On the Characterization of Transition States by Structure–Reactivity Coefficients[1]

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Abstract: Small changes in the position of a transition state may be described by a simple model for the saddle point on an energy surface that is defined in terms of two structure–reactivity parameters, such as α and β_{nuc}. The curvatures and orientation of the saddle point are determined by "Hammond–Marcus" and "Cordes" coefficients that represent second derivatives describing changes in structure–reactivity parameters with changing structure of reactants and catalysts. Changes in α and other parameters resulting from Hammond-type effects are measures of changes in bond length for most reactions, but changes in α resulting from Cordes-type cross-correlation effects also reflect reciprocal electrostatic interactions, so that there is no unique relationship between α and bond length.

We describe here a simple method for the empirical characterization of transition states in terms of structure–reactivity parameters on a three-dimensional energy contour diagram. The energy surfaces of such diagrams will generally be related to but not identical with other energy surfaces that are defined in terms of bond orders, bond lengths, or other parameters for describing the extent of reaction. The structure–reactivity surfaces have the advantage that they are based directly on experimental quantities; they have the disadvantage that the relationship between structure–reactivity parameters and more fundamental quantities may not be simple. Addition–elimination reactions require at least a three-dimensional energy diagram for even a simplified description and other reactions, which commonly are influenced by more than one variable, may be more satisfactorily described by a three-dimensional diagram than by the usual two-dimensional reaction coordinate profile.

The structure–reactivity relationships that characterize the transition state of a chemical reaction are described not only by the first derivatives of log k with respect to some measure of substituent polarity, such as the familiar Brønsted and Hammett coefficients α and ρ, but also by second derivatives of log k with respect to these measures. These second derivatives describe the change in the "effective charge" that is seen by a polar substituent and may describe a change in the position of a transition state along a reaction coordinate or on some reaction surface with changing structure of reactants and catalysts.

There are two classes of such second derivatives, those that describe direct correlations and those that describe cross correlations. The *direct correlations* represent the effect of a substituent in a reacting group on the first derivative coefficient that describes the reactivity of that group, such as $\partial\alpha/\partial \mathrm{p}K_{\mathrm{HA}}$ or $\partial\beta_{\text{nuc}}/\partial \mathrm{p}K_{\text{nuc}}$.[2] We will use the symbol p to designate this Polanyi–Bell–Leffler–Hammond–Thornton–Marcus coefficient[3-6] and define it in such a way that it is positive when an increase in the energy of the products relative to reactants is accompanied by an increase in the parameter describing the extent of reaction; e.g. $p_x = \partial\alpha/\partial \mathrm{p}K_{\mathrm{HA}}$ and $p_y = \partial\beta_{\text{nuc}}/-\partial \mathrm{p}K_{\text{nuc}}$. This positive sign describes the well-known generalization (sometimes called the "Hammond effect") that "hard", endergonic reactions tend to have later transition states that occur further along the reaction coordinate, as measured by structure–reactivity relationships. Positive p coefficients have been treated quantitatively by Bell, Thornton, and Marcus, among others.[3-7] A positive p coefficient is expected for a simple process in which the structural change affects the energy of one end of a reaction coordinate, as a consequence of the negative curvature of the saddle point in the direction parallel to the reaction coordinate in the region of the translation state.[3]

A different kind of behavior, reflecting a negative p coefficient and positive curvature perpendicular to the reaction coordinate,[3] is described by the qualitative generalization that transition states will tend to adjust themselves in such a way as to take advantage of structural changes. For example, it has been suggested that transition states for E2 elimination reactions will adjust themselves to take advantage of electron-withdrawing substituents on the β carbon atom by developing more carbanion character at this atom, an "anti-Hammond" effect.[8]

Cross correlations described by second derivatives involve a change in the structure–reactivity parameter that applies to one reacting group, such as α, when the structure of a different reacting group, such as $\mathrm{p}K_{\text{nuc}}$, is changed. Miller has described the general case of such interaction effects[9] and of the several applications of these correlations that have been reported,[10,11] the interaction coefficients described by Cordes[12,13] are most useful for present purposes. As a consequence of the fact that second derivatives commute, a given Cordes coefficient always describes two equal structure–reactivity relationships, as shown for example by

$$\frac{\partial\alpha}{-\partial \mathrm{p}K_{\text{nuc}}} = \frac{1}{c_2} = \frac{\partial\beta_{\text{nuc}}}{\partial \mathrm{p}K_{\mathrm{HA}}} \tag{1}$$

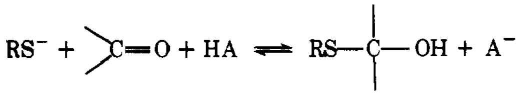
because

$$\frac{\partial^2 \log k}{\partial \mathrm{p}K_{\text{nuc}}\partial \mathrm{p}K_{\mathrm{HA}}} = \frac{\partial^2 \log k}{\partial \mathrm{p}K_{\mathrm{HA}}\partial \mathrm{p}K_{\text{nuc}}}$$

Cordes coefficients for cross correlations are easier to determine experimentally than Hammond coefficients for direct correlations because the determination of $1/c_2$, for example, requires only the measurement of a change in the slope α for a given series of acids as the nucleophile is changed, whereas the determination of a Hammond coefficient requires the determination of a change in slope along a single Brønsted line for different acids that must necessarily be widely different in structure.

The properties of a transition state may be described in terms of a three-dimensional energy contour diagram (Figure 1) in which the height of any point above some standard value represents the Gibbs energy change ΔG for that point (contour lines describing this energy are omitted from Figure 1). Diagrams of this kind were proposed by More O'Ferrall to describe olefin-forming elimination reactions[14] and have been increasingly utilized to provide a qualitative or semiquantitative description of transition states and substituent effects.[13-18] Raising the energy of one side or corner of the diagram, by changing the pK of a reactant, for example, is expected to introduce a perturbation across the energy surface that causes the position of the transition state to move uphill along the direction of the reaction coordinate and downhill perpendicular to the reaction coordinate. Conversely, if changes in the position of the transition state with changing reactant structure are observed experimentally, inferences may be drawn regarding the position and direction of the reaction coordinate on the diagram. Critchlow has described a quantitative treatment of such a diagram for the special case in which the edges of the diagram are linear gradients representing single processes that occur with no activation energy.[15]

For a class e reaction that involves proton transfer to and from an electrophilic reagent, such as the general-acid-catalyzed addition of thiol anions to acetaldehyde



$$RS^- + {>}C{=}O + HA \rightleftharpoons RS{-}\overset{|}{\underset{|}{C}}{-}OH + A^- \quad (2)$$

we can *define* the scale of the x axis of such a diagram by the Brønsted coefficient α and the scale of the y axis by the coefficient $\beta_{nuc} = \partial \log k/\partial pK_{nuc}$ (Figure 1). These coefficients provide a measure of the amount of proton transfer and the amount of S-C bond formation, respectively, in the transition state for most reactions. For most, but not all,[19,20] reactions these coefficients will have a nonlinear, monotonic relationship with other parameters that describe the extent of reaction. A description of the structure-reactivity parameters defines the properties of the transition state on this energy diagram.

A simple approximation to a description of this surface in the region of the saddle point is given by

$$\Delta G/2.303RT = ax^2 + by^2 + cxy + dx + ey + f \quad (3)$$

in which ΔG 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, and increases in the energy of the right edge and top of the diagram are described by increases in d and e, respectively. Although eq 3 will seldom, if ever, describe the entire energy surface, the properties of the surface in the region of the transition state are of primary interest here and it is not unreasonable to assume as a first approximation that changes in the energy of one edge of the diagram produce a linear energy change across the diagram.[3] The coefficients a and b measure the curvature of parabolae and are positive for upward curvature (an energy well) and negative for downward curvature (an energy maximum). The sign of the curvature parameter c is negative for reaction coordinates that lead through saddle points between the lower left and right upper quadrants of the diagram and the quantity $4ab - c^2$ is negative for surfaces that describe a saddle point.

The coordinates of the transition state in the saddle point are obtained by setting the horizontal and vertical derivatives of eq 3 equal to zero and are

$$\alpha = x = \frac{ce - 2bd}{4ab - c^2} \quad (4)$$

$$\beta_{nuc} = y = \frac{cd - 2ae}{4ab - c^2} \quad (5)$$

Harris and Kurz[4] have used a potential function defined in terms of bond length that is of the same form as that of eq 3, and also as that used by Westheimer[21] to treat deuterium isotope effects, to obtain equations similar to 4 and 5 describing changes in bond length in the transition states of S_N2 displacement reactions upon substitution of reactants. Small changes in the position of the transition state that result from changes in the energies of the edges of the diagram are given by the Hammond and Cordes coefficients (the derivatives of α and β_{nuc}) according to

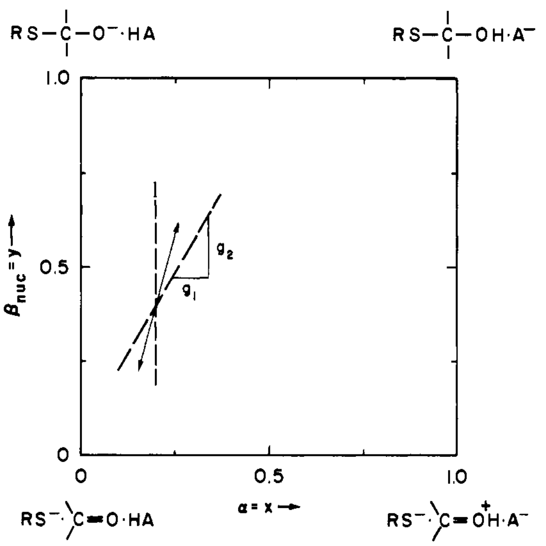


Figure 1. Energy diagram based on structure-reactivity coefficients for the general-acid-catalyzed addition of thiol anions to acetaldehyde, a class e reaction. The x and y coordinates are defined by α and β_{nuc}, respectively; the energy contours are not shown.

$$p_x = \frac{\partial \alpha}{\partial pK_{HA}} = \frac{\partial x}{\partial d} = \frac{-2b}{4ab - c^2} \quad (6)$$

$$p_y = \frac{\partial \beta_{nuc}}{-\partial pK_{nuc}} = \frac{\partial y}{\partial e} = \frac{-2a}{4ab - c^2} \quad (7)$$

$$p_{xy} = \frac{\partial \alpha}{-\partial pK_{nuc}} = \frac{\partial \beta_{nuc}}{\partial pK_{HA}} = \frac{\partial x}{\partial e} = \frac{\partial y}{\partial d} = \frac{c}{4ab - c^2} \quad (8)$$

In eq 6-8 an increase in the energy of the right relative to the left edge of the diagram (Figure 1) results from a decrease in the strength of the acid, $\Delta d = \Delta pK_{HA}$, and an increase in the energy of the top relative to the bottom of the diagram results from a decrease in the basicity of the nucleophile, $\Delta e = -\Delta pK_{nuc}$. Solving these equations for the curvatures a, b, and c (eq 3) gives

$$a = \frac{-p_y}{2(p_x p_y - p_{xy}^2)} \quad (9)$$

$$b = \frac{-p_x}{2(p_x p_y - p_{xy}^2)} \quad (10)$$

$$c = \frac{p_{xy}}{(p_x p_y - p_{xy}^2)} \quad (11)$$

Substituting in eq 3 gives the energy of the transition state in terms of the Hammond and Cordes coefficients, the energies of the right and top edges (d and e, respectively), and a constant, f.

$$\Delta G^{\ddagger}/2.303RT = \frac{cde - ae^2 - bd^2}{4ab - c^2} + f$$
$$= {}^1\!/\!_2 p_x d^2 + {}^1\!/\!_2 p_y e^2 + p_{xy} de + f \quad (12)$$

The energies are expressed in units of $-\log K$ or $-\log k$ and are relative to some reference quantity, for example, $d = pK_{HA} + d_0$ and $e = -pK_{nuc} + e_0$. The constants d_0 and e_0 serve only to place the transition state in its experimentally observed position but do not affect its motion as d and e are changed. The values of d_0 and e_0 are

$$d_0 = -2ax_0 - cy_0$$
$$e_0 = -cx_0 - 2by_0 \quad (13)$$

where x_0 and y_0 are the x and y values extrapolated to both zero pK_{HA} and pK_{nuc} (for the diagram of Figure 1, x and y are α and β_{nuc}, respectively). For the reaction of eq 2 and Figure 1 this gives

$$-\log k = \tfrac{1}{2}p_x pK_{HA}^2 + \tfrac{1}{2}p_y pK_{nuc}^2 - p_{xy} pK_{HA} pK_{nuc} + \alpha_0 pK_{HA} - \beta_{nuc_0} pK_{nuc} + F$$

where $F = d_0^2 + e_0^2 + d_0e_0 + f$. The value of f or F is taken to fit the absolute value of the observed rate constants.

