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Multidimensional Marcus Theory: An Analysis of Concerted Reactions

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Abstract: Equations permitting the application of Marcus theory to reactions with two, three, or four reaction coordinate dimensions have been derived by analogy with the one-dimensional case. All of these equations are based on the quartic approximation to the reaction coordinate; $G_x = ax^2 + bx^3 + cx^4$. The final equations require as input only the energies of each corner intermediate and intrinsic barriers for each dimension. Computer programs have been written to allow finding of the transition state, by numerical search of the high dimensional hyperspace. These programs allow examination of potentially concerted reactions involving multiple processes. Numerical exploration shows that the conditions which must be met for a transition state to involve more than one reaction coordinate become increasingly stringent as the number increases, to the point that it is essentially impossible to have four coordinates changing at once.

Introduction

Marcus[1−3] developed a relationship between the free energy of activation for a chemical reaction and the free energy change for reaction within an encounter complex; this relationship involved an intrinsic barrier, which described the difficulty of bringing about reaction in the absence of a thermodynamic barrier, and two "work terms", the free energy costs of bringing together reactants and products to the encounter complexes. The intrinsic barrier may be interpreted as the activation energy for reaction within an encounter complex when the free energy change for chemical reaction is zero. The most commonly used form of the Marcus equation is:

$$\Delta G^{\ddagger} = \tilde{G}(1 + \Delta G^{\circ}/4\tilde{G})^2 \tag{1}$$

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\mathrm{obs}} - w_{\mathrm{R}}$$

$$\Delta G^{\circ} = \Delta G^{\circ}_{\mathrm{obs}} - w_{\mathrm{R}} + w_{\mathrm{P}}$$

where $\tilde{G}$ is the intrinsic barrier and w_{R}, w_{P} are the work terms for starting material and product.

It has been shown[4−8] that simple quadratic models of the reaction coordinate diagram (intersecting parabolas or inverted parabola) lead to the Marcus equation.

For extremely favorable or extremely unfavorable values of ΔG°, where the rate of reaction in either the forward or reverse direction would become very fast, there is for all but strictly unimolecular processes a change in the rate determining step to either diffusional approach or separation or else solvent relaxation. Thus in general one must use a three-step model, such as Eigen introduced for proton transfer[9] with the Marcus equation describing only the second step. For the extreme cases it is normally assumed[10] for chemical reactions, as opposed to electron transfer processes,[11,12] that for the second step $\Delta G^{\ddagger} = 0$ for $\Delta G^{\circ} < -4\tilde{G}$ and $\Delta G^{\ddagger} = \Delta G^{\circ}$ for $\Delta G^{\circ} > 4\tilde{G}$.

Kurz has shown that in terms of the inverted parabola model, in which free energy is expressed as a function of position along a bond order coordinate, which runs from 0 (starting material) to 1 (product), the free energy is given by

$$G = \alpha x + \beta x^2 \tag{2}$$

and the position of the transition state is given by $x^{\ddagger} = -\alpha/2\beta = 0.5 + \Delta G^{\circ}/8\tilde{G}$ with

$$\Delta G^{\ddagger} = \tilde{G}(1 + 8y + 16y^2) = \tilde{G}(1 + 4y)^2 \tag{3}$$

where $\alpha = \Delta G^{\circ} + 4\tilde{G}$, $\beta = -4\tilde{G}$, and $y = \Delta G^{\circ}/16\tilde{G}$. If the transition state is constrained to fall between 0 and 1, then the limiting values for extremes of ΔG° described in the preceding paragraph are obtained automatically. For $|\Delta G^{\circ}| > 4\tilde{G}$, $x^{\ddagger}$ will lie outside the allowed range; if $\Delta G^{\ddagger}$ is taken as the free energy at the limiting value of x, one gets the expected value.

A more realistic model of the reaction coordinate is provided by a quartic equation,[13−15] which has the correct shape at the three points concerning which we have information, the initial, final, and transition states. By contrast the inverted parabola has the correct shape only at the transition state.

$$G = ax^2 + bx^3 + cx^4 \tag{4}$$

We have shown[15] that $a = 16\tilde{G} + 3\Delta G^{\circ}$, $b = -32\tilde{G} - 2\Delta G^{\circ}$, $c = 16\tilde{G}$, $x^{\ddagger} = -1 -3b/4c = 0.5 + 3\Delta G^{\circ}/32\tilde{G}$, and

$$\Delta G^{\ddagger} = \tilde{G}(1 + 8y + 18y^2 - 27y^4) \tag{5}$$

where $y = \Delta G^{\circ}/16\tilde{G}$. Equation 4 does predict a slightly different transition state position, $x_4^{\ddagger} = 0.5 + 3\Delta G^{\circ}/32\tilde{G}$, instead

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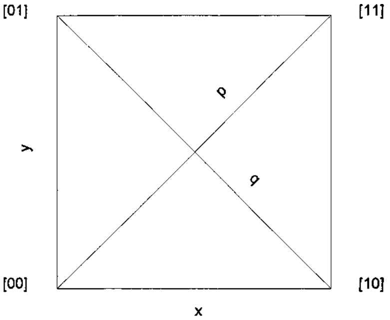


Figure 1. Two-dimensional reaction coordinate diagram. *x* and *y* are the two edge coordinates; *p* is the progress coordinate, and *q* is the disparity coordinate. (0,0) is the starting point, (1,1) is the product, and (1,0) and (0,1) are the corner intermediates corresponding to reaction along only one edge coordinate.

of the value from eq 2, $x_4^{\ddagger} = 0.5 + 4\Delta G°/32\tilde{G}$, and the range of applicability of eq 4 is $|\Delta G°| > 16\tilde{G}/3$. Within this range, eq 4 gives values very similar to those given by eq 2.

In order to discuss concerted reactions, two-dimensional versions of this treatment were derived, both in the quadratic[16] and quartic[15] approximations. This treatment has now been extended to three- and four-dimensional versions, using the quartic approximation. It will be shown that there are abundant chemical examples which require this level of complexity, and that the method can be conveniently applied.

