301-04-2; 2-mercaptoethanol, 60-24-2; lead 2,2′-dithiodiethylurea, 60633-88-7; thioglycolic acid hydrazide, 760-30-5; thioglycolic acid methyl ester, 2365-48-2.

References and Notes

(1) Supported by the National Science Foundation (RANN, Grant G1 3428). Abbreviations used are: DTT, dithiotheitol; DTE, dithioerythreitol; ElIS-SEll, Ellman's reagent, 5,5′-dithiobis(2-nitrobenzoic acid); EllS$^-$, "Ellman's anion", the conjugate dianion of 2-nitro-5-thiobenzoic acid; CysSH, cysteine (or the cysteine moiety of a protein).

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A Simple, Empirical Function Describing the Reaction Profile, and Some Applications

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A simple, algebraic function is derived to represent the reaction profile of a concerted (one-step) reaction: $E = ax^4 + bx^3 - (4a + 3b)x^2/2$, where x is the reaction coordinate. It is shown that this function is in accord with the Hammond postulate and the Polanyi principle. It is used to evaluate the magnitude of the pressure-induced shifts of the transition state predicted by Walling several years ago, and to question the validity of a recent claim of the experimental verification of this effect. Further examination of this pressure effect leads to additional possibilities; among these are the vanishing of activation energies, the creation of certain new intermediates, and the conversion of degenerate sets of rapidly equilibrating structures into resonance hybrids.

The reaction profile showing how the energy of reacting molecules varies as they traverse the reaction coordinate has become a popular pedagogical device. The reason for this is that by means of it, one can conveniently illustrate a multitude of mechanistic phenomena. Concerted vs. stepwise reactions, intermediates vs. transition states, consecutive vs. competing reactions, early vs. late transition states, reversible vs. irreversible reactions, all these can be instantly indicated by means of the familiar curves one finds wherever mechanistically inclined chemists communicate with one another.

On a recent occasion we wished to make a quantitative estimate of pressure induced shifts of the transition state (vide infra), and discovered that none of the books exhibiting these curves records a function representing them.[2] We wish to describe an empirical function here for a simple, single-step reaction. We note its utility by showing, for example, that it behaves in the fashion demanded by the Hammond postulate and the Polanyi principle, and finally employ it to make the estimate referred to above.

The Function and Some of Its Features. We begin by noting that the general quartic

$$E = ax^4 + bx^3 + cx^2 + dx + e$$

is the simplest algebraic function which can have the general features of the reaction profile: a maximum flanked by two minima. E is the potential energy, and we let x represent the "distance" along the reaction coordinate, expressed as a fraction of the total to be traversed between the initial and final states. If we specify that at extreme values of x, E must be positive ($a > 0$), that the curve must pass through the origin ($e = 0$), that it must have a minimum there ($d = 0$) and at $x = 1$ [$c = -(4a + 3b)/2$], we have as the basic function

$$E = ax^4 + bx^3 - \frac{4a + 3b}{2}x^2 \tag{1}$$

Several possibilities are shown in Figure 1; these include reactions with equilibrium constants less than, equal to, or greater than one (curves II, III, and IV, respectively, if we ignore the difference between energy and free energy), as well as extreme cases I and V which are reactions without activation energy. Beside the extrema at $x = 0$ and $x = 1$ (these points will be denoted by x_0 and x_1, respectively), there is a third (at $x^{\neq}$) which represents the transition state; it is found by dividing

$$\frac{dE}{dx} = 4ax^3 + 3bx^2 - (4a + 3b)x = 0$$

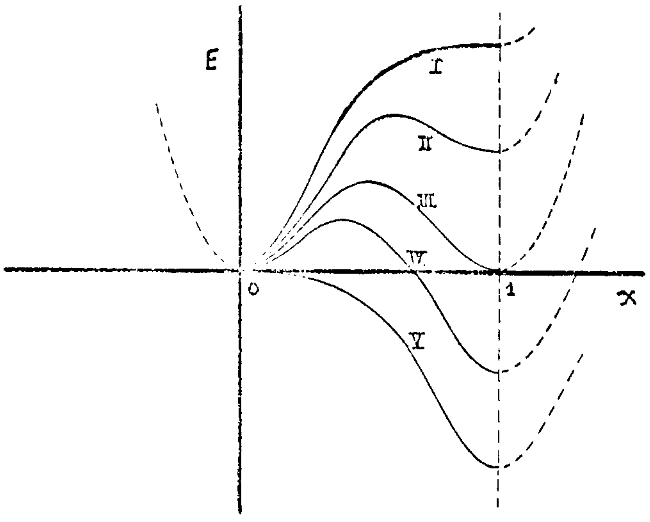


Figure 1. Various reaction profiles described by eq 1.

