

# Energy Surfaces of Sigmatropic Shifts

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Thermal isomerization of small unsaturated hydrocarbons represents an important interface between experimental and theoretical chemistry. Organic chemists have been fascinated by these "no mechanism", uncatalyzed, and solvent-independent processes particularly when the reaction is degenerate where the reactant and product are structurally identical but have interchanged carbons and/or hydrogens.<sup>1</sup> These reactions have also captured the fancy of kineticists who have attempted to understand them in terms of dissociation energies and additivity of group equivalents to thermodynamic properties.<sup>2</sup> In cases where the energy demand of the reaction is far less than expected for complete bond homolysis and where stereospecificity is observed, the notion of concert has been formulated, which led to the development of the Woodward-Hoffmann rules.<sup>3</sup> The advent of sophisticated approximations to the Schrödinger equation and more powerful computers is beginning to allow quantum chemists to calculate energy surfaces for these reactions.<sup>4</sup>

This Account will focus on a few hydrocarbon systems which have been studied in depth; it will examine the question of whether or not these reactions are concerted and thereby provide criteria for concert, and it will pursue substituent effects on the rates of these reactions.

## Energetic Criterion of Concert

Definitions of concert abound in chemistry, but in thermal isomerizations it is possible to identify concerted reactions on the basis of energetics. Any rearrangement requires making and breaking of bonds, and it is always possible, in principle, to characterize these by labeling studies. It is further possible to envision reactions where (a) the bond-making act follows complete bond breaking or (b) the bond-breaking act follows complete bond making. This is illustrated for the 3,3 shift in Figure 1. These reactions should be classed as nonconcerted processes, and the activation energy for these reactions must be equivalent to or higher than the bond dissociation energy (BDE) of the bond being broken in (a) or the energetic demands of bond making in (b). A concerted reaction is one in which the experimental activation free energy is lower than that of either of nonconcerted process (a) or (b). This implies that the bond-breaking and bond-making events occur simultaneously, that is, they are coupled, the extent of which can only be determined by experiment. From a practical point of view it is often difficult to estimate a BDE to better than  $\pm 3$  kcal/mol and likewise for the energy demand of nonconcerted (b), and so the ener-

getic criterion of concert fails when observed activation free energies approach those estimated for nonconcerted paths a or b.

## Stereochemical Criterion

A second criterion of concert is stereospecificity. In a concerted reaction it is reasonable to expect transfer of asymmetry from reactant to product because of the coupling of bond-breaking and bond-making events. The Woodward-Hoffmann rules indicate the mode of transfer; that is, the stereochemistry of the concerted process is predicted by the rules. Unfortunately, the converse is not true. Observation of Woodward-Hoffmann "allowed" stereochemistry is consistent either with a concerted reaction or a two-step process like those depicted in Figure 1 provided that the second step is fast compared with other events that would result in stereorandomization. Thus, stereospecificity is a necessary but insufficient criterion for concert.

In cases where partial stereospecificity is observed but energetics suggest a two-step nonconcerted pathway, there is an important technique popularized by Dolbier which may prove that the reaction has an intermediate and therefore must be stepwise.<sup>5</sup> Judicious placement of a substituent, preferably deuterium, may result in the substituent altering the product distribution (with isotopic substitution, this is the product-determining isotope effect) without affecting the rate of the reaction (the kinetic isotope effect). If this can be demonstrated, then the reaction is not concerted and the first step is rate determining. However, the converse is not true. If the substituent affects both the product distribution and the rate in the same way, then either the reaction is concerted or it is two step, with the second step being rate determining. Nonetheless, in a two-step process there is the opportunity for the intermediate species to partition to two or more products which might be detected by a positive response to a Dolbier experiment. Figure 2 shows the possible reaction coordinate diagrams.

In the case of the concerted reaction a single transition state is usually assumed to relate reactants and products. However, McIver has pointed out that be-

(1) For early reviews see W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963); J. E. Baldwin, *Fortschr. Chem. Forsch.*, **15**, 281 (1970); J. J. Gajewski in "Mechanisms of Molecular Migrations", Vol. 4, B. S. Thyagarajan, Ed., Wiley, New York, 1971.

(2) For summaries, see S. W. Benson, "Thermochemical Kinetics", 2nd ed., Wiley, New York, 1976; H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969); P. J. Robinson and K. A. Holbrook, "Unimolecular Reactions", Wiley-Interscience, New York, 1972.

(3) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(4) See, for instance, D. R. Yarkony and H. F. Schaeffer, III, *J. Am. Chem. Soc.*, **96**, 3754 (1974); J. H. Davis and W. A. Goddard, III, *ibid.*, **98**, 303 (1976); E. R. Davidson and W. T. Borden, *ibid.*, **99**, 2053 (1977); D. A. Dixon, R. Foster, T. A. Halgren, and W. N. Lipscomb, *ibid.*, **100**, 1359 (1978).

(5) W. R. Dolbier, Jr., and S-H. Dai, *J. Am. Chem. Soc.*, **92**, 1774 (1970); **94**, 3946 (1972).

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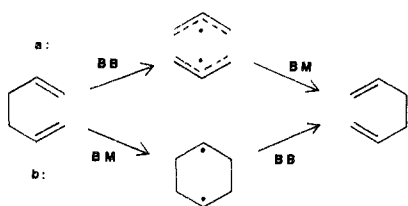


Figure 1.

