Perpendicular Effects on Transition-State Structure: Model and Application to Cycloadditions and Sigmatropic Shifts

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Abstract: Effects of structures perpendicular to the reaction coordinate can be described by a model of an upside-down free energy profile whose minimum is constrained to coincide with the barrier height along the reaction coordinate and its "intrinsic barrier" proportional to that of the profile along the reaction coordinate. The model shows the same quality of semiquantitative agreement with experimental results for sigmatropic shifts and cycloadditions as the models based on two-dimensional "potential-energy surfaces". The model also predicts semiquantitatively the "tightness" of the transition state for hexadiene derivatives, as measured by the secondary kinetic isotope effects.

"Perpendicular" substituent effects in organic reactivity have been popularized in terms of two-dimensional potential energy surfaces.[1-12] The profile along the reaction coordinate (RC) has a maximum (the transition state, TS), which corresponds in a Hammond-like fashion[13] to variations in its end points (reagents and products). Hence stabilizing the products moves the TS closer to reactants (and lowers its energy). The profile perpendicular to the reaction coordinate has a minimum, responding in a "anti-Hammond" manner to perturbations in its asymptotic structures. Stabilization of one of the perpendicular structures moves the TS toward that structure. Such two profiles are depicted in Figure 1. An alternative explanation in terms of curve crossing[14] can also be demonstrated in Figure 1. In this picture G_3 is an excited electronic configuration of the reactants G_1, correlating with the ground electronic configuration of the products, G_2. Similarly G_4 correlates with G_1. The two curves in Figure 1 are generated through the avoided crossing of the curves G_1G_4 and G_3G_2.

To make the discussion more concrete, let us consider the sigmatropic shifts (Cope rearrangements) of 1,5-hexadiene derivatives,[11] as shown in Figure 2. The reaction leading from reactant (structure **1**) to product (structure **2**) involves cleavage of the 1,3 bond and formation of a new bond between carbons 1 and 6. If bond breaking precedes bond making the reaction path is through the intermediate structure **3**. If bond making occurs first, the path is via intermediate **4**. In the general case, these two processes occur simultaneously, and the reaction proceeds in a concerted way. This concerted pathway is the RC, n, which can assume values between 0 and 1. The TS is called "early" if it is close to reactants (small n), and "late" when it is closer to products (n larger than $^1/_2$). The perpendicular coordinate, n^*, may also assume values between 0 and 1. The TS is called "loose" if it resembles structure **3**, where both bonds are broken. Then n^* is smaller than $^1/_2$. The TS is called "tight" when it is closer to structure **4**, where both bonds are made. In terms of Pauling's idea[15] of bond-order conservation, $2n^*$ is the total bond order, whereas n and $1 - n$ are the fractional bond orders of the new and old bonds, respectively.

In addition to substituent effects which probe the structure of the TS, secondary α kinetic isotope effects (KIE) are used.[11c] Deuteration of all or some of the four hydrogens on carbons 1 and 6 lowers the zero-point energy of products (structure **2** in Figure 2) more than that of the reactants (structure **1**). Similarly, the bond-making structure **4** is stabilized in comparison to structure **3**. As a result the rate constant of the deuterated species is larger (and the KIE is larger than unity). The maximal value that the KIE can assume is when the 1,6 bond is fully formed at the TS, and then it equals the equilibrium isotope effect (EIE). Since such a KIE is mainly sensitive to bond making, it was suggested[2b,11c] to use ln (KIE)/ln (EIE) for a thermoneutral reaction ($\Delta G = 0$), as a measure for the "tightness" of the TS, its n value in our notation.

