Relationship between Rates and Equilibria and the Mechanistic Significance of the Brønsted Parameter. A Qualitative Valence-Bond Approach

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The valence-bond configuration mixing (VBCM) model of reactivity is applied to the problem of rate–equilibrium relationships. Reactions are divided into two classes: (a) the special case of two-configuration reactions, such as the S_N2 reaction of methyl derivatives, which can be adequately described by just reactant and product configurations, and (b) multiple-configuration reactions, which incorporate most organic reactions, are exemplified by the S_N2 reaction of benzyl derivatives, and require three or more configurations for an adequate description of the reaction profile. It is demonstrated with simple qualitative arguments that two-configuration reactions are likely to show normal rate–equilibrium behavior if the substituents are adjacent to a site within the molecule at which charge is either generated or destroyed in the product. In such cases the product configuration is stabilized with respect to the reactant configuration in accord with the Bell–Evans–Polanyi model. Anomalous (i.e., $\alpha > 1$) or no rate–equilibrium relationships are anticipated if there is no change in charge adjacent to the substituent site or large steric interactions are generated in the transition state (TS). For multiple-configuration reactions, anomalous rate–equilibrium relationships are likely to result if the substituent change operates on just an "intermediate" configuration but normal rate–equilibrium relationships are expected if the substituent effect operates on the product configuration. The analysis suggests that the Brønsted parameter α (or β) fails to provide a measure of TS structure or charge development for two-configuration reactions but may well provide a relative measure of TS charge development for multiple-configuration reactions. The most striking conclusion is that anomalous α values are really quite common and depend primarily on the position of substitution within a reaction family, rather than on the reaction type.

Because traditionally the factors governing rates of reaction have been less well understood than those governing equilibria, the interest in rate–equilibrium relationships has been an intense one.[2] The existence of such a relationship was first suggested by Brønsted[3] (eq 1) and subsequently discussed by Bell[4a] and Evans and Polanyi,[4b] who proposed eq 2 and 3 linking activation barriers to reaction thermodynamics.

$$\log k = \alpha \log K + C \qquad (\beta \log K + C) \qquad (1)$$

$$\Delta E^{\ddagger} = \alpha \Delta \mathrm{H} + C \qquad (2)$$

$$\Delta G^{\ddagger} = \alpha \Delta G^{\circ} + C \qquad (3)$$

Some years ago in an important conceptual step Leffler[5] extended the mechanistic significance of eq 3 by suggesting that the parameter α may be utilized as a measure of transition state (TS) structure. Values of α close to zero were considered to denote transition states structurally similar to reactants while values of α approaching 1 were considered to denote product-like transition states. The discovery by Bordwell of α values outside the range 0 to 1 in the deprotonation reaction of substituted nitroalkanes, however, undermined such a simplistic view.[6] Bordwell attributed this to a transition state in which negative charge on carbon is greater in the transition state than in the product ground state.[6b] Subsequently, More O'Ferrall[7] and Kresge[8] reaffirmed this idea. Recently, Murdoch, Brauman, et al.[9] observed α values as large as 1.7 in the proton-transfer reaction between 9-alkylfluorenes and 9-alkylfluorenyl anions. This was attributed to both polar and steric effects.

The observation of anomalous α values has led other workers to question the use of α as a measure of TS structure.[10-14] Marcus has demonstrated that if the intrinsic barrier fails to remain constant within a reaction series, anomalous α values are likely to be generated.[10] Jencks has argued that, due to cross-correlation effects there is no unique relationship between α and bond lengths.[11] Murdoch has demonstrated that if the proton-transfer step is incorporated into a multistep mechanism then the measured value of α no longer reflects the degree of proton transfer in the TS.[12] Agmon has presented a related argument suggesting that variation in work terms associated with proton transfer (reflecting solvation fac-

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tors) may lead to anomalous α values and has argued that this occurs in the deprotonation reaction of nitromethane.[13] Jencks et al.[14] and Hupe et al.[15] have also concluded that solvation factors may invalidate the use of β values as a measure of TS structure. This conclusion was based in part, on the large β values observed for phenoxides in their reaction with esters as compared with the small values of β observed for alkoxides;[14,16] this, while other measures of TS structure suggested identical degrees of bond formation.[14,15]

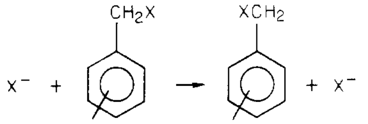
It is apparent, therefore, that at least for multistep reactions and reactions exhibiting unusual solvent effects, α (or β) values do not necessarily relate to the position of the TS along the reaction coordinate. The proposition, however, that we wish to explore is the more basic question: what *is* the mechanistic significance of α for simple *one-step reactions* in which no special solvent effects take place? And more generally, to what extent *can* we expect rates and equilibria to be related for a limited family of reactions?

Central to this entire discussion is the question: how are reaction profiles formed? If we can define the form of an entire reaction profile we may then be able to assess the effect of a substituent on the energies of both the TS and the products and thereby establish the relationship between activation barries and heats of reactions as well as the mechanistic significance of α. In recent papers Pross and Shaik[18] have utilized the method of valence-bond configuration mixing (VBCM)[2,17,18] to build up reaction profiles for substitution,[18a,b,d,e] elimination,[18a,c] as well as proton-transfer[2] reactions. Rules for analyzing any organic reaction were provided.[18c,f,g] In this paper we utilize the approach by building up reaction profiles for some simple organic reactions in order to ascertain (a) which reaction families are likely to exhibit a rate–equilibrium relationship and which are not, and (b) what is the mechanistic significance of α.

Theory

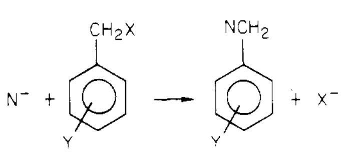
The first point we wish to make is that even for simple one-step reactions, rates and equilibria do not necessarily correlate with one another.[8-13,19]

Consider the identity exchange reaction:



(4)

For a given X, the substituent Y may be altered to provide a family of reactions. For this entire family, K must equal 1. Rates, however, clearly will vary; therefore, a plot of log k vs. log K will yield a straight line with an α value of infinity (eq 1). This simple system clearly illustrates that there is *no inherent reason for rates and equilibria to always be related.* This is not true for just identity reactions. Consider the *nonidentity* reaction family:



(5)

Using the Marcus formulation,[10] the barriers of the identity reactions (i.e., the intrinsic barriers) (eq 4) will also influence the rates of the nonidentity reaction family (eq 5). Thus, the *very same factors* which lead to a breakdown in the rate–equilibrium relationship for identity reactions will at times upset the rate–equilibrium relation for the nonidentity set as well.