For reactions in the reverse direction, in which the reactants are in the upper right corner of the diagram, the observed structure–reactivity coefficients may be normalized and converted to those for the forward direction ($x = \alpha = 1 - \beta$; $y = \beta_{nuc} = 1 - \beta_{lg}$) and the values of x_0, y_0, d_0, and e_0 calculated in the same way. The rate constant is then given by

$$-\log k_r = \tfrac{1}{2}p_x d^2 + \tfrac{1}{2}p_y e^2 + p_{xy}de + f' - d - e \quad (14)$$

The experimental definitions of α and β_{nuc} as $\partial \log k/-\partial pK_{HA} = -\partial \log k/\partial d$ and $\partial \log k/\partial pK_{nuc} = -\partial \log k/\partial e$ are found by differentiating eq 12 to be

$$\alpha = x = p_x d + p_{xy} e$$

$$\beta_{nuc} = y = p_{xy} d + p_y e$$

in agreement with eq 4 and 5.

The points of the surface at the same energy as the transition state form two straight lines ("level lines") through the saddle point. The position relative to the saddle point and angles relative to the x and y axes of these lines are independent of the values of d and e, as is shown by eq 5 of Appendix II. We may solve this equation, in this case $ag_1^2 + bg_2^2 + cg_1g_2 = 0$, to find the slopes of these level lines,

$$g_2/g_1 = \frac{-c \pm \sqrt{c^2 - 4ab}}{2b} \quad (15)$$

relative to the x axis and

$$g_1/g_2 = \frac{-c \pm \sqrt{c^2 - 4ab}}{2a} \quad (16)$$

relative to the y axis, where g_1 and g_2 are the coordinates of a point on one of these lines relative to the transition state; the absolute coordinates are thus $\alpha + g_1$ and $\beta_{nuc} + g_2$. The reaction coordinate through the transition state may be taken as the line with downward curvature that bisects these level lines. Equations 15 and 16 show that if $(4ab - c^2) > 0$ the level lines do not exist; i.e., there is no saddle point.

The analysis of a reaction by eq 3 serves to characterize the transition state in terms of structure-reactivity parameters and its "electronic anatomy", as defined by changes of charge on reacting groups relative to reactants. Such an analysis can be related to other parameters that are measures of the extent of reaction, such as bond length, bond order, and changes in hybridization, but the relationship is not always unique because of the existence of reciprocal electrostatic interaction effects that do not involve changes in bonding.

Changes in α, β_{nuc}, and other parameters that result from Hammond-type effects and are described by p_x and p_y coefficients may be taken as measures of changes in the amount of bond formation or cleavage in the process described by the parameter, except in the unusual cases in which these changes are not monotonic in the course of the reaction.[19,20] It is shown in Appendix I that for changes of this kind the simple assumption that a change in pK_{HA} or pK_{nuc} (for example) is associated with a linear energy change across any reaction coordinate diagram will necessarily mean that the coordinates defining the diagram (such as bond order) are linearly related to α or β_{nuc}. Similarly, in the special case of a parabolic potential maximum (or minimum) in a two-dimensional reaction coordinate profile the application of a linear perturbation gives a linear relationship between a parameter such as α and the amount of shift in the position of the potential maximum along the reaction coordinate.[3,22] The Marcus model or intersecting parabolae models generally give changes in α that have a linear or close to linear relationship with bond order if the curvature and separation of the parabolae are held constant.[6,7]

However, changes in parameters that result from Cordes cross-interaction effects, described by p_{xy} coefficients, do not have the same direct relationship to bond distance or bond order. The energy surface is subject to the same kind of perturbation from Cordes cross-interaction effects as from Hammond-type effects and will give the corresponding changes in position, bond length, and bond order of the transition state. However, polar substituents may *also* act by transmitting electrostatic effects between reacting groups through space or through a rigid molecular framework *with no change in bond length* and thereby give rise to significant cross-interaction coefficients, as described by Hine for electrostatic interactions generally and for the special case of hydrogen bonds.[10] For example, an electron-withdrawing substituent on an acid can change the charge that is "seen" by a polar substituent on a hydrogen-bonded base and therefore change β even if there is no change in the position of the proton or in α. Since β can change with no change in bond length, β is not a unique measure of bond length or bond order when the pK of an acid is changed; the same holds for α when the pK of the base is changed. For this reason, quantitative conclusions cannot be drawn regarding bond distance and the geometry of a transition state from a given value of α or β, nor regarding changes in bond distance from changes in α or β that result from cross-interaction effects. The influence of this direct electrostatic interaction effect ("Hine effect") will be relatively small for nucleophiles and catalysts that are separated by several atoms in the transition state, i.e., for correlations involving β_{nuc} and α in class e reactions; it is larger for correlations involving central atoms that react directly with substituted catalysis or reactants.

Application of Eq 3–16 to Observed Structure–Reactivity Parameters. The general-acid-catalyzed addition of thiol anions to acetaldehyde (eq 2) serves to illustrate the application of the model of eq 3. The structure–reactivity parameters for this reaction[23] are $p_x = 0$, $p_y = \partial\beta_{nuc}/-\partial pK_{nuc} = 0.089$, and $1/c_2 = p_{xy} = 0.026$. Although these numbers are not exact, they do provide a satisfactory description of the observed structure–reactivity behavior of the reaction and a moderate variation in their magnitude does not alter the general conclusions. Substitution of these values into eq 9–11 gives curvatures of $a = 66$, $b = 0$, and $c = -39$. The ratios g_1/g_2 for the level lines (eq 16) are then 0 and 0.58. The tangent of 31° is 0.58, so that the transition state and saddle point may be described as shown in Figure 1 with the reaction coordinate bisecting the level lines at an angle of −15° from the vertical level line.

The absence of an effect of increasing strength of the acid on α ($p_x = 0$) is a consequence of the absence of curvature along the y axis ($b = 0$, eq 6) that is reflected in the vertical position of one level line. The positive curvature along the x axis ($a = 66$) means that there is a potential well along the coordinate for motion of the proton in the transition state that is reflected in the positive slope g_2/g_1 of the second level line. When $b = 0$, this is the *requirement* for a positive sign of p_y ("Hammond behavior", eq 7); if the second level line has a negative slope, there is negative curvature along the x axis (negative a), the sign of p_y is negative (eq 7), and the reaction will exhibit "anti-Hammond behavior".

In general, the magnitude and direction of a shift in the position of the transition state on this surface that results from a change in reactant structure is determined by the magnitude of the energy gradients and the direction of the reaction coordinate. The direction of the shift is determined simply by the position of the two level lines, which are a measure of the ratio of the energy gradients parallel and perpendicular to the reaction coordinate and of the direction of the reaction coordinate.

It is useful to summarize some of the properties of the individual curvatures.

(1) The Cordes interaction coefficient p_{xy} depends on the diagonal curvature c (eq 8). An increase in this curvature (more negative c) corresponds to a more negative curvature along the diagonal between reactants and products and a more positive curvature along the other diagonal; the result is to shift the reaction coordinate toward the diagonal. Thus, c is a measure of the coupling between the processes occurring along the x and y axes.

(2) When $c = 0$ the reaction coordinate is horizontal or vertical, there is no Cordes coefficient p_{xy}, and the reaction will exhibit simple Hammond or anti-Hammond behavior according to the relations $p_x = -1/2a$ and $p_y = -1/2b$ (eq 6-8). The directions of the level lines are determined by the ratio of the horizontal and vertical curvatures according to $g_2/g_1 = \pm(-a/b)^{1/2}$. This is equivalent to the special case treated by Marcus when the curvature a (or b) is negative, the other curvature is positive, and d (or e) is changed; the Marcus treatment reduces to $\partial\alpha/\partial\Delta G_{\mathrm{HA}}{}^{\circ} = {}^{1}\!/_{2}\lambda$, in which $\lambda/4 = \Delta G^{\ddagger\circ}$ is an intrinsic barrier to reaction.[6] An equivalent expression has been given by Thornton for the shift in the position of a transition state when $c = 0$ and either d or e is changed.[3]

(3) The *signs* of the Hammond coefficients p_x and p_y are determined by the curvature *perpendicular* to the direction of the change under consideration, as illustrated by the example just discussed. Thus, when a is positive, $p_y = \partial\beta_{\mathrm{nuc}}/-\partial\mathrm{p}K_{\mathrm{nuc}}$ is positive ($4ab - c^2$ must be negative to give a saddle point) and when b is positive, $p_x = \partial\alpha/\partial\mathrm{p}K_{\mathrm{HA}}$ is positive, so that "Hammond-type" behavior is observed; conversely, negative curvatures give negative coefficients and "anti-Hammond" behavior (eq 6 and 7). A positive value of a means that a horizontal cross section through the transition state represents an energy well (e.g., for motion of the proton in Figure 1) and that there is a level line that is rotated counterclockwise from the horizontal; a positive value of b means that a vertical cross section through the transition state represents an energy well and that there is a level line that is rotated clockwise from the vertical. Negative values of a and b mean that the transition state is at an energy maximum in these cross sections and that the level lines are rotated in the other direction from the horizontal and vertical, respectively. It is of interest that "Hammond-type" behavior for the proton transfer (positive p_x) will be observed when b is positive even if a is also positive, with motion parallel to the x axis for the proton in a potential well; a simple two-dimensional reaction coordinate profile for proton motion alone would, of course, predict "anti-Hammond" behavior for this situation.

(4) The *magnitude* of a Hammond coefficient depends on all curvatures but especially on the curvature *parallel* to the direction of the change under consideration. Thus, the inverse dependence of $p_x = \partial\alpha/\partial\mathrm{p}K_{\mathrm{HA}}$ on the curvature in the direction of proton transfer, a (eq 6), increases as c becomes relatively small and b tends to cancel out.