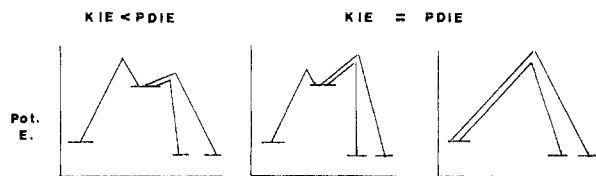


Figure 2.

cause transition states cannot have two negative force constants, symmetric species cannot be a potential-energy maximum but must be a minimum between two unsymmetrical maxima.<sup>6</sup> Each of these maxima as well as the minimum represent species which must have delocalized bonds if the reaction is concerted, and so there would appear to be no opportunity for partitioning of the intermediate species. Thus this situation should have no effect on the interpretation of a positive response to a Dolbier experiment.

### Substituent Effects on Rates

Substituent effects on the rate of hydrocarbon isomerizations depend on the nature of the reaction, concerted or nonconcerted. In particular, for nonconcerted reactions where bond breaking occurs initially, it would appear that placement of radical-stabilizing groups on carbons that will become radical sites must necessarily reduce the activation free energy of the first step by the radical-stabilization energy, RSE. Thus the  $\Delta G^\ddagger$  of the reaction will be reduced by the RSE regardless of whether the first step or second step of path a, Figure 1, is rate determining provided that the substituent does not alter the rate constant for the fast bond-making second step. For nonconcerted reactions where bond making occurs initially, it would appear that radical-stabilizing groups on carbons that will become radical sites will also lower the  $\Delta G^\ddagger$  by the RSE modified for reactant stabilization by these groups.

Concerted reactions present a far greater challenge for prediction of substituent effects. Recent work in our laboratory suggests that concerted transition-state structures change dramatically with radical-stabilizing substituents and that the  $\Delta G^\ddagger$  changes are characterized by nonlinear free energy relationships based on the effect of substituents on each of the two nonconcerted alternative paths, bond breaking and bond making.

### 3,3-Sigmatropic Shifts

In the 3,3 shift of 1,5-hexadiene itself, the  $\Delta G^\ddagger$  for pairwise interchange of C-1 and C-6 with C-3 and C-4 is 41 kcal/mol<sup>7</sup> at 250 °C while that for complete cleavage to two allyl radicals is 57 kcal/mol<sup>8</sup>. The

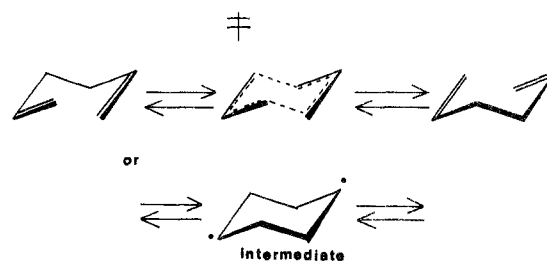


Figure 3.

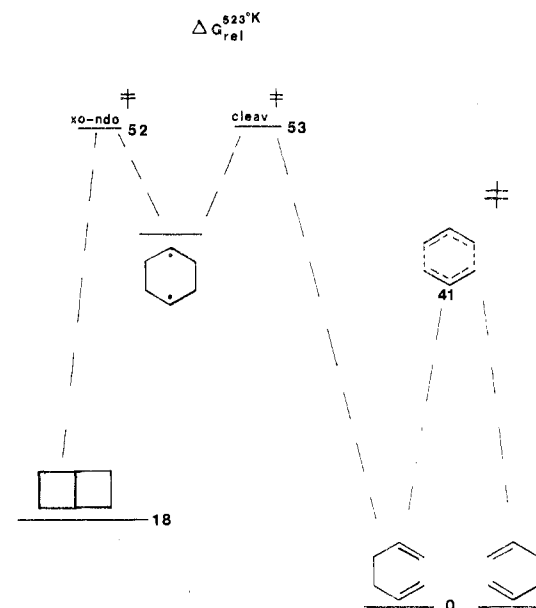


Figure 4.

classic Doering–Roth experiment<sup>9</sup> coupled with observations by Hill<sup>10</sup> indicates that a chairlike transition state is the lowest energy path, but there has been controversy over the extent of bond making between C-1 and C-6 in the transition state. As a result of multiplicative rate increase by placement of phenyl groups at C-2 and C-5 of 1,5-hexadiene (a factor of 50/phenyl), Dewar argued that a cyclohexane-1,4-diyl is involved.<sup>11</sup> Further, MINDO calculations placed this species as a minimum on the 3,3 shift energy surface, suggesting that the 3,3 shift is nonconcerted (Figure 3).<sup>12</sup>

However, consideration of the energy surface for cleavage of bicyclo[2.2.0]hexane studied by Goldstein renders unlikely the diyl nonconcerted pathway.<sup>13</sup> From stereochemical observations, the chairlike cyclohexane-1,4-diyl appears to be involved in this cleavage, and bridgehead double epimerization is a competing process which could also result from the diyl. If the diyl is responsible for both of these reactions, then it must surmount a barrier of 35 kcal/mol relative to bicyclo[2.2.0]hexane to cleave to 1,5-hexadiene. However, the free energy of formation of bicyclo[2.2.0]hexane at 250 °C is 18 kcal/mol above that of 1,5-hexadiene; therefore, 1,5-hexadiene must overcome a 53-kcal/mol barrier to

(6) J. W. McIver, Jr., *J. Am. Chem. Soc.*, **94**, 4782 (1972); J. W. McIver, Jr., *Acc. Chem. Res.*, **7**, 72 (1974).