The implication of the above argument is clear. There are certain types of reactions (and which obviously include *any* series of identity reactions) for which rates and equilibria are unrelated. Furthermore, if a plot of log k vs. log K does yield a straight line (as indeed the *identity exchange* of benzyl derivatives does—here α is infinite) the slope is not necessarily related to the structure of the TS.

What then is the theoretical basis for the rate–equilibrium relationship, and when will it break down? Is α (or β) a measure of TS structure, and if not, what do α values signify?

A. Two Configuration Reactions. S_N2 Reaction of Methyl Derivatives. We begin by analyzing the possibility of rate–equilibrium relationships in S_N2 reactions of methyl derivatives (eq 6). Let us summarize the

$$\text{N} + \text{RX} \rightarrow {}^{+}\text{N–R} + \text{X}^- \qquad (6)$$

manner in which the profile for an S_N2 reaction may be built up. The S_N2 reaction profile of methyl derivatives has been shown to be simply represented, primarily by the avoided crossing of two VB configurations, 1 and 2.[2,20] A

$$\underset{\mathbf{1}}{\text{N: CH}_3\cdot\ \cdot\text{X}} \qquad \underset{\mathbf{2}}{\text{N}\cdot^{+}\ \cdot\text{CH}_3\ \text{:X}^-}$$

schematic energy diagram of the two configurations is illustrated in Figure 1.

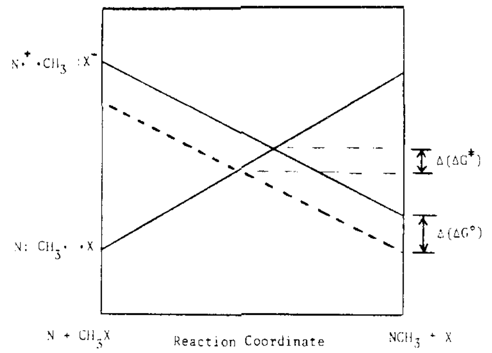


Figure 1. Schematic energy plot of reactant (N: $CH_3\cdot$ ·X) and product (N·$^+$ ·CH_3 :X^-) configurations as a function of reaction coordinate. Effect of a perturbation [$\Delta(\Delta G°)$] on product stability is only partially reflected in the transition state [$\Delta(\Delta G^{\ddagger})$].

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(19) Pross, A. *Tetrahedron Lett.* **1983**, 835.

(20) See ref 18d for a more precise analysis which does take into account the slight mixing of N·$^+$ CH_3:$^-$ ·X and N: CH_3^+ :X^- at the reaction ends.

The fact that the reaction may be simply built up by just two configurations enables us to characterize the reaction in just this way—a *two-configuration reaction.* This is the least number of configurations which is necessary in order to generate a TS *higher* in energy than either reactants or products. The barrier comes about through the avoided crossing of the reactant, 1, and product, 2, configurations.[17,18] We must clarify, however, that reactions defined as two-configuration reactions may actually have some additional configurations mixed in.[20] Strictly, the term two-configuration reaction, only means that intermediate configurations, e.g., the carbocation configuration, N: R$^+$:X$^-$, and the carbanionic configuration, N$\cdot^+$R:$^-$ $\cdot$X, either do not mix significantly into the TS (as for N$\cdot^+$R:$^-$ $\cdot$X) or mix into the TS approximately to the same extent as into reactants and products (as for N: R$^+$:X$^-$). These requirements are met for S_N2 reactions of CH_3X and result in the central carbon in methyl substitution reactions developing neither additional positive charge (due to N: R$^+$:X$^-$) nor negative charge (due to N$\cdot^+$ R:$^-$ $\cdot$X) in the TS.[21]

Let us now assess the relationship between rates and equilibria for a two-configuration system. The effect of a substituent change on the energy of the transition state may be gauged by the energy change of the crossing point of the two configurations.[22] It therefore becomes possible to relate changes in activation energy to changes in the heats of reaction, and by analogy, changes in free energy of activation to changes in free energies of reaction.[23]

Effect of Substituents on the Nucleophile, N. We first introduce a substituent on the nucleophile which makes it more powerful. Since this stabilizes N$\cdot^+$ in the product configuration, 2, this has the effect of stabilizing the product configuration relative to the reactant configuration and is indicated by the dotted line in Figure 1. The argument is essentially the same as that used by Bell and Evans and Polanyi fifty years ago[4] and suggests that the intersection point will be stabilized *less* than the product (i.e., $\Delta(\Delta G)^{\ddagger} < \Delta(\Delta G^\circ)$, Figure 1), leading to the relationship expressed in eq 3. The magnitude of α will, of course, be dependent on the slopes of the intersecting curves.[4d] For the case where the two curves are of equal slopes, as in Figure 1, the value of α will be 0.5 *regardless of the position of the TS.* However, the precise form of the curves will allow α to lie anywhere in the range 0 to 1 leading to normal α values. Since α is a function of curve slopes it becomes apparent that α cannot, on this basis alone, be expected to represent an absolute measure of transition-state structure. By the use of these diagrams, it is a simple matter to generate early transition states with large α values and vice versa, though, clearly, not all these possibilities conform to physical reality. This means that, in order to obtain even a simplistic picture as to the significance of α, at least some qualitative idea regarding curve shapes is required.