(5) When there is no curvature in the direction parallel to the x or y axis, there is no Hammond effect for the process that takes place perpendicular to that direction. For example, when $b = 0$ and $a \neq 0$ there is a vertical level line through the transition state and the Hammond coefficient for proton transfer, $p_x = \partial\alpha/\partial\mathrm{p}K_{\mathrm{HA}}$, is zero (eq 6). This requires that, regardless of the direction of the reaction coordinate, when $\mathrm{p}K_{\mathrm{HA}}$ is changed the vectors for motion of the transition state perpendicular and parallel to the reaction coordinate must sum to zero along the x axis for proton transfer. The Cordes coefficient under these conditions reduces to simply $p_{xy} = -1/c$, the Hammond effect for the vertical process is $p_y = 2a/c^2$, and the Brønsted coefficient is $\alpha = -e/c$. The corresponding conclusions when $a = 0$ and $b \neq 0$ are $p_y = \partial\beta_{\mathrm{nuc}}/-\partial\mathrm{p}K_{\mathrm{nuc}} = 0$, $p_{xy} = -1/c$, $p_x = \partial\alpha/\partial\mathrm{p}K_{\mathrm{HA}} = 2b/c^2$, and $\beta_{\mathrm{nuc}} = -d/c$.

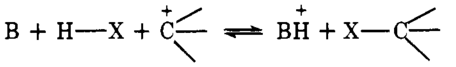
(6) When $a = b = 0$, the two level lines are perpendicular to each other and parallel to the x and y axes so that the direction of the reaction coordinate is diagonal, with maximal coupling of the two processes. There are no Hammond effects, because the vectors for motion of the transition state parallel and perpendicular to the reaction coordinate sum to zero along the x and y axes (eq 6 and 7). However, there must be a positive Cordes coefficient, p_{xy}, because a negative value of c is required in order that there be a saddle point with a reaction coordinate leading from the lower left to the upper right corner. Thus, any reaction that has no Hammond effect ($p_x = p_y = 0$) must have a Cordes cross-interaction effect, although its magnitude may be so small as to make its experimental detection difficult.

Conversely, if $a \neq 0$ or $b \neq 0$ there *must* be at least one Hammond effect with p_x or $p_y \neq 0$. In any hydrogen-bonded transition state of the kind shown in Figure 1, for example, the large angle of the reaction coordinate and level lines relative to the x axis requires that there be a Hammond effect for increasing nucleophile basicity, $p_y = \partial\beta_{\mathrm{nuc}}/-\partial\mathrm{p}K_{\mathrm{nuc}}$. Since $p_y/p_{xy} = -2a/c$ (eq 7 and 8), the Hammond effect should be experimentally detectable when the Cordes effect, p_{xy}, is significant because of the large curvature a for such a transition state.

(7) When the reaction coordinate is diagonal and a and b are both positive, both Hammond coefficients, p_x and p_y, are positive so that "Hammond-type" behavior is observed and the reaction coordinate passes through a relatively narrow pass with a correspondingly negative $\Delta S^{\ddagger}$. When a and b are negative both p_x and p_y are negative, "anti-Hammond" behavior is observed, and the reaction coordinate passes over a ridge with a correspondingly larger $\Delta S^{\ddagger}$.

(8) As the horizontal curvature, a, increases above zero, one level line and the reaction coordinate move counterclockwise and the pass through the saddle point becomes narrower. The horizontal cross section for motion of the proton is then a potential well and as this well becomes narrower the primary deuterium isotope effect may be expected to decrease. Conversely, when a becomes increasingly negative the reaction coordinate becomes more nearly horizontal, the pass through the saddle point becomes wider, and the cross section for motion of the proton is at an energy maximum so that there is a large component of proton transfer in the transition state and a relatively large primary isotope effect. Analogous changes occur with changes in the vertical curvature, b.

Summary of Interaction Coefficients. Definitions of the interaction coefficients for class e reactions of the kind discussed above and for class n reactions, in which catalysis involves proton transfer to and from the nucleophilic reagent in the two directions[24] (eq 17, Figure 2), are summarized in Table I.



$$\mathrm{B} + \mathrm{H{-}X} + \overset{+}{\mathrm{C}}\!\lessdot \rightleftharpoons \mathrm{B}\overset{+}{\mathrm{H}} + \mathrm{X{-}C}\!\lessdot \qquad (17)$$

Structure-reactivity relationships for class n reactions can be treated in the same manner as those for class e reactions with the definitions of the interaction parameters, p, in Table I and the curvatures of the energy surfaces that are described in eq 3-16.

The diagrams are drawn with the unsaturated center in the lower left corner, the addition compound in the upper right corner, proton transfer along the x axis, and bond formation between heavy atoms along the y axis. For a class n reaction

Table I. Structure-Reactivity Parameters for Reactions in Both Directions[a]

Class e reactions	Class n reactions
$\frac{\partial\alpha}{\partial pK_{HA}} = \frac{-\partial\beta}{\partial pK_{HA}} = \frac{\partial x}{\partial d} = p_x$	$\frac{\partial\beta}{-\partial pK_{BH^+}} = \frac{\partial\alpha}{\partial pK_{BH^+}} = \frac{\partial x}{\partial d} = p_x$
$\frac{\partial\beta_{nuc}}{-\partial pK_{nuc}} = \frac{\partial\beta_{lg}}{-\partial pK_{lg}} = \frac{-\partial\rho}{\partial\sigma} = \frac{\partial y}{\partial e} = p_y$	$\frac{\partial\rho}{-\partial\sigma} = \frac{\partial y}{\partial e} = p_y$
$\frac{\partial\beta_{nuc}}{\partial pK_{HA}} = \frac{\partial\alpha}{-\partial pK_{nuc}} = \frac{1}{c_2} = \frac{\partial x}{\partial e} = \frac{\partial y}{\partial d} = p_{xy}$	$\frac{\partial\beta}{-\partial\sigma} = \frac{\partial\rho}{-\partial pK_{BH^+}} = \frac{1}{c_4} = \frac{\partial x}{\partial e} = \frac{\partial y}{\partial d} = p_{xy}$
$\frac{\partial\beta_{lg}}{\partial pK_{HA}} = \frac{\partial\beta}{\partial pK_{lg}} = \frac{1}{c_2} = p_{xy}$	$\frac{\partial\alpha}{\partial\sigma} = \frac{\partial\rho}{-\partial pK_{BH^+}} = \frac{1}{c_4} = p_{xy}$
Diagonal Interactions	
$\frac{\partial\rho}{-\partial\sigma} = \frac{\partial y'}{\partial e'} = p_{y'}$	$\frac{\partial\beta_{nuc}}{-\partial pK_{nuc}} = \frac{\partial y'}{\partial e'} = p_{y'}$
$\frac{\partial\rho}{\partial pK_{HA}} = \frac{\partial\alpha}{-\partial\sigma} = \frac{1}{c_1} = p_{xy'}$	$\frac{\partial\beta_{nuc}}{-\partial pK_{BH^+}} = \frac{\partial\beta}{-\partial pK_{nuc}} = \frac{\partial\alpha}{\partial pK_{lg}} = \frac{1}{c_5} = p_{xy'}$
$\frac{\partial\rho}{\partial pK_{nuc}} = \frac{\partial\beta_{nuc}}{\partial\sigma} = \frac{1}{c_3} = p_{yy'}$	$\frac{\partial\beta_{nuc}}{\partial\sigma} = \frac{\partial\rho}{\partial pK_{nuc}} = \frac{1}{c_6} = p_{yy'}$

[a] Where the reverse reaction is not explicitly indicated, β_{lg}, pK_{lg}, ρ_{lg}, and σ_{lg} may be substituted for the corresponding β_{nuc}, pK_{nuc}, ρ_{nuc}, and σ_{nuc} term. The Cordes coefficients $1/c_2$, $1/c_4$, etc., should be distinguished from the diagonal curvature c of eq 3.

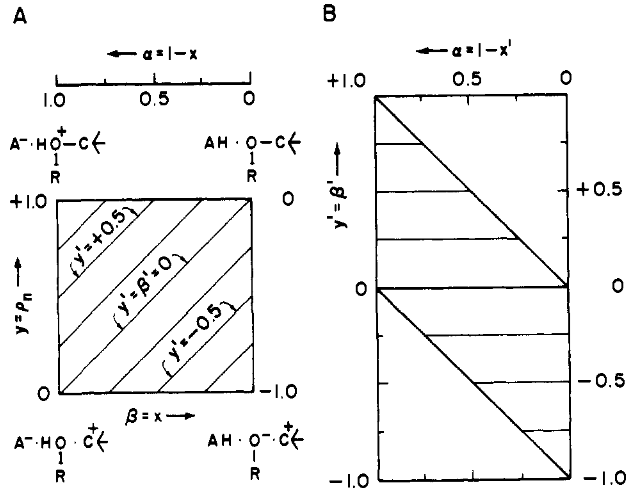


Figure 2. Structure-reactivity diagrams for class n reactions, such as the general-base-catalyzed addition of an alcohol to an electrophilic center or the general-acid-catalyzed hydrolysis of an acetal. A. Rectangular diagram with diagonal lines showing the effects of substituents on the central oxygen atom of the alcohol ($\beta' = \beta_{nuc} = \beta_{lg}$). B. Transformed diagram with perpendicular x' and y' axes for α and β', respectively.

such as the hydrolysis of substituted benzaldehyde acetals,[18] for example, the y axis and the coefficient e may be defined in terms of ρ and σ, respectively, for substituents on a benzene ring attached to a reacting carbon atom. Structure-reactivity coefficients involving central atoms, such as β_{nuc} and β_{lg}, change along a diagonal direction between the lower right and upper left corners as shown in Figure 2. It should be noted that a Brønsted coefficient, β, for proton transfer along the x axis in one direction corresponds to $1 - \alpha$ for the same proton transfer in the reverse reaction. Thus, for a class n reaction such as acetal hydrolysis (Figure 2) movement to the right along the x axis corresponds to an increase in β and a decrease in α.

Coefficients are given in terms of α, β, and pK_a values when possible, but can also be expressed in terms of ρ and σ, which have opposite signs from β and pK_a. For example, the coefficient $\partial\beta_{nuc}/-\partial pK_{nuc} = p_y$ can also be expressed as $-\partial\rho_{nuc}/\partial\sigma_{nuc}$; in the reverse direction $p_y = \partial\beta_{lg}/-\partial pK_{lg}$ or $p_y = -\partial\rho_{lg}/\partial\sigma_{lg}$. Structure-reactivity parameters describing a particular substituent effect in the two directions of a reaction are related by the parameter for the equilibrium constant; e.g., $\beta_{eq} = \beta_{nuc} - \beta_{lg}$, $\rho_{eq} = \rho_f - \rho_r$. A given change in the position of a transition state upon changing the structure of a reactant or catalyst is the same regardless of the direction of the reaction. Thus, the sign and magnitude of the p coefficients in Table I are the same for the reaction in both directions.