Results

Two-Dimensional Systems. First the two-dimensional case will be reviewed, and my treatment will be contrasted with that of Grunwald.[17] I have reported[16] the two-dimensional free energy equation in the quadratic approximation as:

$$G = \alpha x + \beta x^2 + \gamma y + \delta y^2 + \epsilon xy \quad (6)$$

in terms of bond energy coordinates (“edge coordinates”), or after suitable transformation of coordinates as

$$G = (\alpha - \beta + \gamma + \delta)p + (\alpha - \beta - \gamma - \delta + \epsilon)q + (\beta + \delta + \epsilon)p^2 + (\beta + \delta - \epsilon)q^2 + 2(\beta - \gamma)pq + (-2\alpha + \beta + 2\gamma + \delta - \epsilon)/4 \quad (7)$$

in terms of progress (*p*) and disparity (*q*) coordinates, where the “progress coordinate” measures the extent of reaction proceeding directly from starting material to product, and the “disparity coordinate” measures the extent to which the transition state is displaced orthogonal to the “progress coordinate”; see Figure 1.

Grunwald reported a slightly different equation; expressed in terms of progress and disparity coordinates, his equation is:

$$G = c + 4G_{\gamma}p(1 - p) + p\Delta G° - 4G_{\mu}q(1 - q) + q\Delta G' \quad (8)$$

where G_γ and G_μ are used in place of Grunwald’s γ and μ to avoid confusion with terms in (6) or (7). The most obvious difference between eqs 7 and 8 is the absence in eq 8 of a term in *pq*. In terms of eq 7 this can be seen to imply that $\beta = \gamma$, and in turn that $\tilde{G}_x = \tilde{G}_y$. Grunwald’s equation was derived to characterize the region of the transition state, and not to describe the entire energy surface. In fact, examination of eq 8 shows that the energies of the “corner intermediates” in terms of this equation involve both thermodynamic and intrinsic barrier terms. Thus his equation cannot be correct in the vicinity of these corners.

The quartic version of this energy surface has also been reported,

$$G = a_1x^2 + a_2y^2 + a_3x^3 + a_4y^3 + a_5x^4 + a_6y^4 + a_7x^2y^3 + a_8x^3y^2 + a_9x^3y^3 + a_{10}x^2y^2 \quad (9)$$

where

$$a_1 = 16\tilde{G}_x + 3(G_{10} - G_{00})$$

$$a_2 = 16\tilde{G}_y + 3(G_{01} - G_{00})$$

$$a_3 = -32\tilde{G}_x - 2(G_{10} - G_{00})$$

$$a_4 = -32\tilde{G}_y - 2(G_{01} - G_{00})$$

$$a_5 = 16\tilde{G}_x$$

$$a_6 = 16\tilde{G}_y$$

$$a_7 = a_8 = -6(G_{11} - G_{10} - G_{01} + G_{00})$$

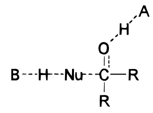
$$a_9 = 4(G_{11} - G_{10} - G_{01} + G_{00})$$

$$a_{10} = 9(G_{11} - G_{10} - G_{01} + G_{00})$$

This equation has been applied to elimination reactions,[15] amide hydrolysis,[18,19] and ester alcoholysis.[20]

Although eq 9 provides an analytical expression for the energy at any point on the reaction surface, it is algebraically intractable if one tries to derive an analytical expression for the position of the transition state. Since there is also the possibility that the analytical solution for the transition state would correspond to a forbidden region with one of the edge coordinates greater than 1 or less than 0 (in which case the free energy of activation would be at a limiting value for at least one dimension), the analytical solution would not be a complete solution to the problem in any case. Numerical solution is used instead and can be applied to this case or the higher dimensional cases now to be considered.

Three-Dimensional Version. It has been pointed out that many reaction mechanisms require a reaction cube[21−24] (Figure 2) for proper analysis, since three microscopic bond-making or -breaking processes are involved in converting starting materials to products. Cases of interest are the addition of nucleophiles to carbonyl compounds in the presence of acidic and basic catalysts,[23]



the water mediated proton switch, which has been found to be

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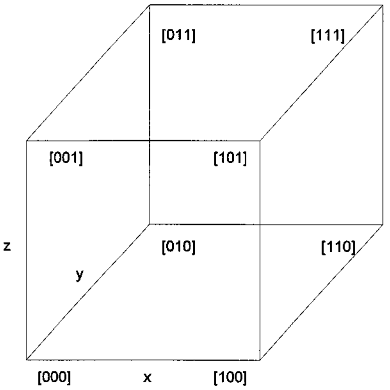
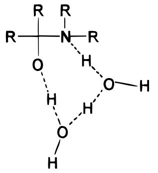
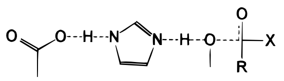


Figure 2. Three-dimensional reaction coordinate diagram. *x*, *y*, and *z* are the three edge coordinates. (0,0,0) is the starting point; (1,1,1) is the product; (1,0,0), (0,1,0), and (0,0,1) are the corner intermediates corresponding to reaction along only one edge coordinate; and (1,1,0), (1,0,1), and (0,1,1) are the corner intermediates corresponding to reaction along two edge coordinates.

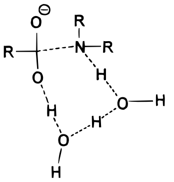
important in various carbonyl reactions or proton exchange processes,[25]



and the proton relay mechanism suggested[26] for serine proteases:

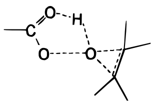


Four-Dimensional Version. Some reactions clearly need more than three reaction coordinates for a complete description. One such was encountered in our analysis of amide hydrolysis in basic solution,[19] where we considered possible concertedness



of a water mediated proton switch converting an anionic tetrahedral intermediate into an anionic zwitterionic intermediate, which would be expected to lose amine rapidly, possible concerted with the proton switch. Since the proton switch alone requires three progress variables, a four-dimensional reaction hypercube is needed to analyze amide hydrolysis; see Figure 3.