The most common approach to analyzing the relationship between $\Delta G^{\ddagger}$ and ΔG° is to treat the intersecting curves as parabolas. Based on a model of intersecting parabolas, Marcus theory[24] does suggest that α values may represent a *relative* measure of TS structure, at least for reaction families sharing a constant intrinsic barrier. In the limits, however, problems arise since the Marcus formulation leads to meaningless values of α for $|\Delta G^\circ| > 4G^{\ddagger}$.[25,26] A model which replaces the parabolic curves by intersecting Morse curves,[27] and which one might expect would be theoretically more valid, is even less satisfactory. Following these inherent deficiencies a number of analytical expressions relating ΔG° and $\Delta G^{\ddagger}$, which at least show proper behavior in the limits, have been proposed.[26,28] These expressions, in much the same way as Marcus theory, allow α to vary between 0 for highly exergonic reactions to 1 for highly endergonic reactions.

Experimental verification of the various models is confusing. The large number of curved Brønsted plots that have been observed over recent years[29a] does lend support to the Marcus idea of a variable TS. However, alternative explanations for curvature have also been proposed[29b,30,31] so that it becomes more difficult to specify unambiguous examples of Marcus curvature. Thus in the absence of a detailed description of configuration curve shapes for a range of reaction types, the precise mechanistic significance of α, for two-configuration reactions at least, remains unclear. Under the circumstances, therefore, we shall attempt to, at least, answer the question, what the α value is *unlikely* to represent.

It appears that for a reaction adequately described by two configurations, α is not in any way related to the *absolute degree of charge development in the TS.* According to the Marcus theory[24] of outer-sphere electron transfer, charge development in the TS is by definition 0.5 and this is independent of the TS geometry. Thus, it is at the TS that electron transfer takes place so that the α value provides *at best* a measure of geometric progression along the reaction coordinate but not of charge progression which is constant at 0.5. (Once a third configuration is incorporated into the analysis this conclusion will be modified.) This analysis was recently extended to the S_N2 reaction, a model two-configuration system,[18e] in a way that focused on the similarity between an S_N2 and electron-transfer reaction. The conclusion reached in that paper was that charge development in the S_N2 TS of methyl derivatives is, as for many electron-transfer reactions, essentially invariant. Both so-called early and late transition states in the geometric sense are about 50% advanced in the charge sense.[18e] Thus, for example, we believe that the α value of ~0.3 obtained by Arnett and Reich[32] for a family of substituted pyridines reacting with

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(21) The absence of charge development on carbon in methyl substitution has recently been discussed by Kevill, D. N. *J. Chem. Soc., Chem. Commun.* **1981**, 421.

(22) This is not strictly true since the actual TS is lower than the crossing point. This is because in the TS region where the configurations appear to cross there is actually an *avoided crossing.* However if we assume that the degree of avoided crossing is constant for the family of reactions then the relative barriers may be obtained from a comparison of crossing point energies.

(23) We make the necessary assumption in any study of reaction rates and equilibria based on potential energy surfaces, i.e., that arguments based on potential energies, *E*, carry over to free energies, *G*, as well.

(24) (a) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155. (b) Marcus, R. A. In "Special Topics in Electrochemistry"; Rock, P. A., Ed.; Elsevier: Amsterdam, 1977. (c) Marcus, R. A. *J. Phys. Chem.* **1963**, *67*, 853. (d) Marcus, R. A. *J. Chem. Phys.* **1963**, *38*, 1858. (e) Weston, R. E.; Schwartz, H. A. "Chemical Kinetics"; Prentice Hall: Engelwood Cliffs, New Jersey, 1972; p 205.

(25) Theoretical calculations by Wolfe and Mitchell have supported the applicability of Marcus theory to S_N2 reactions. See: Wolfe, S.; Mitchell, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7692. Solution studies on methyl derivatives by Albery and Kreevoy also appear to be consistent with Marcus theory. See: Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87.

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(27) Bell, R. P. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 2088.

(28) (a) Miller, A. R. *J. Am. Chem. Soc.* **1978**, *100*, 1984. (b) Agmon, N.; Levine, R. D. *Isr. J. Chem.* **1980**, *19*, 330; *Chem. Phys. Lett.* **1977**, *52*, 197. (c) Rehm, D.; Weller, A. *Ber. Bunsenges. Phys. Chem.* **1969**, *73*, 834; *Isr. J. Chem.* **1970**, *8*, 259. (d) Kurz, J. L. *Chem. Phys. Lett.* **1978**, *57*, 243. (e) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.

(29) (a) For an extended list of examples see ref 7–22 of ref 29b. (b) Murdoch, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 71.

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(31) Agmon, N. *Int. J. Chem. Kinetics* **1981**, *13*, 333.

(32) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1978**, *100*, 2930.

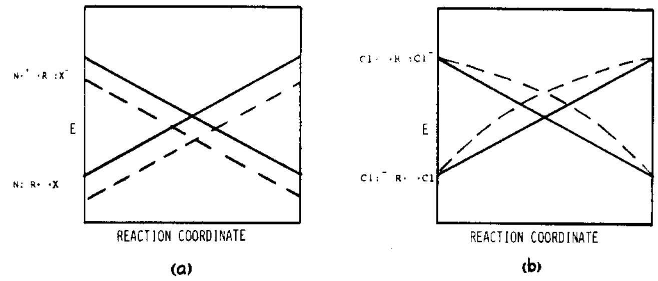

Figure 2. (a) Schematic energy plot of reactant (N: R· ·X) and product ($N\cdot^+$ ·R :X^-) configurations as a function of reaction coordinate. Bold line represents curves before substitution on R, dotted lines represent curves after the effect of a stabilizing substituent on R. (b) Schematic energy plot of reactant (Cl:$^-$ R· ·Cl) and product (Cl· ·R :Cl^-) configurations for the identity exchange reaction $Cl^- + RCl \rightarrow ClR + Cl^-$. Bold lines represent R = methyl, dotted lines represent R = neopentyl.

methyl iodide, tosylate, and triflate is not an absolute measure of TS charge development on the pyridine. Similarly, the β values of $\sim$0.3 obtained by Bordwell[33] for the reaction of substituted fluorenyl anions with 1-butyl chloride may not consitute a measure of TS charge development on the fluorenyl moiety. Paradoxically, it is only for *more* complex systems, requiring at least three configurations, that a clearer mechanistic interpretation of α becomes possible. This will be discussed subsequently.