In order to permit comparison of structure-reactivity coefficients based on different linear free energy relationships, the correlation parameters may be normalized to the range 0 to 1.0 along the x and y axes and −1.0 to +1.0 (or +1.0 to −1.0, for class e reactions) in the diagnonal direction, measured on the y' axis. The normalization along the x and y axes refers to the α, β, or ρ value for the complete reaction at equilibrium; e.g., ρ_{eq}. Normalization for the diagonal coordinate should be based on substituent effects for the equilibrium formation of the intermediates in the upper left and lower right corners of the diagram. The energy scale for the Brønsted coefficients α and β is based on base 10 logarithms; i.e., log K and log k. To convert the Hammett parameter σ to the same scale, σ should be multiplied by ρ_{eq} for the equilibrium constant of the overall reaction, since $\partial \log K/\partial\sigma = \rho_{eq}$. Thus, a coefficient $\partial\rho/\partial\sigma$ is normalized by multiplying by $1/\rho_{eq}^2$ to give $\partial\rho_n/\rho_{eq}\partial\sigma$. The range of α and β values is usually close or equal to 1.0; normalized ρ values may be indicated by the symbol ρ_n. The structure-reactivity relationships are ordinarily expected to apply only within these normalized limits and deviations from linear behavior are likely to occur as the edges of the diagrams are approached. In special cases, however, it may be useful to deal with parameters that fall outside of the range of the rectangular diagram by extending the area of the diagram to curved edges. Intermediates located in the lower right and upper left corners will have coordinates that are close to those of the products on the x and y axes, respectively. They will be shifted in position when the two processes described by the x and y axes are not completely separated; for example, in the

Table II. Effects on Coefficients of a Linear Coordinate Change, Such as That Shown in Figure 2A and B[a]

General case	B in terms of A	A in terms of B
$x = ix' + jy'$	$x = x'$	$x' = x$
$y = mx' + ny'$	$y = x' + y'$	$y' = -x + y$
$a' = ai^2 + bm^2 + cim$	$a' = a + b + c$	$a = a' + b' - c'$
$b' = aj^2 + bn^2 + cjn$	$b' = b$	$b = b'$
$c' = 2aij + 2bmn + c(in + jm)$	$c' = c + 2b$	$c = -2b' + c'$
$d' = di + em$	$d' = d + e$	$d = d' - e'$
$e' = dj + en$	$e' = e$	$e = e'$
$f' = f$	$f' = f$	$f = f'$
$4a'b' - c'^2 = (4ab - c^2)\,det^2\begin{pmatrix} ij \\ mn \end{pmatrix}$		$4ab - c^2 = 4a'b' - c'^2$

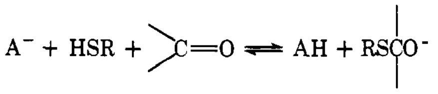
[a] The transformed coefficients are obtained by substituting the values of the original coordinate (e.g., x and y) in terms of the transformed coordinates (e.g., x' and y') into eq 3 and regrouping.

reaction described by Figure 1 the position of the intermediate anionic addition compound in the upper left corner will be shifted to the right along the x axis because of partial proton transfer in the hydrogen-bonded complex $RSCR_2O^-{\cdot}HA$.

Rate constants and transition state Gibbs energies may be calculated for class n reactions from eq 12–14 in the same manner as for class e reactions. In a reaction described by Figure 2, for example, the experimental values of $x = \beta = 1 - \alpha$ and $y = \rho_n$ are extrapolated to zero pK_{BH^+} and to zero σ to obtain x_0, y_0, d_0, and e_0 from eq 13. For this reaction the energy d is based on $-pK_{BH^+}$ and the energy e on $-\sigma$ (the value of σ may be normalized). The identification and sign of d and e may be obtained by inspection of the definitions in Table I.

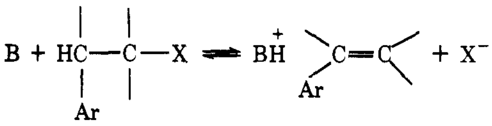
It should be noted that for substituents on a central atom, such as a leaving or attacking alcohol in acetal hydrolysis and other class n reactions, the formal charge is the same in the starting material and products; the change in charge upon forming the transition state is indicated by $y' = \beta_{lg} \sim \beta_{nuc}$. Consequently, the signs of β_{lg} and β_{nuc} are the same and a $-d'$, but not a $-e'$, term is required in the equation corresponding to eq 14 for the calculation of the rate constant of the reverse reaction.

The Cordes cross-interaction coefficients p_{xy} ordinarily have a positive sign as a consequence of the negative signs of c and $4ab - c^2$. However, the cross-interaction coefficients $p_{xy'}$ for central atom effects can be positive or negative because c' can be positive or negative (the coefficients for central atom effects are described more fully in the following section). The positive sign of $\partial\alpha/{-\partial pK_{nuc}} = p_{xy}$ for general acid catalysis of the addition of thiol anions to acetaldehyde,[23] for example, is consistent with the class e mechanism of eq 2; a negative sign of p_{xy} is not expected for this mechanism. From qualitative considerations the opposite structure–reactivity behavior might be expected for the kinetically equivalent mechanism of eq 18.


(18)

However, the same experimental data give a negative sign of $\partial\beta/{-\partial pK_{nuc}} = p_{xy'}$ (Table I) and a positive value of c' for the mechanism of eq 18 and, since negative values of the $p_{xy'}$ coefficient for central atom effects are permitted, this mechanism is not ruled out by this experimental result. Because of this ambiguity, cross-interaction coefficients for structure–reactivity correlations on central atoms frequently cannot be used to resolve kinetically ambiguous mechanisms.

Effects of Substituents on a Central Atom. Structure–reactivity relationships involving substitution on a central reacting atom, such as the general-acid-catalyzed elimination of substituted alcohols from an electrophilic center (eq 17) or olefin-forming elimination with substituents on the β-carbon atom (eq 19), are more difficult to interpret because (1) the


(19)

amount of charge development on the central atom reflects a balance between the interactions with two neighboring atoms with which bonds are forming and breaking, (2) direct electrostatic effects are more important for the short-range interactions involving central atoms than for the longer range interactions between end atoms, and (3) the relationship between structure–reactivity parameters for substituents on central atoms, such as β_{lg} or β_{nuc} (y', Figure 2A) and those for end atoms (x,y) may be complex and, if nonlinear, difficult to deal with mathematically.

In the simplest case substituent effects on the central atom, measured by the y' coordinate, are constant along the diagonal lines as shown in Figure 2A. For example, substituent effects on the rate of acid-catalyzed elimination of substituted alcohols (eq 17) may be described in terms of β_{lg} (or a β_{nuc} in the reverse direction) that can have y' values between -1.0 and $+1.0$ (Figure 2A). We will define β_{lg} or β_{nuc} as β' for convenience.

It is convenient to redraw Figure 2A so that the x' and y' axes are perpendicular in order to visualize more easily the interrelationships between these axes. Such a transformed diagram for the x' and y' coordinates is shown in Figure 2B, in which the x' coordinate $(1 - \alpha)$ is identical with the x coordinate of Figure 2A and the y' axis (β') is vertical. The structure–reactivity relationships in Figure 2B can now be treated with eq 3–16 and can be related to Figure 2A through a linear coordinate change.

The effects of a linear coordinate change on the coefficients of the surfaces are given in Table II for the general case and for the special case of the transformation of A to B in Figure 2. The coefficients a–f refer to the x and y coordinates and a'–f' to the x' and y' coordinates; the x and y axes are perpendicular in Figure 2A, and the x' and y' in Figure 2B. The coefficient e' refers to a substituent on the central atom, such as a change in the pK of a leaving alcohol (eq 17), and represents a change in the energy of the top relative to the bottom edge of Figure 2B and in the energy of the upper left corner relative to the lower right corner in Figure 2A. The coefficient c' can be either negative or positive. The Hammond and Cordes coefficients for α and β' are then given by eq 20–22 in terms of the coordinates for the two diagrams.

$$p_x = \frac{\partial\alpha}{\partial pK_{BH^+}} = \frac{\partial\alpha}{\partial d'} = \frac{-2b'}{4a'b' - c'^2} = \frac{-2b}{4ab - c^2} \qquad (20)$$

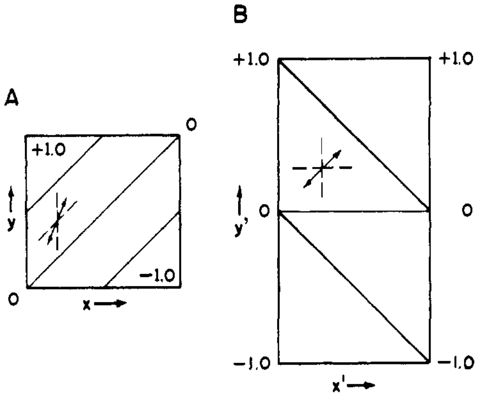


Figure 3. Structure-reactivity diagrams for central atom effects showing the position of the level lines when $p_x = p_{y'} = 0$ and $b = b' = a' = 0$.

$$p_{y'} = \frac{\partial \beta'}{-\partial \mathrm{p}K_{\mathrm{lg}}} = \frac{\partial y'}{\partial e'} = \frac{-2a'}{4a'b' - c'^2} = \frac{-2(a+b+c)}{4ab - c^2} \quad (21)$$

$$p_{xy'} = \frac{\partial \beta'}{-\partial \mathrm{p}K_{\mathrm{BH^+}}} = \frac{\partial \alpha}{\partial \mathrm{p}K_{\mathrm{lg}}} = \frac{\partial \beta'}{\partial d'} = \frac{\partial \alpha}{\partial e'} = \frac{c'}{4a'b' - c'^2} = \frac{c + 2b}{4ab - c^2} \quad (22)$$

The coefficients of the two diagrams are given in terms of the structure–reactivity coefficients by

$$a' = \frac{-p_{y'}}{2(p_x p_{y'} - p_{xy'}{}^2)} \qquad a = \frac{-(p_x + p_{y'} + 2p_{xy'})}{2(p_x p_{y'} - p_{xy'}{}^2)}$$

$$b' = \frac{-p_x}{2(p_x p_{y'} - p_{xy'}{}^2)} = b \quad b = \frac{-p_x}{2(p_x p_{y'} - p_{xy'}{}^2)}$$

$$c' = \frac{p_{xy'}}{p_x p_{y'} - p_{xy'}{}^2} \qquad c = \frac{p_x + p_{xy'}}{p_x p_{y'} - p_{xy'}{}^2}$$

An analogous transformation may be made for the y and y' axes of Figure 2A. It should be noted that Figure 2B is defined solely in terms of the x' and y' coordinates (α and β') and may be used regardless of the relationship between these coordinates and the y coordinate of Figure 2A. It should also be noted that the properties of the level lines for a given saddle point are invariant upon transformation between diagrams such as 2A and 2B, but the properties of the reaction coordinate are not invariant if the reaction coordinate is defined as a line bisecting the two level lines. The coordinates of the level lines are equivalent, according to the relationships in Table II, and define the same structure-reactivity relationships in the two diagrams, but the coordinates of the reaction coordinate that bisects the level lines are not equivalent and do not follow the relationships in Table II because of the change in angles between the two diagrams. This indicates that, in terms of these diagrams, the level lines are a more fundamental property of the surface surrounding the saddle point than the reaction coordinate.