Olefin epoxidation is generally considered to be a concerted reaction,[27,28] which involves four progress variables: (1) transfer



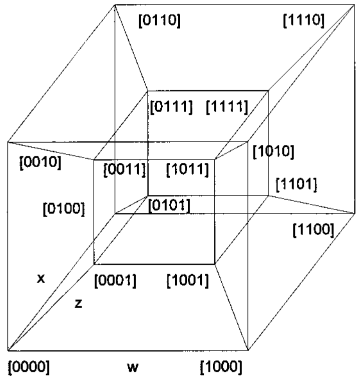
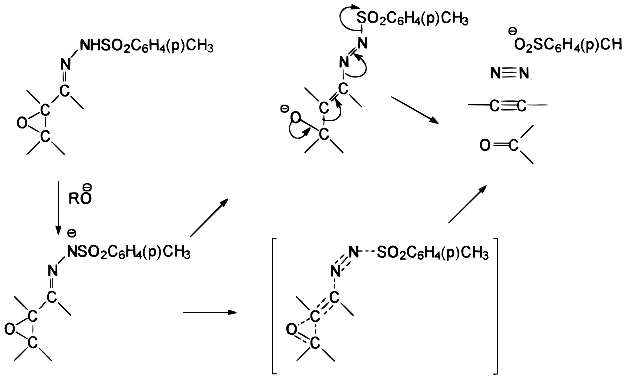


Figure 3. Four-dimensional reaction coordinate diagram. *w*, *x*, *y*, and *z* are the four edge coordinates. (0,0,0,0) is the starting point; (1,1,1,1) is the product; (1,0,0,0), (0,1,0,0), (0,0,1,0), and (0,0,0,1) are the corner intermediates corresponding to reaction along only one edge coordinate; (1,1,0,0), (1,0,1,0), (1,0,0,1), (0,1,1,0), (0,1,0,1), and (0,0,1,1) are the corner intermediates corresponding to reaction along two edge coordinates; and (1,1,1,0), (1,1,0,1), (1,0,1,1), and (0,1,1,1) are the corner intermediates corresponding to reaction along three edge coordinates.

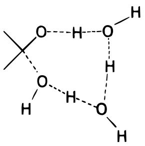
Scheme 1



of a proton between two oxygens; (2) nucleophilic attack by oxygen on the carbon−carbon double bond; (3) nucleophilic attack by carbon on the oxygen which is transferred; (4) cleavage of the oxygen−oxygen bond.

Various fragmentation reactions would, if fully concerted, require four or more progress variables. An example of hydrazone epoxide fragmentation illustrates this (Scheme 1). If the tosylhydrazone anion[29] fragments in a single transition state, then there are four bonds breaking in the process; if the reaction involved two stages, first opening the epoxide to an alkoxide ion intermediate which then fragmented, then for the fragmentation transition state only three progress variables, and a reaction cube, would be needed.

Hydration of carbonyl compounds has been suggested to involve a cyclic process involving three water molecules, one of which adds while the others act as shuttles for a proton so that the zwitterionic intermediate can be avoided.[30,31] With three



water molecules and a cyclic mechanism, there are four progress variables, and analysis of the system requires a hypercube. Thus there are abundant examples of reactions for which detailed analysis of the mechanism to decide whether concerted paths

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are likely to be favored will demand use of a four or even higher dimensional hypercube.

Now it will be shown that the equations for these energy hypersurfaces can be derived in straightforward fashion by analogy with those derived for the two progress variable case, and that with suitable computer programs which have been written, it is possible to find the lowest possible transition state separating reactants from products, provided only that the necessary energies of "corner intermediates" and intrinsic barriers for "edge reactions" are available. This can involve significant effort, for there are two "corner intermediates" for a two progress variable reaction square, six for a three progress variable reaction cube, and 14 for a four progress variable reaction hypercube.

Derivation. The equations to be presented for the reaction hypersurfaces describing potentially concerted reactions follow from four postulates.

1. *Reactants are in equilibrium with starting material or product at each point along each reaction coordinate.* This is one of the starting assumptions of transition state theory.

2. *At each section through the reaction hypersurface for which only one reaction coordinate changes, Marcus theory will apply and will be determined by the initial and final energies, and the intrinsic barrier for that coordinate.* There have been objections,[32] based on theoretical arguments , to the application of Marcus theory to many classes of organic reactions. There seems to be abundant evidence[10,33−37] that Marcus theory meets the empirical test of working in the sense of giving useful correlations and predictions. If Marcus theory can be applied to organic reactions in general, then application to a process involving partial reaction along a perpendicular coordinate follows from postulate 1.

3. *The intrinsic barrier for any reaction coordinate is independent of the values of the other reaction coordinates.* This is a necessary constraint if the equations are to be relatively simple, and the amount of input data required to be manageably small. This constraint is empirically supported.[15,16,18−20]

4. *For any reaction coordinate chosen as progress variable, at fixed values of the other cooordinates, the free energy will be a quartic function of the progress variable.* This is a frequently used assumption about the mathematical nature of reaction coordinate diagrams.[13−15] It then follows that $\Delta G^{\ddagger} = \tilde{G}(1 + 8y + 18y^2 - 27y^4)$, $y = \Delta G^{\circ}/16\tilde{G}$; this is the form of Marcus theory appropriate for quartic reaction surfaces.[15]

Given these postulates, the form of the equations follows. The advantage of using a quartic rather than a quadratic model is that it is more likely to have a realistic shape far from the transition state than would the inverted parabola version of the quadratic model. The quartic model is also likely to be more realistic than the intersecting parabola model, which may be accurate near the ends of the reaction coordinate, but is likely to be too cusp-like at the transition state. This advantage comes at the price of algebraic complexity which commonly precludes analytical solutions.