Effect of Substituents on the Alkyl Group, R. Let us now examine the effect of substituents on the R group. This is the reaction family which includes the set of identity exchange. Within the context of the two-configuration model, we make the simplifying assumption that the electronic perturbation of the substituent is not sufficient to cause intermediate configurations, N: R^+ :X^- and $N\cdot^+$ R:$^-$ ·X, to mix into the TS wave function. The more general multiconfiguration reactions, where this is not the case, will be dealt with in section B. Since the electronic nature of R in both reactant *and* product configurations is identical (i.e., R·) the effect of substituents on reactant and product configurations will be similar (Figure 2a). This means that for substituents on R *no* simple relationship between rates and equilibria can be anticipated. Only for the case where the substituent is situated on the nucleophile or the leaving group is the product configuration displaced in relation to the reactant configuration (see Figure 1) leading to the normal rate–equilibrium relationship of eq 1 and 3.

In practice this suggests that *rate–equilibrium relationships will only be observed for reaction families where the substituent site is adjacent* to some point in the molecule at which charge is either formed or destroyed.[19] It is only for such reactions that the substituent strongly modifies the energy of the product configuration relative to the reactant configuration. For S_N2 reactions this occurs either in the nucleophile or the leaving group and hence gives rise to a normal rate–equilibrium relationship. Substituents on the alkyl group, on the other hand, are less likely to generate a family of reactions obeying the rate–equilibrium relationship, because the formal charge on R has not changed in going from reactants to products. Identity reactions, of course, belong to this latter category.

Let us now consider substituent effects, which are primarily steric in nature. If unfavorable steric interactions arise in the TS, this will manifest itself in the *slopes of the configuration curves*. Let us for example, compare the identity exchange of chloride ion with methyl chloride (eq 7) and with neopentyl chloride (eq 8). As Cl^- approaches

$$Cl^- + CH_3Cl \rightarrow ClCH_3 + Cl^- \qquad (7)$$

$$Cl^- + (CH_3)_3C\ CH_2Cl \rightarrow ClCH_2C(CH_3)_3 + Cl^- \qquad (8)$$

RCl the energy of the reactant configuration, Cl:$^-$ R· ·Cl, will initially increase *more* rapidly for R = neopentyl than for R = methyl. This is illustrated in Figure 2b by the dotted line for R = neopentyl and the bold line for R = methyl. The neopentyl curve rises in energy more rapidly because, in addition to the unfavorable electronic interactions[34] that are taking place for both systems, the neopentyl system experiences enhanced steric repulsions as well. As the reactions pass through the TS region, where crowding is greatest, the release of steric congestion will lead to the reactant configuration, for R = neopentyl increasing in energy *less* rapidly than for R = methyl. By symmetry, an identical argument of course, holds for the product configuration. The argument is analogous to the effect of 3-electron bond strength on S_N2 reactivity.[18d] The net result is apparent. For substrates suffering steric hindrance in the transition state the crossing point is higher and hence a *larger* barrier is expected, as is indeed observed. Neopentyl systems are less reactive than methyl systems to nucleophilic substitution.

What this means is that for the nonidentity S_N2 reaction, substitution of bulky groups on the R group of RX will predominantly affect rates and not equilibria. (Recall, again, for the identity exchange reaction the effect of substitution on equilibria is zero.) Clearly, in such circumstances anomalous rate–equilibrium relationships are likely to be generated with α values greater than 1. Based on the above discussion, we can now propose two rules concerning rate–equilibrium relationships for two-configuration reactions governing both electronic and steric substituent effects.

Rule 1: *For reaction types adequately described by just two configurations, reactant and product, and in the absence of variable steric effects, normal rate–equilibrium relationships will be observed if the substituent is adjacent to a site within the molecule at which charge is either generated or destroyed in the product (e.g., as for a substituent change in either the nucleophile or the leaving group in an* S_N2 *reaction) (Figure 1). Values of* α *will lie in the range 0 to 1 but do not appear to constitute an absolute measure of transition state structure based on either a charge or a geometric criterion. For cases where the substituent is adjacent to a site in which there is no charge change between reactants and products (e.g., as for a substituent change in the R group of an* S_N2 *reaction (Figure 2a) either an anomalous* ($\alpha > 1$) *or no rate–equilibrium relationship is to be expected.*

Rule 2: *Substituent effects which modify the steric congestion in the transition state may lead to larger variations on rates than on equilibria. In such cases anomalous rate–equilibrium relationships (i.e.,* $\alpha > 1$*) may be observed.*

A recent example which illustrates rule 2 is the proton-transfer reaction between 9-alkylfluorenes and 9-alkylfluorenyl anions.[9] Here α values ranging from 0.7 for the unsubstituted parent anion to 1.8 for the 9-(*tert*-butyl)fluorenyl anion were observed. This system is akin to the identity exchange of methyl and neopentyl derivatives in that it provides an additional example where substantial steric interactions are generated in the TS. As a consequence, rates are observed to be more sensitive to sub-

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[33] Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314.

[34] For rules governing the electronic interaction between groups, see ref 18c.

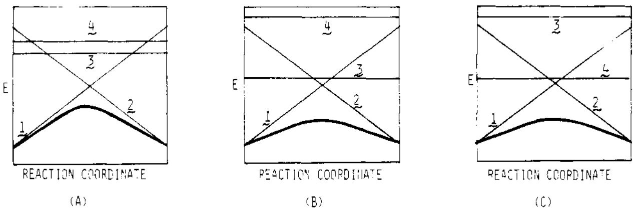

Figure 3. Schematic energy plot of reactant, **1**, product, **2**, and intermediate configurations, N: R^+ :X^-, **3**, and N·$^+$ R:$^-$ ·X, **4** for the S_N2 substitution reaction of (a) benzyl, (b) *p*-methoxybenzyl, and (c) *p*-nitrobenzyl derivatives. Bold curves represent the resultant reaction profile. Due to stabilization of the R^+ configuration in b and R^- configuration in c, barrier heights in b and c are lower than in a.

stituent effects than equilibria (rule 2). Here, again, the rates of the identity proton-transfer reaction are directly related to the steric bulk of the 9-alkyl substituent so that the rates decrease in the order Me > Et > *i*-Pr > *t*-Bu.[9]

B. Multiconfiguration Reactions. S_N2 Reaction of Benzyl Derivatives. The preceding discussion has involved the special case of a two-configuration system. For the majority of organic reactions, however, two configurations are simply inadequate to generate a meaningful reaction profile. At least one additional configuration is required. We will subsequently see that this additional configuration has an important effect on the analysis and leads to the conclusion that the Brønsted coefficient does indeed constitute in many cases a *relative* measure of TS charge development. To illustrate these ideas we now discuss the nucleophilic substitution reaction of benzyl derivatives, a model multiconfiguration system. The benzyl system has attracted continued attention over the years because of the curved Hammett plots generated as a function of substituents in the ring.[35] If the substituent change takes place in the attacking nucleophile, however, linear Hammett plots result indicative of normal rate–equilibrium behavior.