(7) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron Lett.*, **27**, 5299 (1971).

(8) D. M. Golden, N. A. Gac, and S. W. Benson, *J. Am. Chem. Soc.*, **91**, 2136 (1969).

(9) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(10) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

(11) M. J. S. Dewar and L. E. Wade, *J. Am. Chem. Soc.*, **95**, 290 (1973); **99**, 4417 (1977).

(12) M. J. S. Dewar, G. P. Ford, M. L. McKee, H. R. Zepa, and L. E. Wade, *J. Am. Chem. Soc.*, **99**, 5069 (1977); A. Komornicki and J. W. McIver, Jr., *ibid.*, **98**, 4553 (1976).

(13) M. Goldstein and M. J. Benzon, *J. Am. Chem. Soc.*, **94**, 5119 (1972); **94**, 7147 (1972).

Table I

	BM KIE	BB KIE
	$k^{6-D_2}/k^H : 1.06$ $k^H/k^{4-D_2} : -$	$-$ $1.19$
	$k_f^{D_4}/k_f^H : 1.13$ $k_b^H/k_b^{D_4} : -$	$-$ $1.07$
	$k_f^{D_4}/k_f^H : 1.30$ $k_b^H/k_b^{D_4} : -$	$-$ $1.09$
	$k_f^{D_4}/k_f^H : 1.57$ $k_b^H/k_b^{D_4} : -$	$-$ $1.07 \pm 2\%$

form chair cyclohexane-1,4-diyl<sup>14</sup> (Figure 4). Thus the 3,3-shift is 16 kcal/mol lower in energy than cleavage to two allyl radicals and 12 kcal/mol lower than bond making to the diyl and satisfies the energetic criterion for concert within the assumptions indicated above.

If the 3,3 shift is concerted, then to what must be attributed the rate increase with phenyl substitution at C-2 and C-5? An important insight was provided by Neal Conrad who laboriously determined the secondary kinetic isotope effects (KIEs) in the 3,3 shift of various 1,5-dienes. In summary, the inverse isotope effect at the terminal carbons (the BMKIE) expressed as a percentage increase in rate relative to the hydrogen compound is roughly 1.7 times the normal isotope effect at the central carbons (the BBKIE) expressed as a percentage increase in rate relative to the deuterium compound (see Table I). However, this ratio of bond-making to bond-breaking KIEs becomes 3.0 with 2-phenyl-substituted dienes and increases to 8 with 2,5-diphenyl-1,5-hexadiene.<sup>15</sup> In contrast, Humski, Borčić, Molojčić, and Sunko found that the ratio of these KIEs is 0.3 with a 3,3-dicyano-1,5-hexadiene which undergoes the 3,3 shift at only 90 °C.<sup>16</sup> These KIEs are determined at very different temperatures so their absolute magnitudes cannot be compared, but the bond-making to bond-breaking KIE ratios should be relatively temperature independent and certainly indicate very different extents of bond making/bond breaking in the transition states for their 3,3 shifts.

The transition-state structure variation suggested by these results is consistent with chemists' intuition summarized by Thornton in the form of the "perpendicular" effect.<sup>17</sup> That is, the transition state in the 3,3 shift more resembles cyclohexane-1,4-diyl due to stabilization of this species by C-2 and C-5 phenyl substitution, but stabilization of the allyl radicals resulting from C-3,C-4 bond fission will cause the transition state to more resemble this alternative. A More O'Ferrall-Jencks (MJ) diagram nicely summarizes the

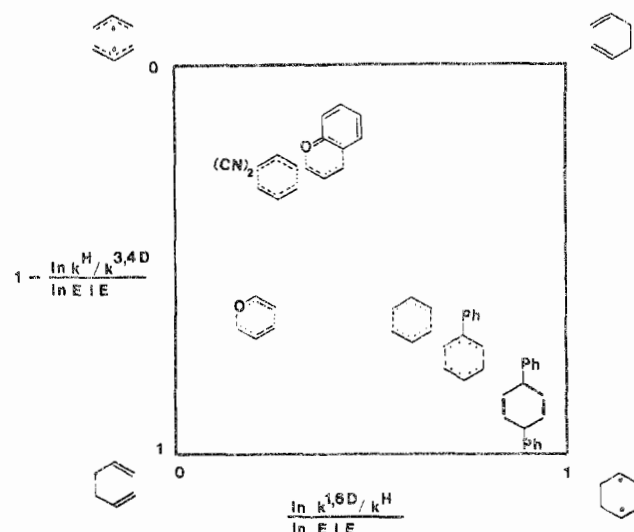


Figure 5.

observation and makes more graphic the perpendicular effect.<sup>18</sup>

The structural coordinates of the MJ diagram are those for bond breaking and for bond making and can be in bond order units. The energy coordinate can be expressed by contour lines but is left implied since the transition states for a number of 3,3 shifts are included in Figure 5. For thermoneutral 3,3 shifts the transition state should lie along the perpendicular diagonal connecting two allyl radicals and cyclohexane-1,4-diyl if there is a single symmetrical transition state. If there are two unsymmetrical transition states as suggested by McIver, then these will be symmetrically displaced about the diagonal. This diagonal represents a very large range of transition-state structure from two weakly coupled allyl radicals to two very strongly coupled ones. By this analysis concerted reactions represent a far greater challenge to chemists who wish to determine transition-state structure than reactions that are two dimensional with only one simple reaction coordinate.

