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A Primer for the Bema Hapothle. An Empirical Approach to the Characterization of Changing Transition-State Structures[1]

WILLIAM P. JENCKS

Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254

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In their search for order, chemists invented Brønsted and Hammett correlations and other linear free energy relationships. The slopes of these correlations are first derivatives of log k, such as β or ρ (eq 1).

$$\beta = \partial \log k / \partial \mathrm{p}K_a \qquad (1)$$

However, these slopes are not always constant. A sense of order can be preserved by describing the change in slope as an interaction coefficient, such as q, C, or p.[2-6] For example, downward curvature in a Brønsted plot for base catalysis (Figure 1A) represents a decrease in the slope, β, as the pK_a of the conjugate acid of the catalyzing base is increased. This is described by the interaction coefficient p_x, which is defined in eq 2. The p$_x$ coefficient is the slope of a plot of β or ρ against a structural parameter, such as pK_a or σ, and is a second derivative of log k (eq 2).

$$p_x = \frac{\partial \beta}{-\partial \mathrm{p}K_a} = \frac{\partial^2 \log k}{\partial \mathrm{p}K_a(-\partial \mathrm{p}K_a)} \qquad (2)$$

A change in the slope, β, for a series of bases can also occur when a substituent is changed in the other reactant. Such a change can be described by a cross-interaction coefficient, p_{xy}. For example, the dependence of the rate constant for a substitution reaction on the basicity of the nucleophile, pK_{nuc}, may be described by the slope, β_{nuc}, of a Brønsted-type plot of log k against pK_{nuc} (Figure 1B). An increase in this slope with a poorer leaving group (increased pK_{lg}) corresponds to a positive cross-coefficient, p_{xy} (eq 3), which is also a second derivative of log k.

$$p_{xy} = \frac{\partial \beta_{nuc}}{\partial \mathrm{p}K_{lg}} = \frac{\partial \beta_{lg}}{\partial \mathrm{p}K_{nuc}} = \frac{\partial^2 \log k}{\partial \mathrm{p}K_{lg} \partial \mathrm{p}K_{nuc}} \qquad (3)$$

The sensitivity of the reaction to the leaving group may be described by β_{lg}, the slope of a plot of log k against pK_{lg}. The same cross-coefficient, p_{xy}, describes the change in β_{lg} as the pK_a of the nucleophile increases (eq 3). Figure 1B shows that this is required directly by the experimental data.[3] The larger slope, β_{nuc}, with the poor leaving group means that there is a smaller dependence of log k on the pK of the leaving group for a basic nucleophile, B_b, than for a less basic nucleophile, B_a; i.e., $\beta_{lg}{}^b$ is less negative than $\beta_{lg}{}^a$. In general, a cross-coefficient such as p_{xy} refers to the effect of a substituent in one reactant (pK_{lg}) on a structure-reactivity parameter for another reactant (β_{nuc}); a direct coefficient such as p_x refers to the effect of a changing substituent (pK_{nuc}) on the slope of the correlation for that substituent (β_{nuc}).

These interaction coefficients can be useful for characterizing a reaction mechanism when the change

After graduation from Harvard Medical School (1951) and internship in the Medical Service at Peter Bent Brigham Hospital (1951–1952), Dr. Jencks spent 2 years in postdoctoral work with Fritz Lipmann at the Massachusetts General Hospital (1952–1953 and 1955–1956). This period was interrupted by 2 years in the Army at the Army Medical Service Graduate School of the Walter Reed Army Medical Center; he was Chief of the Pharmacology Department during the second year. Following this, he spent a year in R. B. Woodward's laboratory at Harvard. In 1957, Dr. Jencks joined the Graduate Department of Biochemistry at Brandeis University, where he has remained since. His research has centered around three areas: (1) the mechanism and mechanism of catalysis of acyl and carbonyl group reactions in water; (2) the mechanisms of acyl transfer and hydrolysis reactions catalyzed by enzymes; and (3) the mechanism of the interaction of small and large molecules with each other in aqueous solution. Recently, he has been particularly concerned with the way in which reaction mechanisms are determined by the lifetime of reaction intermediates in general acid–base catalysis, carbanion, carbocation, and ligand exchange reactions, and the use of structure-reactivity interactions to characterize transition states.

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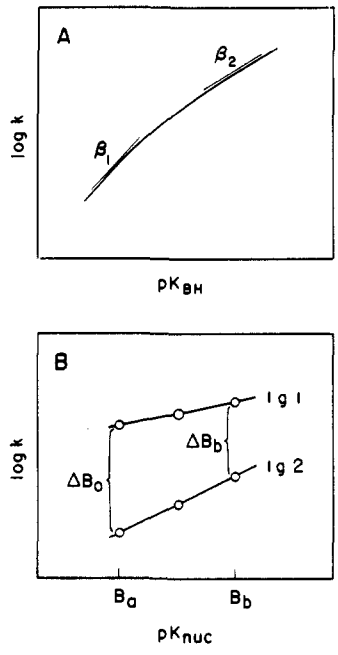


Figure 1. Changes in the β coefficient with changing substituents on the reactants. A: β decreases when the base is stronger. B: β_{nuc} increases when the leaving group is worse (more basic). This result also requires that the dependence of the rate on the structure of the leaving group be smaller for a basic nucleophile, B_b, than for a weaker, less basic nucleophile, B_a, as described by eq 3.

in slope represents a change in the structure of a single transition state, rather than a change in the reaction mechanism, the rate-limiting step, or some property of the reactants other than that being investigated. It is usually easier to evaluate changes in transition-state structure from cross-coefficients (Figure 1B) than from direct interaction coefficients (Figure 1A). It may be difficult to decide whether the experimental data require that a particular structure-reactivity correlation is curved, but it is comparatively easy to establish that a real difference in slope exists for a cross-correlation by comparing the ratios of rate constants for the substrates in the two series. Curvature in a Brønsted correlation is sometimes caused by factors other than basicity that change with the changes in chemical structure of a series of bases. There are also differences in the chemical structures of the substrates used to obtain a cross-coefficient, such as the two different leaving groups for the correlations in Figure 1B, that may cause changes in rate for some reason other than a simple polar substituent effect. It is important to evaluate the role of these differences before an interaction coefficient is interpreted as evidence for a change in transition-state structure that is brought about by a polar substituent effect.[7]

Third derivatives describe changes in interaction coefficients that must (and do) occur but have not been treated systematically.

The nature, and even the existence, of these changes in transition-state structure have provoked much interest and controversy among chemists, so that they require a name. For many years they were called "Hammond effects" and more recently they have been described in terms of Marcus theory.[8,9] However, many workers have provided qualitative or quantitative treatments of these matters and it is not desirable to identify the entire problem with a single theory or

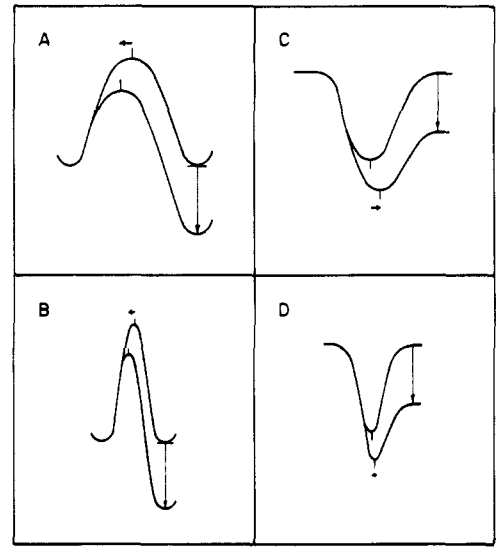


Figure 2. Changes in the position of a transition state when a structure on (or along) the reaction coordinate is stabilized, A and B, and when a structure that is perpendicular to the reaction coordinate is stabilized, C and D.

equation. It is awkward to refer repeatedly to the Bell–Marcus–Hammond–Polanyi–Thornton–Leffler effect,[8-11] which is itself far from complete.[2-6,12-14] Therefore, we have reluctantly acceded to contemporary custom and proposed the acronym Bema Hapothle to describe these effects.[15]

Parallel and Perpendicular Effects on Transition-State Structure

All changes in transition-state structure, and the resulting interaction coefficients, may be divided into two parts:

(1) Systems in which a substituent that raises the energy of a structure causes the transition state to resemble that structure (the "Hammond effect").[16]

(2) Systems in which a substituent that lowers the energy of a structure causes the transition state to resemble that structure (an "anti-Hammond effect").

There has been controversy as to whether all of chemistry fits into only one of these categories, or even whether either of them represents reality, but there is every reason to believe that both of them exist and that they contain information about the nature of a reaction. The first includes the reactivity-selectivity principle, RSP. There has been much discussion whether the RSP is "true" or whether it "fails" in certain reactions, but these may be the wrong questions to ask.[7,17-19] Changes in structure-reactivity parameters and transition-state structure certainly do occur and their direction and size (including effects that are too small to be detected) provide information about the nature of a transition state.

The first kind of behavior, the Hammond effect, is illustrated by the popular, but possibly misleading, picture of a transition state that moves in the direction toward the position of relatively higher energy and becomes earlier as the product becomes more stable relative to the reactant (Figure 2A). The amount or even the existence of a detectable change in the structure of the transition state depends on the sharpness of the curvature of the reaction coordinate at the transition state. A small or broad curvature gives a

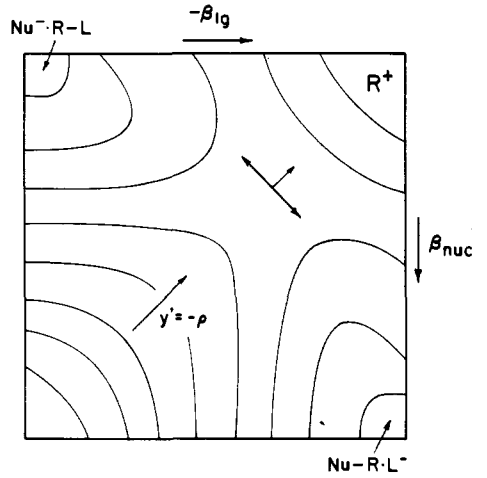


Figure 3. A reaction coordinate diagram to show movement of the transition state perpendicular to the reaction coordinate when the carbocation structure is stabilized.

large change in the position of the transition state when the product is less stable (Figure 2A); a sharp curvature gives little change (Figure 2B).[11] In the Marcus treatment these differences correspond to differences in the intrinsic barriers for identity reactions, $\Delta G_0^{\ddagger}$; a small $\Delta G_0^{\ddagger}$ corresponds to a small curvature and gives a large change in $\Delta G_{obsd}^{\ddagger}$. If the observed change in β or ρ is larger than that calculated from the observed barrier for an identity reaction, the data may be fit to the Marcus equation by including a constant work term, w_r, in $\Delta G_{obsd}^{\ddagger}$. This gives a smaller intrinsic barrier, $\Delta G_0^{\ddagger}$, and a larger change in $\Delta G_{obsd}^{\ddagger}$.[9,20] Other factors and equations can also describe different changes in observed barriers.[14,21,22] These changes describe movement of the transition state along, or parallel to, the reaction coordinate. Interaction coefficients, such as $p_x = \partial\beta/-\partial pK_a$, are defined so that a normal Hammond effect corresponds to a positive sign of the coefficient.

