A Theory of Diastereoisomeric Transition States. Asymmetric Induction

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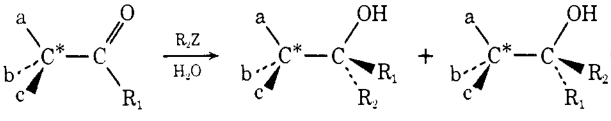
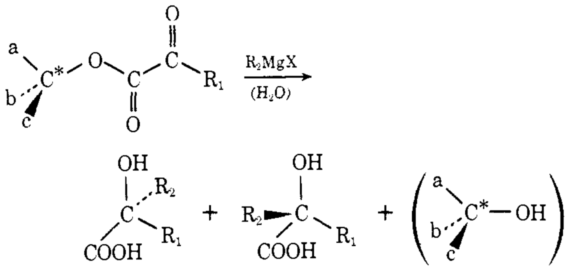
Abstract: The energy difference between diastereoisomeric transition states and the concomitant diastereoisomer ratio are calculated for an achiral reagent $Q(X,Y,Z)$ and a model chiral substrate in which an asymmetrically substituted carbon atom (C*abc) lies in the plane of the prochiral center. The rotation of abc around an in-plane C*d bond in the transition state is assumed to be governed by a ($\cos\theta + \cos 3\theta$)-type potential while the interaction energies between reactant and a, b, c are given respectively by W_a, W_b, W_c which are central-force potentials. Under these assumptions the diastereoisomeric energy difference $\Delta E(\theta)$ for a configuration of the chiral center specified by θ is twice the sum of the algebraic interaction energies between the reagent (in one isomeric transition state) and the fields due to a, b, and c in the direction perpendicular to the plane of prochirality. The *average* energy difference can be calculated under the assumption that in the transition state the reagent sees all thermally available configurations of the chiral group. Various limits are considered. (1) The onefold component of the rotational barrier is smaller than kT; the logarithm of the product ratio for the isomeric approaches Q and Q′ is $\log(c_Q/c_{Q'}) = \text{constant}/(kT)^2$. *The logarithm of the diastereoisomeric ratio is predicted to be proportional to the inverse square of the temperature.* The constant in the numerator depends solely on the physical observables V_a (contribution of substituent a to the onefold potential), F_a (gradient of W_a), r_a (C*–a bond length), etc., which characterize each of the substituents. Its form is different from the "chirality product" suggested by Ruch and Ugi for this type of phenomenon. (2) The onefold component of the rotational barrier is comparable with kT. The average energy difference is proportional to the ratio of two modified Bessel functions of argument $\alpha = V_a/(2kT)$ ($V_a \gg V_b$, V_c) and $\log(c_Q/c_{Q'}) = -(\Delta E_{\max}/kT)(I_1(\alpha)/I_0(\alpha))$, where $\Delta E_{\max}$ is the maximum value of the energy difference, obtained in case 3. (3) The onefold component of the rotational barrier is large relative to kT; the logarithm of the diastereoisomer ratio is proportional to the inverse first power of the temperature. Comparison with experiment shows that information can in principle be obtained (1) on the barrier to rotation of the chiral group and (2) on intermolecular forces, both two-center and three-center, if transition state geometries are known.

The term "asymmetric induction" was coined[2] in 1931 to describe the chirality "induced" in the symmetrical portion of a molecule by an asymmetric center (R) in a different portion of the molecule when the latter reacts with an achiral reagent. Our modern understanding of the phenomenon in terms of the relative energies of diastereoisomeric (RR,RS) transition states dates back to the early 1950's.[3] The entire field of asymmetric reactions has recently been brilliantly reviewed, both in its experimental and in its theoretical aspects.[4] The most thoroughly studied cases of asymmetric synthesis which involve chiral substrates with an achiral reagent are possibly (1) the "1,2-asymmetric induction" addition reactions I of



(I)

chiral aldehydes and ketones with organometallic and metal hydride reagents, which have been interpreted by Cram's rule of steric control of asymmetric induction[3d,5] and by other models;[6] (2) the "1,4-asymmetric induction" addition reactions II of chiral α-keto esters



(II)

with an achiral Grignard reagent, which have been interpreted by Prelog[3e,7] in terms of steric interactions, in the transition states, between R_2 and a, b, c; (3) the "1,3-asymmetric induction" addition reactions III of ketones with organometallics, which can also be interpreted[8] conveniently in terms of steric interactions in the transition state.

The interpretations given[3c,5,7,8] for reactions I–III consider that everything happens *as if* the reagent approaches the keto group more readily on the side of

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(4) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971; (b) R. Bentley "Molecular Asymmetry in Biology," Vol. I Academic Press, New York, N.Y., 1969; Vol. II, 1971.

(5) D. J. Cram and J. D. Knight, *J. Amer. Chem. Soc.*, 74, 5835 (1952); D. J. Cram and F. D. Greene, *ibid.*, 75, 6005 (1953); D. J. Cram and K. R. Kopecky, *ibid.*, 81, 2748 (1959).

(6) (a) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959); (b) G. J. Karabatsos, *J. Amer. Chem. Soc.*, 89, 1367 (1967); (c) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2201 (1968).