A generalized form of the equation for the energy hypersurface will now be presented. In the Supplementary Appendix there is a rigorous if somewhat tedious derivation of these equations from the condition that any section of the hypersurface must be a quartic and must obey the Marcus conditions. The pattern of the terms makes it obvious how one could extend the treatment to still higher dimensions. The numerical coefficients of Γ in the terms involving n reaction dimensions are given by $(-1)^i(3^{n-i})(2^i)$, $i = 0, ..., n$, and the numbers of terms with the same numerical coefficients for a given set of reaction dimensions are given by the coefficients in the binomial theorem expansion for $(a + b)^n$. Thus there are two terms, in $u_j^2u_k^3$ and $u_j^3u_k^2$, with coefficient $-6\Gamma_{jk}$, and six terms, in $u_j^2u_k^2u_l^3u_m^3$, etc., with coefficient $36\Gamma_{jklm}$

$$\begin{aligned}
G = {} & \sum_{i=1}^{N}\{(16\tilde{G}_i + 3\Gamma_i)u_i^2 + (-32\tilde{G}_i - 2\Gamma_i)u_i^3 + 16\tilde{G}_iu_i^4\} + \\
& \sum_{j=1}^{N-1}\sum_{k>j}^{N}\{9\Gamma_{jk}u_j^2u_k^2 + \sum_{h=1}^{h=2}(-6\Gamma_{jk})u_j^{2+\delta_{1h}}u_k^{2+\delta_{2h}} + 4\Gamma_{jk}u_j^3u_k^3\} + \\
& \sum_{j=1}^{N-2}\sum_{k>j}^{N-1}\sum_{l>k}^{N}\{27\Gamma_{jkl}u_j^2u_k^2u_l^2 + \\
& \sum_{h=1}^{h=3}(-18\Gamma_{jkl})u_j^{2+\delta_{1h}}u_k^{2+\delta_{2h}}u_l^{2+\delta_{3h}} + \\
& \sum_{h=1}^{h=3}12\Gamma_{jkl}u_j^{3-\delta_{1h}}u_k^{3-\delta_{2h}}u_l^{3-\delta_{3h}} + (-8\Gamma_{jkl})u_j^3u_k^3u_l^3\} + \\
& \sum_{j=1}^{N-3}\sum_{k>j}^{N-2}\sum_{l>k}^{N-1}\sum_{m>l}^{N}\{81\Gamma_{jklm}u_j^2u_k^2u_l^2u_m^2 + \\
& \sum_{h=1}^{h=4}(-54\Gamma_{jklm})u_j^{2+\delta_{1h}}u_k^{2+\delta_{2h}}u_l^{2+\delta_{3h}}u_m^{2+\delta_{4h}} + \\
& \sum_{h=1}^{h=4}\sum_{\substack{g=2\\ g\neq h\\ g>h}}^{g=4}36\Gamma_{jklm}u_j^{2+\delta_{1h}+\delta_{1g}}u_k^{2+\delta_{2h}+\delta_{2g}}u_l^{2+\delta_{3h}+\delta_{3g}}u_m^{2+\delta_{4h}+\delta_{4g}} + \\
& \sum_{h=1}^{h=4}(-24\Gamma_{jklm})u_j^{3-\delta_{1h}}u_k^{3-\delta_{2h}}u_l^{3-\delta_{3h}}u_m^{3-\delta_{4h}} + \\
& 16\Gamma_{jklm}u_j^3u_k^3u_l^3u_m^3\} + \text{etc.}
\end{aligned}$$

where

$$\Gamma_i = G_{\delta_{i1}\delta_{i2}\delta_{i3}\delta_{i4}\ldots} - G_{0000\ldots}$$

$$\Gamma_{jk} = \sum_{h=0}^{h=1}\sum_{g=0}^{g=1}(-1)^{h+g}G_{\epsilon_1\epsilon_2\ldots\epsilon_i\ldots\epsilon_N}$$

$$\epsilon_i = h\delta_{ij} + g\delta_{ik}$$

$$\Gamma_{jkl} = \sum_{h=0}^{h=1}\sum_{g=0}^{g=1}\sum_{f=0}^{f=1}-(-1)^{h+g+f}G_{\epsilon_1\epsilon_2\ldots\epsilon_i\ldots\epsilon_N}$$

$$\epsilon_i = h\delta_{ij} + g\delta_{ik} + f\delta_{il}$$

$$\Gamma_{jklm} = \sum_{h=0}^{h=1}\sum_{g=0}^{g=1}\sum_{f=0}^{f=1}\sum_{e=0}^{e=1}(-1)^{h+g+f+e}G_{\epsilon_1\epsilon_2\ldots\epsilon_i\ldots\epsilon_N}$$

and

$$\epsilon_i = h\delta_{ij} + g\delta_{ik} + f\delta_{il} + e\delta_{im}$$

with δ_{ij} being the Kronecker delta.

Finding the Transition State Position for a Potentially Concerted Process. The transition state is constrained to lie within the reaction square or cube or hypercube. The transition state is by definition the highest energy point on the lowest

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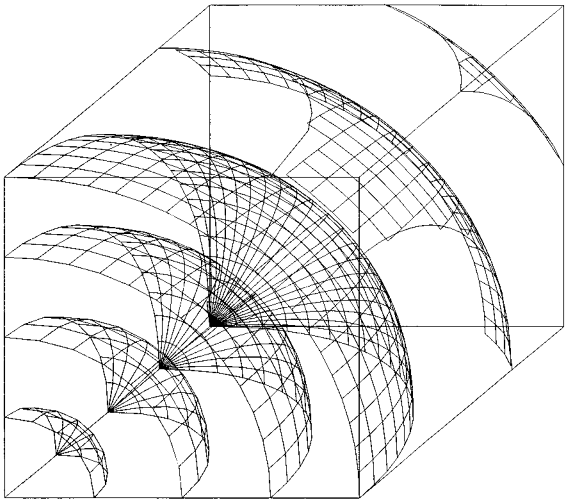

Figure 4. Spherical shells through the reaction hyperspace searched by the program which finds transition states. At each point on the spherical grid the energy at accessible points one step closer to starting point or product is compared to the energy at the test point. If the test point is higher than an accessible point closer to the origin and closer to the product, then it is a candidate transition state and must be tested to see if it is possible to find a path from starting point to product which passes through it and never goes higher in energy.

energy path leading from initial to final state. To find transition states, a set of computer programs were written which search the reaction space, moving out in shells from the initial state; see Figure 4. For each shell, points on a grid defined by polar coordinates are examined; any point which is higher in energy than accessible points both nearer and farther from the origin is a candidate transition state. A further candidate, and the highest energy candidate which need be considered, is the lowest energy stepwise path, which proceeds by a series of edge reactions. Accessible points are those which can be reached by moving no more than one grid step in any coordinate from the test point. Having found a set of candidate transition states, they are sorted and then searched in ascending order of energy, lowest first, to see if, first, there is a path to the final state which never goes higher in energy; and second, if there is a path back to the initial state which never goes higher in energy. This search process is computationally intensive, so first one tests a candidate on a relatively coarse grid, and only tests the successful candidates with finer grids. Although the time required depends on the exact nature of the surface, a four-dimensional search will generally require on the order of 15−30 min on a 50 MHz 486 based computer, but may require as much as 12 h for a difficult case.[44]