The potential energy surfaces described above are usually quantified[5b,11b,12] as a polynomial in n and n^*. Such functions, with one free parameter, were used[11b,12] to evaluate the barrier heights (TS energies) for cycloadditions and sigmatropic shifts. These, unfortunately, did not explain the observed ln (KIE)/ln (EIE) values. There are also some conceptual difficulties with such functions. First, they give a (slightly) different TS energy when evaluated from the side of the product than that calculated from the side of the reactant. Second,[12] they seem to bear no resemblance to potential energy surfaces familiar in molecular dynamics.[16] Third, by postulating such functions, no use is made of the known functions depicting the energy profile along the RC,[17,18] which can realistically describe such profiles on actual potential energy surfaces.[18c] In particular, the perpendicular effect as a variation of "intrinsic barriers",[17] which are the parameters defining reaction series, enters only indirectly.[12]

We therefore feel that it may be helpful to introduce an alternative mathematical procedure that would be directly related to the qualitative features of Figure 1 and would hence provide a quantitative description for both the potential energy surface and curve-crossing models. It would make direct use of the

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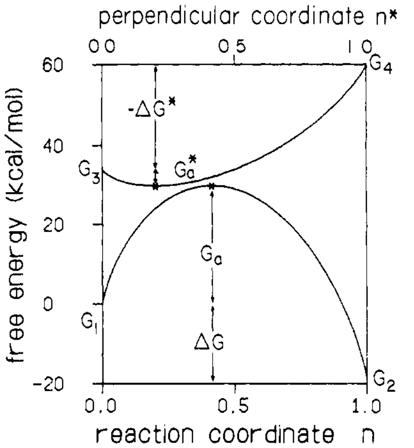

Figure 1. Perpendicular effects on the barrier height by an upside-down free energy profile whose minimum is constrained to coincide with the height of the barrier. These two extrema are denoted by asterisks. The energies are those of reaction 7 in Table I. The two profiles are described by eq 5 and 6. $\Delta G \equiv G_2 - G_1$; $\Delta G^* \equiv G_3 - G_4$; $G_1 \equiv 0$.

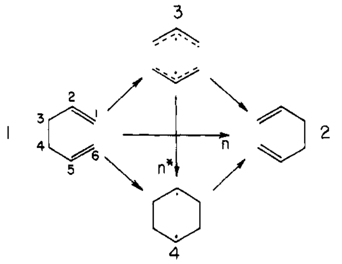

Figure 2. Sigmatropic shift of 1,5-hexadiene. The reaction proceeds from structure **1** to structure **2**, while structures **3** and **4** are possible intermediates. These notations are equivalent to those in Figure 1. The concerted path is the RC,n. The perpendicular coordinate is n^*.

available expressions for the energy profile along the RC and provide a straightforward recipe for intrinsic barrier variations. Finally, it would enable us to fit not only barrier heights but also the KIE data.

Theory

We present a simple model that may give a quantitative, mathematical form to the qualitative behavior demonstrated in Figure 1. The input data for the model are the energies of the four structures. Since one can set the zero of the energy scale arbitrarily (e.g., we put $G_1 = 0$), there are really only three energies involved: $\Delta G = G_2 - G_1$, $\Delta G^* = G_3 - G_4$, and $G_3 - G_1$, which equals G_3 for $G_1 = 0$. What we want to calculate is the barrier height G_a for the lower curve and the well depth G_a^* in the upper curve. We make three simple assumptions:

a. The two energy profiles shown in Figure 1 have the same functional dependence. In particular, each depends on one parameter, the intrinsic barrier. We denote these two parameters by G_a^0 and G_a^{0*}. G_a^0 is the barrier height for the lower curve when $\Delta G = 0$. G_a^{0*} is the well depth in the upper curve when $\Delta G^* = 0$. Note that we have defined ΔG^* to have an opposite sign compared to the usual definition (which is final minus initial value). This is because we view the upper curve as an upside-down reaction coordinate. Stated mathematically, both curves $G = g(n;G_a^0)$ and $G^* = g(n^*;G_a^{0*})$ are given by the same function g. As opposed to the conventional assumption[17] of a constant intrinsic barrier for a reaction series, here both G_a^0 and G_a^{0*} would depend on ΔG and ΔG^*.

