Structure–Energy Relations, Reaction Mechanism, and Disparity of Progress of Concerted Reaction Events

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Abstract: To describe the transition state for many reactions, one needs to specify the progress of two reaction events, such as bond breaking and bond making in bimolecular displacement reactions. A physical description then requires that the reaction coordinate for a reaction series depends on two progress variables; a chemical description requires comparison with two distinct model processes or reference reactions. A theory is developed, based on Marcus' rate-equilibrium theory, which tries to meet these requirements. The normalized progress variables, x and y, are defined so that x measures mean progress and y measures disparity of progress of the two reaction events. The reference reactions are equilibria involving the species at the end points of the progress variables. One reference is the (free) energy change for the reaction itself, reagents = products, as in Marcus' theory. The other is the (free) energy change for the reaction of maximum change of disparity, i = h, where i and h are the alternative intermediates that are formed when the reaction events occur stepwise. An equation is obtained which relates the (free) energy of activation to the (free) energy changes for the reference equilibria and two intrinsic barriers. When the required thermodynamic data exist, rate constants can be predicted for an entire reaction family on the basis of a single kinetic measurement. The theory is applied with encouraging success to (i) symmetrical proton exchange between a series of benzoic acids and methanol, an example of identity reactions, (ii) reaction of hydroxide ion with a series of α-arylnitromethanes, an example of the "nitromethane anomaly", and (iii) general base catalyzed addition of alcohols to formaldehyde, an example of coupled structure–energy relationships.

The prediction of reaction rates and equilibria by means of linear free energy relationships has enjoyed wide success for many years.[1-3] As predicted to date, this method is essentially chemical. Reactions are classified by molecular and mechanistic criteria and predictions are made by simple linear correlations with analogous reference reactions.

Among chemical physicists there are currently two schools of thought concerning these relationships. One school maintains that, being based on chemical analogies, the relationships are extraphysical and will eventually be replaced by structure–energy relationships obtained by physical methods, including those of quantum mechanics. The other school, which includes this paper, maintains that the relationships reproduce an important segment of physical reality and deserve not to be replaced but to be understood on a physical basis. Such basis would need to be of broad scope and not tied to any narrowly defined physical model.

Recent work suggests that the physical rate–equilibrium theory developed by Marcus,[4] originally for outersphere electron-transfer reactions, may fit these requirements. In the particular approach that has come to be called Marcus [rate–equilibrium] theory,[4a,5-11]

one examines energy E as a function of reaction coordinate z and deduces a relationship between the activation energy $\Delta E^\ddagger$ and the energy of reaction $\Delta E°$. (The term "energy" is used here in a generalized sense and E denotes whichever of the energy functions G, H, V, ... is appropriate for the given problem.) Marcus[4] considered particularly a family of barrier functions consisting of intersecting parabolas with equal quadratic coefficients (Figure 1a) and derived eq 1. The energy parameter γ is the *intrinsic*

$$\Delta E^\ddagger = \gamma + \Delta E° /2 + (\Delta E°)^2 / 16\gamma \qquad (1)$$

barrier, i.e., the formal barrier when $\Delta E° = 0$. Subsequently it was hown[5,6] that eq 1 applies not only to intersecting parabolas but also to any barrier of scaled symmetry (defined later; it permits reversing the role of reagents and products), as well as to any barrier that can be transformed into one of scaled symmetry by a suitable redefinition of the reaction coordinate.

A few of the barriers leading to eq 1 are shown in Figures 1 and 2. These examples comprise a remarkable variety of shapes, and since the totality of possible shapes is infinite, one may expect that the range of applicability of eq 1 will be broad. This expectation becomes even greater in situations where the fit of eq 1 need not be mathematically exact: At the transition state, $dE/dz = 0$, and small deviations of real barriers from scaled symmetry should cause little error.

To integrate eq 1 into the framework of linear free energy relations, one must consider its application to a *reaction series*, defined as a set of analogous reactions in which structural changes in the reagents are limited to substitutions outside the formal reaction zone. Interactions between the substituents and the reaction zone then correspond to physical perturbations of the reaction zone.[12] On adopting the approximation that force constants of molecular vibrations are unaffected by external perturbations,[12] one finds that the intrinsic barrier γ is a constant for the reaction series. Marcus showed on this basis that, unless the substituent effects $\delta\Delta E°$ in the reaction series are large, $\delta\Delta E^\ddagger$ varies nearly linearly with $\delta\Delta E°$, with a slope in the range 0–1.[4a] In the terminology of linear free energy relations, eq 1 thus is a rate–equilibrium relationship, reproducing (at least formally) such important relations as the Brønsted catalysis law.[1,2] Moreover, Marcus' theory is consistent with two well-known rules for the description of transition states: Leffler's postulate[13] that the slope

(1) Hammett, L. P. "Physical Organic Chemistry"; McGraw-Hill: New York, 1940.

(2) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963.

(3) (a) Shorter, J. "Correlation Analysis in Organic Chemistry: Introduction to Linear Free Energy Relationships"; Clarendon Press: Oxford, England, 1973. (b) Fujita, T.; Iwamura, H. *Top. Curr. Chem.* **1983**, *114*, 119.

(4) (a) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891. (b) Marcus, R. A. *Discuss. Faraday Soc.* **1960**, *29*, 21.

(5) (a) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2667. (b) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2159. (c) Murdoch, J. R.; Magnoli, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 3792. (d) Magnoli, D. E.; Murdoch, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7465. (e) In private conversation, J. R. Murdoch has described scaled symmetry as being analogous to the symmetry of two congruent right triangles placed back to back so that the apexes coincide.

(6) Kurz, J. L. *Chem. Phys. Lett.* **1978**, *57*, 243.

(7) Miller, A. R. *J. Am. Chem. Soc.* **1978**, *100*, 1984.

(8) (a) Kreevoy, M. M.; Oh, S.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4805. (b) Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *15*, 87. (c) Kreevoy, M. M.; Lee, I. S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550.

(9) Agmon, N.; Levine, R. D. *Chem. Phys. Lett.* **1977**, *52*, 197.

(10) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

(11) (a) Lewis, E. S.; Kukes, S.; Slater, C. D. *J. Am. Chem. Soc.* **1980**, *102*, 1619. (b) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3292. This work appeared after the present manuscript had been completed. It provides data for methyl transfer similar to those of Table I for proton transfer and clearly demonstrates that disparity at the transition state varies with the substituent in S_N2 reactions. As to theory, relative to ref 11a this work moves very close to the present work. The difference is mainly one of formulation rather than of substance.

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

(13) (a) Leffler, J. E. *Science* **1953**, *117*, 340. (b) Leffler, J. E. *J. Org. Chem.* **1955**, *20*, 1202. (c) Leffler, J. E. *J. Chem. Phys.* **1955**, *23*, 2199.
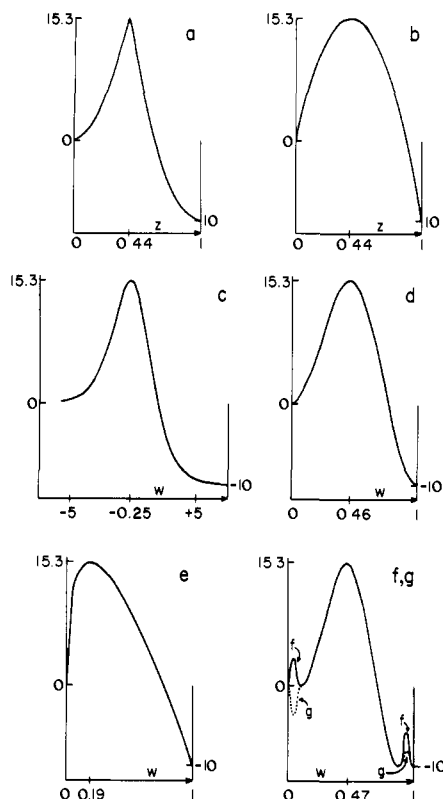
Figure 1. Examples of energy barriers for which $\Delta E^{\ddagger}$ vs. ΔE° is given by eq 1. $\gamma = 20$ kcal, $\Delta E^{\circ} = -10$ kcal. For further details, see the section on Energy Barriers.
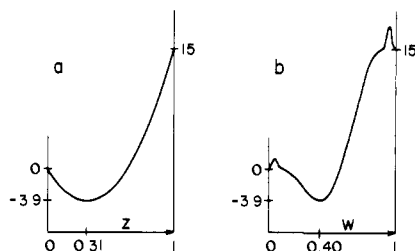

Figure 2. Examples of energy wells for which $\Delta E^{\ddagger}$ vs. ΔE° is given by eq 1. $\gamma = -10$ kcal, $\Delta E^{\circ} = 15$ kcal. Part a is a parabola. Part b uses the transformation function of eq 5 with $A = -0.05$ and $B = 0.05$. To simulate the energy bumps in part b, z must exceed the normalized range 0 to 1.

of a rate–equilibrium relationship measures the position of the transition state along the reaction coordinate and Hammond's postulate[14] that that position is displaced toward the reactants as the reaction becomes more exergonic.