As the number of dimensions increases, there is a rapidly growing number of possible lower dimensional stepwise paths from starting material to products. Since the concerted path must be lower than any of the alternatives if the reaction is to be concerted, the condition for a fully concerted reaction becomes increasingly stringent as the dimensionality increases. In the two-dimensional case, one is in effect asking if the transition states for two processes along parallel reaction coordinates, from starting material to an intermediate and from an intermediate to product, can simultaneously be avoided by way of a transition state lower than either. This is illustrated in Figure 5, for the case $\Delta G_x = \Delta G_y = 15$ kcal/mol, $\tilde{G}_x = 9$ kcal/mol, $\tilde{G}_x = 1$ kcal/mol. When only one intrinsic barrier is substantial and the other is very small, as is the case for Figure 5, then a simple analysis is possible. If one projects the reaction coordinate diagrams involving only the coordinate, x in this case, with the high intrinsic barrier onto a one-dimensional reaction coordinate diagram, as shown in Figure 5, and if there is a crossover point for the limiting curves for $y = 0$ and $y = 1$ which is lower in energy than either of the simple transition states by more than $\tilde{G}_y$, then the reaction will be concerted. If the overall process is higher dimensional, then a similar treatment can be applied, projecting all but one dimension onto the one-dimensional reaction coordinate diagram corresponding to the highest intrinisic barrier. Then the condition for a concerted reaction depends on the effective barrier for the ($N - 1$)-dimensional process, orthogonal to the reaction coordinate with the high intrinsic barrier. Reaction along this ($N - 1$)-dimensional process at the crossover point necessarily has no thermodynamic driving force. This simple analysis, where the overall transition state energy is the sum of the crossover energy and the effective intrinsic barrier for the ($N - 1$)-dimensional process perpendicular to the high intrinsic barrier process is only valid if the ($N - 1$) perpendicular intrinsic barriers are all small. If one or more are large, then the surface is too complicated for this treatment.

It will now be demonstrated that, as the number of dimensions rises, the conditions for fully concerted reaction become more and more severe.[38−40] For a fully symmetrical four-dimensional system, a fully concerted process will have $w^* = x^* = y^* = z^* = 0.5$. One can derive an analytical expression for the activation energy in the most symmetrical case, where all corner intermediates have the same energy and $\Delta G_{\text{reaction}} = 0$. Along any edge, say the v coordinate, one can write an expression for the energy

$$G = a + bv^2 + cv^3 + dv^4$$

When $v^* = 0.5$, then

$$G^*_{v=0.5} = a + b/4 + c/8 + d/16$$

Substituting the expressions for b, c, and d in terms of $\Delta G_v{}^\circ$ and $\tilde{G}_v$, one obtains

$$G^*_{v=0.5} = a + \Delta G_v{}^\circ/2 + \tilde{G}_v$$

which is the energy of the transition state relative to the overall origin. a will depend on the particular coordinate, but is simply the energy of the $v = 0$ end of the coordinate relative to the overall origin. Thus if the coordinate of interest starts at the origin, $a = 0$, $\Delta G_v{}^\circ = \Delta G_{\text{corner}}$, and $G^*_{v=0.5} = \Delta G_{\text{corner}}/2 + \tilde{G}_v$. If the coordinate of interest ends at the product, $a = \Delta G_{\text{corner}}$, $\Delta G_v{}^\circ = -\Delta G_{\text{corner}}$, and $G^*_{v=0.5} = \Delta G_{\text{corner}}/2 + \tilde{G}_v$. If the coordinate of interest proceeds from one corner intermediate to another, then $a = \Delta G_{\text{corner}}$, $\Delta G_v{}^\circ = 0$, and $G^*_{v=0.5} = \Delta G_{\text{corner}} + \tilde{G}_v$.

One can now systematically reduce dimensions until one gets to the overall free energy of activation. The procedure provides a convenient “back of the envelope” analysis in the two-dimensional case where there is at most one large intrinsic barrier: if the two reaction energy diagrams for parallel edge coordinates cross at an energy lower than the two maxima, then the concerted process, if one is allowed, will have an activation energy given by this energy at the crossing point plus the intrinsic barrier for the perpendicular coordinate. Provided that this sum is less than either of edge reactions, the overall process will be concerted. In more than two dimensions, this is not in general a convenient method, because one has not a point of crossing but a line or a surface of crossing.

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(39) Bordwell, F. G. *Acc. Chem. Res.* **1972**, *5*, 374−381.
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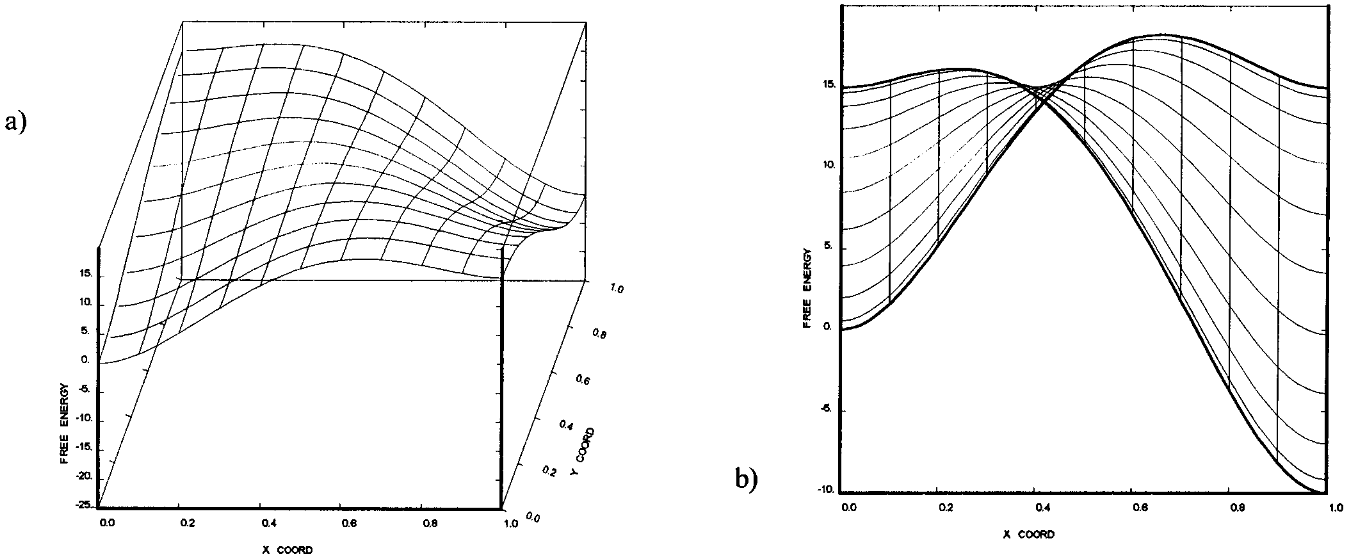