Just how a transition-state structure can be determined from experimental data demands an intuitive leap. Brønsted  $\alpha$ 's in general acid catalysis are interpreted in terms of the fraction of proton transfer. Secondary deuterium kinetic isotopic effects can be similarly related to bond order changes provided steric and reaction coordinate effects do not play a major role.<sup>19</sup> If secondary deuterium isotope effects in a particular case result only from changes in the extent of bonding, then the kinetic effects can be compared to the equilibrium isotope effect in the particular case which should represent the KIE for complete change in bonding. If it is further assumed that the ratio of  $\ln$  KIE to  $\ln$  EIE is directly related to bond order changes,<sup>20</sup> then it is possible to place transition states for the 3,3 shift on the MJ diagram as depicted in Figure 5.

(18) R. A. More O'Ferrall, *J. Chem. Soc. B.*, 274 (1970); W. P. Jencks, *Chem. Rev.*, 72, 705 (1972); see R. Wehrli, H. Schmid, D. E. Bellüs, and H. J. Hansen, *Helv. Chim. Acta.*, 60, 1325 (1977), for the first published application of MJ diagrams to the 3,3 shift.

(19) G. W. Burton, L. B. Sims, and J. C. Wilson, *J. Am. Chem. Soc.*, 99, 3371 (1977); "Isotope Effects in Chemical Reactions", C. J. Collins and N. S. Bowman, Eds., Van Nostrand-Reinhold, New York, 1970.

(20) D. A. Winey and E. R. Thornton, *J. Am. Chem. Soc.*, 97, 3102 (1975), and references contained therein. Our previous papers (ref 14, 15 and 21) used an incorrect, but not highly inaccurate, formulation of the relationship between KIE's and EIE's.

(14) J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, 100, 6268 (1978).

(15) J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, 100, 6269 (1978); 101, 6693 (1979).

(16) K. Humski, R. Molojčić, S. Borčić, and D. E. Sunko, *J. Am. Chem. Soc.*, 92, 6534 (1970).

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

The 3,3 shift of allyl vinyl ether represents an interesting application of this approach since the KIEs correspond to predictions from Thornton's perpendicular effect and from extensions of Hammond's postulate elaborated by Thornton<sup>17</sup> in the form of the "parallel effect". Conrad determined the  $\ln \text{KIE}/\ln \text{EIE}$  ratios for the allyl vinyl ether rearrangement which allows the transition state to be placed on the MJ diagram of Figure 5.<sup>21</sup> It occurs "early", as might be expected for a highly exergonic reaction, and it more resembles the bond-breaking alternative because this species can be estimated to be about 7 kcal/mol more stable than the oxycyclohexane-1,4-diyl bond-formed species. An interesting comparison case is that of the aromatic Claisen rearrangement studied by McMichael.<sup>22</sup> The  $\ln \text{KIE}/\ln \text{EIE}$  ratios indicate that its transition state is more product-like as expected for an endergonic rate-determining 3,3 shift but still resembles the more stable bond-broken alternative (Figure 5).

### Quantification of Substituent Effects

The correspondence of the  $\ln \text{KIE}/\ln \text{EIE}$  ratios to predictions based on the Thornton perpendicular and parallel effects reinforces these hypotheses and suggests an approach to substituent effects on the rates of 3,3 shifts and perhaps other concerted processes. Borrowing from Jencks<sup>23</sup> who tried to mimic and quantify the MJ energy surface in carbonyl addition reactions using quadratic edge potentials and a single coupling term, it is possible to make the simple assumption of linear edge potentials in the form of eq 1. After location of

$$Z = aX + bY + cXY + d \quad (1)$$

the saddle point by setting the partial derivatives with respect to the  $x$  and  $y$  axes equal to zero and after definition of  $a$ ,  $b$ , and  $c$  in terms of  $\Delta G_x^*$ ,  $\Delta G_y^*$  (the  $\Delta G^*$ s for the nonconcerted alternatives, BB and BM) and  $\Delta G_{\text{reaction}}$ , eq 2 results. Included is a scaling factor  $p$

$$\Delta G^* = \Delta G_x^* \Delta G_y^* p / (\Delta G_x^* + \Delta G_y^* - \Delta G_{\text{reaction}}/p) \quad (2)$$

which results from definition of the  $x$  and  $y$  value of the product at point  $(p,p)$  on the surface.<sup>24</sup>

Remarkably, eq 2 reproduces the  $\Delta G^*$  for a number of 3,3 shifts of various substituted 1,5-dienes if  $p$  is a constant equal to 1.5 given reasonable values for the  $\Delta G^*$  of the nonconcerted alternatives in each case. It therefore appears that a suitable correlation of substituent effects in concerted reactions can be found in eq 2. Furthermore the predictions of eq 2 are intuitively reasonable. If a concerted transition state more resembles one over the other of the nonconcerted alternatives due to differences in stability of these, then further stabilization of the more stable alternative will affect the  $\Delta G^*$  of the concerted reaction to a greater extent than the equivalent stabilization of the less stable nonconcerted alternative. In addition, the  $\Delta G_{\text{reaction}}$  affects the  $\Delta G^*$  of the concerted reaction only to a small extent provided it is not large compared to the magnitudes of  $\Delta G_x^*$  and  $\Delta G_y^*$ .