Marcus' rate–equilibrium theory[4a] does have a major limitation, however: the reaction coordinate is assumed to depend on just one variable. While it is always possible to define a single variable which measures progress of reaction in a *single* reaction, it may take two or more independent variables to define progress of reaction *for an entire reaction series*.[8bc,11b,15-21] This is because most molecular reactions are the result of two or more reaction

events (such as bond breaking, bond making, solvent reorganization, ...) whose relative progress along the reaction coordinate varies for different members of the reaction series.

Variables that are suitable for expressing the progress of reaction events will be called *progress variables*. One needs as many progress variables as there are independently variable reaction events at the transition states in the reaction series. Thus, when there are two events, one needs two variables, x and y, and the reaction coordinate becomes a curved path in the x,y plane. The coordinate $z^{\ddagger}$ of the transition state becomes $z(x^{\ddagger},y^{\ddagger})$.

The analysis of energy surfaces in reaction series using two progress variables focussed initially on nuclephilic substitution on carbon.[12,19] Here the S_N2–S_N1 duality of mechanism suggested that the relationship of bond breaking to bond making along the reaction coordinate might be different in formally similar reactions.[8b,17,22] Another productive application was to acid-catalyzed addition, base-catalyzed elimination, and termolecular proton-transfer reactions involving the concerted transfer of two protons.[15,16,21] Such reaction series often give good Brønsted rate-equilibrium plots. It was found, however, that when the reaction coordinates depends on two progress variables, the description of transition states by means of linear free energy slopes becomes complicated. Such well-known simple rules as the Leffler and Hammond postulates[13,14] need no longer apply.[21]

In spite of their obvious relevance, the preceding studies do not fully integrate the physical approach, based on the model of energy surfaces with two progress variables, into the framework of linear free energy relations. I hope that the present paper will provide some missing links.

To apply the methods of linear free energy correlation one needs, above all, analogically suitable reference reactions—as many reference reactions as there are independent variables, or two in the present case of two progress variables. However, to permit a link to the physical model, the reactants and products in the reference reactions must be species or molecular configurations that appear on the energy surfaces. On that basis, one suitable choice of reference reaction is the thermodynamic process, reagents $\rightarrow$ products, i.e., the formal reaction itself. This choice also agrees with that made in the simpler case represented by eq 1 (confirmed by the appearance of ΔE° as an independent variable) and thus provides a desirable continuity of model.

For the second reference reaction there is a process that is particularly suitable as an extreme model of two asynchronous reaction events. As emphasized particularly by More O'Ferrall,[15] energy surfaces with two progress variables generally include two asymptotic reaction paths in which the two events—call them (u) and (v)—take place in consecutive steps: (u) followed by (v) and (v) followed by (u). Completion of the first event on each path represents the formation of a real or virtual intermediate whose energy is in principle predictable. The transformation of one such intermediate into the other may therefore be chosen for the second reference reaction. It will be shown that when this is done, the combination of the two reference reactions provides a natural, direct basis for predicting both the mean progress (eq 8a) and the disparity of progress (eq 8b) of the reaction events at the transition state. It will also be shown that the freedom of the reaction events to progress independently lowers the activation energy. An expression will be obtained for $\Delta E^{\ddagger}$ which consists of the same terms found in eq 1, plus a new, independent term which accounts for this lowering.

Energy Barriers

To judge the validity of structure–energy relations derived by Marcus' approach from energy surfaces with two progress variables, it is helpful first to examine one-dimensional energy barriers, especially those which lead to eq 1.

Parabolic Barriers. Marcus' original barrier[4] was a spline function consisting of two parabolas with equal quadratic coef-

(14) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

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

(16) (a) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705. (b) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937.

(17) (a) Harris, J. M.; Shafer, S. G.; Moffatt, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 3295. (b) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11. (c) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4393.

(18) Critchlow, J. E. *J. Chem. Soc., Faraday Trans. 1* **1972**, *68*, 1774.

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

(20) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2660.

(21) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.

(22) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1981**, *73*, 2700. (b) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667. (c) Bentley, T. W.; Bowen, C. T.; Morton, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466.

ficients joined back to back (Figure 1a). Kurz showed[6] that the inverted parabola shown in Figure 1b and described by eq 2 also agrees with eq 1. Both barriers use a *normalized* reaction coordinate z, defined as a reaction coordinate which varies from zero for the reagents to unity for the products. In eq 2, $\Delta E = E - E_r$ and $\Delta E^\circ = E_p - E_r$; the suscripts r and p denote "reagents" and "products". Both parabolic barriers place the reaction coordinate of the transition state at the position given in eq 3.

$$\Delta E = 4\gamma z(1 - z) + z\Delta E^\circ \tag{2}$$

$$z^* = \tfrac{1}{2} + \Delta E^\circ / 8\gamma \tag{3}$$

Scaled Symmetry. Murdoch[5a] discovered that any barrier function of a normalized reaction coordinate agrees with eq 1 if the barrier has *scaled symmetry*, a kind of symmetry that permits reversing the role of reagents and products. To specify what this means, it is convenient to rewrite the equation for the barrier function by using E rather than ΔE as the dependent variable. For example, the two parabolic barriers indicated in Figure 1, parts a and b, are written in the form of eq 4a,b, where $T[a < b]$ denotes the truth value (unity when the relation is true and zero otherwise) of the relation $[a < b]$.

Figure 1a: $E = (E_r + 4\gamma z^2)T[z < z^*] + E^* T[z = z^*] +$
$$(E_p + 4\gamma[1 - z]^2)T[1 - z < 1 - z^*] \tag{4a}$$

Figure 1b: $\quad E = 4\gamma z(1 - z) + E_p z + E_r(1 - z) \tag{4b}$

In this representation, a barrier function E has scaled symmetry if the simultaneous substitution of E_p for E_r, E_r for E_p, $1 - z$ for z, and $1 - z^*$ for z^* does not change it. A brief inspection will show that both parabolic barriers have scaled symmetry. Murdoch has given tests for scaled symmetry in other representations.[5a,e]

Barrier functions of scaled symmetry can be transformed into other barrier functions of scaled symmetry by suitable redefinition of the reaction coordinate. Let s denote a normalized reaction coordinate and $E(s)$ have scaled symmetry. Murdoch has shown[5a] that for any s there exists a transformation, $s \rightarrow z(s)$, such that $E(z)$ is the inverted parabola expressed by eq 2. In this sense, eq 2 encompasses all barrier functions of a normalized reaction coordinate that have scaled symmetry.

Unsymmetrical Barriers, Unnormalized Reaction Coordinates. Kurz has suggested an elegant method for generating additional barriers that are consistent with eq 1.[6] Let w denote any continuous reaction coordinate in the range w_r to w_p (from reagents to products). Let $z(w)$ be a single-valued function of w which satisfies the conditions that $z(w_r) = 0$ and $z(w_p) = 1$. Substitution of $z(w)$ in eq 2 then generates a function $\Delta E(w)$ which agrees with eq 1. Kurz pointed out that when $z(w) = [\exp(w)]/[1 + \exp(w)]$, the reaction coordinate varies from $-\infty$ for w_r to $+\infty$ for w_p, and substitution in (2) generates an Eckardt barrier (Figure 1c) with parameters γ and ΔE°.[6] When $z = \sin^2(\pi w/2)$, $0 \le w \le 1$, there results a barrier of the type (Figure 1d) often used for representing conformational changes. When $z = w^{1/2}$, $0 \le w \le 1$, there results a barrier of marked asymmetry (Figure 1e).

While $z(w)$ must be a single-valued function of w, the inverse function, $w(z)$, need not be single valued. This allows the construction of barrier functions with two or more maxima, so that the highest maximum conforms to eq 1. Thus Figure 1, parts f and g, shows barriers based on the function (5).

$$z = A \sin^2(10\pi w)T[w \le 0.1] +$$
$$\sin^2(5\pi w/8 - \pi/16)T[0.1 < w \le 0.9] +$$
$$[1 + B \sin^2(10\pi - 10\pi w)]T[0.9 < w]; \; 0 \le w \le 1 \tag{5}$$

In Figure 1f, $A = 0.05$ and $B = -0.05$. In Figure 1g, $A = -0.05$ and $B = -0.02$. In both cases, ΔE° is the energy change for the overall reaction ($w = 0 \rightarrow w = 1$), and the transition state for the overall reaction is represented by the central high maximum. The overall activation energy ΔE^* thus agrees with eq 1. Figure 1f simulates a reaction whose reaction coordinate has two subsidiary energy bumps. Figure 1g simulates a reaction whose reaction coordinate has one bump and one dip. (In the region of the dip, z is negative.)