In contrast to the methyl system which can be adequately represented by two configurations (**1** and **2**) the benzyl system may need to be represented by additional "intermediate" type configurations, N: R^+ :X^- and N·$^+$ R:$^-$ ·X. This is because R^+ and R^-, which are high in energy for R = CH_3, are relatively stabilized for R = benzyl. They will, therefore, mix significantly into the TS, thus playing an important role in governing reactivity.

As has been indicated in a previous publication, intermediate configurations tend to be flat in comparison with reactant or product configurations.[18c] This is because the intermediate configurations both start out and end up as excited configurations along the reaction coordinate. The reactant configuration, by comparison, starts out as a ground configuration but ends up as an excited configuration, while the product configuration does the reverse.

Schematically the configurations of the benzyl system may be represented as indicated in Figure 3a. In addition to reactant and product configurations (N: R· ·X and N·$^+$ ·R :X^-, respectively) the two "intermediate" configurations, N·$^+$ R:$^-$ ·X and N: R^+ :X^-, are now included. We can now assess the effect of substituents on the aromatic ring and compare the result with that for methyl derivatives.

Effect of Ring Substituents. Substitution of an electron-releasing group in the ring (e.g., *p*-CH_3O) will have the effect of stabilizing the carbocationic configuration, N: R^+ :X^-, **3**, compared to the unsubstituted case. This is shown in Figure 3b. It will have negligible effect on reactant and product configurations since no charge is present on R. Stabilization of the carbocationic configuration will lead it to mix into the wave function to a greater extent (rule 7, ref 18c) and this will occur *primarily in the TS region, where the energy gap between the intermediate configuration and reactant and product configurations is least*; as a consequence the TS will be stabilized. The TS can therefore be described in simple valence-bond terms by the resonance forms:

$$\text{N: R}\cdot\ \cdot\text{X} \leftrightarrow \text{N}\cdot^{+}\ \cdot\text{R :X}^{-} \leftrightarrow \text{N: R}^{+}\ \text{:X}^{-} \qquad (9)$$

The result will be enhanced carbocationic character in the TS, an increased reaction rate, and little effect on reaction equilibrium.[36]

If we now substitute the ring with an electron-withdrawing group, (e.g., *p*-NO_2) then the carbanion configuration, N·$^+$ R:$^-$ ·X, will be stabilized, a rate enhancement compared to the unsubstituted benzyl derivative will again occur, and a transition state with carbanionic character will result. The TS may now be described by the resonance forms:

$$\text{N: R}\cdot\ \cdot\text{X} \leftrightarrow \text{N}\cdot^{+}\ \cdot\text{R :X}^{-} \leftrightarrow \text{N}\cdot^{+}\ \text{R:}^{-}\ \cdot\text{X} \qquad (10)$$

The configuration diagram for *p*-nitrobenzyl is illustrated in Figure 3c. In agreement with the above description the rate-enhancement[35] and deduced transition-state character[37] for *p*-nitro- and *p*-methoxybenzyl derivatives have been confirmed experimentally. We see therefore that because for benzyl substitution there are *two* "intermediate" configurations, one carbanionic in character, while one is carbocationic in character, both electron-withdrawing and electron-releasing substituents may induce a rate enhancement. Thus, whereas the conventional view is that curved Hammett plots may result from a *change in mechanism* accompanying a substituent change, the configuration mixing approach predicts *both* the curvature in Hammett plots *and* the change in mechanism. Both are a direct consequence of the dominant influence on the TS of a third (and fourth) configuration.

This third or "intermediate" configuration is also a major ingredient required for observing anomalous rate–equilibrium relationships in multiple-configuration reactions. Since the third configuration mixes into the TS more than into reactants or products, substituent effects operating on this configuration, will lead to wide variations in reaction rate with little or no effect on equilibria. The result is anomalous rate–equilibrium relationships. Clearly, in these cases the α value has no bearing on TS structure,

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(35) Typical examples include: (a) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288. (b) Harris, J. M.; Shafer, S. G.; Moffatt, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 3289. (c) Thorstenson, T.; Eliason, R.; Songstad, J. *Acta Chem. Scand., Ser. A* **1977**, *31*, 276. (d) Thorstenson, T.; Songstad, J. *Ibid.* **1976**, *30*, 724. (e) Ballistreri, F. P.; Maccarone, E.; Mamo, A. *J. Org. Chem.* **1976**, *41*, 3364. (f) Stein, A. R. *Tetrahedron Lett.* **1974**, 4145. (g) Ko, E. C. F.; Leffek, K. T. *Can. J. Chem.* **1972**, *50*, 1297. (h) Brown, H. C.; Ravindranathan, M.; Peters, E. N.; Rao, C. G.; Rho, M. M. *J. Am. Chem. Soc.* **1977**, *99*, 5373. (i) Westaway, K. C.; Waszczylo, Z. *Can. J. Chem.* **1982**, *60*, 2500. (j) Westaway, K. C.; Ali, S. F. *Ibid.* **1979**, *57*, 1354. (k) Yamataka, H.; Ando, T. *J. Am. Chem. Soc.* **1979**, *101*, 266.

(36) An electron-releasing group, in addition to stabilizing the carbocation configuration, will also destabilize the carbanion configuration. A perturbation argument, however, suggests that the stabilizing effect will be larger than the destabilizing effect, leading to rate enhancement. The argument is that since the stabilizing energy, SE (given by eq i) is in-

$$\text{SE} = \frac{\beta^2}{\Delta E} \qquad \text{(i)}$$

versely proportional to the energy gap between the interacting configurations, increasing the energy gap by a predetermined quantity has a smaller effect on SE than decreasing it by the same quantity. In other words stabilizing effects are intrinsically larger than destabilizing ones.

