G_{S_2}(N_2) + \beta_1' G_{S_2}(E_1) - \alpha_1 G_{S_1}(N_1) - \beta_1 G_{S_1}(E_1) \qquad (5)$$

where $\Delta\Delta G^{\ddagger}(E_1)$ represents the free energy difference between the free energy of activation of electrophile 1 with the two nucleophilic systems. In similar fashion:

$$\Delta\Delta G^{\ddagger}(E_2) = \alpha_2 G_{S_2}(N_2) + \beta_2' G_{S_2}(E_2) - \alpha_1 G_{S_1}(N_1) - \beta_2 G_{S_1}(E_2) \qquad (6)$$

where $\Delta\Delta G^{\ddagger}(E_2)$ is the difference in the free energy of activation for electrophile 2 with the same two nucleophilic systems.

We have assumed that the nucleophile desolvation factors α_1 and α_2 in the reactions of nucleophiles 1 and 2 with electrophile 1 are the same for the corresponding reactions with electrophile 2. This assumption is readily justified since nucleophile activation, as noted in the scheme below, takes place in a preequilibrium step in which electrophile solvation is undisturbed. Furthermore, Ritchie has noted an approximate correlation[3i] between N_+ parameters and the changes in rate constant for nucleophilic attack on methyl iodide on changing solvent from methanol to dimethylformamide.[7] Since these changes have been directly attributed to nucleophile solvation differences in the two solvents, the view taken by Ritchie, that N_+ values reflect nucleophile solvation energy, strongly supports the assumption that α_1 and α_2 are electrophile independent. Subtracting (5) from (6):

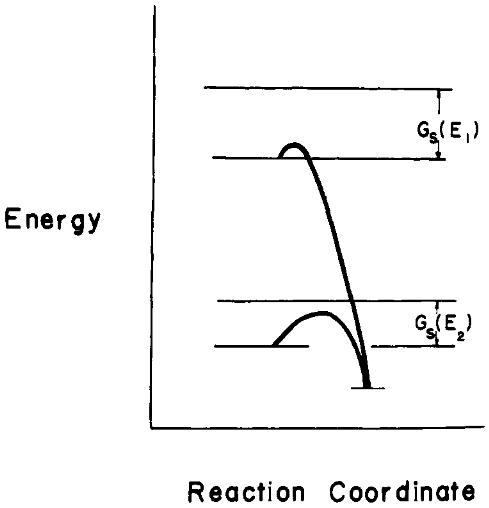


Figure 1. An energy diagram representing the electrophile portion of the electrophile-nucleophile combination reaction. E_1 represents a reactive electrophile while E_2 represents an unreactive electrophile. $G_S(E_1) > G_S(E_2)$.

$$\Delta\Delta G^{\ddagger}(E_2) - \Delta\Delta G^{\ddagger}(E_1) = \beta_2' G_{S_2}(E_2) - \beta_2 G_{S_1}(E_2) - \beta_1' G_{S_2}(E_1) + \beta_1 G_{S_1}(E_1) \qquad (7)$$

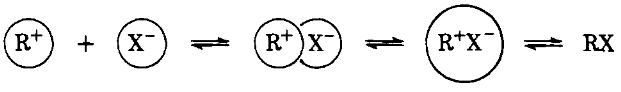
Now the constant selectivity observed for these reactions may be expressed as

$$\Delta\Delta G^{\ddagger}(E_2) - \Delta\Delta G^{\ddagger}(E_1) = 0 \qquad (8)$$

i.e.,

$$\beta_2' G_{S_2}(E_2) - \beta_2 G_{S_1}(E_2) = \beta_1' G_{S_2}(E_1) - \beta_1 G_{S_1}(E_1) \qquad (9)$$

Therefore, based on a model which assumes that the free energy of activation in nucleophile-electrophile combination reactions is attributed to partial desolvation of the nucleophile and the electrophile in the transition state, the relationship expressed in (9) must be satisfied as a precondition to obtaining constant selectivity and the N_+ correlation. The assumption made by Ritchie, that β_1, β_1', β_2, β_2' all equal zero, of course satisfies (9) but is not a *necessary* condition for obtaining the N_+ correlation. The mechanism for cation-anion combination reactions proposed by Ritchie[3i] and represented below is entirely consistent with this model.



Initially solvated ions react to form a solvent-separated ion pair in which the anion has undergone partial desolvation. The solvent-separated ion pair reacts further to form the intimate ion pair. This is the rate-determining step and involves the partial desolvation of the cation. By this account both cation and anion have undergone partial desolvation at the transition state. The scheme is supported by Atkinson[6] who concluded that formation of the one solvent-separated ion pair is anion dependent while formation of the intimate ion pair is cation dependent and anion independent.