Alternatively, the relationships between x' (or x) and y' may be plotted directly on Figure 2A using eq 3-16 and the appropriate coordinates, x' and y'. The coefficients a' and b' then refer to curvatures of lines through the saddle point that are parallel to a diagonal x' axis (at which $y' = 0$) and to a vertical y' axis (at which $x' = 0$), respectively.

In order to interpret the interrelationships illustrated by Figure 2 we consider first the simple case in which there are no Hammond effects, so that $p_x = p_{y'} = 0$. Then eq 20-22 show that $b = b' = 0$, $a' = 0$, and $a = -c = 1/p_{xy'}$. This means that the level lines of zero curvature (eq 15 and 16) are vertical and horizontal, parallel to the x' and y' axes, in Figure 3B and are vertical and diagonal in Figure 3A. A reaction coordinate between the level lines that is diagonal in Figure 3B is therefore intermediate between vertical and diagonal in Figure 3A.

Any other system, in which the level lines are not vertical and diagonal in Figure 3A, requires nonzero values of the Hammond coefficients p_x and $p_{y'}$, respectively. The condition for no Hammond effect on proton transfer, $p_x = 0$, is that there be a vertical level line with $b = 0$, as before; if the line is shifted clockwise, b and p_x become positive, giving Hammond behavior, and if it is shifted counterclockwise b and p_x become negative, giving anti-Hammond behavior. The condition for no Hammond effect with substituents on the alcohol, $p_{y'} = 0$, is that $a' = 0$, giving a horizontal level line in Figure 3B and a diagonal level line in Figure 3A. If this line is shifted clockwise there is a wider pass and a' and $p_{y'}$ become negative giving anti-Hammond behavior; if it is shifted counterclockwise there is a narrower pass and a' and $p_{y'}$ become positive, giving Hammond behavior.

When the level lines are horizontal and vertical in Figure 2A or 3A ($a = b = 0$) and the reaction coordinate is approximately diagonal, there is a large anti-Hammond effect upon changing the leaving group and the Hammond coefficient, $\partial\beta'/-\partial\mathrm{p}K_{\mathrm{lg}}$, is twice as large as the Cordes coefficient, $\partial\beta'/-\partial\mathrm{p}K_{\mathrm{BH^+}} = \partial\beta/-\partial\mathrm{p}K_{\mathrm{lg}}$; i.e., $p_{y'} = -2p_{xy'}$ (eq 21 and 22). Thus, the magnitude of the Hammond coefficient is extremely sensitive to the direction of the level lines and reaction coordinate, changing from 0 to $-2p_{xy'}$ as the angle of the reaction coordinate changes from approximately 67° to 45°. This high sensitivity is a consequence of the diagonal relationship of the x' and y' axes in Figure 2A.

The acid-catalyzed expulsion of substituted alcohols from tetrahedral addition compounds of a phthalimidium ion[17] exhibits an increase in α with increasing basicity of the leaving alcohol and an increase in β_{lg} with increasing acidity of the catalyzing acid that are described by the relationship $1/c_5 = p_{xy'} = 0.07$. The presence of a significant $p_{xy'}$ term and the absence of a detectable change in α with increasing acidity of the catalyzing acid suggest that $p_x \sim 0$ and $b \sim 0$. The diagonal curvature is then given by $c' = -1/p_{xy'} = -14$, if it is assumed that the reaction can be described by the diagrams in Figure 2. The experimental data do not permit a definite decision as to whether β' increases with increasing pK of the leaving alcohol, i.e., $p_{y'} \geqslant 0$. The results are consistent with a direction of the reaction coordinate that is intermediate between diagonal and vertical in Figure 2A or 3A. It is of interest that extrapolation of the Cordes relationship $\partial\beta'/-\partial\mathrm{p}K_{\mathrm{BH^+}} = 0.07$ to the pK of water, 15.7, gives $\beta' = -1.0$, which is on the edge of the diagram and is in accord with the observed value of $\beta_{\mathrm{lg}} = -0.9$ for the "water" reaction.

Electrostatic Effects and "Imbalance" in Transition States. The structure–reactivity relationships described so far provide an incomplete description of substituent effects on central atoms for some, perhaps most, reactions because they neglect direct electrostatic interactions that can affect observed structure–reactivity parameters in the absence of changes in the amount of bond making and bond breaking in the transition state. Electrostatic interactions of this kind have been treated quantitatively by Hine[10] and their contribution to observed rate constants may be described by

$$\Delta \log k = \tau(\mathrm{p}K_{\mathrm{HA}} - \mathrm{p}K_{\mathrm{H_2O}})(\mathrm{p}K_{\mathrm{H_3O^+}} - \mathrm{p}K_{\mathrm{lg}}) - \tau'\sigma(\mathrm{p}K_{\mathrm{H_3O^+}} - \mathrm{p}K_{\mathrm{lg}}) \quad (23)$$

for central atom effects in a class n reaction such as that of eq 17. The coefficient τ describes the transmission of electrostatic interactions through a hydrogen bond between polar substituents on the catalyzing acid and on the central oxygen atom, and τ' describes the transmission of electrostatic interactions between polar substituents on the benzaldehyde moiety and on the central oxygen atom; the sign of these coefficients is positive. Differentiating twice with respect to the appropriate pK values or σ gives

$$\tau = \frac{\partial \alpha}{\partial pK_{lg}} = \frac{\partial \beta'}{-\partial pK_{HA}} \tag{24}$$

$$\tau' = \frac{\partial \rho}{\partial pK_{lg}} = \frac{\partial \beta'}{\partial \sigma} \tag{25}$$

Electrostatic effects on class e reactions may be described similarly, for example by

$$\tau = \frac{\partial \alpha}{\partial pK_{RXH}} = \frac{\partial \beta_{RX}}{-\partial pK_{HA}} \tag{26}$$

$$\tau' = \frac{\partial \beta_{nuc}}{-\partial pK_{RXH}} = \frac{\partial \beta_{RX}}{-\partial pK_{nuc}} \tag{27}$$

where R is a substituent on the central atom X that is protonated by HA. The effect of these electrostatic interactions is to (1) change the amount of charge development and substituent effects on reactants and intermediates and (2) make a contribution to observed Cordes cross-interaction coefficients that is in addition to the effects described by eq 3-16 and by structure-reactivity surfaces such as those shown in Figure 1 and 2.

(1) Equation 24 shows, for example, that the sensitivity to polar substituents on the alcohol, β', will be less for a protonated intermediate that is hydrogen bonded to a base A^- than to water. This will have the effect of reducing the β' value for the formation of the protonated intermediate shown in the upper left corner of Figure 4A. The positive charge on the carbonium ion will produce an opposite effect on β' for the intermediate in the lower right corner of Figure 4A. The electrostatic effects of A^- and the carbonium ion will tend to cancel in the lower left corner and do not exist for the species in the upper right corner. Although the magnitudes of these changes in β' are difficult to estimate, they will have the effect of rotating the edges of the diagram from the positions shown in Figure 2B (shown by the dashed lines in Figure 4A) and thereby squeeze the diagram in its vertical dimension and change the angles of the edges toward the horizontal.

(2) Substituents on a central atom in a class n reaction will change the observed substituent effects for the end atoms, α and ρ, and substituents on end atoms will change the substituent effects on the central atom, β_{lg} or $\beta_{nuc}(\beta')$, through electrostatic interactions that are described by eq 24 and 25. For example, an electron-donating substituent that decreases the strength of the acid (↑pK_{HA}) will give rise to a favorable electrostatic interaction with an electron-withdrawing substituent in the leaving alcohol that decreases β_{lg}. Similarly, an electron-withdrawing substituent on the leaving alcohol (↓pK_{lg}) will cause a favorable electrostatic interaction with an electron-donating substituent on the acid and thereby decrease α with the same proportionality constant, τ. If it is assumed that the distance between these substituents remains constant in the hydrogen-bonded reactants, transition state, and products, the electrostatic effect will be constant for these species. Thus, this direct electrostatic effect may be regarded as an *additional effect of substituents that is independent of bond length effects* and is constant for the different species shown on the diagram; it describes the effects of substituents on the process of bringing reactants from dilute solution (where they are hydrogen bonded to water) to the encounter complexes on the corners of the diagram (where they interact electrostatically with an acid HA, for example). This changes the value of f in eq 3, as described by eq 23, and represents a term that should be added to the substituent effects that are described within the diagram.[27] Equations 24 and 25 are of the same form as the $p_{xy'}$ and $p_{yy'}$ terms, respectively, for class n reactions so that the consequence of the direct electrostatic interaction is to increase the observed $p_{xy'}$ and $p_{yy'}$ terms over the values that are caused by bond length effects and are described by eq 3. It may be convenient to represent the electrostatic effects schematically by shifting the scales of the diagrams according to eq 24 and 25, as shown for changes in the pK of the catalyzing acid and the leaving group in Figures 4B and 4C, respectively; however, such shifted scales should not be used for calculating structure-reactivity relationships within the diagram according to eq 3-16.

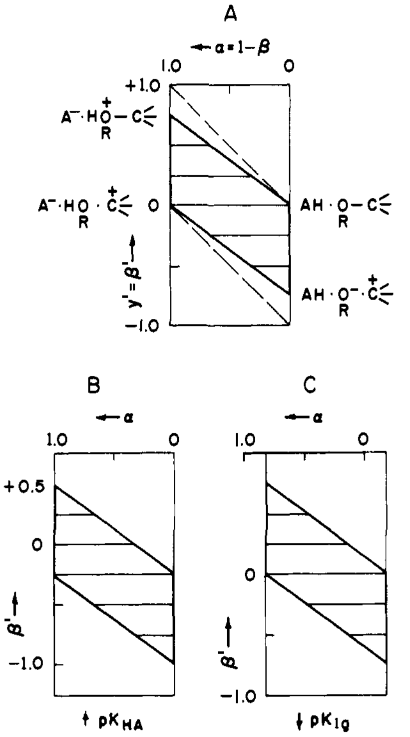


Figure 4. Diagram showing how (A) electrostatic interactions with A^- and $^+C\lessdot$ twist the diagonal lines in a structure–reactivity diagram similar to that of Figure 2B, (B) an electron-donating substituent in the catalyzing acid decreases the observed β' (β_{lg} or β_{nuc}) value by a direct electrostatic interaction, and (C) an electron-withdrawing substituent in the leaving alcohol decreases the observed α value by a direct electrostatic interaction.

The direct electrostatic effect is relatively small for interactions between end atoms because of the greater distance separating substituents on these atoms from each other. The contribution of this effect to an observed p_{xy} coefficient is therefore relatively small; its effect for the reactions of eq 2 and 17, if it is significant, would be to decrease the observed p_{xy} terms.