Table I. Characteristics of Several Curves in Figure 1

	Curve I	III	V
b/a	$-8/3$	-2	$-4/3$
Eq 1; E	$ax^4 - 8/3ax^3 + 2ax^2$	$ax^2(x-1)^2$	$ax^4 - 4/3ax^3$
E_1	$+1/3a$	0	$-1/3a$
$E^{\ddagger}$	$+1/3a$	$1/16a$	0
$x^{\ddagger}$	1	$1/2$	0
$x_{\text{infl.}}$	$1/3$; 1	$1/2 \pm 1/6\sqrt{3}$	0; $2/3$
$\alpha_a{}^a$	1	$1/2$	0
$\alpha_b{}^a$	1	$7/16$	0

[a] See text below.

by $x(x-1)$, which gives

$$x^{\ddagger} = -\left(1 + \frac{3b}{4a}\right) \tag{2}$$

The corresponding activation energy $E^{\ddagger}$ is found by substitution of eq 2 into eq 1:

$$E^{\ddagger} = -a - b\left\{\frac{5}{2} + \frac{9}{4}\left(\frac{b}{a}\right) + \frac{27}{32}\left(\frac{b}{a}\right)^2 + \frac{27}{256}\left(\frac{b}{a}\right)^3\right\} \tag{3}$$

Similarly, the reaction energy

$$E_1 = -\left(a + \frac{1}{2}b\right) \tag{4}$$

Curves I and V are clearly the extreme cases at which the requirement of a vanishing first derivative at x_0 and x_1 still holds. Since in these two curves we also have a zero second derivative (at x_0 and x_1, respectively), we can obtain the limits of b from

$$\frac{\mathrm{d}^2E}{\mathrm{d}x^2} = 12ax^2 + 6bx - (4a + 3b) = 0$$

At x_1, $b/a = -8/3$; at x_0, $b/a = -4/3$. The pertinent data for curves I and V as well as those for the special case of $E_1 = 0$ (curve III) can now rapidly be deduced; they are summarized in Table I. It may be noted that since a is positive, b is negative. The more common types II and IV of course have intermediate values for b/a; once these constants have been chosen one can rapidly determine the corresponding function (from eq 1), E_1 (from eq 4), $E^{\ddagger}$ (from eq 3), and $x^{\ddagger}$ (from eq 2). The reverse process of finding values of a and b appropriate for certain values of E_1, $E^{\ddagger}$, and $x^{\ddagger}$ is also possible, but if $E^{\ddagger}$ is one of the two data specified, the complexity of eq 3 makes this process somewhat cumbersome.

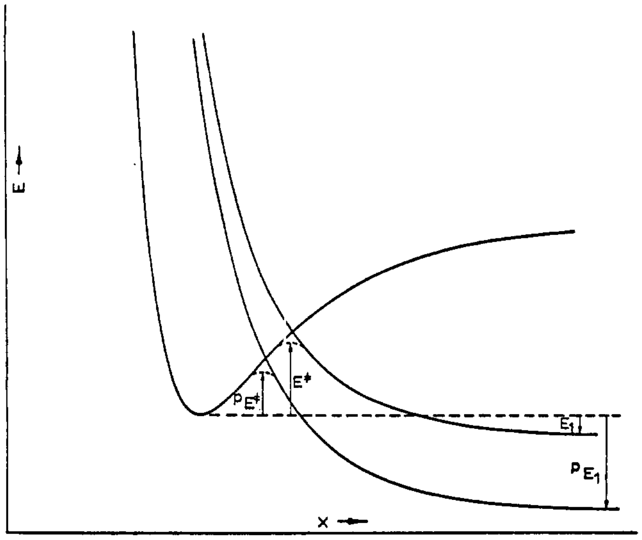


Figure 2. Reaction profiles of two displacement reactions XR + Y (Y′) according to Polanyi et al. (ref 6 and 7).