The second kind of behavior, the anti-Hammond effect, is exemplified by the idea that substituents which stabilize a carbocation will make a transition state resemble the carbocation. A picture of how this stabilization modifies an energy surface to cause such a change was given by Hughes, Ingold, and Shapiro in 1936.[23] Figure 3 shows a reaction coordinate diagram for a substitution reaction at carbon in which the reactants and products are in potential wells in the upper left and lower right corners of the diagram, respectively, and the other two corners correspond to high-energy structures. The horizontal axis describes bond breaking of R–L to give the cation R^+ across the top of the diagram, and the vertical axis describes bond making of R^+ and the nucleophile Nu^- to form Nu–R, on the right-hand side of the diagram. The energy is indicated by contour lines. The transition state for a substitution reaction in which bond breaking and bond making are occurring simultaneously occurs at the saddle point on a diagonal reaction coordinate, shown by the double-headed arrow. There is downward curvature of the surface along, or parallel to, the reaction coordinate as it passes over the saddle point. This is shown in the reaction coordinate profiles of Figure 2A,B, which describes the lowest energy path from the reactants, Nu^-·RL, up to the transition state and down to the products, NuR·L^-. However, there is upward curvature of the surface on the two sides of the saddle, perpendicular to the reaction coordinate. This is shown in the cross section profiles through the saddlepoint of Figure 2C,D.

Complete bond breaking and no bond making gives the carbocation structure R^+ in the upper right corner of Figure 3. This structure may or may not represent a real intermediate in an energy well, with a significant barrier for its collapse. Electron-donating substituents that stabilize this carbocation will lower the energy of the upper right corner of the diagram. The transition state will then tend to slide downhill toward the cation, as shown by the thin arrow in Figure 3. The movement is *toward* the structure of lower energy because the cross section through the energy surface perpendicular to the reaction coordinate is an energy well, with upward curvature at the saddle point. Lowering the energy of R^+ lowers the energy of one side of this energy well and causes the minimum of the well to slide downhill toward the position of lower energy (Figure 2C). Again, the amount of movement is smaller if the curvature of the surface is sharper (Figure 2D).[11,23]

The idea that substituents which stabilize a carbanion in elimination reactions will lead to a transition state that resembles a carbanion, as described by Bunnett,[24] represents another example of a perpendicular effect. Both perpendicular and parallel effects were treated quantitatively by Thornton.[11] More O'Ferrall showed how these effects can be illustrated with energy contour diagrams, analogous to Figure 3, and used to characterize the mechanisms of elimination reactions.[25] Similar diagrams are useful for describing reactions in which two protons are transferred.[26,27]

Perpendicular effects are often responsible for "failures" of the RSP, because they represent changes in structure-reactivity coefficients and transition-state structure that are in the opposite direction from those predicted by the Hammond effect.[28]

Perpendicular effects may also be described in terms of a configuration mixing model, in which a particular configuration or structure contributes more to the transition state than to reactants and products,[29] and a model in which they are described with an upside-down free energy profile and an "intrinsic barrier" proportional to that along the reaction coordinate.[30]

Reaction Coordinates and Structure-Reactivity Parameters

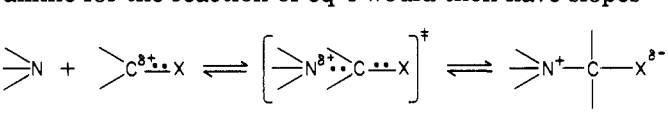
In order to draw pictures like Figures 2 and 3, it is necessary to define axes or "reaction coordinates" that represent the progress of a reaction. A reaction coordinate represents the extent to which some process or combination of processes has taken place; it may be difficult to define quantitatively or in physical terms. Marcus theory, which was originally applied to electron-transfer reactions and their associated changes in solvation, has been applied to organic reactions using the bond energy–bond order (BEBO) model.[9,12] The BEBO model can be applied to simple systems in which the sum of the bond orders is constant at 1.0 throughout the reaction. This is an important contribution because it provides some theoretical basis for structure-reactivity behavior. However, bond orders in transition states are not directly measurable experimentally and the simple BEBO theory may be difficult to apply to complex reactions in which several different processes are occur-

ring more or less concurrently.

Other, related models have been proposed, but it is not clear which of them is most closely related to the chemical and physical changes that take place in the course of the reaction and it is difficult or impossible to choose among these models on the basis of their precision of fit to experimental data.[11-14,22,31,32] In fact, the behavior of almost all models does not differ significantly from the behavior of intersecting parabolas or perturbed simple parabolas, at least over a moderate range of substituent variation.[22,33] It is not surprising that different models will fit curved structure-reactivity plots or other changes in structure-reactivity parameters, in view of the opinion of some investigators that even the existence of such changes is questionable.[7,17,18]

Progress along a reaction coordinate, or bond order, in the transition state is usually estimated from observed structure-reactivity parameters or isotope effects. An empirical approach involves the use of these parameters directly to construct an energy diagram. A justification of this is needed because the validity of structure-reactivity parameters as measures of reaction progress has been questioned.[32,34-36]

Polar substituents exert their effect by a favorable or unfavorable electrostatic interaction with a charge or dipole in a reactant or transition state.[37] If a substituent has a certain effect on the development of a full charge on a neighboring atom, as measured in a reference ionization reaction for example, then if it has half as large an effect on $\Delta G^{\ddagger}$ to reach a transition state it is reasonable to suppose that less than a full charge is developed on that atom in the transition state; if the effect is 0.1 as large, there is still less charge in the transition state. Plots of log k against the pK_a of the amine for the reaction of eq 4 would then have slopes



(4)

of β_{nuc} = 0.5 or 0.1. It is reasonable to say that the reaction behaves *as if* 0.5 or 0.1 positive charge has developed on the nitrogen atom in the transition state; the "effective charge" on nitrogen in the transition state is 0.5 or 0.1. The value of β_{nuc} or the effective charge is certainly not an exact measure of absolute charge or electron distribution in the transition state but can be useful for comparing reactions with early and late transition states.

Charge development and the value of β or ρ are related to the bond orders for forming and breaking bonds and the relationship is monotonic if only one process is occurring, as in eq 4. The value of β or ρ is then an experimental measure of bond order; in the simplest case the relationship might approach linearity. If β or ρ is a measure of bond order, then a change in β or ρ is a measure of a change in bond order.

The value of β or ρ for substituents on a *central atom* that is involved in more than one process will not show such a simple relationship and may not even change monotonically with the overall progress of the reaction. For example, substitution at the benzyl group involves both bond formation and cleavage at the central carbon atom, so that if there is more bond cleavage than bond formation in the transition state there will be an electron deficiency on the central carbon atom relative to both reactants and products and the reaction will be accelerated by electron-donating substituents.[38] Similarly, the ionization of nitroalkanes involves both C–H bond cleavage at the central carbon atom and electron delocalization from the central carbon atom into the nitro group. There can be a larger development of negative charge on the central carbon atom in the transition state than in the product if C–H bond cleavage is ahead of electron delocalization in the transition state; electron-withdrawing substituents will then accelerate the reaction in both directions.[34] Such substituent effects are not direct measures of reaction progress. However, if polar substituent effects measure electrostatic interactions, they are still measures of changes in the distribution of charge in the transition state. They provide important information about the development of charge on the central atom and the *balance* between the extents to which two or more different processes are occurring in the transition state.

An Empirical Method for the Characterization of Transition States

Most quantitative treatments of the Bema Hapothle are based on equations that relate the energy of the transition state directly to the energies of the reactants and products, and sometimes to the energies of intermediates.[9,14,22,31] The equations may be based on theories or models for the reaction course, such as the BEBO theory. The reaction coordinate or reaction surface in these models is often not defined in physical terms, although it may be related to bond orders or bond lengths. A successful fit of structure-reactivity data and, in particular, of changes in structure-reactivity parameters may provide support for a particular theory, model, or equation, or for a particular description of the reaction surface.[27,36,39-41] However, it is difficult to describe the entire course of a reaction or a reaction surface, especially for complex reactions in which several different processes are taking place more or less concurrently, and experimental data can usually be fit satisfactorily by several different models. A good fit to a particular model may be obtained by the use of an additional, adjustable parameter, such as the work term, w_r.

An alternative, empirical approach makes no assumptions about the shape of the entire reaction coordinate or reaction surface and does not attempt to calculate the absolute difference in energy between the transition state and the reactants. Instead, the observed changes in structure-reactivity parameters are used to characterize the nature of the transition state from its observed movements parallel and perpendicular to the reaction coordinate. The reaction coordinate at the transition state is defined in terms of the observed structure-reactivity parameters, which are presumably measures of changes in charge distribution and bond orders. The experimental data characterize the properties of the reaction surface, *but only in the neighborhood of the transition state*; no attempt is made to describe the entire reaction surface. The approach can be useful for distinguishing different reaction mechanisms and for describing the relationship of different processes that are occurring more or less concurrently in complex reactions. The rationale of the method is summarized here. The calculations are described

elsewhere[5] and are outlined in a later section of this review.

Changes in observed structure-reactivity parameters are Hammond and anti-Hammond effects that represent movements of the transition state on the reaction surface parallel and perpendicular to the reaction coordinate, respectively. The magnitude of these movements on a reaction surface that represents two processes, such as bond breaking and bond making in Figure 3, depends on (1) the *direction* of the reaction coordinate, which determines the relative contributions of changes in energy parallel and perpendicular to the reaction coordinate when a polar substituent on a reactant or catalyst changes the energy of an edge or corner of the diagram, and (2) the *curvatures* of the surface parallel and perpendicular to the reaction coordinate, which determine how much movement of the transition state is brought about by a given change in energy (Figure 2).

For example, stabilization of the carbocation structure in the upper right corner of Figure 3 with an electron-donating substituent will cause only a perpendicular movement of the transition state toward the carbocation if the reaction coordinate is diagonal; the amount of this movement is determined by the curvature of the surface perpendicular to the reaction coordinate (Figure 2C,D). However, changing the energy of an edge of the diagram changes the energy in the directions that are both perpendicular and parallel to the direction of a diagonal reaction coordinate, so that the transition state will move in directions both perpendicular and parallel to the reaction coordinate.