(37) Ko, E. C. F.; Parker, A. J. *J. Am. Chem. Soc.* **1968**, *90*, 6447.

other than specifying the TS contains within it character largely absent in both reactant and product. So it is important to note that for a one-step process *the character of the transition state is not necessarily intermediate between that of reactants and products.* The transition state may take on characteristics which are only weakly present or even totally absent in both reactants and products, and this will occur for those reactions in which "intermediate" configurations (such as N: R$^+$:X$^-$ or N$\cdot^+$ R:$^-$ $\cdot$X) mix strongly and preferentially into the TS. The idea that transition states may exhibit character absent in both reactants and products is well established.[11,26,38] However we believe that through the VBCM model this "foreign" character is introduced quite naturally, and as such, augments the various two-curve treatments.

The effect of substituents which primarily influence the "intermediate" configuration may be described by the following rule.

Rule 3: *Substituent effects operating on a low energy "intermediate" configuration will have a large effect on rates with little or no effect on equilibria. For such systems either no correlation between rates and equilibria will occur* (*as for the identity exchange of ring substituted benzyl derivatives*) *or anomalous slopes* (*i.e.*, $\alpha > 1$) *are likely to occur* (*e.g., as for the deprotonation of nitroalkanes*).

In more practical terms this means that anomalous rate–equilibrium relationships will be expected for families where substituents are located adjacent to a site at which charge is *built up and then recedes* along the reaction coordinate. This build up of charge results from the influence of the intermediate configuration. This is what occurs for benzyl derivatives where positive charge may build up on C_α for electron-releasing ring substituents or negative charge for electron-withdrawing ring substituents.

Effect of Substituents on the Nucleophile, N. The effect of substituents on the nucleophile (or the leaving group) is likely to yield a normal rate–equilibrium relationship. This is because now the energy of the product configuration, N$\cdot^+$ $\cdot$R :X$^-$, is being modified with respect to the reactant configuration. This is similar to the two-configuration case. However, the influence of the substituents on the third configuration does modify the situation somewhat. Let us first consider the case of a family of nucleophiles reacting with *p*-nitrobenzyl derivatives (Figure 3c). For the nucleophilic substitution reaction of *p*-nitrobenzyl derivatives the major configurations describing the TS are the reactant configuration, N: R$\cdot$ $\cdot$X, the product configuration, N$\cdot^+$ R$\cdot$:X$^-$, and the carbanion configuration, N$\cdot^+$ R:$^-$ $\cdot$X (eq 10). A substituent change in the nucleophile (let us presume one stabilizing N$\cdot^+$, e.g., *p*-$OCH_3C_6H_4$) will stabilize *both* the product configuration, N$\cdot^+$ $\cdot$R :X$^-$, as well as the intermediate configuration, N$\cdot^+$ R:$^-$ $\cdot$X. This is illustrated in Figure 4, where the dotted lines indicate the stabilized configurations. Since *both* perturbed configurations will have an influence on the stability of the TS, a large variation in rate will result leading to a large β value. This is in comparison to the corresponding situation for methyl (Figure 1) where only one configuration (the product one) is effectively stabilized and hence a moderate rate increase is observed (i.e., equivalent to a lower β value). Or expressed differently, since the TS for *p*-nitrobenzyl derivatives may be represented by the resonance hybrids of eq 10, in which *two* contributing forms contain N$\cdot^+$, substituent effects on N will have a large influence on rate.

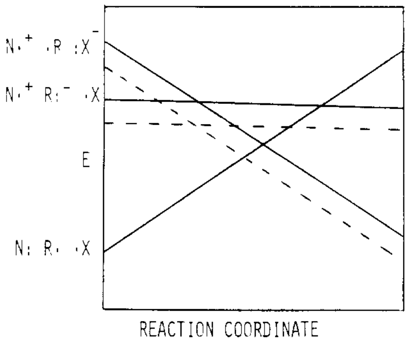

Figure 4. Schematic energy plot of reactant (N: R$\cdot$ $\cdot$X), product (N$\cdot^+$ $\cdot$R :X$^-$), and carbanion (N$\cdot^+$ R:$^-$ $\cdot$X) configurations for the nucleophilic substitution of a *p*-nitrobenzyl derivative. Dotted lines indicate the stabilizing effect of a substituent on the nucleophile for product and carbanion configurations.

For the case of *p*-methoxybenzyl derivatives where the third configuration is now the carbocationic configuration, N: R$^+$:X$^-$, the transition state is represented by the resonance hybrids of eq 9, where only *one* form of the three contains N$\cdot^+$. As a consequence substituent effects on N will have only a slight effect on reaction rate—experimentally, this translates as a low β value.

The interesting observation from the above discussion is that whereas for two-configuration reactions, the Brønsted coefficient is primarily a function of curve slopes, for multiconfiguration reactions the relative mix of the various configurations will play an important role in determining the magnitude of α (or β) values. This means that for systems which require a third configuration to describe the reaction profile, α values, though *not* an *absolute* measure of charge development in the TS, may well provide a *relative* measure of charge development. Thus the fact that β values derived from substituted anilines, in their reaction with a variety of *p*-substituted benzyl chlorides,[35e] increase in the order *p*-OCH_3 < *p*-CH_3 < H < *p*-Cl < *p*-NO_2, is mechanistically significant. The large β value observed in the nucleophilic attack on *p*-nitrobenzyl derivatives[35e] does signify *more* charge transfer from the nucleophile due to the third configuration, whereas the small β value observed for *p*-methoxybenzyl derivatives[35e] does imply *less* charge transfer in the corresponding transition state in comparison to unsubstituted benzyl derivatives. *We believe much of the confusion surrounding the question of whether α and β values measure charge development and TS structure derives from this different pattern in two- and three-configuration systems.* This may be summarised as a rule.