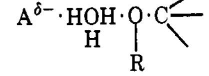
The acid-catalyzed expulsion of substituted phenols from a series of benzaldehyde methyl aryl acetals[18] exhibits a large interaction coefficient for substituents on the central atom and on the catalyzing acid, with $1/c_5 = p_{xy'} \sim 0.2$. The Brønsted plots exhibit no significant curvature for catalysis by carboxylic acids but show a negative deviation for the proton, i.e., $\partial\alpha/\partial pK_{HA} = p_x \gg 0$. The increase in α with electron-withdrawing substituents on the benzaldehyde group and the increased (less negative) ρ with strong acids[18] give a normalized Cordes interaction coefficient of $1/c_4 = p_{xy} = 0.11$. The ρ values were normalized based on a ρ value of -3.6 for the equilibrium formation of oxocarbonium ions from acetophenone acetals.[28] For a reaction that is described by the simple structure-reactivity relationships of eq 6, 8, and 22, the relationship of p_{xy} and $p_{xy'}$ is given by $p_{xy'} = p_{xy} - p_x$. The experimental fact that $p_x \gg 0$ means that $p_{xy'}$ should be equal to or smaller than p_{xy}. The observed ratio of $p_{xy'}/p_{xy} \sim 2$ means that the substituent effects in this reaction are not adequately described by eq 6, 8, and 22. The effect of a direct electrostatic interaction is to increase the magnitude of the $p_{xy'}$ term (eq 24) but not the p_{xy} term, which does not involve central atoms. Thus, it is likely that the direct electrostatic effect makes a significant contribution in this reaction that accounts for part, or possibly all, of the observed increase in the $p_{xy'}/p_{xy}$ ratio over 1.0.

However, there are several pieces of evidence that direct electrostatic interactions do not account for all of the observed substituent interaction effects and that there are significant changes in the structure of the transition state with changing substituents in acetal hydrolysis. (1) The large interaction coefficient for substituents on the end atoms for the hydrolysis of benzaldehyde methyl aryl acetals,[18] with $p_{xy} = 0.11$, cannot be accounted for by direct electrostatic interactions because such interactions will generally be small for substituents on end atoms and have the effect of decreasing rather than increasing the p_{xy} interaction term in this reaction. For the same reason, the significant p_{xy} term in the class e reaction of eq 2 is evidence for a change in transition state structure and cannot be accounted for by a direct electrostatic interaction. The absence of an increase in α with increasing acid strength ($p_x \gg 0$, $b \gg 0$) and of detectable curvature in the $\rho\sigma$ correlations[29] ($a \sim 0$) suggest that there is an important diagonal component to the reaction coordinate on the diagram describing the hydrolysis of benzaldehyde methyl aryl acetals.[18]

(2) The continued increase in α with increasing basicity of the leaving group (positive $p_{xy'}$) is consistent with the apparent specific acid catalysis ($\alpha = 1.0$) for the hydrolysis of benzaldehyde dimethyl acetal. The large inverse deuterium isotope effect of $k_{H^+}/k_{D^+} = 0.33$ for the dimethyl acetal is evidence for specific acid catalysis, with complete proton transfer in the transition state, and the fact that this isotope effect is significantly different from the value of $k_{H^+}/k_{D^+} = 0.62$ for benzaldehyde methyl *p*-methoxyphenyl acetal[18] suggests that there is a significant difference in the structure of the transition state, and not just a different electrostatic effect, in the transition states for these reactions. (3) When the reaction coordinate is forced over to the left edge of the diagram with $\alpha = 1.0$ it will be essentially vertical. This is consistent with the large increase in secondary isotope effect with electron-withdrawing substituents on the aldehyde (k_H/k_D increases from 1.04 to 1.15 in going from *p*-methoxy- to *p*-nitrobenzaldehyde diethyl acetal), as expected for an increase in carbonium ion character in the transition state with a harder reaction; i.e., a normal Hammond effect and positive p_y.[26] (4) An important vertical component to the reaction coordinate is also suggested by the increased secondary isotope effect, implying more carbonium ion character in the transition state, with electron-donating substituents on the leaving group for the proton-catalyzed hydrolysis of 2-(substituted phenoxy)tetrahydropyrans;[26] a diagonal reaction coordinate with horizontal and vertical level lines in Figure 2A would be expected to give a change in the opposite direction.

In conclusion, the existence of direct electrostatic effects that give rise to significant interaction coefficients in the absence of changes in bond length means that observed $p_{xy'}$ and $p_{yy'}$ coefficients cannot be interpreted directly in terms of changes in bond length, although they are likely to include such changes. Thus, the existence of a significant $p_{xy'}$ or $p_{yy'}$ term does not, in itself, prove that there is motion along both axes for proton transfer and heavy atom transfer in a transition state for a concerted reaction. Other evidence, some of which has been referred to above, supports a concerted reaction mechanism for the expulsion and addition of alcohols and water in acetal hydrolysis and related reactions.[17,18] Direct electrostatic interactions, changes in interaction coefficients that are associated with nonlinear relationships between structure–reactivity coefficients, and edge effects that cause such changes as the transition state approaches the edge of the surface can give rise to an apparent "imbalance" in the extent to which different processes have occurred in a transition state and to nonadditivity of the "effective charges" on the reacting atoms that are estimated from observed substituent effects.[25]

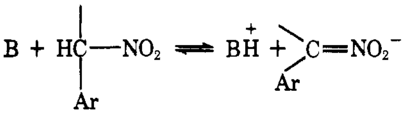
The hydrolysis of benzaldehyde methyl aryl acetals[18] provides a striking example of such a nonlinear relationship and imbalance. The ρ value of -2.8 for this reaction and the β_{lg} value of -0.58 for catalysis by pivalic acid are in the range expected if leaving group expulsion were somewhat more than half complete in the transition state with little or no proton transfer to the leaving oxy anion, yet the α value of 0.75 suggests that there has been extensive proton transfer from the catalyzing acid. This nonlinear relationship or imbalance[25] can itself be described by a three-dimensional energy diagram;[15,25,30] the outline of a mathematical treatment of multidimensional energy diagrams is given in Appendix II (supplementary material). Such nonlinear relationships can be represented on three-dimensional diagrams by curved lines and edges that describe the relationship of the different coefficients to each other. A possible chemical explanation for this imbalance is that a significant positive charge is carried by the proton or by a water molecule between HA and the leaving alcohol that resembles H_3O^+ in the transition state (1).



$$A^{\delta-}\cdot\underset{H}{\overset{\delta+}{HOH}}\cdot\underset{R}{\overset{\delta-}{O}}\cdot\overset{\delta+}{C}\!\!<$$

1

Multiple Interaction Effects. Three-dimensional energy diagrams are useful for describing the properties of other reactions in which more than a single variable influences the properties of the transition state and have been used to describe imbalance in the extent to which resonance, solvation, rehybridization, and other factors influence the stability of transition states and products.[15,25] As an example we describe an analysis of the base-catalyzed ionization of nitroalkanes:

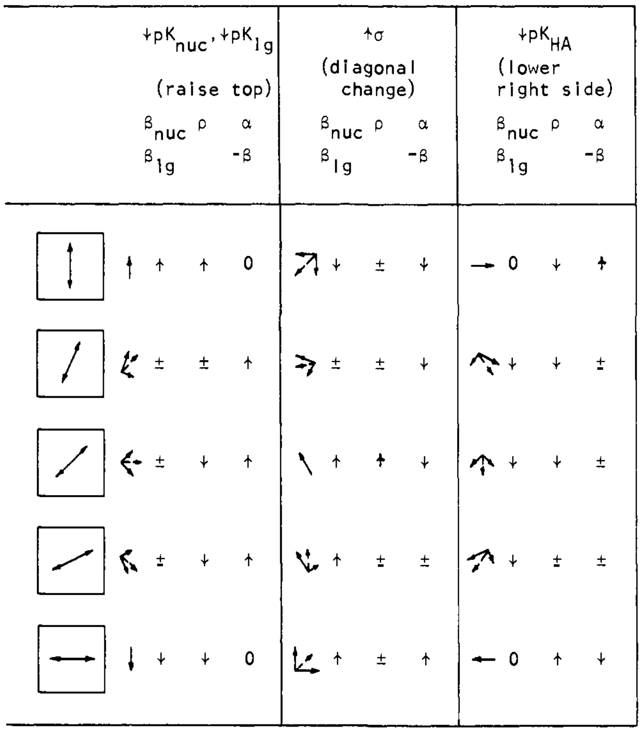


$$B + \underset{Ar}{HC}{-}NO_2 \rightleftharpoons \overset{+}{B}H + \underset{Ar}{>}C{=}NO_2^-$$

The analysis is crude but may serve to illustrate the point. The effects of polar substituents on a benzene ring attached to the ionizing carbon atom of nitroalkanes are larger for the rate than for the equilibrium constants ($\alpha > 1.0$), suggesting that there is more delocalization of negative charge into the nitro group from this carbon atom in the product than in the transition state.[19,20]

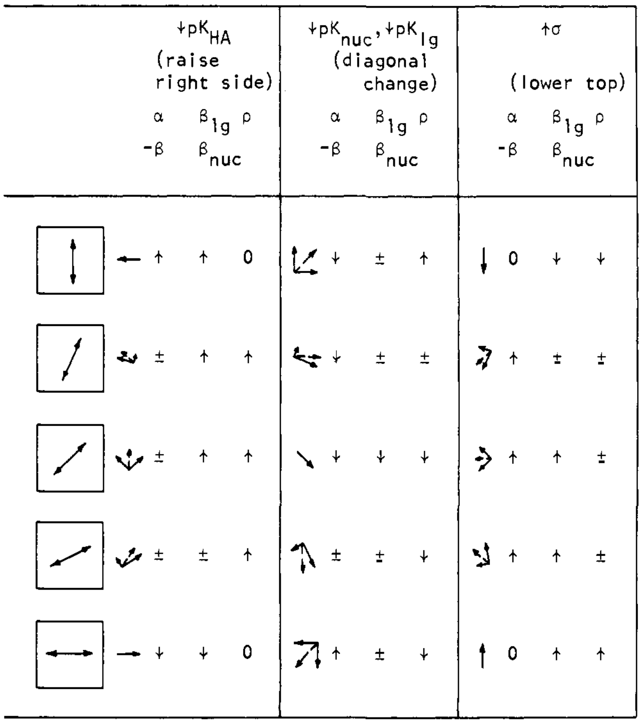
In Figure 5 the horizontal axis represents proton transfer, as measured by the Brønsted slope β, and the vertical axis represents the effect of polar substituents on the carbon atom that undergoes ionization, as measured by the normalized parameter ρ_n. If the value of ρ for carbanion formation without delocalization into the nitro group is taken as 7.0 ± 1.0, based on the equilibrium ionization of 2-substituted fluorenes,[31] the value of $\rho = 1.03$ for the equilibrium ionization of 2-substituted fluorenes,[31] the value of $\rho_n = 0.16$, suggesting that there is approximately 84% delocalization of negative charge into the nitro group in the nitronate anion product. The lower solid line in Figure 5 represents a direct path from reactants to products and the upper diagonal line represents a reaction with no delocalization in either the transition state or product. The distance of any point above the lower solid line is a measure of the amount of negative charge development on carbon that is less delocalized than in the product; the dotted line represents 50% delocalization of the developing negative charge into the nitro group. The dashed curved line is based on Kresge's proposi-

Table III. Effect of Direction of the Reaction Coordinate on Shifts in Transition State Position on a Structure–Reactivity Surface with an Electron-Withdrawing Substituent for Class e Reactions (Figure 1)