Applications. 1. The Hammond Postulate. This rule was recently discussed by Farcasiu.[3] The original statement by Hammond[4] is that if two states occurring consecutively during a reaction process have similar energies, they will have similar structures; but most chemists are probably more familiar with the corollary due to Melander,[5] who essentially derived the statement that for a given type of reaction, increased exothermicities imply earlier transition states. For our present purpose, we consider the energy of the starting material zero and relate the structure of the transition state $x^{\ddagger}$ to $E^{\ddagger}$ and E_1. From Figure 1 and Table I it is clear that the Hammond postulate is obeyed in the extremes; we now examine whether it applies at any intermediate value of $x^{\ddagger}$. We wish to show that for any given value of $E^{\ddagger}$, $x^{\ddagger}$ increases as E_1 increases; in other words

$$\left(\frac{\partial x^{\ddagger}}{\partial E_1}\right)_{E^{\ddagger}} > 0$$

Elimination of b/a between eq 2–4 leads to

$$E_1 = E^{\ddagger}\frac{(1 - 2x^{\ddagger})}{(x^{\ddagger} - 2)}\left(\frac{1}{x^{\ddagger}}\right)^3$$

Hence

$$\left(\frac{\partial x^{\ddagger}}{\partial E_1}\right)_{E^{\ddagger}} = \frac{\{x^{\ddagger 3}(x^{\ddagger} - 2)\}^2}{x^{\ddagger 3}(x^{\ddagger} - 2)(-2) - (1 - 2x^{\ddagger})(4x^{\ddagger 3} - 6x^{\ddagger 2})}\Big/E^{\ddagger} = \left[\frac{x^{\ddagger 2}(x^{\ddagger} - 2)}{(x^{\ddagger} - 1)}\right]^2\Big/6E^{\ddagger}$$

which is clearly positive since $E^{\ddagger} > 0$.

2. The Polanyi Principle. Horiuti and Polanyi[6] considered reaction profiles as the resultants of attractive and repulsive potential energy curves (see Figure 2). Their analysis, initially applied to ionic displacement reactions, clearly implied a correlation between $E^{\ddagger}$ and E_1. In time the generalized proposition that in a series of closely related reactions greater product stability meant proportionately faster reaction and vice versa became one of the cornerstones of mechanistic chemistry:

$$E^{\ddagger} = \alpha E_1$$

or

$$\frac{\partial E^{\ddagger}}{\partial E_1} = \alpha$$

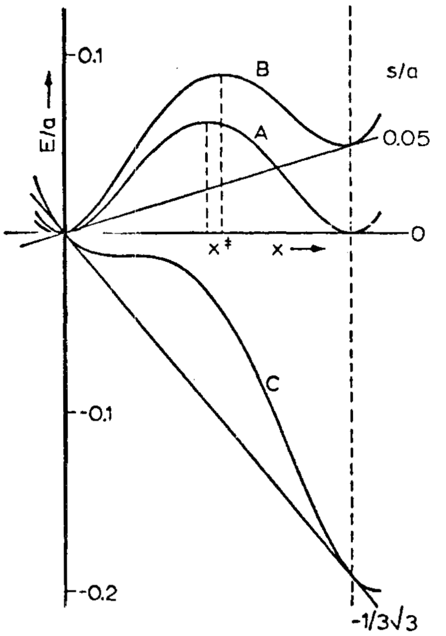


Figure 3. Pressure induced transition state progression.

Polanyi et al.[6] suggested that the proportionality factor α is about ½, but Evans[8] later concluded that it could be as low as ⅓. A relation of this sort can be derived from eq 1. Thus, if we eliminate b/a between eq 3 and 4, we obtain

$$\frac{E^{\ddagger}}{a} = -1 + 2\left(\frac{E_1}{a} + 1\right)\left\{\frac{5}{2} - \frac{9}{2}\left(\frac{E_1}{a} + 1\right) + \frac{27}{8}\left(\frac{E_1}{a} + 1\right)^2 - \frac{27}{32}\left(\frac{E_1}{a} + 1\right)^3\right\}$$

Then the derivative

$$\alpha_{\mathrm{a}} = \left(\frac{\partial E^{\ddagger}}{\partial E}\right)_{\mathrm{a}} = 5 - 18\left(\frac{E_1}{a} + 1\right) + \frac{81}{4}\left(\frac{E_1}{a} + 1\right)^2 - \frac{27}{4}\left(\frac{E_1}{a} + 1\right)^3$$

$$= 5 + 9\frac{b}{a} + \frac{81}{16}\left(\frac{b}{a}\right)^2 + \frac{27}{32}\left(\frac{b}{a}\right)^3$$