Energy Wells. Magnoli and Murdoch[5d] have generalized the method of Kurz[6] in two respects: First, they showed that the barrier function into which $z(w)$ may be substituted can be any member of a quadratic family of functions, described by them, which includes eq 2. This generalization further increases the diversity of barrier functions $\Delta E(w)$ which agree with eq 1. Second, they found that the energy parameter γ may be negative, so that the "barrier" function $\Delta E(w)$ becomes an energy well. Both conceptions were tested by applying eq 1 to the formation of proton-bound dimers in gas-phase proton-transfer reactions.[5d]

When γ is negative and the "barrier" is an energy well, the "activation energy" ΔE^* computed from eq 1 is negative and unrelated to any real rate constant. Nevertheless, the concept that an energy well is equivalent to a negative barrier will be quite useful when there are two progress variables. It will be noted, therefore, that energy wells have the same attributes for transformability into parabolic shape as do energy barriers. Examples of a model energy well and the parabolic function into which it can be transformed are shown in Figure 2.

Deviations from Equation 1. Validity of eq 1 requires appropriate barrier shapes for all members of the reaction series and reaction coordinates that depend on a single progress variable. The latter implies that γ for the reaction series is a function of $|\Delta E^\circ|$ and, in particular, that γ is practically constant if $|\Delta E^\circ|$ is of the order of γ or less. Supposing for the moment that the requirement of a single progress variable is met, it is convenient to discuss the other issues together.

It follows from eq 2 and 3 that, in order for reagents and products to lie on opposite sides of the parabolic maximum (Figure 1b), $|\Delta E^\circ|$ must be less than 4γ. For the accommodation of high values of $|\Delta E^\circ|$, the parabola must become steeper, and γ thus loses its constancy and increases with $|\Delta E^\circ|$.[23] Also because of the high $|\Delta E^\circ|$, the reaction coordinate of the transition state approaches that of either the reagents or products, and the barrier's scaled symmetry may deteriorate because the encounter step gains in importance relative to the chemical transformation step on one side of the barrier but not on the other. Scaled symmetry and effective constancy of γ therefore tend to be lost together.

Although the frequent success of Marcus' theory in fitting experimental trends and propensities in reaction series shows that this theory is often a good first approximation, the assumption that the reaction coordinate depends on a single progress variable, it seems to me, is *always* an oversimplification. Marcus' theory should be most nearly correct for reactions with physically simple interaction mechanisms (such as triatomic displacement reactions, for which the BEBO theory, in which bond order is assumed to be conserved,[24] also gives acceptable fits).

It is desirable at this point to introduce a specific reaction series for which a single progress variable is clearly not sufficient, and which may later serve as a vehicle for calculations with two progress variables. I have chosen a series of proton-transfer identity reactions, eq 6, in which X is a variable substituent.[25a,b] Methanol is the solvent. Reagents and products are non-ionic, so that solvation effects will be in the normal range.
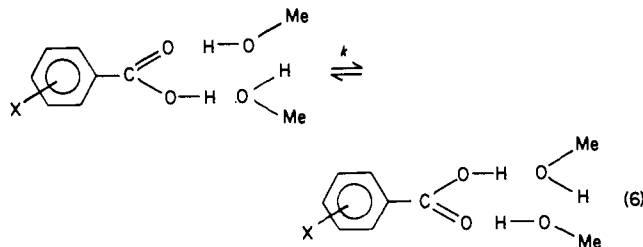
(23) (a) Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224. (b) Reference 5c, especially footnote 55. (c) See also ref 8a, ref 10.

(24) (a) Johnston, H. S.; Parr, C. *J. Am. Chem. Soc.* **1963**, *85*, 2544. (b) Although there are two bond orders, $n(1)$ and $n(2)$, in the BEBO theory there is only one independent progress variable because $n(1) + n(2) = 1$.

(25) (a) Grunwald, E.; Jumper, C. F. *J. Am. Chem. Soc.* **1963**, *85*, 2047. (b) Grunwald, E.; Jumper, C. F.; Meiboom, S. *J. Am. Chem. Soc.* **1962**, *84*, 4664. (c) Gandour, R. D.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 6967.

Table I. Data for Proton Exchange of Benzoic Acids in Methanol:
Eq 6 and 17a

	substituent				
	H	m-NO$_2$	p-NO$_2$	3,5-(NO$_2$)$_2$	o-NO$_2$
$10^{-5}k$, s^{-1}	0.66	1.8	2.25	8.0	9.5
p$K_a{}^a$	9.41	8.34	8.33	(7.28)	7.56
p$K_b{}^a$	23.4	24.1	(24.2)	(24.8)	[24.5]
$\Delta G'$, kcal	19.1	21.5	21.6	23.9	23.1
$\Delta G^{\ddagger}$, kcal	10.88	10.28	10.15	9.40	9.30
$\Delta W^{\ddagger}$, kcal	−1.96	−1.10	−1.21	−0.53	−1.01
μ, kcal	8.97	8.42	8.63	8.04	8.75
$(\Delta G')^2/16\mu{}^b$	2.65	3.36	3.39	4.15	3.88
γ, kcal	13.53	13.64	13.54	13.55	13.18
$\delta\Delta G^{\ddagger}$, eq 16	(0.00)	−0.71	−0.74	−1.50	−1.23
$\delta\Delta G^{\ddagger}$, obsd	(0.00)	−0.60	−0.73	−1.48	−1.58

^{a} Values in parentheses were estimated by linear free energy rela-
tions. The value in brackets is a mean estimate based on two models.
^{b} A mean value of μ = 8.6 kcal was used.

Rate constants k are listed in Table I. They are low enough
to indicate that the reaction is activation rather than diffusion
controlled. Although reactions with two or more proton transfers
can also proceed by stepwise mechanisms,[25c] the present reaction
mechanism is very likely concerted.[25a,b] With the possible ex-
ception of *o*-nitrobenzoic acid, steric hindrance effects are constant.

Polar effects involving the substituents are known to be small
perturbations. Thus, if a single progress variable were sufficient,
and because ΔE° = 0, constancy of γ could be expected. As a
result, k (and the corresponding free energy of activation $\Delta G^{\ddagger}$)
would be constant throughout the series. In fact (Table I), k varies
by more than a factor of 10! The next section will show that this
variation can be accounted for by introduction of a second progress
variable.

Because of the accuracy with which rate constants for pro-
ton-transfer identity reactions can be measured by dynamic NMR
and hydrogen isotopic exchange, numerous series of identity re-
actions have been examined.[26] I do not know of a single series
in which substituent effects on $\Delta G^{\ddagger}$ are experimentally insignificant
and which thus conforms rigorously to the model of a single
progress variable.

Energy Surfaces with Two Progress Variables

Choice of Progress Variables. As stated in the introduction,
in case of two progress variables one needs two analogically
suitable reference reactions whose reagents and products are
species that appear on the energy surfaces. Moreover, in order
to apply Marcus' theory, the reagents and products of any ref-
erence reaction must appear at the end points of a progress
variable. To obtain variables which satisfy these conditions, the
diagram shown in Figure 3 provides a convenient starting point.
For illustration I shall use the concerted proton-transfer reaction
7, which is a simplified version of (6) with only one molecule of
methanol.

(7)
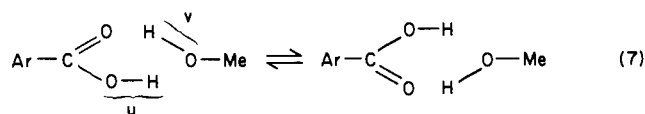
The u,v axes and the species shown at the corners in Figure
3 correspond to parts of a More O'Ferrall diagram.[15] By hy-
pothesis, the reaction consists of two, more or less concerted,
reaction events. The coordinates u and v measure the progress
of these events on a scale from 0 to 1. [In eq 7, u and v might
be bond orders of the indicated O–H bonds.] The points (0,0)
and (1,1) in the u,v plane represent the reagents and products,
respectively, and thus define a suitable reference reaction. The
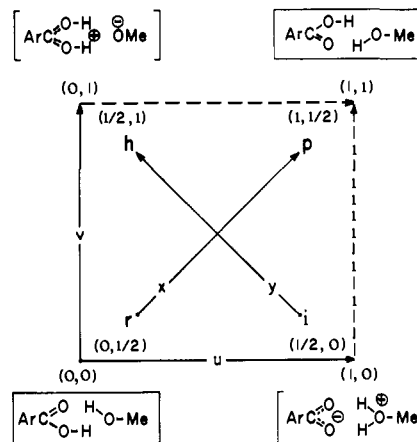points (1,0) and (0,1) in the u,v plane [the two ion-pair species

(26) (a) Grunwald, E.; Ralph, E. K. "Dynamic Nuclear Magnetic
Resonance"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New
York, 1975; pp 621–647. (b) Murdoch, J. R.; Bryson, J. A.; McMillen, D.
F.; Brauman, J. I. *J. Am. Chem. Soc.* **1982**, *104*, 600.