	↓pK_{nuc}, ↓pK_{lg} (raise top)				↑σ (diagonal change)				↓pK_{HA} (lower right side)			
		β_{nuc} β_{lg}	ρ	α −β		β_{nuc} β_{lg}	ρ	α −β		β_{nuc} β_{lg}	ρ	α −β
↕	↑	↑	↑	0	→↓↙	↓	±	↓	→	0	↓	↑
⤢	↗↙↘	±	±	↑	→↘↙	±	±	↓	↖↘↓	↓	↓	±
⤢	←↖↙	±	↓	↑	↖	↑	↑	↓	↙↗↓	↓	↓	±
⤢	↖↘↓	±	↓	↑	↑↘↙	↑	±	±	↙↘	↓	±	±
↔	↓	↓	↓	0	↑↗→	↑	±	↑	←	0	↑	↓

Table IV. Effect of Direction of the Reaction Coordinate on Shifts in Transition State Position on a Structure–Reactivity Surface with an Electron-Withdrawing Substituent for Class n Reactions (Figure 2A)



	↓pK_{HA} (raise right side)				↓pK_{nuc}, ↓pK_{lg} (diagonal change)				↑σ (lower top)			
		α −β	β_{lg} β_{nuc}	ρ		α −β	β_{lg} β_{nuc}	ρ		α −β	β_{lg} β_{nuc}	ρ
↕	←	↑	↑	0	↑↗→	↓	±	↑	↓	0	↓	↓
⤢	←↘↙	±	↑	↑	←→↘	↓	±	±	↗↙↓	↑	±	±
⤢	↑↖↗	±	↑	↑	↘	↓	↓	↓	←↗↘	↑	↑	±
⤢	↑↗↙	±	±	↑	↖↓↘	±	±	↓	↖↑↘	↑	↑	±
↔	→	↓	↓	0	←↓↙	↑	±	↓	↑	0	↑	↑

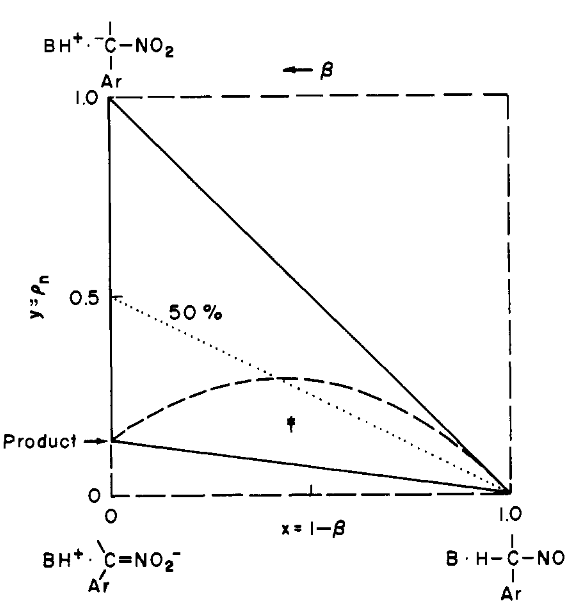


Figure 5. Structure-reactivity diagram for nitroalkane ionization with axes for proton transfer to the base, $x = 1 - \beta$, and for charge development on the ionizing carbon atom, $y = \rho_n$. The dotted line represents 50% delocalization of the developing negative charge into the nitro group.

tion[20] that the fraction of charge delocalization at some point along the reaction path is equal to the amount of C–H bond breaking and rehybridization (measured here by β), times 0.84, the fraction of charge delocalization in the product; the dashed curve is calculated from this fraction and the charge that would be developed on carbon if there were no delocalization (shown by the upper diagonal line). The position of the transition state is indicated for $\alpha = 1.35$ (the average of observed values of 1.15 and 1.54 for phenylnitroethanes and phenylnitromethanes, respectively; $\alpha = \rho/\rho$ (equib)).[19] Although there is more charge development in the transition state than in the product, this charge is small compared to what would be expected if there were no delocalization in the transition state and Kresge's proposition is more than adequate to account for the observed substituent effects.

The available data indicate that the Hammond and Cordes coefficients are small and that the curvatures in the saddle point are large, so that the directions of the level lines and reaction coordinate cannot be evaluated. The linearity of Brønsted slopes over a range of 11.6 pK units for ethyl nitroacetate and similar data for other nitroalkanes[32,22] give a value of $\partial\beta/-\partial pK_{BH^+} = p_x \sim 0$ and more limited data for different nitroalkanes[19,33] suggest that $\partial\rho/\partial pK_{CH} \sim \partial\alpha/\partial pK_{CH} = p_y \sim 0$. The essentially constant value of $\beta \simeq 0.55$ for nitroalkanes differing in acidity over a range of 20 pK units[19,34] indicates that the value of the Cordes coefficient is $\partial\beta/\partial pK_{CH} = p_{xy} \sim 0$. The same Cordes coefficient describes the change in ρ or α with changing pK of the catalyzing base, so that the value of $\partial\alpha/-\partial pK_{BH^+} = p_{xy}$ must also be $\sim$0; this is consistent with the essentially constant value of ρ with nitrogen bases differing in pK over 3.5 units (the slightly larger value for hydroxide ion may be attributed to an electrostatic effect[19]).

Qualitative Evaluation of Reaction Coordinates and Level Lines from Structure–Reactivity Coefficients. The position of a transition state on a structure-reactivity surface is determined by the values of the first derivative structure-reactivity coefficients, such as α and β_{nuc}, along the x and y axes of the diagram. The direction of a reaction coordinate through this transition state is determined by the second derivative structure-reactivity coefficients and, in simple systems, can be estimated even if only the signs of these coefficients are known. A summary of the changes in first derivative coefficients, such as α and β_{nuc}, for different directions of the reaction coordinate when an electron-withdrawing substituent is added to various positions in the reactants is shown in Tables III and IV for class e and class n reactions, respectively. It is apparent from Tables III and IV that the direction of the reaction coordinate may be estimated from the presence, absence, and sign of these

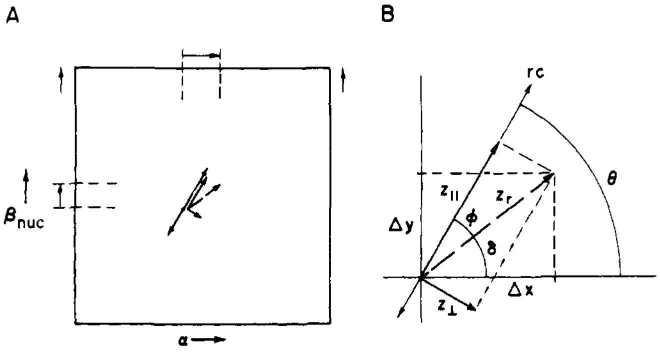


Figure 6. Structure-reactivity diagram for a class e reaction showing how an electron-withdrawing substituent on the nucleophile raises the energy at the top of the diagram and shifts the position of the transition state in directions perpendicular and parallel to the reaction coordinate.

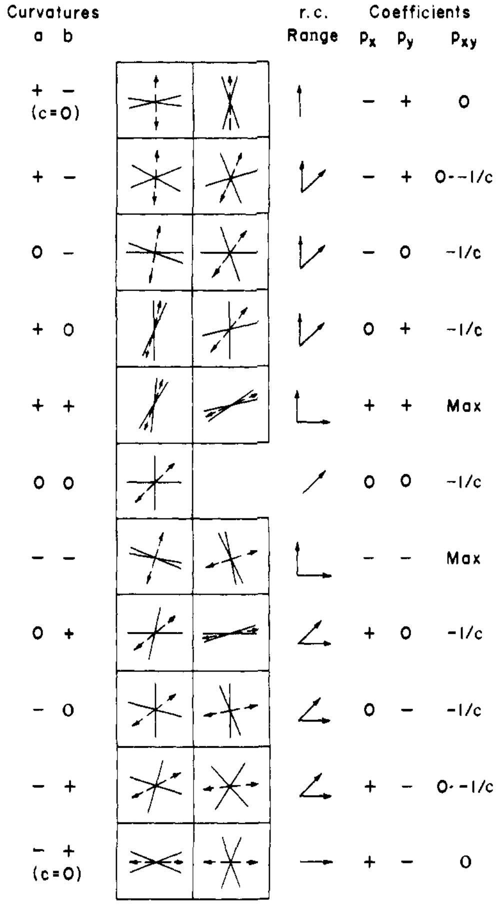
changes regardless of the gradients and magnitude of the changes in the diagram (remembering, of course, that failure to detect a change does not prove that a small change does not exist).

Three reservations must be kept in mind for even the qualitative interpretation of reaction coordinate direction from diagrams of this kind; these reservations are important mainly for the interpretation of substituent effects on central atoms. First, Cordes-type cross-interaction effects may include a contribution of a direct electrostatic interaction between polar substituents[10] that is not dependent on changes in bonding or transition state geometry. Such an interaction can, therefore, lead to an incorrect estimation of the diagonal contribution to the reaction coordinate. Second, the reaction coordinate (in contrast to the level lines) is not uniquely defined for structure-reactivity diagrams and may have different coordinates depending on the geometry of the diagram that is chosen to describe the data. For example, a diagonal reaction coordinate that bisects perpendicular level lines and follows a line of $\beta' = y' = 0$ in Figure 2A will give a positive Cordes interaction coefficient, $p_{xy'}$, but in Figure 2B the same interaction coefficient and level lines will give a reaction coordinate that is rotated counterclockwise from the horizontal and does not follow the line of $y' = 0$. A horizontal reaction coordinate that does follow $y' = 0$ in Figure 2B will give a value of $p_{xy'} = 0$. Third, nonlinear relationships between the different structure-reactivity parameters will give curved lines and edges in the diagrams and can lead to apparent inconsistencies when the direction of the reaction coordinate is estimated from two sets of structure-reactivity relationships.

The directions of the reaction coordinate shown in Tables III and IV refer to the diagrams of Figures 1 and 2, respectively. For each direction of the reaction coordinate and structural change, the dashed arrow indicates the direction of movement of the transition state in response to that change, as determined by the vectors for movement in directions parallel and perpendicular to the reaction coordinate. The symbols following refer to the direction of the change in particular structure-reactivity coefficients: the symbol ± means that the change is ambiguous, depending on the ratio of the energy gradients and the exact direction of the reaction coordinate.

The shifts upon changing the energy of an edge or corner of the diagram are evaluated as follows, taking the addition of an electron-withdrawing substituent to the nucleophile in a class e reaction as an example (Figure 6).

(1) An electron-withdrawing substituent on the nucleophile raises the energy of the top relative to the bottom of the diagram, as indicated by the small arrows at the top of Figure 6A. The resulting change in the gradient along the y axis is divided into its components in the directions parallel and perpendicular to the reaction coordinate. (This change corresponds to an increase in e of eq 3. The changes parallel and perpendicular to the reaction coordinate are $\Delta e \sin \theta$ and $\Delta e \cos \theta$, respectively, where θ is the angle between the reaction coordinate and the x axis, as shown in Figure 6B).



Curvatures a	Curvatures b	p_x	p_y	p_{xy}
+	− (c=0)	−	+	0
+	−	−	+	0--1/c
0	−	−	0	−1/c
+	0	0	+	−1/c
+	+	+	+	Max
0	0	0	0	−1/c
−	−	−	−	Max
0	+	+	0	−1/c
−	0	0	−	−1/c
−	+	+	−	0--1/c
−	+ (c=0)	+	−	0

Figure 7. Range of level lines, reaction coordinates, and structure-reactivity coefficients for different curvatures in rectangular diagrams.