(21) J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **101**, 2747 (1979).

(22) K. McMichael and G. L. Korver, *J. Am. Chem. Soc.*, **101**, 2746 (1979).

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

(24) J. J. Gajewski, *J. Am. Chem. Soc.*, **101**, 4393 (1979).

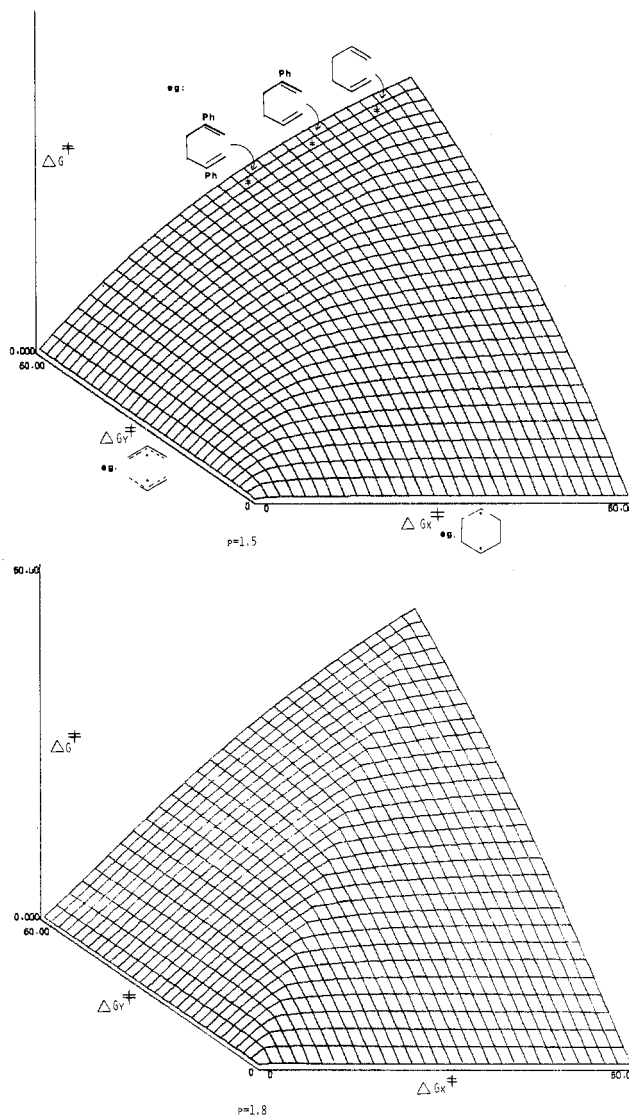


Figure 6. Activation free energy response surfaces with various values of  $p$  according to eq 3 and 4.

There are problems with eq 2 in that it does not give the same transition-state free energy when calculated in the endothermic direction and in the exothermic direction, but the deviations are small for most reactions of interest. Equation 2 also does not give correct values for  $\Delta G^*$  when the two nonconcerted alternatives are not coupled, and so ad hoc addition of a second term gives eq 3 which does better, and if the parameter  $q$  is linearly

$$\Delta G^* = \text{eq 2} \times [1 - q(\Delta G_x^* - \Delta G_y^*) / (\Delta G_x^* + \Delta G_y^* - \Delta G_{\text{reaction}}/p)] \quad (3)$$

$$q = 1.3p - 1.85 + \Delta G_{\text{reaction}}/75 \quad (4)$$

related to  $p$ , it is related by eq 4 from consideration of the behavior of eq 3 when it is applied to uncoupled nonconcerted alternatives.<sup>25</sup>

Equations 3 and 4 also mimic the relative rates of Diels-Alder addition of various cyano-substituted dienophiles to cyclopentadiene with  $p = 1.8$  and an  $\alpha$ -cyano stabilization energy of 8 kcal/mol throughout.<sup>25</sup> The success of eq 3 in reproducing  $\Delta G^*$  of concerted reactions suggests that the activation free-energy re-

(25) J. J. Gajewski, unpublished work.

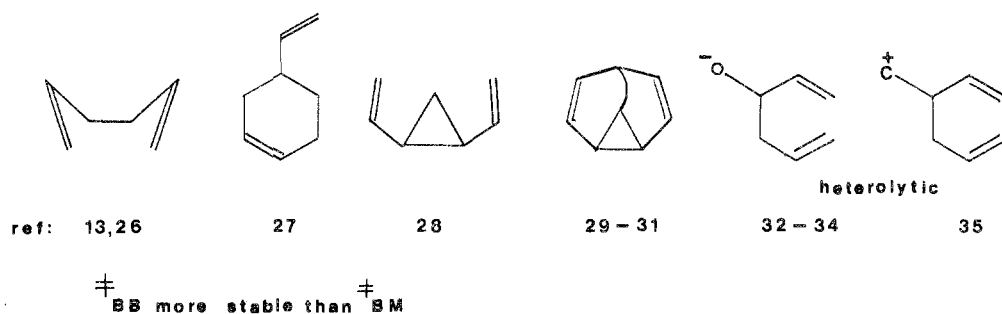


Figure 7.