Figure 3. Coordinate diagram for two reaction events. The normalized
coordinates u and v represent the progress of the individual events. The
normalized coordinates x and y represent mean progress and disparity
of progress; see eq 8. The x,y axes are rotated by 45° relative to the u,v
axes, and their origins are moved so that x and y intersect at $(^1/_2,^1/_2)$.

in Figure 3] represent the two kinds of reaction intermediate that
are possible when the two reaction events occur stepwise rather
than simultaneously. The transformation of one intermediate into
other is a chemical reaction and a natural choice as reference
reaction, because it provides a standard of reference for asyn-
chronism of the reaction events.

Accordingly, an x,y coordinate system has been drawn in Figure
3 so that the x axis links reagents and products and the y axis
links the two intermediates. The x,y coordinates are produced
from the u,v coordinates by a 45° rotation, translation of the origin,
and re-normalization. The result is (8). Thus x measures the

$$x = (v + u)/2 \qquad (8a)$$

$$y = (v - u)/2 + \tfrac{1}{2} \qquad (8b)$$

mean progress and $(y - ^1/_2)$ measures the disparity of progress
for the two reaction events. The (x,y) coordinates are $(0,^1/_2)$ for
the reagents r, $(1,^1/_2)$ for the products p; $(^1/_2,0)$ for intermediate
i, and $(^1/_2,1)$ for intermediate h.

I shall use the following notation. The reference reaction r →
p is the *main reaction*. The reference reaction i → h is the
disparity reaction. Motion along x is the *mean progress mode*.
Motion along y is the *disparity mode*; see Figure 3. Energy
parameters for the main reaction are ΔE°, $\Delta E^{\ddagger}$, and γ, as before.
The analogous energy parameters for the disparity rection are $\Delta E'$,
$\Delta W^{\ddagger}$, and μ. $\Delta E'$ is defined as $E(\text{h}) - E(\text{i})$; $\Delta W^{\ddagger} = E^{\ddagger} - E(\text{i})$.
The reaction coordinate for the disparity reaction normally de-
scribes an energy well. The parameter μ is the intrinsic well depth
and is defined to be a positive number.

Equation for Energy Surfaces. We have seen that a wide variety
of energy barriers and wells based on a single progress variable
can be transformed into parabolas. It is reasonable to assume
that many energy surfaces based on two progress variables can
similarly be transformed into quadratic equations. Following
others, I shall initially represent $E(x,y)$ for a reaction series by
eq 9, in which c is a constant depending on the choice of zero level
for the energy. Equation 9 can be simplified and its parameters

$$E = \\ c + ax(1 - x) + bx + dy(1 - y) + ey + f(x - \tfrac{1}{2})(y - \tfrac{1}{2}) \quad (9)$$

related to energy parameters of the reference reactions by applying
Marcus' theory and appropriate boundary conditions, as follows.

(1) For those reactions in the series for which $u = v$ at all points
$z(x,y)$ along the reaction coordinate, $y = ^1/_2$ (eq 8b) and the
reaction coordinate coincides with the x axis. Thus, when $z =
x$ and $y = ^1/_2$, (9) must reduce to (2). It follows that $a = 4\gamma$ and
$b = \Delta E^\circ$.

(2) A similar argument can be made to obtain d and e from
energy parameters for the disparity reactions. Since each main
reaction has a complementary disparity reaction (Figure 3), the
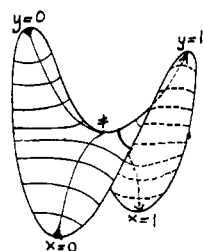
Figure 4. A hyperbolic paraboloid representing $E(x,y)$ according to eq 11. $\Delta E° = \Delta E' \approx 0$.

existence of a reaction series implies the existence of a series of disparity reactions. For each disparity reaction there is a reaction coordinate z' which runs from i ($x = \frac{1}{2}$, $y = 0$) to h ($x = \frac{1}{2}$, $y = 1$). Although z' needs to coincide with the y axis only at the end points, one may expect that there will be a group of disparity reactions for which z' coincides with the y axis at all points. For instance, all disparity reactions that are complementary to identity reactions belong in this group. The mathematical condition for membership in this group is $z'(x,y) = z'(\frac{1}{2},y)$, $0 \leq y \leq 1$. When this condition is met, (9) must reduce to (10), which is the analogue of (2) for disparity reactions. The quadratic term in (10)

$$E = \text{constant} - 4\mu y(1 - y) + y\Delta E' \qquad (10)$$

appears with a negative sign because the "barrier" of the disparity reaction normally is an energy well; see below. It then follows that $d = -4\mu$ and $e = \Delta E'$.

(3) When the given magnitudes of $\Delta E°$ and $\Delta E'$ are small enough so that γ and μ may be treated as intrinsic constants, the related perturbations of $E(x,y)$ may be treated as linear perturbations and are accounted for by the linear terms bx and ey in eq 9. Under such conditions the coefficient f in eq 9 is also an intrinsic constant.[27a]

This property enables us to evaluate f. The relevant boundary condition is that for any identity reaction in the series, the y,E plane at $x = \frac{1}{2}$ is a plane of symmetry. The cross term in $(x - \frac{1}{2})(y - \frac{1}{2})$ in (9) must therefore vanish. It follows that $f = 0$.[27c]

The final quadratic equation for $E(x,y)$ is (11).

$$E = c + 4\gamma x(1 - x) + x\Delta E° - 4\mu y(1 - y) + y\Delta E' \qquad (11)$$

Equation 11 represents a distinct gain over eq 9 because the significance of the coefficients is no longer purely formal; there is now a clear connection to energy parameters of the reference reactions. Equation 11, and particularly the subsequent eq 14 and 16, are in full agreement with equations obtained by Murdoch[20] using an approach in which disparity of progress of the reaction events is treated as a perturbation of the intrinsic barrier for the main reaction.

Equation 11 differs formally from an earlier treatment due to Critchlow[18] because the coefficients of the quadratic terms are no longer constrained to be equal. It differs formally from the treatment of Jencks and Jencks[21] by imposing the boundary condition that the series includes identity reactions, which eliminates the independent cross term in xy. Thus eq 11 constrains the reaction coordinates of all main reactions to be parallel to the x axis at the transition state, while the treatment of Jencks and Jencks, when applied to unsymmetrical reaction series, allows for variability of direction.[21,27c]

Transition States. Rate Equations. Figure 4 shows the energy surface according to (11) for an intrinsic reaction, which is now defined by the condition that both $\Delta E°$ and $\Delta E'$ are zero. The figure is a hyperbolic paraboloid normal to the x,y plane whose axis of symmetry passes through the point of intersection of the x and y axes. The reaction coordinate for the main reaction (in this case, the x axis) is the path of least energy from reagents to products: At any point $z(x,y)$, $\partial E/\partial y = 0$, while $\partial E/\partial x \neq 0$ except at the transition state.

The reaction coordinate for the disparity reaction (the y axis in Figure 4) is the path along the saddle from $y = 0$ to $y = 1$ and thus is the path of greatest energy linking the species i and h. This

becomes obvious when Figure 4 is turned upside down and the path along the saddle turns into a typical energy barrier. Thus, for the reaction coordinate of the disparity reaction, $\partial E/\partial x = 0$, while $\partial E/\partial y \neq 0$ except at the transition state.

The transition state for either reaction is defined by the dual condition that $\partial E/\partial x$ and $\partial E/\partial y$ are both zero. Since energy surfaces consistent with (11) have only one point at which this condition is met, this point must be the common transition state for both reactions. This is important: The main reaction and its complementary disparity reaction have the same transition state!

The condition that $\partial E/\partial x = \partial E/\partial y = 0$ at the transition state leads to the following coordinates (12).

$$x^* = \frac{1}{2} + \Delta E°/8\gamma \qquad (12a)$$

$$y^* = \frac{1}{2} - \Delta E'/8\mu \qquad (12b)$$

On substituting in (11), one obtains the following expressions for the energy.

Reagents: $E(0,\frac{1}{2}) = -\mu + \frac{1}{2}\Delta E' + c$ $\qquad$ (13a)

Products: $E(1,\frac{1}{2}) = \Delta E° - \mu + \frac{1}{2}\Delta E' + c$ $\qquad$ (13b)

Transition state: $E(x^*,y^*) =$
$$\gamma + \frac{1}{2}\Delta E° + (\Delta E°)^2/16\gamma - \mu + \frac{1}{2}\Delta E' - (\Delta E')^2/16\mu + c \qquad (13c)$$

Transition state − reagents:
$$\Delta E^* = \gamma + \frac{1}{2}\Delta E° + (\Delta E°)^2/16\gamma - (\Delta E')^2/16\mu \qquad (14)$$

Many problems involve relatively small changes in ΔE^*. By deriving the differential form of (14) and substituting finite increments for differentials one obtains eq 15.

$$\delta\Delta E^* = \frac{1}{2}\delta\Delta E° + (\Delta E°/8\gamma)\delta\Delta E° - (\Delta E'/8\mu)\delta\Delta E' \qquad (15)$$

Finally, by solving (11) for $E(i) = E(\frac{1}{2},0)$ and $E(h) = E(\frac{1}{2},1)$ and subtracting $E(r)$ and $E(p)$, one obtains eq 16, which states that the two intrinsic "barriers" for a reaction family are *not* independent. However, in practical tests of eq 14 it may be

$$\gamma + \mu = \frac{1}{2}[E(h) + E(i) - E(r) - E(p)] \qquad (16)$$

advisable to set aside eq 16 and treat γ and μ as independent parameters, especially when $[E(h) + E(i) - E(r) - E(p)]$ are not known with good accuracy.