Figure 5. Simple analysis for the two dimensional case. (a) Reaction surface for the case $\Delta G_{\mathrm{reaction}} = -10$ kcal/mol, $\Delta G_x = \Delta G_y = 15$ kcal/mol, $\tilde{G}_x$ =9 kcal/mol, $\tilde{G}_y = 1$ kcal/mol. (b) Projection of the surface in (a) along the *y*-coordinate. The lines for $y = 0$ and $y = 1$ are heavier; these lines cross at $x = x^*$. For $x = x^*$, the free energy change along the *y*-coordinate is 0.0, so the additional activation barrier, above the crossover point, is $\tilde{G}_y = 1$ kcal/mol. In this case the concerted path is favored, because it is possible to avoid the maxima on both of the limiting reaction paths ($y = 0$, and $y = 1$).

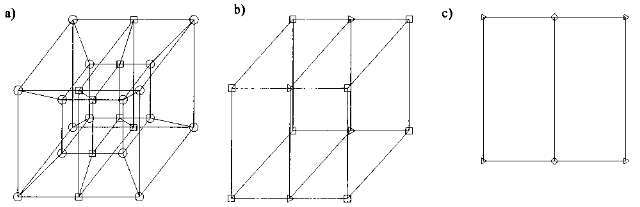

Figure 6. Analysis for the special case of a four-dimensional reaction path where all corner energies are equal, $\Delta G_{\mathrm{reaction}} = 0$, and all intrinsic barriers are equal and small. (a) Section through the hypercube at $w = 0.5$. (b) The reaction cube corresponding to the section through the hypercube from (a), with a section drawn at $x = 0.5$. (c) The reaction square corresponding to the section through the cube from (b), with a section drawn at $y = 0.5$. The overall transition state will be at $z = 0.5$ on the corresponding one-dimensional reaction coordinate diagram.

Now this process will be illustrated for a four-dimensional reaction hypercube reaction diagram, as shown in Figure 6. Let us start with *w*. There are eight edges of the hypercube parallel to the *w* axis. The midpoints of these eight edges define an *xyz* reaction cube. Proceeding as described above the energies of these eight corners are:

$$G_{0.5,0,0,0} = \Delta G_{\mathrm{corner}/2}$$

$$G_{0.5,1,0,0} = G_{0.5,0,1,0} = G_{0.5,0,0,1} = G_{0.5,1,1,0} = G_{0.5,1,0,1} = G_{0.5,0,1,1} = \Delta G_{\mathrm{corner}} + \tilde{G}_w$$

$$G_{0.5,1,1,1} = 0$$

The midpoints of the four edges of the *xyz* cube parallel to the *x* axis define a *zy* reaction plane. Proceeding as described above, the energies of these four corners are:

$$G_{0.5,0.5,0,0} = G_{0.5,0.5,1,1} = \Delta G_{\mathrm{corner}}/2 + \tilde{G}_w + \Delta G_{\mathrm{corner}}/4 + \tilde{G}_x = 3\Delta G_{\mathrm{corner}}/4 + \tilde{G}_w + \tilde{G}_x$$

$$G_{0.5,0.5,1,0} = G_{0.5,0.5,0,1} = \Delta G_{\mathrm{corner}} + \tilde{G}_w + \tilde{G}_x$$

Now we do the same process again to define the *z* reaction diagram

$$G_{0.5,0.5,0.5,0} = G_{0.5,0.5,0.5,1} = 3\Delta G_{\mathrm{corner}}/4 + \tilde{G}_w + \tilde{G}_x + \Delta G_{\mathrm{corner}}/8 + \tilde{G}_y = 7\Delta G_{\mathrm{corner}}/8 + \tilde{G}_w + \tilde{G}_x + \tilde{G}_y$$

Finally the overall energy is

$$G_{0.5,0.5,0.5,0.5} = 7\Delta G_{\mathrm{corner}}/8 + \tilde{G}_w + \tilde{G}_x + \tilde{G}_y + \tilde{G}_z$$

Unless one of the intrinsic barriers is quite large (in which case concerted reaction is impossible), the rate-determining process for the best stepwise edge reaction will be the progression form one corner intermediate to another, with $\Delta G^* = \Delta G_{\mathrm{corner}} + \tilde{G}_v$. For small intrinsic barriers, there will be essentially no kinetic barrier for progression from starting point to a corner intermediate, and by hypothesis all intermediates have the same energy. If the intrinsic barriers are not all the same, then *v* will correspond to the smallest. Thus the condition for a concerted reaction is that

$$7\Delta G_{\mathrm{corner}}/8 + \tilde{G}_w + \tilde{G}_x + \tilde{G}_y + \tilde{G}_z < \Delta G_{\mathrm{corner}} + \tilde{G}_v$$

or

$$\tilde{G}_w + \tilde{G}_x + \tilde{G}_y + \tilde{G}_z < \Delta G_{\mathrm{corner}}/8 + \tilde{G}_v$$

If $\tilde{G}_w = \tilde{G}_x = \tilde{G}_y = \tilde{G}_z = \tilde{G}$, then the condition is $\Delta G_{\mathrm{corner}} > 24\tilde{G}$. This is a severe condition and will normally prevent fully concerted processes. In fact, there is an even more severe constraint, because of the possibility of a semiconcerted path, involving two successive two-dimensional processes, which under the assumed conditions have the same activation energy. If this alternative process has a lower activation energy than the fully concerted process, then this semiconcerted process will be preferred. The algebraic solution for the two-dimensional process is not practical in the quartic approximation; in the quadratic approximation analytical solution is possible[16] and leads to a transition state energy of $(\Delta G_{\mathrm{corner}} + 4\tilde{G})^2/(\Delta G_{\mathrm{corner}} + 8\tilde{G})$ which for small $\tilde{G}$ can be less than $\Delta G_{\mathrm{corner}} + \tilde{G}$, the transition state energy for the one-dimensional alternative.