(2) These changes in gradients cause shifts in the position of the transition state toward the direction of higher energy (uphill, Hammond effect) parallel to the reaction coordinate and toward the direction of lower energy (downhill, anti-Hammond effect) perpendicular to the reaction coordinate.[3] (The amounts of these shifts depend on proportionality constants that are determined by curvatures in the saddle point (eq 3), force constants,[3] or the "intrinsic barriers" of the Marcus treatment.[6] For proportionality constants m the shifts, z, parallel and perpendicular to the reaction coordinate are given by $z_{\parallel} = m\Delta e \sin \theta$ and $z_{\perp} = m'\Delta e \cos \theta$, respectively.)

(3) The change in the position of the transition state is the resultant (vector sum) of these changes. (The angle ϕ between the vector for this change and the reaction coordinate is given by $\tan \phi = z_{\perp}/z_{\parallel}$; the length of the vector is $z_r = z_{\parallel}/\cos \phi$.)

(4) The change in the position of the transition state is divided into its components along the x axis, α, for proton transfer, and along the y axis, β_{nuc}, for bond formation to carbon. (The angle δ between the vector describing the change and the x axis is given by $\delta = \theta - \phi$. The shifts along the x and y axes are given by $\Delta x = z_r \cos \delta$ and $\Delta y = z_r \sin \delta$, respectively. These shifts may also be obtained directly by vector addition of the components of $z_{\parallel}$ and $z_{\perp}$ along the x and y axes.)

The result of the changes illustrated in Figure 6 is that there is an increase in both α and β_{nuc}. The increase in α is required by the direction of the reaction coordinate, but the increase in β_{nuc} depends on the relative length of the vectors perpendicular and parallel to the reaction coordinate, so that a smaller gradient and larger vector perpendicular to the reaction coordinate could result in no change or even a decrease in β_{nuc}.

Qualitative Predictions for the Level Lines. A more specific characterization of the reaction surface from observed substituent effects is possible if the positions of the level lines of zero curvature in the saddle point are taken into account. The interrelationships between the directions of the level lines and structure-reactivity coefficients for the x and y axes (defined in Table I) are summarized in Figure 7. Permitted directions of the reaction coordinate, assuming that the reaction coordinate bisects the level lines, are shown by double-headed arrows and the range of possible reaction coordinate directions is indicated to the right of the diagrams. Note that the Hammond coefficients, p_x and p_y, can be either positive or negative for any direction of the reaction coordinate, except for the limiting values of 0 and 90°.

The relationships of substituent effects on central atoms to the curvatures (a', b', and c') and directions of the level lines are the same as those shown in Figure 7 when these substituent effects are described by a diagram with rectangular coordinates, such as Figure 2B. A summary of these relationships for a square diagram with diagonal axes, such as Figure 2A, is shown in Figure 8. The direction of the reaction coordinate is not shown in Figure 8 because this direction is not independent of the angle between the x' and y' axes; however, the reaction coordinate presumably passes between the lower left and upper right quadrants of the diagrams in Figure 8 in a direction that is close to, if not identical with that of the line bisecting the angle between the level lines. It is of interest, as shown in the bottom diagram, that when a' and b' have opposite signs and define a sufficiently narrow pass along the diagonal direction, the terms c' and $p_{xy'}$ approach zero so that there is no Cordes-type effect for substituents on the central atom; a qualitative examination of the reaction coordinate direction would predict a significant $p_{xy'}$ term for a diagonal reaction coordinate. Relationships analogous to those shown in Figure 8 hold for structure-reactivity correlations involving the y and y' coordinates, as defined in Table I.

Appendix I

Demonstration of the Linear Relationship of Brønsted-Type Coefficients and the Coordinates of the Transition State for a Linear Energy Perturbation. We consider an energy surface in n parameters $(x_1, \ldots, x_n) = \mathbf{x}$ depending on the heights $(b_1, \ldots, b_n) = \mathbf{b}$ of the edges of the surface by a linear energy gradient; i.e., the energy of a point $\mathbf{x}$ of the surface with edges at heights $\mathbf{b}$ is $E(\mathbf{x},\mathbf{b}) = E(\mathbf{x}) + \Sigma b_i x_i$. Then we will prove that the coordinates $\mathbf{x}^{\ddagger}$ of a critical point of this surface where all the x_i derivatives vanish, such as a saddle point, are identical with Brønsted-type coefficients, $\alpha_i = \partial E(\mathbf{x},\mathbf{b})/\partial b_i$. First we let $f(\mathbf{x},\mathbf{b})$ be the vector-valued function $(\partial E(\mathbf{x},\mathbf{b})/\partial x_1, \ldots, \partial E(\mathbf{x},\mathbf{b})/\partial x_n)$ and assume that its x_i derivatives, i.e., $(\partial^2 E(\mathbf{x},\mathbf{b})/\partial x_i \partial x_j)$, form a nonsingular matrix and that for some value of $\mathbf{b}$ and $\mathbf{x}$, $f(\mathbf{x},\mathbf{b}) = 0$, so that there is at least one critical point; the first assumption is justified because an arbitrarily small change in E will make it true. Then the implicit function theorem for functions of several variables shows the existence of a function $\mathbf{x}(\mathbf{b})$ such that $f(\mathbf{x}(\mathbf{b}),\mathbf{b}) = 0$; evidently $\mathbf{x}(\mathbf{b})$ gives the coordinates of the critical point with the edges at heights $\mathbf{b}$.

Now,

$$\alpha_i = \frac{E(\mathbf{x}(\mathbf{b}),\mathbf{b})}{\partial b_i} = \sum_{j=1}^{n} \frac{\partial E}{\partial x_i}(\mathbf{x}(\mathbf{b}),\mathbf{b})\frac{\partial x_i(\mathbf{b})}{\partial b_i} + \sum_{n=1}^{n} \frac{\partial E}{\partial b_k}(\mathbf{x}(\mathbf{b}),\mathbf{b})\frac{\partial b_k}{\partial b_i} = \frac{\partial E}{\partial b_i}(\mathbf{x}(\mathbf{b}),\mathbf{b}) = x_i(\mathbf{b})$$

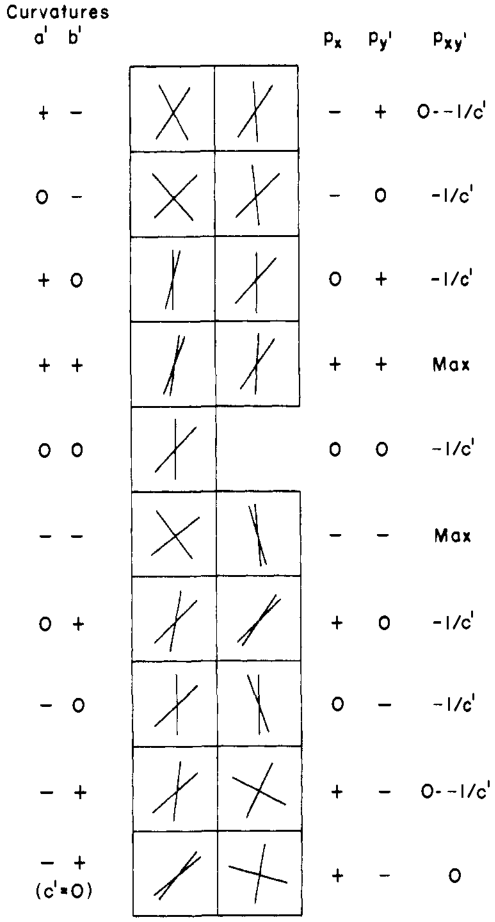


Figure 8. Examples of level lines and coefficients for substituent effects on central atoms.

since $(\partial E/\partial x_i)(\mathbf{x}(\mathbf{b}),\mathbf{b}) = 0$ by assumption. This is what we set out to prove.

Supplementary Material Available: Appendix II, outline of a mathematical treatment of multidimensional energy diagrams (3 pp). Ordering information is given on any current masthead page.

References and Notes

(1) Supported by grants from the National Science Foundation (GB-31740) and the National Institute of General Medical Sciences of the National Institutes of Health (GM20888).

(2) The term β_{nuc} represents the slope of a plot of log k against the pK values of the conjugate acids of a series of nucleophiles, pK_{nuc}.

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Nucleophilic Character of the Alkyl Radicals. 16. Absolute Rate Constants and the Reactivity–Selectivity Relationship in the Homolytic Aromatic Alkylation

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Abstract: The rate constants for the homolytic alkylation of protonated heteroaromatic bases (4-methyl- and 4-cyanopyridine, 4-methylquinoline, benzothiazole, and quinoxaline) were measured from 15 to 80 °C. A good agreement was obtained with two different kinetic models involving 5-hexenyl and *n*-heptyl radicals. The high values of the rate constants (a range of 10^5–10^8 M^{-1} s^{-1} was obtained) explain the great synthetic interest of these reactions. On the contrary the homolytic alkylation of benzene derivatives has lower rate constants (10^2 L mol^{-1} s^{-1}), and shows a very poor synthetic interest. The observed failure of the reactivity-selectivity principle (RSP) was discussed in terms of polar effects and frontier orbitals theory.

Free-radical reactions are often considered somewhat suspiciously by the synthetic organic chemists owing to their poor selectivity. This suspiciousness is largely justified by the fact that transient radicals[2] (the most important from the synthetic point of view) are very reactive species, and that the reactivity-selectivity principle (RSP) is generally held to be valid in either free-radical or ionic reactions.

We[3] have recently described several reactions of transient radicals characterized by very high positional and substrate selectivity, which, in agreement with the RSP, should be characterized by low reactivity. On the contrary, the qualitative behavior suggested not only that these reactions were fast, but also that the selectivity increased with the reactivity.[3]

In particular, the homolytic alkylation of protonated heteroaromatic bases must be considered among the most important substitution reactions of this class of aromatic compounds owing to its high yields and selectivity, its cheap availability of a large variety of free-radical sources, and its very simple experimental conditions.[3,4] As no hydrogen abstraction takes place from alkyl groups in protonated heteroaromatic bases (also with high conversions) and alkyl radicals intermediate in the Hofman–Löffler–Freitag rearrangement have been successfully used in the homolytic alkylation of protonated heteroaromatic bases,[4] this last reaction must be very fast. Actually the value[5] of the rate constant for the chlorine transfer (eq 1) in Hofman–Löffler–Freitag rearrangement is higher than 10^4 L mol^{-1} s^{-1} at 30 °C and the attack of the radical I to protonated heteroaromatic bases successfully competes with the very fast reaction of eq 1.

$$\underset{\textstyle\text{I}}{RN^+H_2(CH_2)_3\dot{C}H_2} + R_2N^+HCl \rightarrow RN^+H_2(CH_2)_3CH_2Cl + R_2N^{+\cdot}H \qquad (1)$$

Moreover, the homolytic alkylation of protonated heteroaromatic bases also takes place in the presence of cupric salts,[10] which oxidize the alkyl radicals with a high rate (the rate constants[6,7] for the oxidation of primary alkyl radicals by $Cu(OAc)_2$ and $CuCl_2$ were estimated respectively as 1.2×10^6 and 1.1×10^9 L mol^{-1} s^{-1} at 25 °C). The knowledge of the absolute rate constants of the homolytic aromatic alkylation