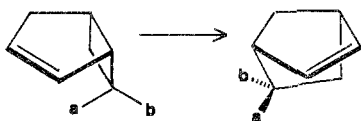


Figure 8.

sponse surface, AFERS, represented by eq 3 and 4, is the three-dimensional, concerted reaction analogue of the two-dimensional Hammett or Brønsted plot, and  $p$  is the concerted reaction equivalent of the Hammett  $\rho$  or the Brønsted  $\alpha$  or  $\beta$ . Other models for the AFERS are being pursued, but it is instructive to visualize the current AFERS model with various values of  $p$  (Figure 6).

In a number of other 3,3-shifts that have been studied, the bond-breaking alternative is more stable than the bond-making alternative. These are shown in Figure 7 along with expectations for some ionic 3,3 shifts.<sup>26-35</sup>

### 1,3 Shifts

Allylic rearrangement such as those of vinylcyclopropane to cyclopentene<sup>36a</sup> and vinylcyclobutane to cyclohexene<sup>36b</sup> have been studied kinetically and stereochemically not only in the parent cases but in bicyclic systems<sup>36c</sup> (Figure 8). In almost every case the activation free energies are 5–10 kcal/mol higher than that expected for pure bond breaking, suggesting a stepwise nonconcerted reaction. However, these reactions almost invariably occur with stereospecificity in the suprafacial-inversion mode as predicted by the Woodward–Hoffmann rules for concerted 1,3 shifts. The stereospecificity is less than 100% in most cases,

(26) K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.*, **100**, 654 (1978).

(27) W. von E. Doering, M. Franck-Newman, D. Hasselman, and R. L. Kaye, *J. Am. Chem. Soc.*, **94**, 3833 (1972); W. von E. Doering and D. M. Brenner, *Tetrahedron Lett.*, 899 (1976).

(28) J. M. Brown, B. T. Golding, and J. J. Stofko, Jr., *J. Chem. Soc., Chem. Commun.*, 319 (1973).

(29) G. Schröder, *Angew. Chem., Int. Ed. Engl.*, **2**, 481 (1963); A. Allerhand and H. S. Gutowsky, *J. Am. Chem. Soc.*, **87**, 4092 (1965).

(30) W. von E. Doering, B. M. Ferrier, et al., *Tetrahedron*, **23**, 3943 (1967); F. A. L. Anet and G. Schenk, *Tetrahedron Lett.*, 4237 (1970); H. Kessler and W. Ott, *J. Am. Chem. Soc.*, **98**, 5014 (1976).

(31) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, **88**, 183 (1966); A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *ibid.*, **96**, 2887 (1974).

(32) D. A. Evans and A. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).

(33) D. A. Evans, Abstracts, 25th National Organic Chemistry Symposium, June 19–23, 1977, Morgantown, WV; M. L. Steigerwald, W. A. Goddard III, and D. A. Evans, *J. Am. Chem. Soc.*, **101**, 1994 (1979).

(34) Professor John E. Bartmess points out that the EA of allyl radicals is 10–15 kcal/mol greater than that of  $\alpha,\beta$ -unsaturated carbonyl compounds.

(35) P. Yates and P. Eaton, *Tetrahedron Lett.*, 5 (1960); Y. Fujise, T. Katatsu, A. Kakamura, and S. Ito, *ibid.*, 4393 (1978); R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.*, **94**, 2111 (1972).

(36) (a) G. D. Andrews and J. E. Baldwin, *J. Am. Chem. Soc.*, **98**, 6705 (1976). (b) L. M. Jordon, Ph.D. Thesis, Yale University, 1974. (c) J. A. Berson, *Acc. Chem. Res.*, **5**, 406 (1972).

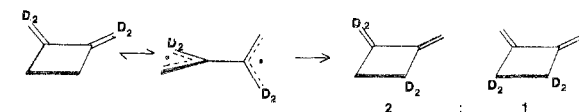


Figure 9.

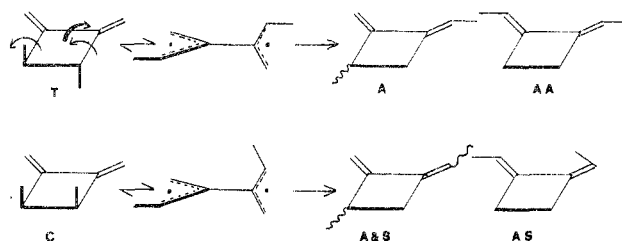


Figure 10.

but even then the next most traveled path is a Woodward–Hoffmann “forbidden”, Berson–Salem “allowed”,<sup>36c</sup> suprafacial-retention process which is utilized more than a stereorandom path. Recognition that there is the possibility of suprafacial or antarafacial use of the three-carbon component and inversion or retention of the one-carbon migrating group leads to the expectation of four distinct stereopaths—all of which should be utilized equivalently in a stereorandom reaction. Thus, 1,3 shifts have often been characterized as proceeding by separate concerted routes and not via biradicals—at least not stereorandomized biradicals.