Similarly

$$\alpha_b = 1 - \frac{9}{4}\left(\frac{b}{a}\right)^2 - \frac{27}{16}\left(\frac{b}{a}\right)^3 + \frac{81}{256}\left(\frac{b}{a}\right)^4$$

Both factors reach a maximum of +1 for curve I and a minimum of 0 for curve V. Throughout the intermediate region, α is positive, as can be shown, for example, from

$$\frac{\mathrm{d}\alpha_a}{\mathrm{d}(b/a)} = 9 + \frac{81}{8}\left(\frac{b}{a}\right) + \frac{81}{32}\left(\frac{b}{a}\right)^2 = 0$$

which has roots of $(b/a) = -4/3$ and $-8/3$ (note Table I). For curve III, α_{a} has the value ½, and it is equal to ⅓ for $b/a = -1.8493$.[9]

3. Pressure Induced Shifts in the Transition State. Since the absolute value of the activation volume is rarely more than 30 cm^3/mol or so and since 1 cm^3 atm is only 2.4 × 10^{-5} kcal, the $p\Delta V^{\ddagger}$ term is a vanishingly small part of $\Delta H^{\ddagger}$ or $\Delta G^{\ddagger}$ in reactions carried out under room conditions; however, at high pressures (e.g., 10 kbar ≈ 10^4 atm) the work term is no longer negligible. As was pointed out by Walling in 1963[10] and supported by Hamann[11] in 1964, this may in fact have the effect of shifting the position of the transition state, as is shown in Figure 3 (curve B). This illustrates a reaction with a positive activation volume and reaction volume carried out under high pressure; it is subject to a $p\Delta V$ term of increasing magnitude as the reaction coordinate is traversed. This additional term raises the entire curve above where it would be at zero pressure (A), and the maximum shifts somewhat to larger x. Thus, pressure in such a case has the effect of bringing about a later transition state.

It is perhaps unfortunate that this proposal came as a part of polemics centered on the question of whether the thermodynamic compressibility $(-1/V)(\partial V/\partial p)_T$ of a transition state might be adequately expressed by the Tait equation or not.[12] Walling's proposal led to such terms as "abnormal compressibility"[10] and "negative compressibility"[11] of transition states; furthermore, in their critical assessment of the magnitude of the effect, Benson and Berson[13] used a model involving the compression of a very weak bond, which may suggest that shifts of the transition state would necessarily be in the direction of a shorter bond. It seems preferable to the present authors to refer to Walling's phenomenon as a pressure induced progression of the transition state. The opposite phenomenon, occurring in cases of a monotonic volume decrease, would be retrogression of the transition state.

In the following discussion, the activation volume $\Delta V^{\ddagger} = V^{\ddagger} - V_0$, the reaction volume $\Delta V_1 = V_1 - V_0$, and $\Delta V = V_x - V_0$. Equation 1 allows us to make an estimate of the magnitude of the effect. If we assume for the moment that the work term obeys

$$w = p\Delta V = sx$$

then the enthalpy becomes

$$H = ax^4 + bx^3 - \frac{4a + 3b}{2}x^2 + sx$$

and the slope is

$$\frac{\mathrm{d}H}{\mathrm{d}x} = 4ax^3 + 3bx^2 - (4a + 3b)x + s$$

The three roots of this equation will ordinarily be real, and can rapidly be evaluated by the trigonometric method of solving cubics. One of them represents the new value of $x^{\ddagger}$, which will be denoted by ${}^px^{\ddagger}$. The others give the new values of ${}^px_0$ and ${}^px_1$.

The solution of a cubic is too complicated to permit the writing of a general expression for the exact shift of $x^{\ddagger}$ as a function of a, b, and s; however, a few numerical examples may suffice. For the special case that $E_1 = 0$ at atmospheric pressure, for instance, if we have $E^{\ddagger} = 22.5$ kcal/mol, so that $a = 360$ kcal/mol^1, $b = -720$ kcal/mol, and $\Delta V_1 = 45$ cm^3/mol (such values may be encountered in reverse Diels–Alder reactions, for example[14]), then the value of s at $p = 10$ kbar is 10.75 kcal/mol and the points of minimum and maximum enthalpy are the roots of