The magnitudes of the movements can be calculated from the changes in energy and the curvatures parallel and perpendicular to the reaction coordinate, if it is assumed that a change in energy causes a linear perturbation along the reaction surface and that the curvatures in the immediate vicinity of the transition state can be described by parabolas.[11] It is reasonable to describe the curvatures by parabolas, at least for small perturbations. The changes parallel and perpendicular to the reaction coordinate are most easily calculated by using curvatures that are defined in the coordinates of the contour diagram. If the coordinates are defined by normalized structure-reactivity parameters, such as β and ρ, the energy perturbation at the transition state when the energy of an edge is changed corresponds to a linear energy perturbation across the diagram, according to the definition of β or ρ. Conversely, it can be shown that a linear energy perturbation gives a linear relationship of Brønsted-type coefficients and the coordinates of the transition state.[42] The calculations are straightforward and are equivalent to relating a change in energy of an edge or corner of a diagram (e.g., Figure 3), which results from a change in substituent, to the changes in energy parallel and perpendicular to the reaction coordinate that cause movement of the transition state (Figure 2).[5]

Since movements of the transition state with changes in substituents depend on the direction of the reaction coordinate and the curvatures of the surface at the saddle point, the procedure can be reversed and the direction and curvatures can be calculated from the observed movements of the transition state, as measured by changes in structure-reactivity parameters. These changes in structure-reactivity parameters are described by direct interaction coefficients, such as $p_x = \partial\beta/-\partial pK_a$, and cross coefficients, such as $p_{xy} = \partial\beta_{nuc}/\partial pK_{lg}$.

The basic assumption of the method is that the shape of the saddle point remains constant, so that transition states of different structure in a series of reactions will behave in the same way. This is equivalent to the assumption that changes in transition-state structure can be described by second derivatives or interaction coefficients, such a p_x and p_{xy}. This assumption certainly does not hold for very large changes in structure. It fails when the interaction coefficients are not constant, i.e., when there are significant third derivative effects and changes in the curvatures of the surface at the saddle point.

It may be useful to indicate the position of the transition state and the direction of the reaction coordinate on the diagram, as in Figure 3. Each perturbation that moves the transition state produces a new diagram, just as it produces a new reaction profile (Figure 2). However, it is often convenient to use the diagram also as a map in order to show the positions to which the transition state moves.

This procedure is clearly a crude oversimplification of the real situation for most reactions. However, it is less of a simplification than the combination of all parameters of the reaction into a single reaction coordinate, the use of two coordinates with the assumption that two processes are balanced in such a way that the actual reaction coordinate is always at an angle of 45° on a reaction surface, or the assumption that all of the different processes that are taking place in a complex reaction in solution can be described by a simple equation. It is based on few assumptions and makes no assumptions about the direction of the reaction coordinate. The contributions, or coupling, of different components of the reaction in the transition state, such as proton transfer and heavy-atom motion, are likely to be different in different types of reactions. The direction of the reaction coordinate at the transition state will then be different for the different reactions, because it is determined by the relative contributions of the two processes, each of which is represented by movement along one coordinate. Most of the assumptions of the method arise when the structure-reactivity behavior is interpreted in terms of bond orders and bond lengths. These assumptions are described in the preceding section. This approach provides an empirical method to describe the properties of transition states, as manifested in structure-reactivity behavior, that can be useful for describing and distinguishing the mechanisms of reactions in which several different processes are involved.

This approach to the Bema Hapothle is best illustrated by example. This review describes some changes in transition-state structure that are manifested by changes in observed structure-reactivity parameters or isotope effects for several different classes of reactions. The changes are described qualitatively and, in some cases, semiquantitatively, with energy contour diagrams.

Substitution at Carbon

Nucleophilic displacements on carbon have provided much of the experimental material for qualitative

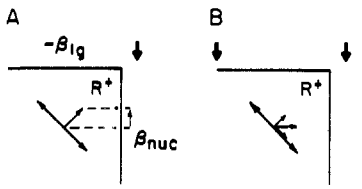
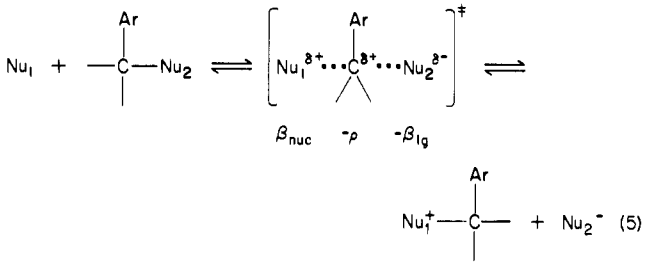


Figure 4. Portions of Figure 3 to show the effects of stabilization of the cation structure, A, and of the nucleophile, B.

analysis of changes in transition-state structure, following Ingold et al.[23] The substituent effects that characterize the differences in charge distribution between the reactants and transition state may be described by β_{nuc} and β_{lg}, the slopes of plots of log k against pK_{nuc} and pK_{lg}, respectively, and ρ, from a plot of log k against σ for substituents on an aryl group attached to the central carbon atom (Ar in eq 5). The



reaction coordinate diagram of Figure 3 can be related to experimental measurements by defining the horizontal axis for leaving group departure across the top of the diagram as $-\beta_{lg}$, the vertical axis for nucleophilic attack down the right side of the diagram as β_{nuc}, and a diagonal axis from the lower left to the upper right corner (y') as $-\rho$, a measure of the total amount of bonding to the central carbon atom (eq 5). The parameters may be normalized by dividing by the β or ρ value for the corresponding equilibrium process. The lower left corner of this diagram corresponds to a pentavalent addition intermediate, which is not ordinarily significant for nucleophilic substitution at carbon.

Electron-donating substituents on the central carbon atom that stabilize a carbocation can increase the cationic character of the transition state for a concerted substitution reaction by increasing bond breaking to the leaving group and by decreasing bond making to the nucleophile.[11,13,19,23,24,40,43,44] The movement of the transition state toward the carbocation, perpendicular to the diagonal reaction coordinate of Figure 3, corresponds to movement upward and to the right when the energy of the carbocation structure in the upper right corner is decreased by an electron-donating substituent. Figure 4 shows the upper right corner of Figure 3. A substituent with a decreased σ value decreases the energy of R^+, as indicated by the heavy arrow in Figure 4A. This decreases the energy in the perpendicular direction from the reaction coordinate, so that the transition state moves toward the position of lower energy (Figure 2C). This movement toward the cation corresponds to a decreased (more negative) value of ρ.

This description illustrates the use of Figure 3 as both an energy contour diagram and a map. Figure 3 shows a reaction coordinate in a saddle point at a certain position on the diagram. It also shows movement of the transition state to a new position, perpendicular to the reaction coordinate. This results in a new energy diagram in which the saddle point is at a different position; however, the contours of the new diagram are not shown. Note that the cationic structure R^+ need not be an intermediate in an energy well; in fact, it is likely that it does not exist as an intermediate with a significant barrier for collapse on the energy diagram for concerted substitution reactions at carbon.[45]

The amount of bond making to the nucleophile in the transition state might be estimated from the value of β_{nuc}. The amount of bond making and β_{nuc} are decreased when the transition state moves upwards toward R^+, as shown in Figure 4A. This decrease in β_{nuc} upon stabilization of the cation can be described by a positive value of the interaction coefficient $p_{xy'}$ in eq 6.[46] The $p_{xy'}$ coefficient describes the relationship be-

$$p_{xy'} = \frac{\partial\beta_{nuc}}{\partial\sigma} = \frac{\partial-\rho}{-\partial pK_{nuc}} = \frac{\partial\rho}{\partial pK_{nuc}} \qquad (6)$$

tween changes in the amount of bond formation, as measured by β_{nuc}, and in carbocation character, as measured by a $\sigma\rho$ correlation for substituents on the central carbon atom that is indicated by the diagonal y' axis leading toward the cation (Figure 3).[19] It is important to realize that there are no mathematical or other assumptions in eq 6; the relationship is similar to that shown in Figure 1B and arises directly from the experimental data.[3,5]

The other term in eq 6, $\partial-\rho/-\partial pK_{nuc}$, corresponds to an increase in carbocation character, i.e., movement of the transition state toward the carbocation, when the nucleophilic reagent becomes weaker. A weaker, less basic nucleophilic reagent results in a decrease in the energy of the top relative to the bottom edge of the diagram (Figure 3) because electron-withdrawing substituents stabilize the nucleophile relative to the products. This is indicated by the heavy arrows in Figure 4B. For a diagonal reaction coordinate this tends to move the transition state toward the right, with an increase in the amount of bond-breaking and carbocation character.

This can be analyzed by considering the expected movements of the transition state parallel and perpendicular to the reaction coordinate, which depend on the direction of the reaction coordinate and the curvatures parallel and perpendicular to it. In this case the decrease in the energy of the top of the diagram means that the movement of the transition state perpendicular to the reaction coordinate will be toward the upper right corner of Figure 4B. This occurs because a cross section through the saddle point perpendicular to the reaction coordinate decreases in energy toward the upper right corner and the transition state moves toward this position of lower energy, as shown in Figure 2C. The movement parallel to the reaction coordinate is toward the lower right corner. This occurs because a cross section through the saddle point along the reaction coordinate increases in energy toward the lower right corner and the transition state moves toward this position of higher energy, as shown in Figure 2A. The observed movement to the right is the resultant, or vector sum, of these two movements (Figure 4B). Thus, the diagram predicts that when the reaction coordinate is diagonal, there will be more bond breaking in the transition state when the nucleophile becomes weaker because both the perpendicular and the parallel movements of the transition state are toward the right.

This corresponds to an increase in carbocation character (more negative ρ) that arises from an increase in bond breaking (more negative β_{lg}). However, there is a partial or complete cancellation of the vectors on the scale for β_{nuc}, so that a small or no change in this parameter is predicted.

The diagram predicts that cross coefficients, such as $p_{xy'}$, should be larger than direct coefficients, such as p_x, when the reaction coordinate is diagonal. If the curvatures of the surfaces are not the same parallel and perpendicular to the reaction coordinate, a change in β_{nuc} will occur when the pK_a of the nucleophile is changed.[5] For example, if the curvature perpendicular to the reaction coordinate were smaller, movement of the transition state toward the cation, perpendicular to the reaction coordinate, would predominate (compare parts B and C of Figure 2). This would give a decrease in β_{nuc} (an anti-Hammond effect) rather than the increase in β_{nuc} that is usually expected when the nucleophile becomes weaker.