This derivation is for an artificially simple reaction scheme, but suffices to show that there are severe constraints limiting concerted processes of high dimensionality, unless the corner intermediates are high in energy relative to the intrinsic barrier.

Thus fully concerted reactions either involve very low intrinsic barriers or are inherently slow.

At each stage the crossover energy must be lower than either of the simple transition states by more than the sum of the intrinsic barriers for the perpendicular dimensions. These conditions are very severe and, in fact, make it unlikely for real processes to be synchronously concerted in four or more dimensions, and any that are will be inherently slow because of the requirement for high energy corner intermediates to give an adequate gap. The condition is still severe for three-dimensional processes, but much less so for two-dimensional processes. This shows that our four postulates necessarily imply that “multibond reactions cannot normally be synchronous” as Dewar has argued from quite different grounds.[40]

In numerical exploration of the consequences of the equations derived above, it has been found that it is indeed possible to have synchronous four-dimensional processes, but either the intrinsic barriers must be very low, or the corner intermediates must be high in energy and the overall process slow.

Discussion

The procedures described above have been applied to a number of reaction systems to be reported separately: examining cyclic concerted proton transfer processes,[25] hydration of carbonyl compounds,[41] hydrolysis of benzoyl chloride,[42] and hydrolysis of *N*-methylformanilide.[43] This has been found to be a useful procedure for determining both the energy and nature of the transition state when suitable input information is available.

Numerical exploration of the nature of the hypersurface shows that very often one or more of the possible reaction dimensions is 0 or 1 at the transition state; i.e., the reaction is less concerted than it might be, and the reaction hypersurface could be reduced in dimensionality. In some cases, notably water mediated proton switch reactions,[25] the preferred reaction path often involves a series of stepwise processes, each involving only one reaction dimension. A great virtue of the approach reported above is that the calculation performed to look for a concerted process can give the result that the process is not concerted. In cases where there was independent evidence concerning the concerted nature of the preferred reaction path, our approach led to consistent predictions of concerted transition states.[15,20]

Reactions will be characterized as fully concerted if all reaction coordinates have values near 0.5 at the transition state. Reactions for which all reaction coordinates are changing at the transition state, but some are far from 0.5, are described as nonsynchronous concerted. If one or more of the reaction coordinates are either 0 or 1 at the transition state, then the transition state is of reduced dimensionality. If only one reaction coordinate is changing at the transition state, then one has an edge reaction.

In the 2D case with $\Delta G_{\text{reaction}} = 0.0$ kcal/mol, and ΔG for the corner intermediates = 25 kcal/mol, then with both intrinsic barriers the same it is possible to get fully concerted reactions with $\tilde{G}_x = \tilde{G}_y \leq 7$ kcal/mol, but only edge reaction for larger intrinsic barriers. If one of the intrinsic barriers is always 1, then fully concerted reactions are found for $\tilde{G}_x \leq 44$ kcal/mol. If the overall driving force for the reaction is increased by making $\Delta G_{\text{reaction}} = -10.0$ kcal/mol, then with both intrinsic barriers the same we find that fully concerted reactions occur with $\tilde{G}_x = \tilde{G}_y \leq 7$ kcal/mol, but only edge reaction for larger intrinsic barriers. If one of the intrinsic barriers is always 1, then concerted reactions are found for $\tilde{G}_x \leq 29$ kcal/mol, with edge reactions for larger intrinisc barriers. The concerted reactions have both reaction coordinates in the range 0.4−0.6 for $\tilde{G}_x \leq 20$ kcal/mol, but are increasingly nonsynchronous for larger intrinsic barriers. With ΔG for the corner intermediates = 15 kcal/mol, the pattern is very similar, except that concerted reactions are only found for smaller intrinsic barriers. These calculations are summarized in Table 1.

Table 1. Two-Dimensional Case: Relation of the Nature of the Transition State to the Overall Free Energy Change and the Intrinsic Barriers

corner energy	$\Delta G_{\text{reaction}}$	$\tilde{G}_x$		$\tilde{G}_y$	nature of the transition state
25	0	≤7	=	≤7	fully concerted
25	0	>7	=	>7	edge
25	0	≤44		1	fully concerted
25	0	≥45		1	edge
25	−10	≤7	=	≤7	fully concerted
25	−10	>7	=	>7	edge
25	−10	≤28			fully concerted
25	−10	29		1	nonsynchronous concerted
25	−10	≥30		1	edge
15	0	≤15		1	fully concerted
15	0	≥16		1	edge
15	−10	≤5	=	≤5	fully concerted
15	−10	>5	=	>5	edge
15	−10	≤10		1	fully concerted
15	−10	11≤, ≤13		1	nonsynchronous concerted
15	−10	>14		1	edge

Table 2. Three-Dimensional Case: Relation of the Nature of the Transition State to the Overall Free Energy Change and the Intrinsic Barriers

corner energy	$\Delta G_{\text{reaction}}$	$\tilde{G}_x$		$\tilde{G}_y$		$\tilde{G}_z$	nature of the transition state
25	0	≤3	=	≤3	=	≤3	fully concerted
25	0	≥4	=	≥4	=	≥4	edge
25	0	≤4		1		1	fully concerted
25	0	5≤, ≤9		1		1	essentially 2D
25	0	≥10		1		1	edge
25	−10	≤5		1		1	fully concerted
25	−10	6≤, ≤10		1		1	nonsynchronous concerted
25	−10	≥11		1		1	edge
15	0	≤1		1		1	fully concerted
15	0	≥2		1		1	edge
15	−10	≤3		1		1	fully concerted
15	−10	4≤, ≤7		1		1	nonsynchronous concerted
15	−10	≥8		1		1	edge