b. The minimum in the upper curve, at $n^{*\ddagger}$, has the same energy as the maximum in the lower curve, which occurs at some $n^{\ddagger}$. Mathematically, $G^*(n^{*\ddagger};G_a^{0*}) = G(n^{\ddagger};G_a^0)$. This is clear from the potential energy surface model described above, since both $n^{\ddagger}$ and $n^{*\ddagger}$ are the location of the col where the TS is located. Written explicitly, this becomes

$$G_a + G_a^* = G_3 \qquad (1)$$

c. For similar reactions, there is a relation between the two intrinsic barriers. For simplicity, we assume that they are proportional to each other. We have found that a good fit, which produces the results discussed below, is obtained for

$$G_a^0 = 3G_a^{0*} \qquad (2)$$

Using these assumptions, one may derive results at several levels of sophistication. In the most primitive version of structure–reactivity correlations, valid for small values of ΔG and ΔG^*, one assumes a linear correlation of kinetics and thermodynamics

$$G_a = G_a^0 + \tfrac{1}{2}\Delta G \qquad G_a^* = G_a^{0*} + \tfrac{1}{2}\Delta G^* \qquad (3)$$

Inserting this relation into condition 1, while using assumption 2, leads to an explicit expression for the intrinsic barrier G_a^0

$$G_a^0 = \tfrac{3}{4}[G_3 - \tfrac{1}{2}(\Delta G + \Delta G^*)] \qquad (4)$$

which, as we have mentioned above, is generally not constant. The final relation for the barrier height G_a is obtained by inserting this result into eq 3.

A more realistic description of the energy profiles is obtained in ref 18. The profile is generally described by a linear interpolation plus a convex function which accounts for the barrier

$$G(n) = n\Delta G + G_a^0 M(n) \qquad (5)$$

When the "mixing function" $M(n)$ is an entropy function,

$$M(n) = -[n \ln n + (1 - n) \ln (1 - n)]/\ln 2 \qquad (6)$$

the following relations for the barrier height and location are obtained

$$G_a = -G_a^0 \ln (1 - n^{\ddagger})/\ln 2 \qquad (7)$$

$$n^{\ddagger} = [1 + \exp(-\Delta G \ln 2/G_a^0)]^{-1} \qquad (8)$$

According to our first assumption, the same relations hold for the upper curve, i.e., for the quantities with asterisks. The curves shown in Figure 1 were actually drawn according to eq 5 and 6. In contrast to the simple structure–reactivity model of eq 3, eq 1 cannot be solved explicitly for the intrinsic barrier G_a^0. Instead, it has to be solved numerically: G_a^0 is varied systematically until equality in eq 1 is obtained.

We now show that for profiles given by the general relation 5, and for symmetric reactions, $\Delta G = 0$, one has approximately

$$\ln (\text{KIE})/\ln (\text{EIE}) = n^{*\ddagger} \qquad (9)$$

Denoting by δ changes due to isotopic substitution, we want to show that

$$\delta G_a = n^{*\ddagger}\delta\Delta G \qquad (10)$$

The proof would only utilize the general properties of $M(n)$, namely[18b] that it is a symmetric function of n, maximal for $n = {}^1/_2$ and zero for $n = 0$ or 1.

As discussed in the introduction, isotopic substitutions on carbons 1 and 6 stabilize structures **2** and **4**, where a 1,6 bond is present, to a larger extent than structures **1** and **3**. Hence $\delta\Delta G$ is negative and equals $-\delta\Delta G^*$, while $\delta G_3 = 0$. (G_3 is actually the energy difference between G_3 and G_1, the latter being defined as zero.) Equation 1 now implies that $\delta G_a^* = -\delta G_a$. The variation of eq 5 at its extremum ($n^{\ddagger}$ or $n^{*\ddagger}$), together with the abovementioned conditions, yields

$$\delta G_a = \delta G_a^0 + \tfrac{1}{2}\delta\Delta G \qquad (11a)$$

$$\delta G_a^* = -n^{*\ddagger}\delta\Delta G + M(n^{*\ddagger})\delta G_a^0/3 \qquad (11b)$$