An energy diagram which illustrates the electrophile desolvation process for both a reactive and an unreactive electrophile is presented in Figure 1. For simplicity, the anion desolvation portion of the curve has been excluded. The diagram shows that in spite of the fact that the reactive electrophile is more strongly solvated, its energy level still remains above the corresponding energy level for the less reactive electrophile. As a consequence, application of the Hammond postulate[4] implies that since the transition state for the more reactive electrophile is more "reactant-like", the degree of desolvation β will be smaller than for the less reactive electrophile. In other words, "inherent reactivity" (which may be considered the energy level of the unsolvated or free electrophile) is dominant over the solvation energy in its ability to influence the reactivity pattern of the electrophile. This means that the energy term for electrophile desolvation, $\beta G_S(E)$, is reduced for more reactive electrophiles because β, which is dependent on "inherent reactivity", is more sensitive to electrophile structure than $G_S(E)$, at least for those solvents studied. Therefore, even though the reactive electrophile is more strongly solvated, it exhibits greater reactivity. This competition between "inherent reactivity" and solvation energy is most aptly demonstrated by reference to halogen anion nucleophilicity.[8] Thus in aprotic solvents where "inherent reactivity" is dominant, the relative order of halide nucleophilicity is $Cl^- > Br^- > I^-$ in spite of the fact that the solvation energy runs in the same order.[9] In protic solvents, however, this order is inverted, since now solvation energy is sufficiently large to override the "inherent reactivity". The situation for electrophile desolvation indicates that for the solvents studied the pattern is similar to that for halogens in aprotic solvents; i.e., "inherent reactivity" is dominant. The anomalous results observed by Ritchie are consistent with this model. Thus the key anomaly discussed by Ritchie is the large range in absolute rate constants observed for the reaction of a particular nucleophile with different electrophiles. For cation-anion of magnitude. Since the free energy of activation of the reaction of an electrophile and a nucleophile is electrophile dependent (eq 3), then variation in the magnitude of $\beta G_S(E)$ will clearly influence the rate of reaction. For reactive electrophiles, $\beta G_S(E)$ will be relatively small, while for unreactive electrophiles, $\beta G_S(E)$ will be relatively large. The anomalous Bronsted slope (~0.5) and ρ values observed for nucleophile-electrophile reactions, as discussed earlier, are also consistent with the present model since they indicate that cation desolvation is well under way in the transition state. Up to this point, the model produces a consistent mechanism which rationalizes Ritchie's results. However, the relation between this model and the reactivity-selectivity principle remains obscure. The incorporation of a simplifying assumption into (9) leads to a surprising and instructive relationship.

Let us assume that $\beta_1 = \beta_1'$ and $\beta_2 = \beta_2'$. This assumption is not arbitrary It suggests that β is a measure of electrophile reactivity and that the degree of electrophile desolvation in the transition state is dependent only on the electrophile and *not* on the solvent. Equation 9 simplifies to

$$\beta_2[G_{S_2}(E_2) - G_{S_1}(E_2)] = \beta_1[G_{S_2}(E_1) - G_{S_1}(E_1)] \quad (10)$$

or

$$\beta[G_{S_2}(E) - G_{S_1}(E)] = \text{constant} \quad (11)$$

Equation 11 states that the degree of desolvation in the transition state for a particular electrophile is inversely proportional to the difference in solvation energy of that electrophile in two solvents. If this difference, $G_{S_2}(E) - G_{S_1}(E)$, is thought of as a measure of electrophile solvation, then (11) takes on physical significance. Reactive and therefore strongly solvated electrophiles [i.e., large $G_{S_2}(E) - G_{S_1}(E)$] will undergo only slight desolvation in the transition state (β close to 0), while unreactive and therefore weakly solvated electrophiles [i.e., small $G_{S_2}(E) - G_{S_1}(E)$] will undergo considerable desolvation in the transition state (β close to 1). The physical significance of the above conclusion is that this behavior is perfectly explicable, based on the Hammond postulate,[4] since a reactive electrophile is expected to produce a "reactant-like" transition state which is still considerably solvated. We conclude, therefore, that the constant selectivity observed in the N_+ relationship may be viewed as resulting from the cancellation of two opposing effects. On the one hand, a reactive electrophile is strongly solvated, a factor which would tend to increase selectivity. On the other hand, the transition state for a reactive electrophile is "reactant-like", resulting in a decrease in selectivity. In the absence of complicating solvent effects, this latter influence operating alone would produce the normal reactivity-selectivity relationship.

We feel that while the above analysis does restore a measure of validity to the reactivity-selectivity principle, it does so to a limited extent only. The proposed model indicates that solvent effects may mask its wider applicability and, therefore, that a thorough examination of all apparent failures in the principle be conducted with the aim of establishing more clearly the limitations to which the principle may be bound.

Acknowledgment. I am very grateful to Professor C. D. Ritchie for comments and criticisms of an early draft of this manuscript and to Dr. D. Kost for helpful discussions.

References and Notes

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