There is clearcut experimental evidence for the behavior illustrated by Figure 4A,B in the reactions of substituted thiol anions, anilines, and carbanions with benzyl derivatives, with a value of $p_{xy'} \simeq 0.045$ for the aniline reaction.[18,19,47,48] The relationship between the leaving group and the amount of carbocation character in the transition state is described by the analogous relationship of eq 7.

$$p_{yy'} = \frac{\partial -\beta_{lg}}{\partial \sigma} = \frac{\partial -\rho}{\partial pK_{lg}} \qquad (7)$$

The decrease in ρ that results from electron-donating substituents on the central atom represents a perpendicular movement of the transition state toward the carbocation (Figures 3 and 4A) and is described by a negative value of the direct interaction coefficient $p_{y'}$ for the diagonal y' axis (eq 8). Many S_N2 reactions

$$p_{y'} = \partial -\rho / \partial \sigma \qquad (8)$$

show little or no effect of polar substituents on the central atom.[40] However, the value of $\rho = -2.9$ for the S_N2 reaction of azide ion with substituted 1-phenylethyl chlorides shows that there is a large amount of carbocation character in the transition state.[45] 1-Phenylethyl derivatives undergo solvolysis through a carbocation intermediate if there are electron-donating substituents on the aryl group and might be expected to take advantage of the electron-donating character of the aryl and methyl groups to stabilize the transition state for S_N2 substitution. These substituents stabilize the carbocation structure in the upper right corner of the diagram so that the transition state moves toward the upper right corner, perpendicular to the reaction coordinate, and develops carbocation character. The U-shaped Hammett plots for substitution on benzyl derivatives can be accounted for by opposing resonance and electrostatic effects, at least with anionic nucleophiles.[19] However, there is also evidence from secondary isotope effects for a direct perpendicular effect that gives a looser transition state with electron-donating substituents on the benzene ring.[45,48,49]

Substitution reactions of methyl derivatives show little or no change in transition-state structure with changes in the nucleophile or leaving group.[50] This may be explained, at least in part, by the great instability

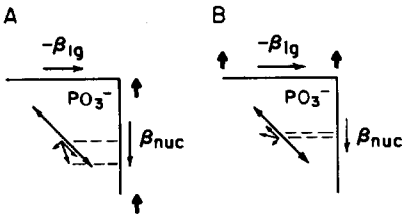


Figure 5. Portions of a reaction coordinate diagram for phosphoryl transfer to show the effect of destabilization of the leaving group, A, and destabilization of the nucleophile, B.

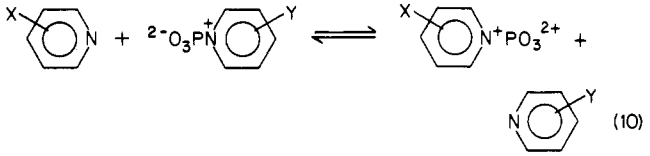
of the methyl cation, CH_3^+, which gives rise to steep upward curvature of the energy surface toward the upper right corner of the diagram, perpendicular to the reaction coordinate, and inhibits movement of the transition state (Figure 2D).[19,23]

Phosphoryl Transfer

The reactions of amines with phosphate monoesters and phosphorylated pyridines exhibit an increased selectivity toward the nucleophile when the leaving group becomes worse and an increased selectivity for the leaving group when the nucleophile is weaker.[51,52] These cross-interactions between the nucleophile and the leaving group are described by a positive p_{xy} coefficient (eq 9), with a value of $p_{xy} = 0.014$ for the reactions of

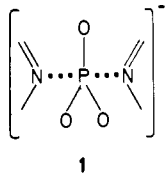
$$p_{xy} = \frac{\partial \beta_{nuc}}{\partial pK_{lg}} = \frac{\partial \beta_{lg}}{\partial pK_{nuc}} \qquad (9)$$

pyridines with phosphorylated pyridines (eq 10).[52] They correspond to the behavior shown in Figure 1B.



(10)

Phosphoryl transfer reactions are described by a diagram similar to Figure 3 for substitution at carbon, except that the structure in the upper right corner is PO_3^- instead of R^+. There is evidence that the reactions of pyridines with phosphorylated pyridines are concerted, perhaps because the PO_3^- ion is too unstable to have a significant lifetime as an intermediate in the presence of pyridines. However, the transition state 1



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is open or "exploded" and resembles PO_3^-, with a large amount of bond cleavage and little bond formation.[51-53] The weak bonding in the transition state may facilitate changes in the structure of the transition state, as in the transition states for substitution at carbon that resemble the carbocation.

Figure 5 shows the upper right corner of a diagram for substitution at phosphorous. A worse (more basic) leaving group raises the energy of the right edge of the diagram, as shown by the heavy arrows in Figure 5A. This leads to movement of the transition state toward the lower right, which is the direction of increased energy parallel to the reaction coordinate, and toward the

lower left, the direction of decreased energy perpendicular to the reaction coordinate. The resulting downward movement corresponds to the observed increase in β_{nuc}.

These two movements reinforce each other to give downward movement but tend to cancel each other with respect to horizontal movement, so that there should be a smaller or no change in β_{lg} with changing pK_{lg} (Figure 5A).[11,52] A similar cancellation occurs with changing nucleophilicity of the pyridine (Figure 5B). An increased basicity of the nucleophile increases the energy of the top relative to the bottom of the diagram. This results in a net movement to the left, with a decrease in bond breaking, but a partial or complete cancellation of the vectors for vertical movement so that little or no change in β_{nuc} is expected with increasing pK_{nuc}.

These are direct interactions that correspond to small values of the coefficients $p_x = \partial\beta_{nuc}/-\partial pK_{nuc}$ and $p_y = \partial-\beta_{lg}/\partial pK_{lg}$. This kind of cancellation is expected for all direct interaction coefficients, as noted above, and may help to explain why such coefficients are often small, in addition to being hard to detect for experimental reasons.[7,11,44,54] In fact, the Brønsted-type plots of log k against pK_{nuc} for pyridines show little or no curvature;[52,53] the value of p_x is certainly smaller than that of p_{xy}.

The small direct Hammond effects p_x and p_y, compared with the cross-interaction effects p_{xy} and $p_{xy'}$, reflect the tendency of a reaction to seek the lowest energy pathway when this is made possible by the existence of several variables or degrees of freedom in these complex reactions. Perpendicular effects represent the ability of the transition state to *take advantage* of changes in reactant structure. Thus, when the nucleophile becomes stronger, the movement of the transition state perpendicular to the reaction coordinate makes the transition state tighter, in order to take advantage of the increased bonding ability. This tendency to increase the amount of bonding and S_N2 character in the transition state counteracts the normal Hammond effect for the nucleophile, with movement parallel to the reaction coordinate, but reinforces the Hammond effect for leaving group departure so that the direct effect p_x is small and the cross-interaction effect p_{xy} is large.

The reaction coordinate for phosphoryl transfer between pyridines in Figure 5 has an angle of 45° because the reaction is symmetrical. If the curvatures of the surface perpendicular and parallel to the reaction coordinate were equal, the corresponding movements of the transition state would be equal and there would be no net movement corresponding to the p_x and p_y coefficients; these coefficients would be zero. However, if the reaction coordinate passes through a relatively narrow valley at the saddle point, with steeper curvature upwards of the walls (perpendicular to the reaction coordinate, Figure 2D) than downwards (along the reaction path, Figure 2A), there will be a larger movement of the transition state along the reaction coordinate than perpendicular to the reaction coordinate. This can give a normal Hammond effect, as shown in Figure 5B. The curvatures of the surface in the region of the saddle point can be calculated from the value of $p_{xy} = \partial\beta_{nuc}/\partial pK_{lg} = 0.014$ and an upper limit for $p_x = \partial\beta_{nuc}/\partial pK_{nuc} = p_y \leq 0.006$. A value of $p_x > 0$ corresponds to a small Hammond effect. These p_{xy}, p_x, and p_y coefficients were used to calculate the movements of the transition state shown in Figure 5 and the rate constants for the different nucleophiles and leaving groups, which agree well with the experimental data.[52] However, the data are also consistent with $p_x = p_y = 0$, which would give equal movements parallel and perpendicular to the reaction coordinate and no Hammond effect.

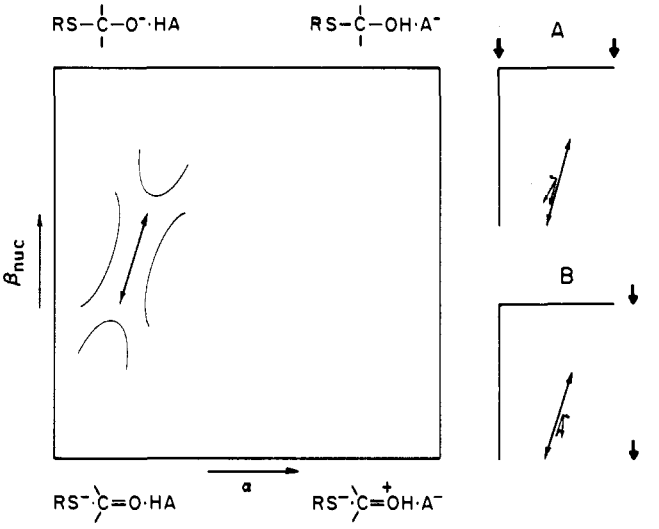
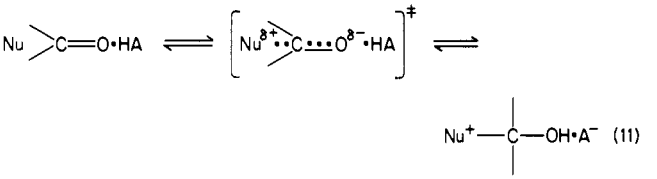


Figure 6. Reaction coordinate diagram for general acid catalysis of the addition of thiol anions to acetaldehyde. The effect of increased basicity of the thiol anion is shown in A and the effect of increased acidity of the catalyst in B.

General Acid Catalysis of Addition to the Carbonyl Group

The addition of weakly basic nucleophiles to carbonyl compounds is assisted by stabilization of the developing charge on the carbonyl oxygen atom by hydrogen bonding to a buffer acid (eq 11). This class e reaction



(11)

involves proton donation to the oxygen atom on the electrophilic reagent through either a concerted or a stepwise mechanism. These reactions characteristically show an increase in the Brønsted α value for general acid catalysis as the nucleophile becomes less basic and a corresponding increase in β_{nuc} as the catalyst becomes less acidic, as described by a positive p_{xy} coefficient (eq 12).[4,5] The addition of thiol anions to acetaldehyde shows this behavior, with an increase in α from <0.09 to 0.26 and a value of $p_{xy} = 0.026$.[5,55]

$$p_{xy} = \frac{\partial\alpha}{-\partial pK_{nuc}} = \frac{\partial\beta_{nuc}}{\partial pK_{HA}} \qquad (12)$$

Figure 6 shows an energy contour diagram for this reaction (only a few contour lines around the saddle point are shown). The axes of this diagram are defined so that the progress of proton transfer from the acid to the carbonyl group is along the x axis, as measured by

the Brønsted coefficient, α, and the progress of bond formation to the nucleophile is along the y axis, as measured by the slope of a plot of log k against pK_{nuc}, i.e., by β_{nuc}. In the reverse direction, proton transfer to the base catalyst is measured by β and bond cleavage at carbon is measured by β_{lg}. Note that the reactants are in the lower left corner and the products in the upper right corner, according to this convention.

A positive p_{xy} coefficient suggests that there is significant diagonal character to the reaction coordinate. This leads to movement of the transition state in a direction orthogonal to the perturbation when the energy of one edge of the contour diagram is increased. For example, an increased basicity of the nucleophile stabilizes the top relative to the bottom of the diagram, as shown by the heavy arrows in Figure 6A. This would not cause horizontal movement of a vertical reaction coordinate, in which only S–C bond formation is taking place in the transition state. However, if the reaction coordinate has a significant diagonal component, it will give net movement to the left with a decrease in α, as shown in Figure 6A. The energy decreases at the upper left, perpendicular to the reaction coordinate, and increases toward the lower left, parallel to the reaction coordinate. Both the perpendicular and the parallel movements of the transition state will then correspond to movement toward the left, with a decrease in proton transfer.