$$4x^3 - 6x^2 + 2x + 0.03 = 0$$

The solutions are ${}^px_0 = -0.0144$, ${}^px^{\ddagger} = 0.5301$, and ${}^px_1 = 0.9843$. Thus a shift of $100[(0.5301 + 0.0144)/(0.9843 + 0.0144) - 0.5000]/0.5000 = 9.0\%$ would occur in the location of the transition state relative to the initial state. A slightly less accurate but more convenient procedure is to make use of a Taylor series expansion of the enthalpy:

$$H - H^{\ddagger} = \frac{\mathrm{d}H}{\mathrm{d}x}\delta x + \frac{1}{2}\frac{\mathrm{d}^2H}{\mathrm{d}x^2}(\delta x)^2 + \frac{1}{6}\frac{\mathrm{d}^3H}{\mathrm{d}x^3}(\delta x)^3 - - - - + s\delta x$$

where $\delta x = x - x^{\ddagger}$. Near the transition state, the first term vanishes, as does the derivative

$$\frac{\mathrm{d}(H - H^{\ddagger})}{\mathrm{d}(\delta x)} = 0 \approx \frac{\mathrm{d}^2H}{\mathrm{d}x^2}\delta x + s$$

Hence

$$\delta x \approx \frac{-s}{12ax^2 + 6bx - 4a - 3b}$$

For $x = \frac{1}{2}$, $b/a = -2$, one finds

$$\delta x \approx s/a = 0.0300$$

so that $x^{\ddagger}$ shifts to ${}^{p}x^{\ddagger} = 0.5300$. This value and the new values of ${}^{p}x_0$ and ${}^{p}x_1$ agree to three decimal places with those obtained by exact solution of the cubic equation.

The use of $w = sx$ is of course arbitrary. An especially simple solution is available if we replace it by a pressure contribution

$$w = r\left(x^3 - \frac{3}{2}x^2\right)$$

This curve—like the reaction profile itself—has been designed to have zero slope at x_0 and x_1, so that it will produce no changes in x at either extremity (see Figure 4). The constant r is defined by $H_1 = s = r(1 - \frac{3}{2})$, and so we may rewrite the pressure contribution as

$$w = -2sx^3 + 3sx^2 \tag{5}$$

Now the enthalpy

$$H = ax^4 + (b - 2s)x^3 + \left(3s - \frac{4a + 3b}{2}\right)x^2$$

has a slope

$$\frac{dH}{dx} = 4ax^3 + (3b - 6s)x^2 + (6s - 4a - 3b)x$$

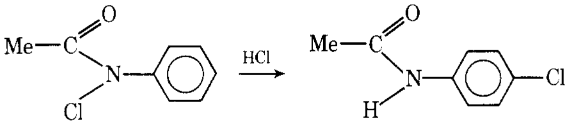
which equals zero at x_0, x_1, and at

$${}^{p}x^{\ddagger} = -\left(1 + \frac{3b}{4a}\right) + \frac{3s}{2a}$$

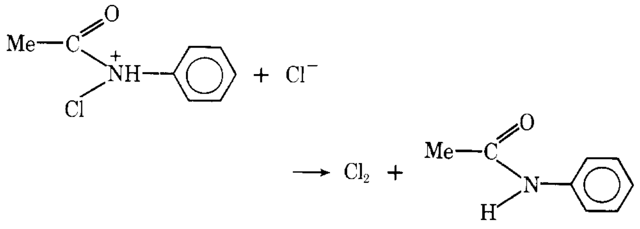
The shift in $x^{\ddagger}$ therefore now simply equals $3s/2a$, = 0.0450, or 9.0%.

However the shifts are evaluated, they are not very large. For instance, if we examine the effect of using $E_1 = -7.2$ kcal/mol ($a = 414$ and $b = -813.6$ kcal/mol), the shift in $x^{\ddagger}$ is now from 0.474 to 0.500; if E_1 is taken as -22.5 kcal/mol ($a = 522$ and $b = -999$ kcal/mol), then $x^{\ddagger}$ changes from 0.435 to 0.456. Very large shifts can of course be designed by assuming ever larger values of $p\Delta V^{\ddagger}$ and $p\Delta V_1$; however, it should be remembered that volume differences are not independent of pressure, and they invariably become smaller as the pressure is raised. It is quite common for $|\Delta V^{\ddagger}|$ to change, say, from 30 cm^3/mol at atmospheric pressure to 10 cm^3/mol at 5 kbar, and even less than that at still higher pressures. The assumption made above (of $\Delta V_1 = 2\Delta V^{\ddagger} = 45$ cm^3/mol *at 10 kbar*) is already so generous as to strain credulity, and still larger estimates have simply no counterpart in reality (except for some reactions of macromolecules). Further controlled increases in pressure are eventually ruled out for various experimental reasons.