Rule 4: *Substituent effects operating on reactant or product configurations in multiconfiguration reactions will generate normal rate–equilibrium relationships. In such cases the value of α may provide a relative measure of charge development in the transition state but not necessarily a measure of geometric progression along the reaction coordinate.*

Effect of Intermediates. If for a given reaction the "intermediate" configuration is particularly strongly stabilized then an intermediate will result along the reaction coordinate.[18c] This is illustrated in Figure 5. For example, if the carbocationic configuration is strongly stabilized then the profile becomes one of an S_N1 reaction, with the intermediate formation of a carbocationic type intermediate. Now, of course, the reaction is a two-step reaction, each of which is described by the intersection of two configurations. The first step is described by the intersection of

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[38] (a) Critchlow, J. E. *J. Chem. Soc., Faraday Trans. 1* **1972**, *68*, 1774. (b) Farcasiu, D. *J. Chem. Ed.* **1975**, *52*, 76. (c) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4393. (d) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

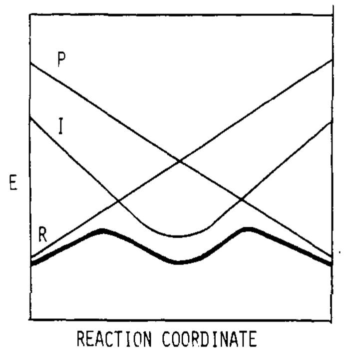


Figure 5. Schematic energy diagram of reactant (R), product (P), and intermediate (I) configurations for a reaction in which an intermediate is generated. Bold curve represents the resultant reaction profile.

reactant and intermediate configurations while the second is described by the intersection of intermediate and product configurations. Since each step is described by just two configurations, on the basis of rule 1, we would expect each step to conform to a rate–equilibrium relationship. This, indeed, appears to be the case. It is widely recognized, for example, that stable carbocations are formed faster than unstable ones implying the existence of a rate–equilibrium relationship for the rate-determining step.

An additional point of importance: it now becomes clear that the nature of the "intermediate" configurations will define the mechanistic bounds of a given reaction. In the extreme situation where say N: R^+ :X^- dominates the reaction pathway then an S_N1 process will occur. If $N\cdot^+$ $R:^-$ $\cdot X$ dominates the reaction pathway, then in the limit a radical anion mechanism will occur. The entire substitution spectrum may therefore be contained within these bounds—S_N1 at one end, S_N2 in the middle (no "intermediate" configurations), and electron transfer at the other end. For reactions constrained to just two configurations (e.g., a range of substitution reactions on methyl derivatives) substituent changes cannot induce changes in mechanism—only changes in reactivity. This is because the TS will mainly be described by a mixture of reactant- and product-like character. Additional configurations, which generate the mechanistic variety, are not involved.[18f]

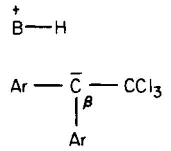
This discussion throws light on a question of recent interest—concerted vs. stepwise pathways. The preceding analysis suggests that concerted pathways are enforced simply when intermediate configurations are too high in energy to affect the reaction pathway. Once an intermediate configuration is sufficiently accessible, the reaction takes advantage of the lower energy pathway that becomes available and an intermediate is formed. These ideas are entirely consistent with views recently expressed by Jencks.[39]

C. Anomalous α Values. In the introductory section it was pointed out that anomalous α values have been explained in a variety of ways. Essentially all presume that "well-behaved" systems generate normal α values ($0 < \alpha < 1$) and that it is some extraneous effect that leads to deviations from normality. Thus unusual solvent effects, preequilibria, and variation in work terms are some typical foreign factors that have been proposed to explain α values greater than 1.

Application of the VBCM model[18] to the makeup of organic reaction profiles has suggested that so-called anomalous Brønsted coefficients constitute an integral part of chemical reactivity. Thus just as certain reactions exhibit positive ρ values and some negative ones, with neither considered to be anomalous, we believe that substitution at certain sites generates normal Brønsted coefficients while substitution at other sites in the same system will generate anomalous Brønsted coefficients.

Even the widespread view that anomalous α values are relatively rare does not really appear to be justified. If rates and equilibria correlate at all, anomalous α values are likely to be observed in any reaction family where the substituent is adjacent to a site which bears the same formal charge in both reactants and products, and this was simply demonstrated in the nucleophilic substitution reaction of benzyl derivatives. Substitution within the nucleophile or leaving group generates normal α values while substitution in the benzyl group is likely to generate anomalous α values. For the special case of identity exchange the α value is infinity, highlighting the intrinsic deficiencies of the rate–equilibrium relationship.

In order to emphasize the widespread nature of anomalous α values we now examine the family of elimination reactions. In a typical system, McLennan and Wong[40] found that the rates of dehydrochlorination of $Ar_2CH{-}CCl_3$ derivatives are sensitive to ring substituents while the equilibria are not. This observation represents, in qualitative form, an anomalous α value. In this system, the substituent is adjacent to a site (the β-carbon) which has the *same* formal charge in both reactants and products. As a result, anomalous α values are to be anticipated. In fact, this family of compounds, which was found to react via an E2–$E1_{CB}$ pathway, is a clear example of a three-configuration system. In addition to reactant and product configurations, the reaction is governed by the carbanion configuration, **5**, as well. Thus, even though the formal charge on C_β is zero in both reactants and products, for electron-withdrawing substituents there is likely to be negative charge development on C_β in the TS region—and this is due to the mixing in of **5** into the TS wave function. As a result, a family of substituents which primarily affects the stability of this configuration will have a large influence on reaction rates with little influence on equilibria, as observed. On the basis of this analysis we would predict anomalous α values for a family of substituents located on C_α as well. Here the third configuration would be the carbocationic one so that substituents which could stabilize this configuration (e.g., *p*-methoxyphenyl) would enhance rates while having little effect on equilibria. Note again, there is no change in the formal charge at C_α between reactants and products. Of course substituents, which are located on the nucleophile or the leaving group, where the charges in reactant and product are different, will exhibit normal rate–equilibrium relationships with $0 < \alpha < 1$ and indeed many such examples exist.[41]



$$\overset{+}{B}{-}H \qquad Ar{-}\underset{\beta\,|\,Ar}{\bar{C}}{-}CCl_3$$

5

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[39] (a) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161. (b) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789. (c) For a similar discussion of the concerted vs. stepwise process using different terminology, see: Metiu, H.; Ross, J.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 377.