The addition of thiol anions to acetaldehyde also exhibits decreased selectivity toward the nucleophile as it becomes more basic.[55] This is a normal Hammond effect that is described by a positive p_y coefficient (eq 13). It suggests that the reaction coordinate is predominantly vertical so that the transition state moves downward, along the reaction coordinate, when the thiol anion becomes more basic, as shown in Figure 6A. If the reaction coordinate were predominantly horizontal, it would move upward toward the top of the diagram (perpendicular to the reaction coordinate) with increasing basicity of the nucleophile.

$$p_y = \partial\beta_{nuc}/-\partial pK_{nuc} \quad (13)$$

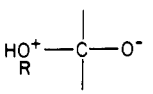
There is no significant change in the Brønsted α value with increasing acidity of the catalyst for this reaction, so that the direct interaction coefficient for proton transfer p_x (eq 14) is close to zero.[56] This indicates that

$$p_x = \partial\alpha/\partial pK_{HA} \quad (14)$$

movements of the transition state toward the right and bottom of the diagram when the energy of the right side is decreased give little or no net horizontal movement, as shown in Figure 6B. The parallel and perpendicular movements toward the left and right, respectively, tend to cancel so that no movement along the coordinate for proton transfer is observed.

These characteristics of the reaction are determined by the direction of the reaction coordinate and the curvatures of the surface at the saddle point and can be used to calculate these parameters. The resulting reaction coordinate in Figure 6 is rotated clockwise from the vertical by 15° and passes through a moderately narrow col. This is consistent with a mechanism in which the reaction coordinate represents primarily nucleophilic attack of the thiol anion, with assistance by a small component of proton transfer from the catalyst through hydrogen bonding to the carbonyl oxygen atom as it develops negative charge in the transition state.[5,55] When the nucleophile becomes weaker there is more development of negative charge and hydrogen bonding becomes more significant.

As the nucleophile becomes still weaker, there is increased proton transfer, with an increased α value, and the reaction must eventually become concerted when the addition compound becomes so unstable, in the absence of proton transfer, that it cannot be an intermediate in the reaction. The Brønsted α values for the addition of alcohols to formaldehyde are in the range 0.28–0.36 and increase to α = 0.50–0.59 for the addition of alcohols to acetaldehyde; in both series there is a positive p_{xy} coefficient, with an increase in α as the basicity of the alcohol decreases. The reactions of acetaldehyde, and probably formaldehyde, must be concerted because some of the rate constants that are required to account for a reaction through the dipolar addition intermediate **2** are too large to be consistent with the existence of an intermediate with a significant lifetime.[57,58]



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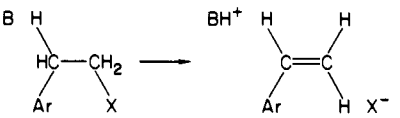
Changes in the stability of the carbonyl compound relative to its addition compound change the energy of the top relative to the bottom of the energy diagram in a manner similar to changes in the basicity of the nucleophile. The greater stability of the addition compounds for formaldehyde compared with acetaldehyde corresponds to a lower energy at the top of the diagram. This is expected to cause movement of a transition state on a diagonal reaction coordinate toward the lower left and upper left corners of the diagram, as shown in Figure 6A. The net result is a decrease in α, which is consistent with the smaller α values for the addition of alcohols to formaldehyde compared with acetaldehyde.[57,58]

Grunwald has shown that the structure-reactivity data for the addition of alcohols to formaldehyde can also be accounted for by a model with an additional dimension that corresponds to proton transfer from the attacking alcohol to water in the transition state.[59]

Elimination Reactions

Olefin-forming eliminations are also class e reactions, in which a proton is removed from the electrophilic reagent in the elimination direction (eq 15). They are



(15)

similar in several respects to carbonyl-forming elimination reactions, which are the reverse of carbonyl addition reactions.

Structure-reactivity correlations and their interpretation with More O'Ferrall's energy contour diagrams have made a major contribution to our understanding of the mechanism of olefin-forming elimination reactions.[11,25,60-62] Most of the effects are illustrated by the general-base-catalyzed reactions of 2-arylethyl derivatives in 60% Me_2SO/H_2O;[63] however, virtually all of

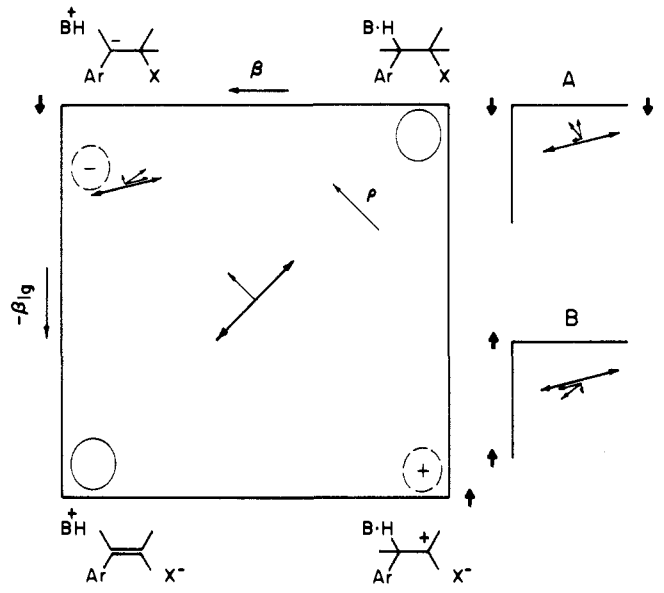


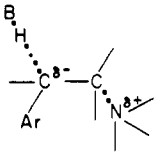
Figure 7. Reaction coordinate diagram for olefin-forming elimination reactions with predominantly diagonal or horizontal reaction coordinates. The effect of an increase in basicity of the leaving group is shown in A and the effect of a decrease in the pK_a of the catalyst in B.

them have been demonstrated previously in at least one system.[60,61] Figure 7 shows a reaction coordinate diagram for this reaction, in which the x axis for proton transfer is defined by β, the y axis for leaving group departure is defined by $-\beta_{lg}$, and the development of negative charge that is stabilized by electron-withdrawing substituents on the β-carbon atom is measured by ρ, which defines an approximately diagonal axis.

The increase in carbanionic character of the transition state for E2 elimination of 2-arylethyl bromides with carbanion-stabilizing substituents on the aryl group is illustrated by the increase in the Brønsted β value for proton removal when electron-withdrawing substituents are added at the β-position.[63] Decreasing the energy of the carbanion in the upper left corner of Figure 7 moves the transition state downhill toward the carbanion, perpendicular to the diagonal reaction coordinate in the center of the figure. This gives a significant movement of the transition state to the left, with an increase in β. It corresponds to a positive $p_{xy'}$ coefficient in eq 16. Little or no movement of the transition state parallel to the reaction coordinate is expected from a change in energy of the corner of the diagram if the reaction coordinate is diagonal.

$$p_{xy'} = \frac{\partial\beta}{\partial\sigma^-} = \frac{\partial\rho}{\partial \mathrm{p}K_{BH}} \qquad (16)$$

Different behavior is expected if the transition state 3 closely resembles the carbanion, with a more horizontal reaction coordinate and a larger component of proton transfer, as shown at the top of Figure 7.



3

Stabilization of the carbanion will then tend to move the transition state parallel to the reaction coordinate, away from the carbanion. This Hammond effect counteracts the perpendicular, anti-Hammond effect so that there is no longer an increase in β with increasing σ; in fact, there is a small decrease. This corresponds to a change in the sign of the $p_{xy'}$ coefficient (eq 16) from positive to negative and shows that there is a large increase in the horizontal component of the reaction coordinate, compared with that for 2-arylethyl bromides. A change of this kind has been observed with a series of (2-arylethyl)ammonium ions, which are believed to have a larger component of proton transfer in the transition state,[63] and with 2-arylethyl halides that have strongly electron-withdrawing substituents on the aryl group.[64] Such a change in the direction of the reaction coordinate represents a third derivative effect, as noted above, because it is a change in the second derivative coefficient $p_{xy'}$.

A poorer leaving group lowers the energy of the top relative to the bottom of the diagram, as shown by the heavy arrows in Figure 7A. A reaction coordinate with significant diagonal character will then tend to move toward the top of the diagram, perpendicular to the reaction coordinate, and toward the left, parallel to the reaction coordinate. This gives a net movement to the left, which corresponds to an increase in carbanion character and in ρ. It is described by a negative $p_{yy'}$ coefficient in eq 17. This behavior suggests that there

$$p_{yy'} = \frac{-\partial\rho}{\partial \mathrm{p}K_{1g}} = \frac{\partial -\beta_{1g}}{\partial\sigma^-} \qquad (17)$$

is an important horizontal component for proton transfer as well as a vertical component for leaving group expulsion in the reaction coordinate. It has been observed within the series of (2-arylethyl)ammonium ions, along with the complementary manifestation of a decrease in C–N bond breaking ($-\beta_{1g}$) with electron-withdrawing substituents on the β-phenyl group (eq 17).[61,63] A horizontal reaction coordinate of an E1cB mechanism that involves only proton transfer in the transition state and is already at the top of the diagram would not be expected to show such behavior. A vertical reaction coordinate would be expected to move toward the bottom of the diagram, parallel to the reaction coordinate.

The interaction between proton removal by the base catalyst and bond cleavage to the leaving group in a concerted E2 elimination is expected to give more bond cleavage with a weaker base catalyst, corresponding to a positive p_{xy} coefficient (eq 18). Figure 7B shows that

$$p_{xy} = \frac{\partial\beta_{1g}}{\partial \mathrm{p}K_{BH}} = \frac{\partial\beta}{\partial \mathrm{p}K_{1g}} \qquad (18)$$

a decrease in the pK_a of the base raises the energy of the left side of the diagram, so that the transition state on a reaction coordinate with significant diagonal character will tend to slide down toward the bottom and climb up toward the left edge of the diagram. This produces a net downward movement, with an increase in bond cleavage to the leaving group and a more negative value of β_{1g}. This behavior has been observed with buffer bases and with hydroxide ion in water–Me_2SO mixtures.[63] The complementary manifestation of the p_{xy} coefficient is an increase in the Brønsted β for proton removal with a poorer leaving group (eq 18).