While eq 12 and 13 are specific for quadratic energy surfaces of the form of (9) with $f = 0$, eq 14 and 15 are more general, applying to any series of energy surfaces which can be transformed into this quadratic form. This property is inherently less common for two-dimensional surfaces than for one-dimensional barriers, but the scope of transformability may still be broad, especially if the fit of eq 14 and 15 need not be mathematically exact. As in the case of one-dimensional barriers, the quality of fit may deteriorate, however, for reactions whose transition states lie near the edges of the coordinate diagram, where theoretical requirements of scaled symmetry on the energy surfaces may not be met in adequate approximation.

A Numerical Example. For an initial test of validity, eq 14 will be applied to the proton-transfer identity reactions in (6). The generalized energy E will be represented by the Gibbs free energy G. Since $\Delta G°$ is identically zero, eq 14 reduces to (17a).

$$\Delta G^* = \gamma - (\Delta G')^2/16\mu; \; \Delta G° = 0 \qquad (17a)$$

$\Delta G'$ for the disparity reaction will be obtained from data for acid (K_a) and base (K_b) dissociation of benzoic acids. Acid

$$ArCOOH + MeOH = ArCOO^- + MeOH_2^+ \qquad (K_a)$$

$$ArCOOH + MeOH = ArC(OH_2)^+ + MeO^- \qquad (K_b)$$

dissociation constants K_a have been measured for a series of benzoic acids directly in methanol.[25b] Base dissociation constants K_b have been reported in water, based on Hammett's acidity

function and measurements in strongly acidic aqueous solutions;[28a] values for additional meta- and para-substituted acids,[28a] and the effect of the change of solvent from water to methanol,[28b] were estimated with adequate accuracy by applying appropriate $\rho\sigma$ and mY_0 equations. pK_b for o-nitrobenzoic acid was estimated from measured results by two models: (i) that for o-NO_2, the steric effect on pK_b is the same as that on pK_a; (ii) that the ortho/para ratio of K_b for nitro is the same as that for methyl. The two methods gave similar results; the mean estimate was used. All values to be used for pK_a and pK_b are listed in Table I.

Although the intermediates shown in Figure 3 are ion pairs, I shall choose the disparity reaction to be (17b), which involves free ions. The extension of the end points of the disparity mode

$$ArCOO^- + MeOH_2^+ = ArC(OH)_2^+ + MeO^- \quad (17b)$$

$$\Delta G' = 2.303RT(pK_b - pK_a) \quad (17c)$$

from ion pairs to free ions undoubtedly complicates the shapes of the energy functions that one hopes to transform into parabolas. However, it need not spoil the transformability, and the choice of (17b) permits the use of well-defined data, which do not exist when the end points are ion pairs. Results obtained in this way for $\Delta G'$ are listed in Table I.

The next three rows of data in Table I were calculated according to eq 18. Equation 18b follows from the definition of $\Delta W^{\ddagger}$, which

$$\Delta G^{\ddagger} = -RT \ln k + RT \ln (k_B T/h) \quad (18a)$$

$$\Delta W^{\ddagger} = \Delta G^{\ddagger} - 2.303RTpK_a \quad (18b)$$

$$\Delta W^{\ddagger} = -\mu + \tfrac{1}{2}\Delta G' - (\Delta G')^2/16\mu \quad (18c)$$

$$\mu = \Delta G'/4 - \tfrac{1}{2}\Delta W^{\ddagger}(1 + [1 - \Delta G'/\Delta W^{\ddagger}]^{1/2}) \quad (18d)$$

here takes the form $\Delta W^{\ddagger} = G^{\ddagger} - G(ArCOO^-) - G(MeOH_2^+)$. Equation 18c is analogous to eq 1 but applies to the disparity mode. Equation 18 d is the solution of (18c) for μ and was used in the calculations. The values thus obtained for μ (Table I) are essentially constant; the fluctuations are consistent with the probable errors of $\Delta G'$ and $\Delta W^{\ddagger}$.

The next two rows in Table I list values obtained for $(\Delta G')^2/16\mu$ based on the average μ (8.6 ± 0.3 kcal) and for γ based on eq 17a. The last two rows compare $\delta\Delta G^{\ddagger}$ as predicted by (17a) with the experimental values.

Because the energy well μ was treated as an intrinsic constant and a mean value was used, the test of eq 17a involves one parameter to fit five data points. By the standards of linear free energy relations, the fit is good. The mean deviation is 0.12 kcal, which corresponds to 20% mean deviation for the rate constant k and equals the mean fit of Hammett's $\rho\sigma$ equation.[28c] The most deviant point is that for o-nitrobenzoic acid, where $\Delta G'$ is relatively uncertain.

Reaction Mechanism and Disparity

Description of Transition State. Structure–reactivity relationships have been used to help characterize reaction mechanisms for well over half a century. In the present approach, the reaction mechanism is defined by the number of progress variables and the nature of the disparity reactions. Ideally, the correct mechanism will fit the given structure–reactivity data and other mechanisms will not. Returning to reaction 6, the data for

Table II. Transition-State Coordinates in Symmetrical Proton Exchange of Benzoic Acids in Methanol[a]

	substituent				
	H	m-NO_2	p-NO_2	3,5-$(NO_2)_2$	o-NO_2
$x^{\ddagger\,b}$	$^1/_2$	$^1/_2$	$^1/_2$	$^1/_2$	$^1/_2$
$y^{\ddagger\,b}$	0.222	0.188	0.186	0.153	0.164
$u^{\ddagger\,c}$	0.778	0.812	0.814	0.847	0.836
$v^{\ddagger\,c}$	0.222	0.188	0.186	0.153	0.164
η^{d}	0.56	0.62	0.63	0.69	0.67

[a] Based on the mechanism in Figure 3 and data in Table I. [b] Equation 12. [c] Equation 8. [d] Equation 19.

$(\Delta G')^2/16\mu$ in Table I show that disparity makes a numerically important contribution to $\Delta G^{\ddagger}$, both absolutely and relatively. A change of mechanism, say from proton transfer to hydride transfer, would require a change of disparity reaction and thus would lead to diagnostically different values for $(\Delta G')^2/16\mu$.

Given the reaction mechanism, description of the transition state by specifying the progress coordinates is straightforward. In case of two progress variables the relevant equations are (12) and (8). For an example, Table II lists values obtained for $x^{\ddagger}$, $y^{\ddagger}$, $u^{\ddagger}$, and $v^{\ddagger}$ for reaction 6. Because the reaction series is limited to identity reactions, $x^{\ddagger}$ is identically $^1/_2$, but $y^{\ddagger}$ and the initial progress variables $u^{\ddagger}$ and $v^{\ddagger}$ (Figure 3) are different from $^1/_2$ and vary considerably with the substituent. For identity reactions, $u^{\ddagger} + v^{\ddagger}$ add up to unity, but in general that is not true.

The numbers listed in Table II show that the transition state has substantial methyloxonium benzoate ion-pair character, progress of proton transfer from the carboxyl O–H bond being well ahead of that from the methanol O–H bond. In interpreting the numbers it should be remembered that the full scales range from 0 to 1, and that the coordinates have been projected from a quadratic energy surface. Thus the coordinates cannot automatically be identified with such intuitive measures of reaction progress as bond order or partial charge. Fortunately, the topological relationships among the points representing the transition states are invariant to transformation of the progress variables, so that the *relative* values *do* have mechanistic significance. Thus one may conclude from the numbers in Table II that in reaction 6, electron-removing substituents tend to increase the methyloxonium benzoate character of the transition state by significant amounts.

It is convenient to express disparity at the transition state in terms of a single parameter by defining a *disparity index* η according to (19). Note that the definition employs the *magnitude* of ΔE°. In terms of the original variables, $\eta = (u^{\ddagger} - v^{\ddagger})/(u^{\ddagger} + v^{\ddagger})$ for reaction in the *exoergic* direction. In terms of Figure 3, η ranges from +1 to −1 as the transition state moves along the disparity coordinate from state i to state h. Values of η for reaction 6 are included in Table II.

$$\eta = (\Delta E'/4\mu)/(1 - |\Delta E^\circ|/4\gamma) \quad (19)$$

Constancy of Transition-State Coordinates. A reaction mechanism, as defined here, is specified by the number of progress variables and by the nature of the disparity reactions. An array of reactions which, by this definition, all proceed with the same mechanism will be called a *mechanistic family*. Such an array is multi-dimensional, the number of dimensions being equal to the number of reagent species and environmental variables that can be varied independently without changing the mechanism. A reaction series is a particular row or column of such an array in which only one of the variables is changing. A mechanistic family thus comprises a large number of reaction series.