In eq 11a we have used the fact that when $\Delta G = 0$, $n^{\ddagger} = {}^1/_2$ and $M({}^1/_2) = 1$.[19] Consider now two possible situations. If $n^{*\ddagger}$ is close either to 0 or to 1, $M(n^{*\ddagger})$ is close to zero, so that the equality of δG_a and $-\delta G_a^*$ gives the desired result, eq 10. If $n^{*\ddagger}$ is close

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[19] Note that a variation with respect to n (n^*) vanishes by definition at $n^{\ddagger}$ ($n^{*\ddagger}$).

Table I. Application of the Model to Sigmatropic Shifts and Cycloadditions to Cyclopentadiene (All Energies in kcal/mol)

		data[11b]			intrinsic barriers		barrier heights						extremum location		
							G_a								
		ΔG	ΔG^*	G_3	$G_a{}^\circ$	$G_a{}^{\circ e}$	*a*	*b*	*c*	*d*	*e*	$G_a{}^*$	$n^\ddagger$	$n^{*\ddagger}$	ln (KIE)/ ln (EIE)[f]
	sigmatropic shifts														
1.	1,5-hexadiene	0.0	4	57	41.2	41.2	41.0	41.2	40.9	41.2	41.2	15.8	0.50	0.55	0.64
2.	2-phenyl-1,5-hexadiene	0.0	15	57	36.0	37.1	35.5	36.3	34.5	36.0	37.1	21.1	0.50	0.70	0.75
3.	2,5-diphenyl-1,5-hexadiene	0.0	26	57	29.0	33.0	31.0	30.1	27.0	29.0	33.0	28.0	0.50	0.87	0.87
4.	3,3-dicyano-1,5-hexadiene	−4.5	−16	37	34.0	35.4	32.0	31.6	27.8	31.8	33.2	5.2	0.48	0.27	0.25
5.	3,4-dimethyl-1,5-hexadiene	−4.5	0	53	41.4	41.4	39.0	38.7	36.8	39.2	39.2	13.8	0.48	0.50	
6.	3,4-diphenyl-1,5-hexadiene	−4.5	−18	35	32.8	34.7	31.0	30.6	26.5	30.6	32.5	4.4	0.48	0.24	
7.	*cis*-1,2-divinylcyclobutane	−19.0	−26	34	38.6	42.4	28.0	28.6	22.4	29.9	32.9	4.1	0.42	0.20	
8.	allyl vinyl ether	−17.0	−6	47	43.3	45.4	33.0	33.6	27.9	35.4	35.4	11.6	0.43	0.43	
9.	allyl phenyl ether	5.0	−22	47	39.3	41.6	42.0	43.2	43.9	41.9	44.1	5.1	0.52	0.24	
10.	allyl acetate	0.0	−15	52	43.6	44.6	45.0	43.9	44.5	43.6	44.6	8.3	0.50	0.33	
11.	*cis*-1,2-divinylcyclopropane	−20.0	−18	35	38.3	40.5	21.0	27.5	20.0	29.2	30.5	5.9	0.41	0.27	
12.	allyl silyl enol acetate	−20.0	−6	47	44.3	44.2	25.0	33.0	26.6	35.0	34.2	11.9	0.42	0.43	
13.	3-oxyanion-1,5-hexadiene	−19.0	−27	26	32.1	36.7	26.0	23.4	24.9	23.6	27.2	2.5	0.40	0.15	
	cycloadditions														
14.	ethylene	−20.0	0	40	36.8	37.5	30.0	27.7	28.9	27.7	27.5	12.3	0.41	0.50	
15.	acrylonitrile	−20.0	9	40	32.9	34.1	24.0	23.8	24.0	23.9	24.1	16.1	0.40	0.64	
16.	fumaronitrile	−20.0	0	31	29.9	30.7	21.3	20.6	20.1	21.1	20.7	10.0	0.39	0.50	
17.	maleonitrile	−20.0	0	31	29.9	30.7	21.1	20.6	20.1	21.1	20.7	10.0	0.39	0.50	
18.	1,1-dicyanoethylene	−20.0	18	40	27.7	30.7	17.8	18.9	18.3	19.0	20.7	21.1	0.38	0.79	
19.	1,1,2-tricyanoethylene	−20.0	9	31	25.8	27.4	16.3	16.6	15.3	17.1	17.4	13.9	0.37	0.67	
20.	1,1,2,2-tetracyanoethylene	−20.0	0	22	22.9	24.0	13.9	13.7	11.4	14.4	14.0	7.6	0.35	0.50	