This corresponds to the movement toward the left in Figure 7A and has also been observed experimentally.[63]

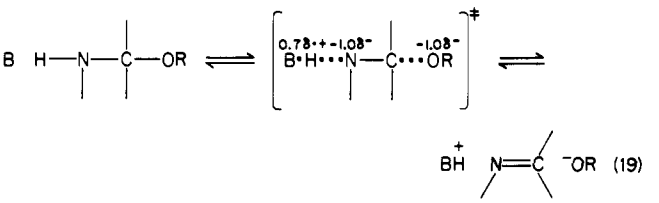
These interaction effects are not observed for the E1cB irreversible reaction of (2-(*p*-nitrophenyl)ethyl)-ammonium ions, which involves only proton transfer in the transition state. Thus, they provide a useful experimental method for distinguishing the stepwise E1cB from the concerted E2 mechanism.[63] The absence of a p_{xy} effect shows that there is no detectable weakening of the C–N bond in the transition state for proton removal,[65] in spite of the large β values for this reaction, and no significant Hammond effect on the β value for proton removal when the leaving group is changed.

The observed interaction coefficients for the E2 elimination reactions of (2-arylethyl)ammonium ions are $p_{xy} = 0.018$, $p_{yy'} = -0.09$, and $p_{xy'} = -0.07$. These values are normalized assuming a value of $\rho = 5$ for the formation of the carbanion at equilibrium. These three coefficients correspond to the diagonal reaction coordinate shown at the top of Figure 7, which is rotated 24° counterclockwise from the horizontal. A value of $\rho = 7$ gives a reaction coordinate that is rotated 30° counterclockwise. The calculation is crude and should not be taken too seriously. However, it supports the conclusion that the transition state lies on the reaction coordinate for a concerted E2 elimination mechanism that involves mainly proton transfer but includes significant bond breaking to the leaving group.[63] This generally agrees with earlier conclusions for this class of reaction.[60,61]

The positions of the transition states and reaction coordinates on the diagram of Figure 7 are difficult to reconcile with the coexistence of concerted E2 and stepwise E1cB mechanisms for elimination reactions of (2-arylethyl)ammonium ions. The Brønsted β values in the range 0.8–1.0, β_{lg} values of –0.16 to –0.36, and ρ values of 3.0–4.3 show that there is a large amount of proton removal and carbanion character, but comparatively little bond breaking, in the transition state of the concerted reaction. The transition states are located very close to the expected position of the carbanion in Figure 7 and some of them have structures that are very similar to those observed for stepwise E1cB elimination. It does not appear likely that an energy maximum for the transition state of the E2 reaction and an energy well, with two transition states for formation and breakdown of the carbanion intermediate of the E1cB reaction, can exist together for a single compound at almost the same position on the diagram of Figure 7. The simplest explanation of the structure-reactivity data is that the two mechanisms do not coexist and that the concerted E2 mechanism appears when the carbanion intermediate of the E1cB mechanism becomes so unstable that a stepwise mechanism is impossible. In other words, there is a *transformation* from a stepwise E1cB to a concerted E2 mechanism of elimination that is enforced by the disappearance of an energy well for the carbanion intermediate.[63]

Rate constants for the base-catalyzed E2 elimination reactions of ring-substituted 1-phenylethyl chlorides pass through a minimum on a Hammett plot. This is the behavior expected for the diagonal reaction coordinate of a concerted reaction. Electron-donating and electron-withdrawing substituents on the central atom stabilize the carbocation and carbanion structures at the two corners of the reaction diagram, respectively. The transition state slides downhill toward these structures, perpendicular to the reaction coordinate, when they are stabilized, so that the transition state increasingly resembles a carbocation or carbanion and is stabilized by substituents that stabilize these species.[66]

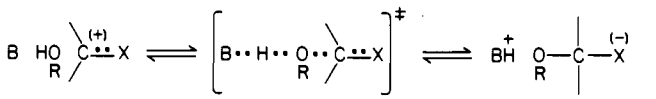
The analogous base-catalyzed elimination to form imines (eq 19) occurs through a concerted E2 mechanism with a large amount of proton transfer ($\beta = 0.7$ for base catalysis and $\beta_N = -1.0$ for substituents on the nitrogen atom) and a large amount of charge development on the leaving oxygen atom ($\beta_{lg} = -1.0$). The constant value of $\beta = 0.7$ over a range of 10 pK units for the substrate amine corresponds to a value of $p_{xy'} \approx 0$. This suggests that the reaction coordinate has significant diagonal character. Its direction may be intermediate between those for the two olefin-forming elimination reactions shown at the center and top of Figure 7, which have positive and negative values of $p_{xy'}$, respectively.[67,68]



(19)

Base-Catalyzed Addition of ROH and Related Reactions

The addition of water or alcohols to carbonyl groups, carbocations, and other unsaturated or electron-deficient centers is frequently catalyzed by buffer bases (eq 20). This important group of reactions represents class n catalysis, in which a proton is removed from the nucleophile; in the reverse direction it involves general acid catalysis of ROH expulsion.



(20)

These reactions characteristically show an increased Brønsted β value for base catalysis (or decreased α value for acid catalysis, in the reverse direction) as ROH becomes more acidic. This is described by a positive value for the $p_{xy'}$ coefficient of eq 21.[69-76] In many cases

$$p_{xy'} = \frac{\partial\beta}{-\partial \mathrm{p}K_{nuc}} = \frac{\partial\beta_{nuc}}{-\partial \mathrm{p}K_{BH^+}} = \frac{\partial\alpha}{\partial \mathrm{p}K_{lg}} \qquad (21)$$

the Brønsted lines cross, so that the dependence of the rate on the basicity of ROH, β_{nuc} or β_{lg}, changes sign as the catalyst becomes a stronger base. This corresponds to the complementary $\partial\beta_{nuc}/-\partial pK_{BH^+}$ term in eq 21. It reflects the role of RO as the central group in the transition state, with a net charge that is determined by the relative amounts of proton transfer to the base and bond formation to carbon.

The reaction may be described by the diagram of Figure 8, in which the horizontal axis represents proton transfer (α or β), the vertical axis represents C–O bond formation and cleavage (ρ), and a diagonal axis, from the lower right to the upper left corner, represents

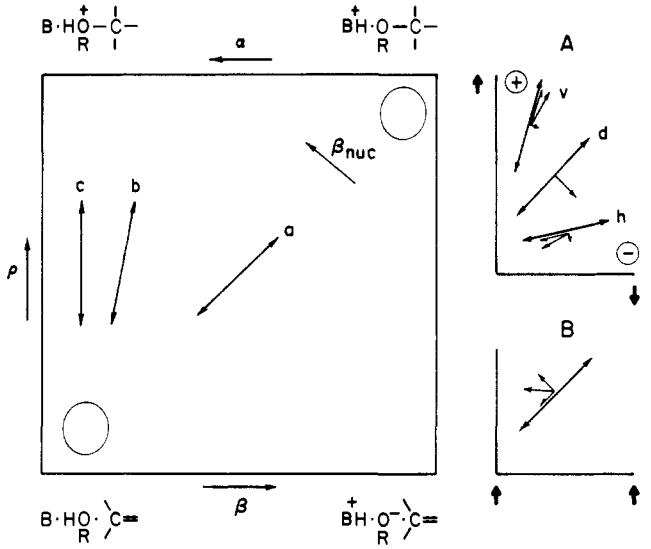


Figure 8. Reaction coordinate diagram for the base-catalyzed addition of ROH to an electrophile and the reverse, acid-catalyzed reaction. The effect of increased acidity of ROH on predominantly vertical, diagonal, and horizontal reaction coordinates is shown in A and the effect of destabilization of the electrophile in B.

charge development on the central oxygen atom (β_{nuc} or β_{lg}). The diagonal, y', axis refers to 1− charge on oxygen in the lower right corner, 1+ charge on the upper left corner, and no charge along a diagonal line from reactants to products.

A positive $p_{xy'}$ coefficient is consistent with a diagonal reaction coordinate on the diagram and requires a reaction coordinate with an important vertical component. An electron-withdrawing substituent on RO^- stabilizes the RO^- group in the lower right corner, as shown by the heavy arrows in Figure 8A. A diagonal or a more vertical reaction coordinate will then slide down toward this corner and may climb toward the upper right corner, with a net movement to the right and an increase in β for proton removal. This is shown by the reaction coordinates d and v in Figure 8A. However, a predominantly horizontal reaction coordinate, h, would undergo a shift of the transition state toward the left and give a decrease in β, because movement of the transition state parallel to the reaction coordinate must cause such a shift (Figure 8A).

The movement of the transition state on a diagonal reaction coordinate toward the lower right corner also corresponds to a decrease in β_{nuc} with decreasing basicity of ROH, which gives upward curvature in a plot of log k against pK_{nuc}. This is described by a negative $p_{y'}$ coefficient for the reaction (eq 22). There are in-

$$p_{y'} = \frac{\partial\beta_{nuc}}{-\partial pK_{nuc}} = \frac{\partial\beta_{lg}}{-\partial pK_{lg}} \qquad (22)$$

dications of such a change in several reactions and the dependence of log k on pK_{ROH} follows a U-shaped curve for the reaction of alcohols and formaldehyde. This U-shaped curve represents the balance between the amount of C–O bond formation and O–H bond cleavage in the transition state, which changes with changing substituents. This is itself strong evidence for a concerted mechanism that involves both processes in the transition state.[57]

However, there is usually no significant curvature of the Brønsted plots for general base catalysis, so that the p_x coefficient (eq 23) is close to zero. The values of $p_{xy'}$

$$p_x = \partial\beta/-\partial pK_{BH^+} \qquad (23)$$

= 0.09, $p_{y'}$ = −0.20, and p_x = 0 for the formaldehyde reaction give a reaction coordinate that is rotated 48° clockwise from the vertical, close to diagonal, as shown in *a* of Figure 8. This is consistent with a fully concerted or coupled reaction mechanism, in which C–O bond formation or cleavage and proton transfer are both occurring in the transition state.[57] In fact, the data for this reaction can also be fit by a simple model of the entire reaction surface that assumes a 45° angle of the reaction coordinate.[59]

The interaction between RO and the carbon electrophile is described by the $p_{yy'}$ coefficient of eq 24, in

$$p_{yy'} = \frac{\partial\rho}{-\partial pK_{nuc}} = \frac{\partial\beta_{nuc}}{-\partial\sigma} \qquad (24)$$

which ρ (the y axis of Figure 8) is a measure of the amount of bond formation to carbon in the transition state. For the reaction of alcohols and formaldehyde there is a decrease in the amount of bonding to carbon in the transition state with decreasing pK of the alcohol, as measured by secondary deuterium isotope effects, that is described by a negative $p_{yy'}$ coefficient.[77] This corresponds to downward movement of the transition state in Figure 8. It requires a reaction coordinate with an important horizontal component, d or h in Figure 8A, that gives such downward movement with decreasing pK of the alcohol. It is inconsistent with the predominantly vertical reaction coordinate, v, that would be expected for catalysis by hydrogen bonding, with the proton in an energy well and only C–O bond formation along the reaction coordinate.[78] A vertical reaction coordinate would be expected to give increased bonding to carbon as the alcohol becomes less basic, according to a normal Hammond effect (Figure 8A).