[40] McLennan, D. J.; Wong, R. J. *J. Chem. Soc., Perkin Trans 2* **1974**, 1818.

[41] See, for example: Alunni, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2052.

The point we wish to emphasize therefore is that *anomalous rate–equilibrium relationships are likely to be found in any family of reactions and the so-called normality of the relationship between rates and equilibria is governed by the nature of the site at which substitution takes place, rather than the nature of the reaction itself.* The fact that there are many more examples of normal Brønsted coefficients than anomalous ones is simply due to the selection of substituent sites that most workers have deliberately chosen in the course of their mechanistic studies.

A detailed discussion of the nitroalkane system, the most studied example of anomalous Brønsted coefficients, is outside the scope of this paper and will appear elsewhere.[18g]

Conclusion

We have attempted to illustrate in this paper that the VBCM model can provide insight into the way rates and equilibria are related and to the significance of the Brønsted parameter. An examination of a number of basic reaction types indicates that the correlation between rates and equilibria is governed more by the position of substitution than the reaction type. For the special case of a two-configuration system, such as the S_N2 reaction of methyl derivatives, rates and equilibria are expected to be related on the basis of the Bell–Evans–Polanyi argument. The mechanistic significance of the Brønsted parameters in such cases remains obscure. It appears unlikely that Brønsted parameter represents a measure of charge development and is uncertain as to whether it represents a geometric measure of TS structure.

For more complex reactions which require at least three configurations to describe them adequately, i.e., at least one "intermediate" configuration, in addition to reactant and product configurations, both normal and anomalous rate–equilibrium relationships are likely to be observed, depending on the position of substitution. Typical examples are the S_N2 reaction of benzyl derivatives and borderline elimination reactions, i.e., E2–E1$_{CB}$ and E2–E1 pathways.

Normal behavior will be observed if the substituent change primarily affects the product configuration (e.g., a leaving group or nucleophile change in the S_N2 reaction of benzyl derivatives). Remarkably, in such cases our analysis for the benzyl system suggests that α (or β) values obtained from a series of nucleophiles, though certainly not an absolute measure of TS structure, may provide a *relative* measure of charge development in the TS. Thus the larger absolute value observed for substituted anilines reacting with *p*-nitrobenzyl halides compared to that for benzyl halides does signify *more* charge transfer in the former case (i.e., due to $N\cdot^+ \; R{:}^- \cdot X$). The basic reason for the difference between the three-configuration reaction, where the Brønsted parameter does provide a measure of charge development, and the two-configuration reaction where it does not, is that substituents will modify the relative mix of the three configurations in the TS region. For two-configuration reactions, by contrast, the mix at the TS is necessarily comprised of 50% of each of the two configurations *regardless* of the substituent, and therefore no such pattern is observed.

Substituent effects which operate on the "intermediate" configuration (e.g., on the hypothetical benzyl cation or anion in the S_N2 reaction of benzyl derivatives) will invariably generate large rate variations with little or no effect on equilibria. This is the classical recipe for observing anomalous rate–equilibrium behavior, with α values exceeding 1. These values have an indirect bearing on TS structure. The magnitude of the substituent effect on rates (measured by α or ρ) signifies the extent to which the "intermediate" configuration mixes into the reaction pathway and thereby constitutes an important mechanistic tool. α or ρ for these cases are a measure of the extent to which charge builds up at the substituent site and rightfully enables reaction mechanisms to be assigned. Thus the U-shaped Hammett plots for benzyl derivatives reveal that for electron-withdrawing substituents (where ρ is positive in sign) negative charge builds up on the central carbon, while for electron-releasing substituents (where ρ is negative) positive charge builds up on the central carbon. Similarly E2–E1$_{CB}$ and E2–E1 pathways may be assigned from substituents adjacent to the carbanionic and carbocationic sites respectively.

The most striking conclusion we have derived, however, is that so-called anomalous Brønsted parameters ($\alpha > 1$) are extremely common. In fact, *for essentially any reaction family either anomalous or normal Brønsted parameters may be obtained depending on the position of substitution within the reaction complex.*

A final note is required. Considerable effort has been spent in developing analytical expressions for describing reaction profiles and relating rate and equilibrium constants.[26,28,42] A large majority of these have been based on the assumption that the TS is intermediate in character between reactants and products. The key point of this article has been that only a small fraction of all reactions can be satisfactorily viewed in this way and that the majority of reactions, both ionic and pericyclic, of necessity require at least one additional component in order to provide an adequate description. In this sense we are reflecting the profound impact of the potential energy surface models[38a,43-46] which have been recently developed by Thornton,[43] More O'Ferrall,[44] Jencks,[45] and Kurz.[46] The intermediate configuration in our terminology serves the same goal as the "perpendicular" effects of the potential energy surface models, i.e., both introduce character into the TS which is *absent* in reactants and products. We believe that an important intermediate goal in the search for greater understanding of reactivity will focus on the ways such a third component can be quantitatively incorporated into existing treatments.

Acknowledgment. I thank the Australian National University for a Visiting Fellowship, and the University of Auckland for a Visiting Lectureship. Most helpful discussions with Professor Duncan McLennan, Dr. Leo Radom, and Dr. Sason Shaik are gratefully acknowledged.

Note Added in Proof: A paper recently submitted by Kreevoy and Lee reaches similar conclusions to our own. These workers demonstrate that "perpendicular" effects can modify α values from their "true" value. This is equivalent in the terminology of this paper to substituent effects on intermediate configurations. See: Kreevoy, M. M.; Lee, I.-S. H. *J. Am. Chem. Soc.*, in press. We thank Professor Kreevoy for kindly providing us with a preprint.

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(42) For a recent discussion and pertinent references, see: Scandola, F.; Balzani, V.; Schuster, G. B. *J. Am. Chem. Soc.* **1981**, *103*, 2519.

(43) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915.

(44) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274.

(45) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705.

(46) Harris, J. C.; Kurz, J. L. *J. Am. Chem. Soc.* **1970**, *92*, 349.