As a conclusion from the discussion in the introduction to this account, stereospecificity is not a sufficient condition for concert in a reaction. And in these cases where various products are presumed to be formed by separate concerted processes, the application of a Dolbier experiment might provide a distinction between concert and a stepwise pathway involving a biradical resulting from bond cleavage which partitions to various products. In related systems with similar stereospecificity, it has been demonstrated that a biradical intermediate can be formed with at least partial stereospecificity, and it closes to products via preferential traversal of a least motion path to give net suprafacial inversion stereochemistry. The facts will be elaborated below, but it is clear that they do not require that all 1,3 shifts be nonconcerted; they merely demonstrate that this is a possibility and that more evidence for concert needs to be provided than just stereochemistry.

Stereospecific generation of 1,4 biradicals occurs in the degenerate rearrangement of 1,2-dimethylcyclobutane (DMCB) studied by Chung Nan Shih<sup>37</sup> and by Doering and Dolbier.<sup>38</sup> The activation free energy

(37) J. J. Gajewski and C. N. Shih, *J. Am. Chem. Soc.*, **89**, 4532 (1967).

(38) W. von E. Doering and W. R. Dolbier, Jr., *J. Am. Chem. Soc.*, **89**, 4534 (1967).

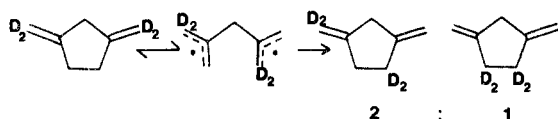


Figure 11.

is 8–15 kcal/mol higher than that predicted for complete C-3,C-4 bond fission, and a rapidly central bond rotating or fixed orthogonal 2,2'-diallyl biradical can account for the deuterium distribution<sup>37</sup> (Figure 9). Of course, a 2:1 ratio of concerted 1,3 and 3,3 shifts could also account for the label distribution, but this would be most fortuitous.

Surprisingly, pyrolysis of *trans*- and *cis*-3,4-dimethyl-DMCB leads to very different product distributions which are consistent with conrotatory ring opening in each case and closure faster than loss of stereointegrity of the allyl radicals<sup>39</sup> (Figure 10). Furthermore, the *trans* isomer reacts only twice as fast as the *cis* isomer; this does not correspond to expectations based on conrotatory ring opening of the 1,2,3,4-tetramethylcyclobutenes where the rate factor is roughly 40. A convenient rationalization for this behavior involves a third rotation about the C-1,C-2 bond in a "bevel" sense to relieve the potential steric difficulty in the conrotatory opening of the *cis* compound. It is not unreasonable that this stereomode of ring opening occurs in the *trans* case although pyrolysis of optically active *trans* material gives racemic 1,3-shift product which indicates that either the orthogonal biradical recloses with a rate slower than that for central bond rotation or that the "bevel" rotation does not occur in the ring opening of *trans* isomer.<sup>41</sup> Nonetheless the fact of conrotatory opening to a diradical indicates that 1,4-biradicals can be generated stereospecifically. Just why this is the case can be rationalized in terms of the least motion, sterically least encumbered path to a more stable conformation of the 1,4-biradical. Hasselman's excellent work with 6-methylenebicyclo-[3.2.0]heptenes may be similarly interpreted.<sup>42</sup> Electronic coupling has been proposed to account for the behavior of DMCB,<sup>43</sup> but the same stereospecificity is observed in the formation of 1,5-biradicals where the coupling effect should be substantially smaller.

Partial stereospecific conrotatory-bevel generation of 1,5-biradical and least motion inversion of configuration of the migrating carbon in a 1,3 shift have been observed by Jose Salazar, who studied the degenerate rearrangement of 1,3-dimethylenecyclopentane, DMCP. Like the rearrangement of DMCB, DMCP gives a 2:1 ratio of 1,3- and 3,3-shift products consistent with intervention of a 2,2'-diallylmethane biradical. The activation free energy is the same as the estimated  $\Delta G^\ddagger$  for complete bond fission<sup>44</sup> (Figure 11).

Likewise, pyrolysis of *trans*- and *cis*-4,5-dimethyl-DMCP gives different products consistent with a 3–10-fold preference for conrotatory ring opening as de-

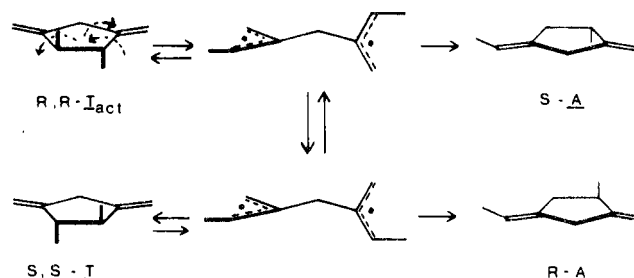


Figure 12.

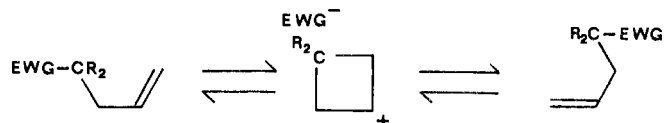


Figure 13.

termined from an extensive kinetic analysis which is required since *cis* and *trans* isomers interconvert slowly under the reaction conditions. Again the *trans* and *cis* isomers react with almost equivalent rates, indicating a third rotation in the "bevel" sense. Pyrolysis of optically active *trans* material gives the 1,3-shift product with 11.9% excess inversion of the migrating carbon after correction for racemization of starting material.<sup>44</sup> Thus, W-H predicted stereospecificity is observed, suggesting that the biradical formed by conrotatory-bevel motion closes in a least motion path competitive with stereorandomization by rotation about bonds to the central carbon (Figure 12).