The base-catalyzed reaction of alcohols and acetaldehyde shows increased Brønsted β and decreased β_{lg} and β_{nuc} values compared with the formaldehyde reaction. Substitution of the methyl group of acetaldehyde for the H of formaldehyde stabilizes the carbonyl group of acetaldehyde and corresponds to a decrease in σ, so that this result is additional evidence for a negative $p_{yy'}$ coefficient (eq 24). Again, the decrease in β_{lg} and β_{nuc} with increasing stability of the carbonyl compound is in the opposite direction from that expected from a simple Hammond effect and is evidence for an important role of proton transfer in the concerted reaction mechanism. This role is supported by the increased Brønsted β values for the acetaldehyde reaction.[58]

It may be useful to think of these reactions in terms of electrophilic attack on the central oxygen atom by an acid and by the carbon electrophile.[77,79] A diagonal cross section from the upper left to the lower right corner of Figure 8 describes the amount of bonding of oxygen to the proton and to carbon and places the diagonal reaction coordinate, a, in an energy well. An electron-withdrawing substituent on RO will stabilize the RO^- anion in the lower right corner and decreases the amount of bonding of RO^- to both the proton and carbon as the transition state slides downhill. A stronger acid or a more reactive carbon electrophile increases the amount of bonding to oxygen in the transition state and β_{nuc}, as described by the positive

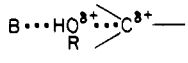
$p_{xy'}$ and negative $p_{yy'}$ coefficients.

As the carbon electrophile becomes less stable there is a tendency for the transition state to move toward the left with a decrease in the Brønsted β (or increase in α), as described by a positive p_{xy} coefficient (eq 25).[71,72,74,77,80] Increasing the energy of the electrophile

$$p_{xy} = \frac{\partial\rho}{-\partial \mathrm{p}K_{\mathrm{BH}^+}} = \frac{\partial\beta}{-\partial\sigma} = \frac{\partial\alpha}{\partial\sigma} \qquad (25)$$

at the bottom of the diagram will tend to shift the transition state toward the upper left corner, perpendicular to the reaction coordinate, and toward the lower left corner, parallel to the reaction coordinate, to give a net movement toward the left as shown in Figure 8B. This corresponds to an increase in the Brønsted α value for acid catalysis of the expulsion of ROH, which has been observed in several reactions of this kind. The increase in α leads to a progressive decrease in the importance of general acid catalysis as the electrophile becomes less stable, as occurs for the formation of oxocarbonium ions in the acid-catalyzed cleavage of acetals.[58,71,74,80-83]

The addition of alcohols to substituted 1-phenylethyl carbocations shows an increase in β_{nuc} with increasing stability of the carbocation that corresponds to a *positive* value of $p_{yy'} = 0.10$ (eq 24).[76] This indicates a small component of proton transfer in the transition state and a shift to a largely vertical reaction coordinate, as shown in *b* of Figure 8. Stabilizing the cation and the bottom edge of the diagram now causes the transition state to move upward, parallel to the reaction coordinate, to give a larger amount of bond formation. This is a normal Hammond effect and suggests that C–O bond formation is the predominant process that is taking place in the transition state. The change in direction may arise simply from an approach of the reaction coordinate to the left edge of the diagram, where a diagonal reaction coordinate is no longer possible. The catalysis can be accounted for by stabilization of the developing positive charge on ROH in the transition state by hydrogen bonding to the base catalyst (4).



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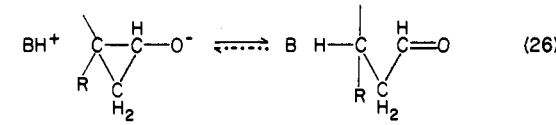
With a further decrease in stability of the carbocation the transition state moves further to the left until the value of β becomes zero, as shown in *c* of Figure 8. The reaction then shows no catalysis in the addition direction and specific acid catalysis in the cleavage direction ($\alpha = 1.0$). The transition state for attack of ROH on the unstable cation is early, so that there is little development of positive charge on ROH and no significant stabilization by hydrogen bonding to buffer bases. In the limit, the reaction with ROH is diffusion controlled and there is no buffer catalysis. In the cleavage direction, protonation of the leaving group occurs before rate-limiting diffusional separation of ROH from R^+, so that specific acid catalysis is observed.

The general acid catalyzed cleavage of cyclopropanol anions (eq 26) shows a decrease in α with increasing acidity of the leaving carbon atom that is accepting a proton. This corresponds to a positive $p_{xy'}$ coefficient (eq 21). This reaction is analogous to the addition and loss of ROH (eq 20) and involves electrophilic displacement on the central atom, carbon in this case, by



(26)

the proton in one direction or by the carbonyl group in the other. The concerted electrophilic catalysis avoids the formation of an unstable carbanion and might possibly be a model for avoiding unstable carbanions in enzymic catalysis.[84]

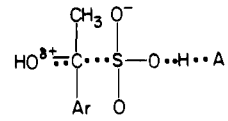
The decomposition of carbamates of weakly basic amines is catalyzed by general acids (eq 27), with α =

(27)

0.84 for *p*-nitroaniline as the leaving group.[85,86] There is a decrease in β_{1g} (and also in β_{nuc}, in the addition direction) with increasing basicity of the leaving amine. This corresponds to a positive sign of $p_{y'} = \partial\beta_{1g}/-\partial pK_{1g}$ (eq 22), which is opposite to that for the cleavage of formaldehyde hemiacetals. It supports a mechanism with a predominantly vertical reaction coordinate in which the catalysis occurs by an initial proton transfer to the leaving amine and by hydrogen bonding to the protonated amine in the transition state (eq 27). There is an increase in α as the leaving amine becomes more basic that corresponds to a positive coefficient $p_{xy'} = \partial\alpha/\partial pK_{1g}$ (eq 21). This results in the disappearance of buffer catalysis with basic amines, as α approaches 1.0. The Brønsted plot is linear over 17 pK units, which gives $p_x = \partial\alpha/\partial pK_{\mathrm{HA}} = 0$.

The reaction appears to involve mainly C–N bond formation or cleavage, which gives a normal Hammond effect, and a relatively small component of proton movement in the transition state. With basic amines there is more bond cleavage and less positive charge on the leaving amine, so that there is no significant stabilization by hydrogen bonding to the base in the transition state. The approximate values of $p_{y'} = 0.053$, $p_{xy'} = 0.034$, and $p_x = 0$ for the interaction coefficients correspond to a reaction coordinate that is rotated only ~20° clockwise from the vertical axis for C–N bond cleavage.[86]

The acid-catalyzed cleavage of bisulfite addition compounds of substituted acetophenones, and of the corresponding *O*-methyl compounds, shows a decrease in α with electron-withdrawing groups on the carbonyl compound that corresponds to a negative sign of $p_{xy} = -0.18$. Again, this is opposite to the behavior of fully coupled, concerted addition–elimination reactions of carbonyl compounds and alcohols. It is consistent with the behavior that would be expected for a mechanism in which the acid stabilizes the transition state by simple hydrogen bonding to the leaving sulfite ion (**5**).[87]



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The α values in the range 0.3–0.5 and the solvent isotope effect of $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 2.2$ for this reaction are consistent with the values expected for a hydrogen-

bonded proton in a broad single well or a rapidly exchanging double well.[78,87,88] The proton appears to move away from the substrate, perpendicular to the reaction coordinate, when electron-withdrawing substituents are added to the acetophenone. The electrophile in this reaction is extremely unstable and probably reacts with SO_3^{2-} at a diffusion-limited rate. It is conceivable that in the addition direction the base catalyst simply increases the effective concentration of SO_3^{2-} adjacent to the electrophile by accepting a proton from HSO_3^- and stabilizing the SO_3^{2-} dianion by hydrogen bonding to an oxygen atom; in the cleavage direction the acid could help the escape of the leaving group by hydrogen bonding.

Calculations

The procedure for calculating the direction of the reaction coordinate and the curvatures of the surface at the transition state from the observed interaction coefficients is described in detail elsewhere.[5] A brief summary of the rationale and procedure is given here.

A transition state is at a saddle point on an energy surface with an energy maximum along the direction of the reaction coordinate and an energy minimum perpendicular to the reaction coordinate, between the two sides of the saddle. The change in the position of an energy maximum or an energy minimum when a linear perturbation of the energy is applied depends on the sharpness of the curvature at the maximum or minimum (Figure 2A–D). Small changes in position can be calculated making the reasonable assumption that the curvature can be approximated by a parabola, as described by Thornton.[11]

The application of this procedure to a transition state on an energy surface corresponds to (1) evaluation of the energy perturbations parallel and perpendicular to the reaction coordinate when the energy of an edge or corner of the diagram is changed, (2) calculation of the resulting parallel and perpendicular movements of the transition state, and (3) conversion of these movements to the amount of movement of the transition state along the x and y axes of the diagram. The movements depend on the direction of the reaction coordinate as well as the curvatures of the surface. If one edge of the diagram is increased in energy, for example, the direction of the reaction coordinate determines the amounts of the perturbations that are parallel and perpendicular to the reaction coordinate and the curvatures determine the amount of movement that each perturbation brings about. Conversely, the direction of the reaction coordinate and the curvatures at the saddle point can be calculated from observed changes in the structure-reactivity parameters that define the x and y axes. Three interaction parameters, such as p_x, p_y, and p_{xy}, determine the direction and the two curvatures of the reaction coordinate at the saddle point.

A reaction coordinate diagram in which the x and y axes are measures of two processes may be described in the region of the saddle point by eq 28, in which ΔG

$$\Delta G/2.303RT = ax^2 + by^2 + cxy + dx + ey + f \quad (28)$$

is the Gibbs energy of a point (x,y) on the surface relative to the origin, a and b define the curvatures of the saddle point parallel to the x and y axes, respectively, c is a measure of the diagonal curvature that is not described by a and b, increases in the energy of the right edge and top of the diagram are described by increases in d and e, respectively, and f is a constant.[5] The x and y axes are defined by experimental measures of reaction progress, usually normalized structure-reactivity parameters such as β and ρ. Changes in d and e are usually taken from changes in structure-reactivity parameters, such as pK_a or σ, which are measures of changes in the energy of structures on one edge of the diagram when polar substituents are added. The coordinates of the transition state at the saddle point are defined by setting the horizontal and vertical derivatives of eq 28 equal to zero. Changes in these coordinates with changing energy of the edges of the diagram, d and e, may be calculated similarly. The amounts of these changes correspond to the interaction coefficients p_x, p_y, and p_{xy} and may be calculated from the curvatures a, b, and c. Conversely, the curvatures a, b, and c may be calculated from three observed interaction coefficients, such as p_x, p_y, and p_{xy}.[5]

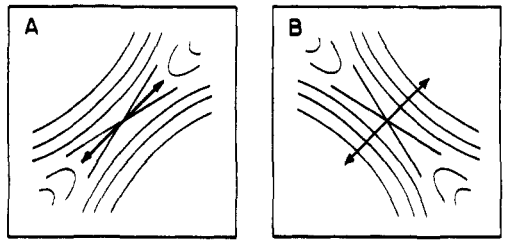

Figure 9. Level lines of constant energy that pass through the saddle point of an energy contour diagram. The level lines show where the curvature of the surface changes from negative to positive. A reaction coordinate is drawn to bisect the level lines, along the direction of negative curvature. The reaction coordinate may pass through a narrow col, A, or over a broad ridge, B.