Mean progress and disparity of progress at the transition state need not be constant, even within the relatively narrow confines of a reaction series. In the case of two progress variables this is clear from eq 12, since both ΔE° and $\Delta E'$ may vary with the reaction. In many reaction series these changes are relatively small, however, so that the coefficients $\Delta E^\circ/8\gamma$ and $\Delta E'/8\mu$ in eq 15 remain nearly constant. In such series the transition-state coordinates are essentially constant. A number of extensive reaction series of this type were documented recently by Bordwell

(27) (a) When $|\Delta E^\circ|/\gamma$ and/or $|\Delta E'|/\mu$ are so large that the approximation of linear perturbations becomes inadequate, f becomes a function of $\Delta E^\circ \Delta E'$. It is likely that in a power series expansion of f, the leading term is of higher than first power in $\Delta E^\circ \Delta E'$. (b) When γ and μ may be regarded as intrinsic constants, it follows from ref 16 that substituent effects on $[E(h) + E(i) - E(r) - E(p)]$ vanish. For identity reactions it then follows that $\delta[E(h) - E(r)] = -\delta[E(i) - E(r)]$. (c) A symmetry-independent alternate condition for $f = 0$ is that the disparity $|v - u|$ goes through a maximum at the transition state.

(28) (a) Stewart, R.; Yates, K. *J. Am. Chem. Soc.* **1960**, *82*, 4059. (b) $pK_a(HA^+,MeOH) - pK_a(HA^+,HOH) = 0.8$ (estimate). $pK_b(HA,MeOH) = 16.92 - pK_a(HA^+,MeOH)$. 16.92 is the pK(autoprotolysis) of MeOH. (c) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.

adn Hughes[29] and interpreted in terms of constancy of transition-state coordinates. The present view differs from theirs, however, in that the constancy is thought to be fundamentally approximate rather than exact.

The disparity coordinate at the transition state can be expected to vary widely within a reaction series when the energies $E(i)$ and $E(h)$ of *both* disparity species happen to be only slightly greater than that of the transition state. In that case μ is necessarily small, and changes of normal magnitude in $\Delta E'$ according to (12b) cause relatively large changes in y^*. As a result the transition states within a reaction series move easily along the disparity coordinate and those transition-state properties that depend on resemblance to a disparity species vary considerably.

In the comparison of formally similar reactions it may be difficult to distinguish between a constant mechanism with a highly variable disparity at the transition state and a genuine change of mechanism. For instance, if μ is small and y^* approaches either zero or unity, a change whose normal effect might be that of a perturbation can shift the reaction mechanism from concerted to stepwise. Some nucleophilic substitution reactions at a saturated carbon atom, including those of *tert*-butyl[22b] and α-phenylethyl[30] halides, manifest borderline mechanisms that seem to fit this description.

Energy of Disparity Species. The disparity coordinate of the transition state according to (12b) varies linearly with $\Delta E'$ and thus depends on both the magnitude and sign of $\Delta E'$. By contrast, the activation energy according to (14) varies linearly with $(\Delta E')^2$ and thus depends only on the magnitude of $\Delta E'$. While the more stable disparity species thus has the greater weight in determining the structure of the transition state, both species have symmetrical status in determining the activation energy. In quantitative applications the energies of both disparity species must be known.

Because of the exotic nature of many disparity species, it is not usual for the energies of both species to be known by direct measurement, and some of the required values must be predicted. Fortunately one can rely on semiquantitative methods for making such predictions in many problems of interest. However, instead of giving a review of such methods I shall, in the following, discuss two kinds of cases that strike me as inherently difficult: First, the kind in which the More O'Ferrall plane is essentially a triangle because only three of the corners are occupied by definable chemical species; they are the reagents r, the products p, and one disparity intermediate i. The fourth corner is not a species but corresponds to the asymptotic limit of a repulsion branch. In the second kind of cases to be discussed, the nature of the reaction events is such that one or both of the disparity "intermediates" are unstable states rather than metastable species.

When the More O'Ferrall plane is essentially a triangle, let the (x,y) coordinates be $(0,^{1}/_{2})$ for the reagents r, $(1,^{1}/_{2})$ for the products p, and $(^{1}/_{2},0)$ for the disparity species i. Assume, as before, that $E(x,y)$ in the triangle is reproduced by a quadratic equation of the form of (11) with parameters γ, μ, and $(\Delta E')'$. Let $E(x,y)$ be extrapolated outside the triangle and let $E(h)'$ denote the extrapolated value of the energy at the corner point $(^{1}/_{2},1)$. Apply eq 16 and assume that $\gamma + \mu$ is constant for the reaction series, that is, $\delta(\gamma + \mu) = 0$. On that basis, $(\delta\Delta E')'$ is given by (20a). While direct application of (14) may not be feasible,

$$(\delta\Delta E')' = \delta[E(h)' - E(i)] = \delta[2E(i) - E(r) - E(p)] \qquad (20a)$$

changes in reactivity within the reaction series are then given by (20b), which is analogous to (15). The parameter s' corresponds to $(\Delta E')'/8\mu$.

$$\delta\Delta E^* =$$
$$^{1}/_{2}\delta\Delta E^\circ + (\Delta E^\circ/8\gamma)\delta\Delta E^\circ - s'\delta[2E(i) - E(r) - E(p)] \qquad (20b)$$

Unstable States as Disparity Species. In Figure 3, the ion pairs at the end points of the disparity mode are metastable species—species which occupy stationary states on the untransformed energy surfaces. After transformation to quadratic energy surfaces,

however, the points representing the ion pairs are no longer stationary points.

Reflection will show that there is no basic reason for requiring the end points of the disparity mode to be stationary states.[17b] It is sufficient that the electronic and molecular structures at the end points be clearly defined and that the energy surface between the end points be transformable into quadratic form. Thus the disparity reaction need not be a real reaction involving metastable intermediates. It may be a virtual reaction involving any two molecular configurations that provide natural models for asynchronism of the presumed reaction events.

This liberalization enlarges the scope of the present theory. While not changing any mathematical requirements on the energy functions, it eliminates physical constraints as to the nature of the concerted reaction events. For instance, reactions in which a bond-breaking event occurs simultaneously with an electronic rearrangement can now be treated, at least in principle, as will be illustrated in the next section. However, when one or both end points of the disparity mode are unstable configurations, it becomes difficult to obtain absolute energy parameters for the disparity reactions, and the use of eq 14 is practically precluded. On the other hand, relative energies $\delta\Delta E'$, such as substituent and medium effects, can often be predicted by methods of analogy, using structurally similar but stable species as models. The use of eq 15 may therefore be practical. The factor $\Delta E'/8\mu$ in (15) then becomes an adjustable parameter.

Proton Transfer of α-Nitrotoluene. The reaction of meta- and para-substituted α-nitrotoluenes with hydroxide ion in water, eq 21, proceeds with electronic rearrangement, the product being the nitronate anion rather than the electronically unrearranged carbanion conjugate base.[31] Brønsted plots of log k vs. log K for
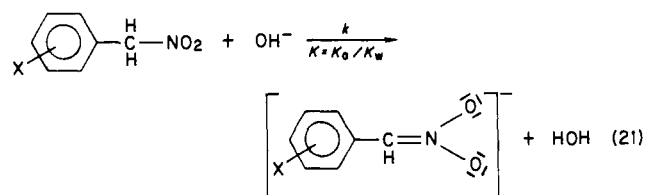
this series, as well as for other reaction series in which a proton is removed from α-nitro carbon acids, have slopes lying outside the theoretical limits, 0 to 1, established for a single progress variable.[31,32] For the reaction series in (21), for example, the Brønsted slope $\alpha = 1.54$. Since Brønsted slopes for a series of proton-transfer reactions normally fall within the theoretical limits, the phenomenon has been called the "nitromethane anomaly".[32a]

Jencks and Jencks[21] have shown that when there are *two* progress variables, Brønsted slopes lying outside the range 0 to 1 become theoretically possible. For α-nitro carbon acids in particular, they suggested that the two reaction events, proton transfer and electron rearrangement, exist in large disparity at the transition state, and that this accounts for the anomalous Brønsted slopes. I wish to develop their suggestion in terms of the present theory. For definiteness I shall proceed in a quantitative manner. However, whatever validity this development may have is qualitative.

The coordinate diagram for reaction 21, based on proton transfer and electronic rearrangement as the reaction events, is shown in Figure 5. The end points of the disparity mode are the species that result from proton transfer without electronic rearrangement: the nitronic acid from the products and the α-nitrobenzyl anion from the reagents. The former is probably a metastable and perhaps isolable species; the latter represents an unstable configuration.

The generalized energy E in the theoretical equations will be specialized to the free energy G. Because the reaction series

(29) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314.