Further demonstration that a biradical is involved was provided by a Dolbier experiment. When optically active *trans* material is pyrolyzed with and without four deuteriums on the exomethylenes, virtually no change in the rate of loss of optically active starting material, i.e., no KIE, is observed, but with deuterium the starting material is more extensively racemized and the 1,3- and 3,3-shift products are formed to a correspondingly smaller extent, indicating an isotope effect in the product distribution. This isotope effect is not a bonding change secondary effect but a rotational primary effect since its origin is in the reaction coordinate motion that converts the biradical to product.<sup>5,45</sup>

Analysis of 1,3 shifts in terms of a MJ diagram presents difficulty in describing the bond-making non-concerted alternative. A hypervalent carbon is required, and in simple hydrocarbon cases this would appear to be very unstable and force the potential concerted transition state to resemble the bond-breaking biradical alternative, which seems to be the case. However, if a MJ analysis applies to 1,5 shifts as well, then the hypervalent atom bond-making alternative must be accessible since the transition state cannot resemble the bond-breaking, biradical species. A case in point is the 1,5-hydrogen shift in cyclopentadiene. The BDE of the C-5,H bond is roughly 75 kcal/mol but the activation energy is only 25 kcal/mol.<sup>46</sup> A similar but not quite so dramatic situation occurs with 1,5-alkyl shifts in spiro[4.4]nona-1,3-dienes studied by Semmelhack.<sup>47</sup> Further, in 1,3-carbon shifts dramatic rate accelerations accompany substitution of electron-withdrawing groups

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in the migrating carbon.<sup>48</sup> In these cases the bond-making alternative may resemble the species involved in the solvolysis of allylcarbinyl derivatives and may be more stable than the bond-breaking alternative (Figure 13). Clearly work needs to be done to understand these reactions and to determine if the analysis above is appropriate.

### Concluding Remarks

Through the use of  $\alpha$  secondary deuterium isotope effects, the extent of bond breaking and bond making in the transition state for the concerted 3,3 shift of 1,5-hexadienes has been examined. Remarkably, the KIEs reveal a dramatic change in transition-state structure upon substitution in a manner consistent with expectations based on Hammond's postulate (Thornton's parallel effect) and on Thornton's perpendicular effect. Diagrammatic representation of this behavior in terms of a More O'Ferrall-Jencks energy surface has led to a quantitative relationship between the activation free energy for various 3,3 shifts and the activation energies for the bond-breaking and bond-making non-

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concerted alternatives that appears to be the concerted reaction analogue of the Hammett equation.

Studies of some degenerate 1,3 shifts indicate that though Woodward-Hoffmann allowed stereochemistry is observed, suggesting concert, the rearrangement is best interpreted in terms of least motion generation and closure of a biradical intermediate. Whether or not other 1,3 shifts are also nonconcerted will require execution of experiments designed by Dolbier to reveal a two-step process. Analysis of 1,3-, 1,5-, and 2,3-sigmatropic shifts in terms of the relative amounts of bond breaking and bond making provides an insight to mechanism that indicates the direction of further work.

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## Flavin Coenzymes: At the Crossroads of Biological Redox Chemistry

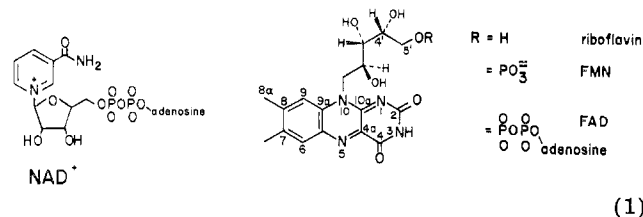
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### Nature and Scope of Flavoenzyme Redox Catalysis

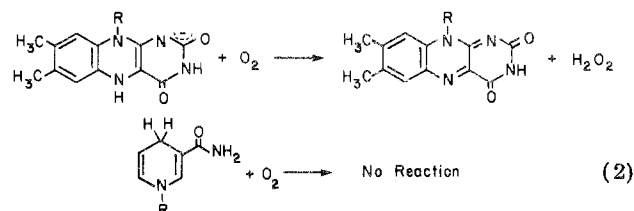
Riboflavin, vitamin B<sub>2</sub>, is a yellow tricyclic (isoalloxazine) molecule which in biological systems is phosphorylated and then adenylylated further to the two active redox coenzyme forms FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide). Flavins and nicotinamide coenzymes (eq 1) (NAD/



NADH, NADP/NADPH) are the primary acceptors for electron pairs removed from the vast majority of

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functional groups in soluble metabolites undergoing cellular oxidation or, in the reverse direction, reduction. Their substrates include amines, amino acids, alcohols, sugars, hydroxy acids, dithiols, aldehydes, ketones, and acids. These oxidations are net two-electron redox processes, and in a stoichiometric sense either flavin or nicotinamide coenzymes can be used for the same reaction. However, the tricyclic flavins are much more versatile catalysts than the monocyclic nicotinamides, as evinced by two related properties: (a) nicotinamides appear restricted to two electron pathways while flavins can undergo both facile two-electron and one-electron chemistry; (b) dihydronicotinamides are inert to oxygen, but dihydroflavins, with a central dihydropyrazine ring system, are highly reactive for reductive oxygen metabolism (eq 2). These chemical features place flavin



coenzymes squarely, and uniquely, at the crossroads of