[a] Experimental data as collected from literature in ref 11b. [b] Gajewski's calculation.[11b] [c] Murdoch's calculation.[12] [d] Present work, full model. [e] Present work, simplified version, eq 3 and 4. [f] Data of ref 11a,c. EIE is KIE ratio for the forward and reverse reactions.

to $^1/_2$, eq 11 implies that $\delta G_a{}^0 = 0$, again leading to the result in eq 10. As a conclusion we have shown that for $\Delta G = 0$, eq 9 is approximately obtained for any value of $n^{*\ddagger}$.

Results

Results shown in Table I are for sigmatropic shifts and cycloadditions. The first three columns show the input data for the calculation, taken from ref 11b. The next two columns give the intrinsic barrier as calculated from the full model and from the simplified expression in eq 4. The next five columns give the barrier height according to experiment, the two models in the literature, and our full and simplified versions. Next come results from our full calculation for the well depth on the upper curve and the two parameters which determine the TS location. Finally we show the experimental estimate for ln (KIE)/ln (EIE).

From this table we see that our calculation of the barrier height, G_a, shows on the average the same quality of agreement with experiment as the two models in the literature.[11b,12] The fact that all models are equally good in this respect is not surprising in view of the fact that even our very simplified model, eq 3 and 4, gives almost as good results. Roughly speaking, it differs from the full calculation by $0.1(\Delta G + \Delta G^*)$. This number is significant only for a few entries, such as 3, 7, 9, and 13, where usage of this version increases the error by 2–4 kcal/mol. In one case (entry 13), the simplified version is even better, probably due to some cancellation of errors.

Finally, an agreement not obtained by any other model is seen in the comparison of the experimental values for ln (KIE)/ln (EIE) with our calculation of $n^{*\ddagger}$, for the first four entries, which are nearly symmetric reactions. The agreement is not completely quantitative for all reactions, but the qualitative trends in the "tightness" of the TS are clearly there.

Conclusion

We have shown that it is possible to generalize the models for energy profiles along the RC by adding an upside-down profile which describes the energy perpendicular to the RC. We have introduced three simple assumptions relating these two curves. The only assumption that is not intuitively evident is the proportionality of the two intrinsic barriers. This assumption should be further tested in the future. The assumptions enabled us to explain in a self-consistent way both Hammond and anti-Hammond effects. For the instructive example of cycloadditions and sigmatropic shifts, we were able to explain trends in barrier height variations, in two levels of sophistication, and, for the first time, demonstrate a semiquantitative agreement with KIE results as well.

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Registry No. 1, 592-42-7; **2**, 7399-52-2; **3**, 7283-49-0; **4**, 92014-36-3; **5**, 4894-63-7; **6**, 4403-14-9; **7**, 16177-46-1; **8**, 3917-15-5; **9**, 1746-13-0; **10**, 591-87-7; **11**, 2984-58-9; **13**, 71256-01-4; **14**, 74-85-1; **15**, 107-13-1; **16**, 764-42-1; **17**, 928-53-0; **18**, 922-64-5; **19**, 997-76-2; **20**, 670-54-2; 1,3-cyclopentadiene, 542-92-7.