(30) Richard, R. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361.
(31) Bordwell, F. G.; Boyle, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 3907.
(32) (a) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897. (b) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 491.
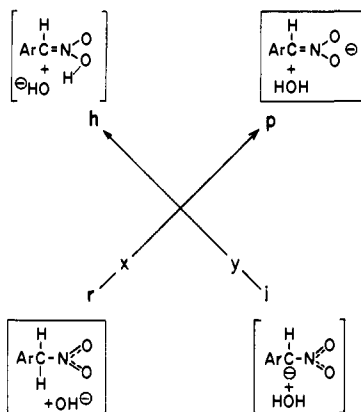
Figure 5. Coordinate diagram for reaction of meta- and para-substitued α-nitrotoluenes with hydroxide ion. The reaction events are proton transfer and electronic rearrangement.

comprises a series of meta and para substituents, it is convenient to proceed on the basis of Hammett $\rho\sigma$ equations. All $\delta\Delta G$ terms will therefore be written in the form $-2.303RT\rho\delta\sigma$. On substituting in (15) and eliminating the common factor $-2.303\ RT\ \delta\sigma$, one obtains (22). Experimental values are $\rho^* = 1.28$, $\rho(r \to p)$

$$\rho^* = \rho(r \to p)/2 + [\Delta G°/8\gamma]\rho(r \to p) - [\Delta G'/8\mu]\rho(i \to h)$$
(22a)

$$\alpha = \rho^*/\rho(r \to p)$$
(22b)

= 0.83, and α = 1.54.[31] For unsubstituted α-nitrotoluene, $\Delta G°$ = -9.71 kcal and ΔG^* = 14.42 kcal.[31] On substituting in eq 1, one obtains γ = 19.0 kcal. (This is a minimum value because eq 1 does not allow for the second progress variable. A more likely value, for subsequent use, is γ = 22 kcal.)

To estimate $\rho(i \to h)$, it is convenient first to estimate ρ for the "normal" proton transfers $r \to i$, and $h \to p$. A reasonable model for $r \to i$ is the reaction of hydroxide with meta- and para-substituted phenols; hence $\rho(r \to i) = 2.11$.[28c,33a] For $h \to$ p, I shall try two models: hydroxide + ArCH=NOH; $\rho = 0.86$.[28c] And multiplying ρ for phenols by an attenuation factor for the CH=N group. The attenuation factor is 0.46 on the basis of cinnamic/benzoic acids.[28c] This model gives $\rho(h \to p)$ = 0.97. The mean estimate is $\rho(h \to p)$ = 0.92. Accordingly, $\rho(i \to h)$ = $\rho(r \to p) - \rho(r \to i) - \rho(h \to p)$ = -2.20.

Unfortunately there are no simple, apt models for estimating $\Delta G'$ and μ, either individually or in ratio. I shall therefore use the preceding data to calculate $\Delta G'/8\mu$ from eq 22 and the disparity index η from eq 19 and then examine the results for physical acceptability and plausibility. Results are $\Delta G'/8\mu$ = 0.41 and η = 0.9.[33b] Both are less than their upper limits of $^1/_2$ and 1, respectively, and are physically acceptable. As to plausibility, the experimental facts are anomalous in their field. If one wishes to explain them in terms of disparity of two reaction events at the transition state, perhaps one ought not be surprised if the disparity index is high. By comparison, for the proton transfer reaction 6, which is *not* regarded as anomalous, η was found to be in the range 0.56–0.69 (Table II).

If the preceding mechanism is valid, several conclusions follow. (1) The data establish unambiguously the *sign* of the disparity. At the transition state, the progress variable for proton transfer is ahead of that for electron rearrangement.

(2) On substitution in (12), one finds that at the transition state, $x^* = 0.45$ and $y^* = 0.09$. Transforming from x,y to u,v coordinates (Figure 3 and eq 8) one finds that u^* (progress variable for proton transfer) = 0.86 and v^* (progress variable for electronic rearrangement) = 0.04. The transition state therefore resembles a carbanion. However, even though electronic rearrangement is not far advanced, the freedom, for it to occur at all, results in a significant lowering of ΔG^*.

(3) Because the main reaction and the disparity reaction share a common transition state, the geometrical structure of the transition state must be such that the proton can form weak bonds
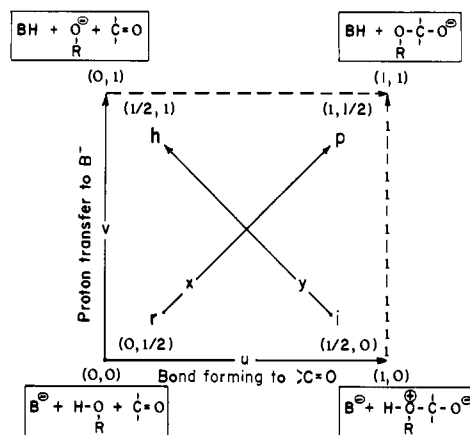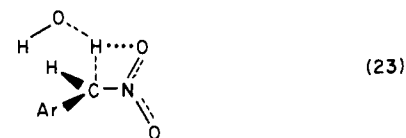

Figure 6. Coordinate diagram for base-catalyzed addition of alcohols to carbonyl compounds. The reaction events are nucleophilic addition of ROH to >C=O and proton transfer from ROH to B⁻.

to both carbon and oxygen, as in (23). This places constraints on the directions from which hydroxide ion may attack.

(23)

(4) Because of the high disparity index, one may infer that the transition state and the electronically unrearranged α-nitrobenzyl anion have nearly the same energy; $|\Delta W^*|$ is probably less than 2 kcal. Hence the free energy change for electronic rearrangement $\Delta G(er) \approx \Delta G^* - \Delta G°$ = 24 kcal.

**Structure–Energy Relations**

When $\Delta E°/8\gamma$ and $\Delta E'/8\mu$ may be regarded as constant, eq 15 is formally identical with a conventional linear free energy relation in which a given reaction series is compared with two model reaction series in linear combination.[2] The connection to

$$\delta\Delta E^* = \frac{1}{2}\delta\Delta E° + (\Delta E°/8\gamma)\delta\Delta E° - (\Delta E'/8\mu)\cdot\delta\Delta E'$$
(15)

conventional linear free energy relations is much closer, however, than mere identity of mathematical form. Like any reaction, the main and disparity reactions can be represented as sums and differences of subsidiary reactions, and $\Delta E°$ and $\Delta E'$ can be represented accordingly as sums and differences of the subsidiary energy changes. It is often possible to demonstrate in this way that eq 15 is equivalent to established linear free energy relations. More important, this method leads to explicit equations which identify the empirical slopes of the linear free energy relations in terms of energy parameters for specific reactions.

To illustrate this method, I shall use a reaction whose kinetics and mechanism have been much studied,[34,35] the base-catalyzed addition of alcohols to carbonyl compounds, eq 24. The concerted

(24)
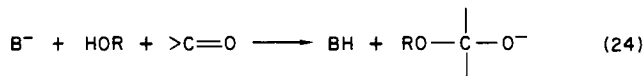
reaction events are thought to be proton transfer from HOR to B⁻ and nucleophilic addition of HOR to the carbonyl group.[35] The coordinate diagram for this mechanism is shown in Figure 6, and the disparity reaction is eq 25. To generate previously used[35] structure–energy relations, I shall relate ΔG^* for reaction 24 to

(33) (a) Prof. W. P. Jencks has pointed out that this estimate may be too small, judging by substituent effects on pK_a of 2-substituted fluorenes. pK_a values for these carbon acids have been reported by Bowden et al. and Borwell et al. [Bowden, K.; Cockerill, A. F.; Gilbert, J. R. *J. Chem. Soc. B* **1970**, 179. Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391]. (b) If $\rho(r \to i) > 2.11$, the correct results will be <0.41 and <0.9, respectively.
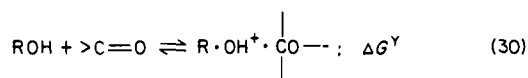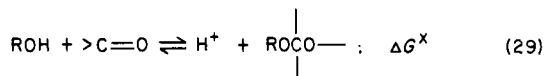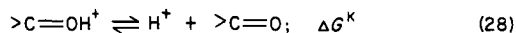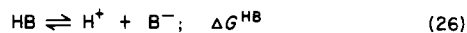(34) Bell, R. P. "The Proton in Chemistry"; 2nd ed.; Cornell University Press: Ithaca, NY, 1973; pp 183–190.
(35) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444.

$$B^- + R \cdot OH^+ \cdot \overset{|}{\underset{|}{C}}O^- \longrightarrow BH + RO^- + >C=O \qquad (25)$$

ΔG^{HB} for acid dissociation of HB and to ΔG^{HOR} for acid dissociation of HOR.