One claim for a shift of this sort has been made to date. Fujii[15] has mentioned it in a recent paper describing a study of the Orton rearrangement in water containing up to 16 wt % ethanol:



The rate-determining step is



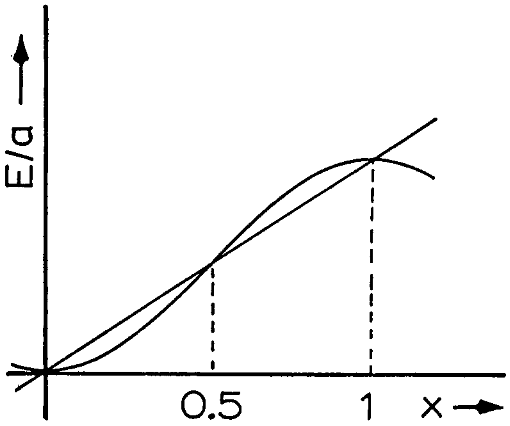


Figure 4. Equation 5: The straight line $w = sx$ is given for comparison; the integrated areas under the curves from x_0 and x_1 are the same.

The author used the relation between ln k and the dielectric constant D (Scatchard's equation)[16] to calculate $r_{\mathrm{N^+\cdots Cl^-}}$; the necessary variation in D was achieved by applying changes in solvent composition. Since the change in D with pressure for these media is unknown, the Owen–Brinkley equation[17] was used to calculate it. The result was a change in r from 2.6 to 3.6 Å over a range of a mere 2 kbar, and this result was considered to confirm the operation of the Walling effect. However, the change seems far too large, especially if the modest pressure range and activation volume (+5 cm^3/mol) are considered; furthermore, since the ionic and van der Waals radii of chlorine are 1.80 Å, and the covalent radii of chlorine and nitrogen are about 1.0 and 0.7 Å, respectively, it is hard to see how the distance between the ionic centers could be much less than 3.7–4.7 Å at any stage, unless we assume that the rate-limiting step is a front-side displacement (at chlorine by chloride). It seems likely that the observation is a manifestation of the special solvent effects that are known[18] to operate in highly aqueous organic media, and which were not considered. As may be obvious from the discussion here, the Walling effect is going to be small even under the most favorable circumstances, and hence difficult to demonstrate; perhaps pressure sensitivity of the chlorine (35/37) isotope effect will be the method of choice.

An interesting phenomenon may be encountered if reactions of low $E^{\ddagger}$ and large, negative $\Delta V^{\ddagger}$ are studied at high pressures. We illustrate this by means of the symmetrical curve III. At the inflection points, the energy is $(\frac{1}{36})a$, and the slope reaches maxima there of $\pm (\frac{1}{9})a\sqrt{3}$. Since $E^{\ddagger}$ is $(\frac{1}{16})a$, one can readily show that the transition state vanishes altogether if $E^{\ddagger} < -(\frac{3}{16})s\sqrt{3}$. Thus, if $\Delta V^{\ddagger} = -22.5$ cm^3/mol and $\Delta V_1 = -45$ cm^3/mol at 10 kbar, in a reaction of activation energy less than 3.5 kcal/mol at atmospheric pressure, the starting material would pass over into product without having to pass a barrier at all at 10 kbar (see curve C of Figure 3). A phenomenon of this sort has been alluded to by Libby.[19]

Finally, it may be noted that it is not necessary that ΔV vary monotonically along the reaction coordinates; it may exhibit extremum behavior as does E itself.[10] Displacement reactions involving no net change of charge, and Diels–Alder reactions involving secondary orbital interactions, are examples of reactions in which $\Delta V^{\ddagger}$ is more negative than ΔV_1. In such reactions, as Figure 5 demonstrates, the addition of E and $p\Delta V$ may lead to a new minimum. In fact, by working at high pressure, we would have stabilized a transition state to the point that it is a reactive intermediate instead. In the displacement example, this might be a molecule containing a pentacovalent carbon atom, or an ion triplet; in the Diels–Alder reaction, a diradical would be indicated. A particularly