The direction of the reaction coordinate and the ratio of the curvatures of the surface parallel and perpendicular to the reaction coordinate are determined by the direction of two lines of constant energy that pass through the saddle point, the "level lines". These level lines define the angles at which the curvature of the saddle point changes from positive to negative. For a reaction coordinate that passes through a narrow col, with sharp curvature upward on the two sides and small downward curvature along the reaction coordinate, the two level lines are close to the reaction coordinate (Figure 9A). For a reaction coordinate that passes over a broad ridge, with small upward curvature on the two sides and sharp downward curvature along the reaction coordinate, the two level lines diverge (Figure 9B). The directions of the level lines are calculated from the curvatures a, b, and c. A reaction coordinate may be drawn that bisects these lines in the direction of negative curvature (Figure 9).

The fit of experimental data to a set of interaction coefficients may be calculated from eq 29, which is derived from eq 28.[5,52] In eq 29, x_0 and y_0 are the values

$$-\log k = \tfrac{1}{2}p_x d^2 + \tfrac{1}{2}p_y e^2 + p_{xy}de + x_0 d + y_0 e + F \quad (29)$$

of the normalized structure-reactivity parameters x and y when $d = e = 0$; d and e are parameters related to energy, such as pK_a or σ, which may also be normalized; and F is a constant.

We have adopted the conventions for addition–elimination reactions that the reaction proceeds from the

lower left to the upper right corner, with an unsaturated substrate at the origin, and that proton transfer occurs along the x axis. A diagonal axis y', from the lower right to the upper left corner of the diagram, describes the effects of substituents or isotopes on the central atoms. For general base catalysis of the addition of ROH to electrophiles it is defined by β_{nuc} (Figure 8) or by β_{lg} in the reverse direction. For olefin-forming elimination reactions it is defined by ρ (Figure 7). This diagonal axis is similar to the tightness[40,41] or disparity index.[27] The diagonal axis can be described on the same diagram as the x and y axes or on a transformed diagram that gives rectangular coordinates. Calculations involving the y' axis are most conveniently carried out on a transformed diagram, by the same procedure as for the x and y axes of the original diagram. Changing the substituents on the central atom changes the energy of the corners of the original diagram and the edges of the transformed diagram; it produces a linear perturbation along the y' axis.[5,77]

For substitution reactions we have followed the usual convention that bond breaking occurs along the horizontal axis and bond making along the vertical axis, so that the x and y axes of Figure 3 are rotated 90° clockwise compared with those of Figures 7 and 8. The diagonal y' axis, from the lower left to the upper right corner on such a diagram, refers to the effects of polar substituents on the central atom or to isotope effects that may provide a measure of the total amount of bonding to the central atom.

It is frequently an approximation to identify a particular structure-reactivity parameter with a single axis, such as y. For example, the equilibrium constants for the addition of an amine or a thiol anion to a carbonyl group, without proton transfer to neutralize the negative charge on the carbonyl oxygen atom (y axis, Figure 6), follow a value of $\beta_{nuc} = 0.8–0.9$. There is a further increase in β_{nuc} of 0.1–0.2 when the oxygen anion is protonated (x axis, Figure 6).[89] The error introduced by such approximations is often small compared with other uncertainties; a more exact calculation may be warranted in some cases.

Imbalance

In view of the complexity of most organic reactions we should be surprised if their properties can be described by an energy contour diagram in which the progress of all of the different components of the reaction is measured by only two coordinates and amazed if they can be described by an energy profile with only one coordinate for reaction progress. Failure to account for all of the properties of a transition state with one or two coordinates on a reaction coordinate cross section or diagram may be called *imbalance*; it occurs when the different processes that take place in the course of the reaction are not perfectly correlated. It has recently been called the "Principle of Imperfect Synchronization" (PIS).[90] In some examples of imbalance the sum of the "effective charges" in the transition state that are being probed by structure-reactivity correlations is not equal to the net charge of the reactants or products.

The best known example of imbalance is the nitroalkane anomaly, in which resonance delocalization of electron density into the nitro group and solvation of the nitronate anion lag behind proton transfer to the base, so that there is an excess of negative charge on the central carbon atom in the transition state.[34] There is a similar lag in the development of resonance that produces an imbalance between polar and resonance substituent effects in the transition state for the formation of 1-phenylethyl carbocations.[91] This may be a general phenomenon that arises from the small amount of delocalization that can occur until there is a change in geometry accompanying rehybridization. For example, if there is 50% bond breaking, 50% rehybridization, 50% delocalization of charge, and 0.5 development of negative charge on the nitroalkane moiety in the transition state for the ionization of nitroalkanes, there will be only 0.25 charge delocalized into the NO_2 group and 0.25 charge on the central carbon atom. When rehybridization and delocalization are complete, in the product, there can be relatively less (or even absolutely less) negative charge on the central carbon atom because a larger *fraction* of the charge is delocalized into the $-NO_2^-$ group.[5,92]

Imbalances in the development or loss of solvation compared with other processes are likely to cause anomalous structure-reactivity behavior in many reactions.[93] For example, nucleophilic attack of an alkoxide ion on a carbonyl group or a carbon acid in aqueous solution presumably requires removal of one or more solvating water molecules from RO^-_s, to form RO^-_d, before the reaction can take place (eq 30). Removal

$$RO^-_s \underset{\pm H_2O}{\overset{K_d}{\rightleftharpoons}} RO^-_d \rightleftharpoons [RO^{\delta-}\cdots{>}C\overset{\cdot\cdot}{-}O^{\delta-}] \qquad (30)$$

of solvating water is more difficult when RO^- is more basic, so that the value of β_d for the equilibrium constant K_d is negative (eq 30). If β_n is the β value for attack of RO^-_d on the substrate, the observed β value is equal to $\beta_d + \beta_n$. The observed β value will then be smaller than β_n and is not a direct measure of the amount of bond formation to a carbonyl group or a proton. This requirement for desolvation of basic oxygen anions probably contributes to the decrease in β for attack on esters and carbon acids from $\beta \approx 0.7$ for phenolate anions, for which desolvation is less important, to $\beta \approx 0.2$ for basic alkoxide anions.[93] In the reverse direction the same phenomenon corresponds to a lag in the development of solvation and gives values of β_{lg} that are more negative than expected from the amount of bond cleavage that has occurred in the transition state. For example, the value of β_{lg} is −1.1 for the expulsion of RO^- from the anions of formaldehyde hemiacetals, although C–O cleavage is certainly not complete in the transition state.[57]

If the negative β_d for desolvation is larger than β_n for nucleophilic attack, the observed value of β will be negative. This can occur in reactions that have only a small amount of bond formation in the transition state, such as the reactions of substituted quinuclidines with phosphate esters and phosphorylated pyridines.[94]

A requirement for desolvation of basic nucleophiles can give rise to curvature in structure-reactivity correlations that can be mistaken for a change in transition-state structure with increasing basicity of the nucleophile, such as a Hammond effect or positive p_y coefficient.[93]

Solvation effects may also mask direct interaction coefficients such as $p_x = \partial\alpha/\partial pK_{HA}$. Suppose that an

increase in the acid strength of HA increases the strength of a hydrogen bond between H–A and solvating water and increases the bond length of H–A. There may also be an increase in the bond length of HA with increasing acid strength in a transition state for catalysis by HA that is stabilized by hydrogen bonding. However, this will not give a curved Brønsted plot or a significant p_x coefficient if the two effects are similar in magnitude, because the effects in the transition state and in the reference ionization reaction will cancel.[95]

Normalized structure-reactivity parameters for a reaction, such as β, β_{nuc}, and ρ, may be used to define the x, y, and y' axes of a diagram and the interaction coefficients p_x, p_y, $p_{y'}$, p_{xy}, $p_{xy'}$, and $p_{yy'}$. If the different processes described by these coefficients are balanced, all of the processes can be described by the same diagram and the coefficients are related by eq 31–34.[77] If

$$p_{y'} = p_x + p_y - 2p_{xy} \quad (31)$$

$$p_{yy'} = p_y - p_{xy} \quad (32)$$

$$p_y = p_x + p_{y'} + 2p_{xy'} \quad (33)$$

$$p_{yy'} = p_{y'} + p_{xy'} \quad (34)$$

the processes measured by different structure-reactivity parameters have occurred to different extents in the transition state, the reaction is not balanced and eq 31–34 will not be followed. Additional diagrams or additional dimensions are then required to describe the reaction.

For example, base-catalyzed addition reactions of ROH (eq 20) show an imbalance between proton transfer from ROH to the base and other processes in the transition state and do not follow eq 31. The reaction behaves as if there is an overall tightening of the transition state when RO becomes more basic, with a larger movement of the proton than of the carbon electrophile toward the alcohol.[77]

It is not surprising that such a complex reaction, in which five atoms are undergoing changes in bonding and solvation, cannot be adequately described with only two coordinates for reaction progress. A complete description would require a separate coordinate for each change. Nevertheless, it is often useful to describe reactions with x, y, and y' coordinates. It is often helpful to use separate diagrams, in which these parameters are described by one of the axes, to describe the effects of changing solvation or electron delocalization in the course of the reaction.[96]

Imbalance should not be regarded as a "failure" of structure-reactivity relationships. On the contrary, it provides additional information about the nature of the reaction and its transition state.

Simple Electrostatic Interactions

Simple electrostatic interactions provide a quite different reason for an apparent imbalance or a misinterpretation of structure-reactivity data. The electrostatic interaction of a polar substituent on one reactant with a charge or dipole on another molecule will give a change in $\Delta G^{\ddagger}$ with changing substituents on either reactant. Such electrostatic interactions can cause changes in β or ρ and give rise to significant interaction coefficients, such as $p_{xy'}$, in the absence of any changes in bond length or transition state structure.[5,6,37]

For example, the favorable electrostatic interaction of an electron-donating substituent on a nucleophile with an electron-withdrawing substituent on an electrophile will stabilize the transition state and increase the observed rate constant. This increase in the rate constant for compounds with large σ values will increase ρ, even if there is no change in transition-state structure. Fortunately, such effects are generally small and are often opposite in direction from observed interaction coefficients.[97] The value of the electrostatic interaction coefficient, $\tau = \partial\beta_{eq}/\partial\sigma = \partial\rho/\partial pK_{ROH}$, for the equilibrium formation of substituted 1-phenylethyl alcohols and ethers is 0.10 for the reaction in 0–50% trifluoroethanol in water (v/v).[98]

Conclusion

There may be more to the Bema Hapothle than meets the eye, but one picture is worth more than a thousand words.

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