In the 3D case with $\Delta G_{\text{reaction}} = 0.0$ kcal/mol, and ΔG for all corner intermediates = 25 kcal/mol, fully concerted reactions occur with $\tilde{G}_x = \tilde{G}_y = \tilde{G}_z \leq 3$ kcal/mol, and edge reactions for larger intrinsic barriers. With all but one of the intrinsic barriers = 1, fully concerted reactions are found with $\tilde{G}_x = \leq 4$ kcal/mol, but essentially 2D concerted reaction for intrinsic barriers >4 but <10 kcal/mol, and edge reaction for larger intrinsic barriers. If the overall driving force for the reaction is increased by making $\Delta G_{\text{reaction}} = -10.0$ kcal/mol, then with two of the intrinsic barriers always 1 kcal/mol, fully concerted reactions are found for $\tilde{G}_x \leq 5$ kcal/mol, nonsynchronous concerted reactions are found for $6 \leq \tilde{G}_x \leq 10$ kcal/mol, and edge reactions for larger intrinisc barriers. With ΔG for the corner intermediates = 15 kcal/mol, the pattern is very similar, except that concerted reactions are only found for smaller intrinsic barriers. These calculations are summarized in Table 2.

Likewise in the 4D case, with $\Delta G_{\text{reaction}} = 0.0$ kcal/mol, ΔG for all corner intermediates = 25 kcal/mol, and all intrinsic

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(42) Guthrie, J. P. To be submitted for publication.

(43) Guthrie, J. P. *Can. J. Chem.* **1993**, *71*, 2109−2122.

(44) The source code for these FORTRAN programs is available from the author: please send an MS-DOS formatted disk, $3^1/_2$" or $5^1/_4$". The executable forms of these programs are large, 0.5, 0.6, and 1.1 MByte, and require Windows 3.x or a memory manager.

Table 3. Four-Dimensional Case: Relation of the Nature of the Transition State to the Overall Free Energy Change and the Intrinsic Barriers

corner energy	$\Delta G_{\mathrm{reaction}}$	$\tilde{G}_w$	$\tilde{G}_x$	$\tilde{G}_y$	$\tilde{G}_z$	nature of the transition state
25	0	0.01	0.01	0.01	0.01	concerted
25	0	$1 \le, \le 2 =$	$1 \le, \le 2 =$	$1 \le, \le 2 =$	$1 \le, \le 2$	essentially 2D
25	0	≥ 3	≥ 3	≥ 3	≥ 3	edge
25	0	1	1	1	1	essentially 3D
25	0	2	1	1	1	2D
25	0	≥ 3	1	1	1	edge
25	-20	1	1	1	1	fully concerted
25	-20	2	1	1	1	nonsynchronous concerted
25	-20	≥ 3	1	1	1	edge
35	-20	1	1	1	1	fully concerted
35	-20	$2 \le, \le 3$	1	1	1	nonsynchronous concerted
35	-20	≥ 4	1	1	1	edge
45	-20	≤ 2	1	1	1	fully concerted
45	-20	$3 \le, \le 4$	1	1	1	nonsynchronous concerted
45	-20	≥ 5	1	1	1	edge
55	-20	≤ 2	1	1	1	fully concerted
55	-20	$3 \le, \le 6$	1	1	1	nonsynchronous concerted
55	-20	≥ 7	1	1	1	edge
65	-20	≤ 3	1	1	1	fully concerted
65	-20	$4 \le, \le 7$	1	1	1	nonsynchronous concerted
65	-20	≥ 8	1	1	1	edge
75	-20	≤ 3	1	1	1	fully concerted
75	-20	$4 \le, \le 9$	1	1	1	nonsynchronous concerted
75	-20	≥ 10	1	1	1	edge

barriers the same, fully concerted reactions are only found with $\tilde{G}_w = \tilde{G}_x = \tilde{G}_y = \tilde{G}_z \le 0.01$ kcal/mol; 2D concerted reaction are found for intrinsic barriers of 1 or 2 kcal/mol, and edge reactions for larger intrinsic barriers. If all but one of the intrinsic barriers were 1 kcal/mol, then with $\tilde{G}_w = 1$ kcal/mol, the reaction is essentially 3D, with $\tilde{G}_w = 2$ kcal/mol the reaction is essentially 2D, and with larger $\tilde{G}_w$ edge reactions are found. If the overall driving force for the reaction is increased by making $\Delta G_{\mathrm{reaction}} = -20.0$ kcal/mol, then with three of the intrinsic barriers always 1 kcal/mol, fully concerted reactions are found for $\tilde{G}_w = 1$ kcal/mol, nonsynchronous concerted reactions are found for $\tilde{G}_w = 2$ kcal/mol, and edge reactions for larger intrinisc barriers. With $\Delta G_{\mathrm{reaction}} = -20.0$ kcal/mol, the effect of increasing the corner energies was explored to see if fully concerted reactions would be found with one intrinsic barrier in the range found for heavy atom bond forming reactions. As Table 3 shows such concerted reactions could be found but only for high corner energies.

Thus what is found is that fully synchronous concerted processes only occur for high-dimensional processes when the intrinsic barriers are all very low, or when the reaction is so slow as to be of no practical significance. Fully concerted processes in two-dimensonal reactions are much more common. Thus one expects that the vast majority of reactions which seem to demand a three- or four-dimensional reaction diagram will have at most two reaction coordinates changing at the transition state, a few will have three reaction coordinates changing at the transition state, and none will have four or more reaction coordinates changing at the transition state. This has been proposed before,[38−40] but it has not previously been recognized that it is a necessary consequence of the simple postulates stated above.

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Supporting Information Available: An Appendix giving a deriviation of the equation for the energy hypersurface (13 pages). See any current masthead page for ordering and Internet access instructions.

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