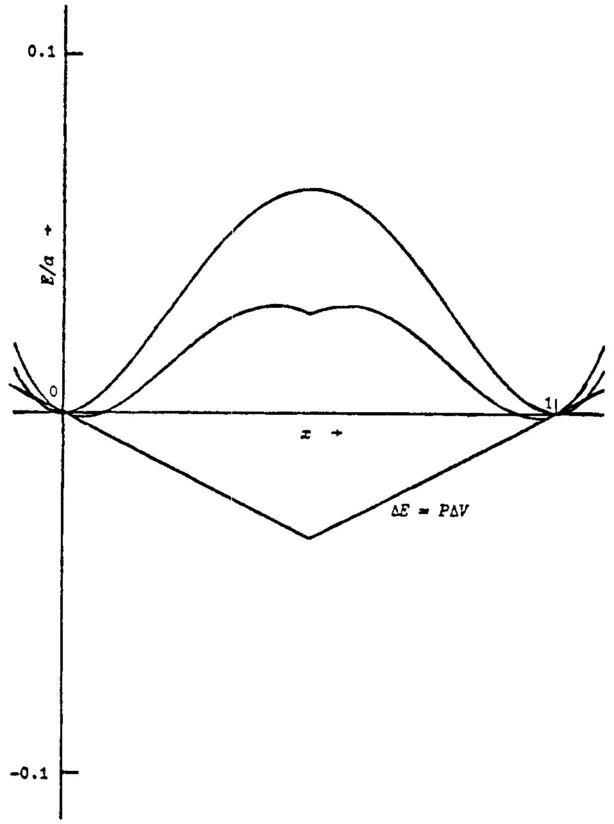
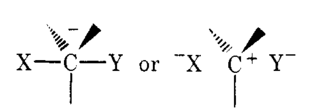
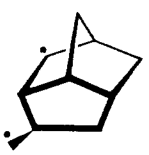
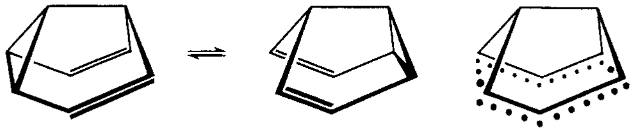


Figure 5. The pressure induced creation of an unstable intermediate.


$$X{-}\overset{-}{C}{-}Y \quad \text{or} \quad {}^{-}X \quad C^{+} \quad Y^{-}$$



interesting case would be the application of very high pressures to rapidly equilibrating valence isomers such as semibullvalene.[20] The activation energy for the degenerate isomerization is only a few kcal/mol; the [3,3] sigmatropic shift is characterized by a negative activation volume and a minimum in the pressure profile.[21] Conversion into a pressure stabilized resonance hybrid (sought by means of substituents in recent years[22]) is thus conceivable.



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References and Notes

(1) (a) At Stony Brook. (b) Molecular Dynamics Fellow at Stony Brook, 1974–1975; correspondence to this author should be addressed to 201 Service Memorial Institute, University of Wisconsin, Madison, Wis. 53706. (c) At Melbourne.
(2) The Eckart potential is an exception; see J. Eckart, *Phys. Rev.*, **35**, 1305 (1930). Its principal virtue has been the fact that its substitution into the wave equation gives a differential equation which can readily be integrated. The solution has been useful in theoretical analyses of tunnelling: J. J. Weiss, *J. Chem. Phys.*, **41**, 1120 (1964). The authors are indebted to an unknown referee for acquainting them with this literature. The Manning potential has been used in the analysis of the ammonia inversion; see M. F. Manning, *J. Chem. Phys.*, **3**, 136 (1935).
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(9) It may be noted here in passing that eq 1 may also be used to relate resonance energies with conventional structures. In this application, a is negative and b has values between $-(4/3)a$ and $-(8/3)a$, so that the curves, now the mirror images of those in Figure 2, lie below the x axis; $x^{\ddagger}$ now represents the "resemblance" of the hybrid with the contributing structures x_0 and x_1; the resonance energy is the difference between E_0 or E_1 (whichever is lower) and $E^{\ddagger}$. It should at once be obvious that $x^{\ddagger}$ will be closest to the canonical structure of lowest energy; if E_1 is also zero, the hybrid is exactly intermediate and the resonance energy reaches a maximum.
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