In applying eq 14 and 15, "energy" will be specialized to free energy. It is convenient to introduce the following subsidiary reactions. Free energy changes for reactions 26–30 have been

$$HB \rightleftharpoons H^+ + B^-; \quad \Delta G^{HB} \qquad (26)$$

$$ROH \rightleftharpoons H^+ + RO^-; \quad \Delta G^{HOR} \qquad (27)$$

$$>C=OH^+ \rightleftharpoons H^+ + >C=O; \quad \Delta G^K \qquad (28)$$

$$ROH + >C=O \rightleftharpoons H^+ + RO\overset{|}{\underset{|}{C}}O-; \quad \Delta G^X \qquad (29)$$

$$ROH + >C=O \rightleftharpoons R \cdot OH^+ \cdot \overset{|}{\underset{|}{C}}O-; \quad \Delta G^Y \qquad (30)$$

reported for several reaction series.[35] ΔG° for (24) and $\Delta G'$ for (25) are related to them according to (31) and (32).

$$\Delta G^\circ = -\Delta G^{HB} + \Delta G^X \qquad (31)$$

$$\Delta G' = -\Delta G^{HB} + \Delta G^{HOR} - \Delta G^Y \qquad (32)$$

The main reaction, 24, involves three reagents whose structures can vary independently: B^-, HOR, and $>C=O$. I shall therefore let ΔG^{HB}, ΔG^{HOR}, and ΔG^K be the independent variables of the structure–energy relationship. As a consequence, ΔG^X and ΔG^Y become *dependent* variables; they depend on HOR and $>C=O$. I shall represent them as functions of ΔG^{HOR} and ΔG^K, as indicated in (33). The desired structure–energy relations 35–39 are obtained from (34) by substitution of 31–33 and partial differentiation. The partial first derivatives β and β_{Nuc} are slopes of (possibly curved) Brønsted relations. The partial second derivatives are proportional to structure–reactivity coefficients as defined by Jencks and Jencks.[21]

$$\Delta G^X = \Delta G^X(\Delta G^{HOR}, \Delta G^K); \quad \Delta G^Y = \Delta G^Y(\Delta G^{HOR}, \Delta G^K) \qquad (33)$$

$$\Delta G^\ddagger = \gamma + \tfrac{1}{2}\Delta G^\circ + (\Delta G^\circ)^2/16\gamma - (\Delta G')^2/16\mu \qquad (34)$$

$$\beta = -\frac{\partial \Delta G^\ddagger}{\partial \Delta G^{HB}} = \frac{1}{2} + \frac{\Delta G^\circ}{8\gamma} - \frac{\Delta G'}{8\mu} \qquad (35)$$

$$\beta_{Nuc} = -\frac{\partial \Delta G^\ddagger}{\partial \Delta G^{HOR}} =$$
$$-\left(\frac{1}{2} + \frac{\Delta G^\circ}{8\gamma}\right)\frac{\partial \Delta G^X}{\partial \Delta G^{HOR}} + \left(\frac{\Delta G'}{8\mu}\right)\left(1 - \frac{\partial \Delta G^Y}{\partial \Delta G^{HOR}}\right) \qquad (36)$$

$$\frac{\partial^2 \Delta G^\ddagger}{\partial (\Delta G^{HB})^2} = \frac{1}{8\gamma} - \frac{1}{8\mu} \qquad (37)$$

$$\frac{\partial^2 \Delta G^\ddagger}{\partial \Delta G^{HB}\,\partial \Delta G^{HOR}} = \frac{1}{8\gamma}\frac{\partial \Delta G^X}{\partial \Delta G^{HOR}} - \frac{1}{8\mu}\frac{\partial \Delta G^Y}{\partial \Delta G^{HOR}} \qquad (38)$$

$$\frac{\partial^2 \Delta G^\ddagger}{\partial (\Delta G^{HOR})^2} = \frac{1}{8\gamma}\left(\frac{\partial \Delta G^X}{\partial \Delta G^{HOR}}\right)^2 +$$
$$\left(\frac{1}{2} + \frac{\Delta G^\circ}{8\gamma}\right)\frac{\partial^2 \Delta G^X}{\partial (\Delta G^{HOR})^2} -$$
$$\frac{1}{8\mu}\left(1 - \frac{\partial \Delta G^Y}{\partial \Delta G^{HOR}}\right)^2 + \frac{\Delta G'}{8\mu}\frac{\partial^2 \Delta G^Y}{\partial (\Delta G^{HOR})^2} \qquad (39)$$

The structure–energy relations 35–39 divide themselves into two groups: direct and conditional. Equations 35 and 37 are direct relationships; they do not depend on the existence of additional structure–energy relations. Equations 36, 38, and 39 are conditional relationships; they require that partial derivatives of ΔG^X

and ΔG^Y with respect to ΔG^{HOR} exist. There is a high a priori probability that this condition is satisfied when eq 34 applies, because reactions 24, 25, 29, and 30 involve the same kind of species; but there is no physical *necessity*.

In their experimental study,[35] Funderburk, Aldwin, and Jencks used formaldehyde as the carbonyl substrate and allowed ROH and B^- to vary independently, generating a two-dimensional array of rate constants. Their results may be summarized for the present purpose as follows. (1) For any given ROH, a plot of $\Delta G^\ddagger$ vs. ΔG^{HB} is essentially a straight line whose slope $-\beta$ varies smoothly with ΔG^{HOR} of the alcohol. Thus $\partial^2 \Delta G^\ddagger/\partial(\Delta G^{HB})^2 \approx 0$ and $\partial^2 \Delta G^\ddagger/\partial \Delta G^{HB}\partial \Delta G^{HOR} \neq 0$. (2) For any given HA, a plot of $\Delta G^\ddagger$ vs. ΔG^{HOR} is essentially a smooth, curved line which passes through a real maximum in the experimental range. Because the changes of alcohol structure are known to be mild, constancy of reaction mechanism may be assumed. The plots therefore indicate the need for a basic physical theory, such as the present one, which permits nonlinear relationships even when the reaction mechanism is constant.

From a different perspective, perhaps the most important feature of the results is simply that the relationships are smooth. This shows that the derivatives on the left-hand sides of eq 35–39 really exist and that necessary physical conditions for the existence of structure–energy relations are satisfied. Contingent upon the sufficiency of two progress variables, eq 34 will therefore apply.

Equations 35–39 can explain why the plots of $\Delta G^\ddagger$ vs. ΔG^{HB} might be straight lines while those of $\Delta G^\ddagger$ vs. ΔG^{HOR} are curved. Equation 37 indicates that a plot of $\Delta G^\ddagger$ vs. ΔG^{HB} will be an accurate straight line if γ and μ are equal. In terms of eq 35, this is because the difference $(\Delta G^\circ - \Delta G')$ is independent of ΔG^{HB}; see eq 31 and 32. However, because it is difficult to ascertain the curvature of experimental plots, the plots may be indistinguishable from straight lines even when γ and μ differ considerably. In any event, barring numerical coincidences, eq 38 predicts that the slopes $(-\beta)$ will vary with the alcohol.

Equation 36 shows, on the other hand, that plots of $\Delta G^\ddagger$ vs. ΔG^{HOR} are curved, except in improbable special cases. Among the reasons for curvature, $(\Delta G^\circ - \Delta G')$ is *not* independent of ΔG^{HOR}. Also, $\partial \Delta G^X/\partial \Delta G^{HOR}$ and $\partial \Delta G^Y/\partial \Delta G^{HOR}$ are nonzero; numerical estimates are 0.2 and −0.8, respectively. Depending on the magnitudes and signs of ΔG° and $\Delta G'$, the equation permits plots of $\Delta G^\ddagger$ vs. ΔG^{HOR} to show maxima. Thus the potential exists that this complicated phenomenology can be reproduced. Numerical tests are in progress and look encouraging.

When combined with eq 12 and 8, eq 35 and 36 relate the empirical slopes β and β_{Nuc} to progress variables at the transition state. In particular, $-\beta = x^\ddagger + y^\ddagger - \tfrac{1}{2} = v^\ddagger$ and thus is constrained to lie in the range 0–1. In terms of Figure 6, $-\beta$ is a vector whose direction coincides with that of the v axis.

On the other hand, $-\beta_{Nuc} = x^\ddagger \partial \Delta G^X/\partial \Delta G^{HOR} + (y^\ddagger - \tfrac{1}{2})(1 - \partial \Delta G^Y/\partial \Delta G^{HOR})$ and can have values outside the range 0–1. Using estimates of 0.2 and −0.8 respectively for the partial derivatives, one predicts that when $y^\ddagger = \tfrac{1}{2}$, $-\beta_{Nuc}$ is in the range 0–0.2; when $x^\ddagger = \tfrac{1}{2}$, $-\beta_{Nuc}$ is in the range −0.8 to 1.0. In terms of Figure 6, $-\beta_{Nuc}$ does *not* measure progress along the u axis.

Concluding Remarks. If the present theory is valid, it will enhance the precision with which structure–energy relationships can be used in the definition of reaction mechanisms. It will also lead to the revision of some traditional beliefs about the possible complexity of structure–energy relationships for a constant reaction mechanism. Further tests of the theory, and its extension to include more than two reaction events, are in progress. It seems possible, indeed probable, that a broad basis for the derivation of structure–energy relations from physical principles can be built in this way.