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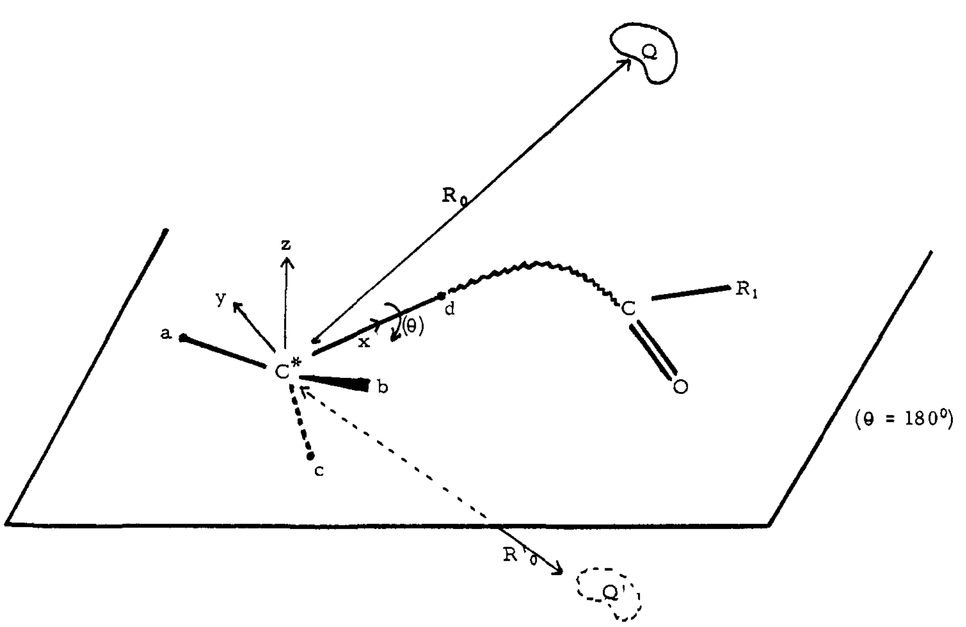
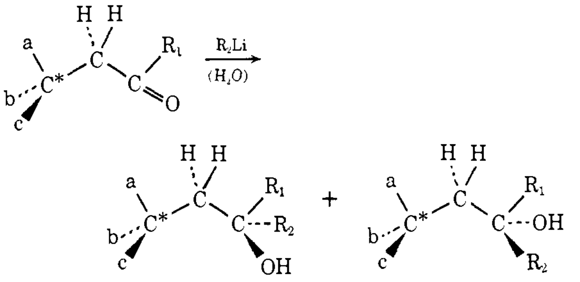


Figure 1. Model for diastereoisomeric transition states in asymmetric induction (Q and Q′ represent the two diastereoisomeric approaches of the chiral reagent).



(III)

C*abc which is less hindered, *i.e.*, nearer to whichever of a, b, and c is smallest. To determine the preferred side of attack, it is generally assumed that the largest of the substituents a, b, and c is locked in the plane of the keto group so that the reagent can choose simply the smaller of the two remaining substituents. *There is no pretense that these models are an accurate description of the real transition states.*[9] In practice, for instance, the chiral group C*abc may be rotating.

In view of the vast amount of experimental data on asymmetric organic syntheses, it is surprising that attempts to establish a theoretical framework for these reactions have been few and far between. Ruch and Ugi have proposed[10] that for asymmetric inductions of types II and III the logarithm of the diastereoisomeric ratio should be of the form

$$\log \frac{c_{RR}}{c_{RS}} = \rho(\lambda_a - \lambda_b)(\lambda_b - \lambda_c)(\lambda_c - \lambda_a) \qquad (1)$$

where λ_a, λ_b, and λ_c are "chirality parameters" characteristic of the substituents a, b, and c and which should be transferable from one reaction to another, while ρ would depend on the type of reaction and on the external conditions. The "chirality product" (1) is attractive in that it has the proper symmetry of the problem. However, it also has serious drawbacks: although λ is clearly homogeneous to a free energy, there is *no knowledge of the physical observables which enter* λ. Furthermore a simple product of differences is not the only conceivable functional which satisfies the symmetry of the problem. Recently, chirality products have been used[11] in the interpretation of free energy differences between the conformers of asymmetric ethanes.

It is our purpose to evaluate the energy difference between diastereoisomeric transition states in terms of physical observables such as temperature, interatomic forces, bond lengths, etc. As model for reactions I, II, and III we assume a prochiral center (keto group, for instance) determining a plane of prochirality which also contains the chiral center C*abc. The fourth bond C*d to the asymmetric center is also assumed to be in the plane of prochirality (Figure 1). Rotation of C*abc is assumed to occur around this bond. The manner in which atom d and the carbon atom C of the prochiral center are related will depend on whether the reaction is a "1,2-asymmetric induction" (d ≡ C), a "1,3-asymmetric induction" (d adjacent to C), or a "1,4-asymmetric induction" (d is β to C).

The potential energy curve $V^{\ddagger}(\theta)$ for rotation of abc around C*d in the *transition state* will be some complicated function. Its maxima and minima are essentially determined by the interactions between a, b, and c and the neighboring center d in the geometries which they adopt at the transition state. The potential will contain an intrinsic, familiar threefold component $V_3^{\ddagger}$ of periodicity 120°, together with a onefold component $V_1^{\ddagger}$ of periodicity 360°. This onefold component represents, in a sense, the asymmetry of the

$$V^{\ddagger}(\theta) = V_1^{\ddagger}(\theta) + V_3^{\ddagger}(\theta)$$

$$V_1^{\ddagger}(\theta) = \frac{V_a}{2}\cos\theta + \frac{V_b}{2}\cos\left(\theta + \frac{2\pi}{3}\right) + \frac{V_c}{2}\cos\left(\theta + \frac{4\pi}{3}\right) \qquad (2)$$

$$V_3^{\ddagger}(\theta) = V_3 \cos 3\theta$$

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(9) (a) D. J. Cram, private communication, 1970; (b) V. Prelog, private communication, 1971.

(10) (a) E. Ruch and I. Ugi, *Top. Stereochem.*, 4, 99 (1969), and references therein; (b) E. Ruch, *Accounts Chem. Res.*, 5, 49 (1972).

(11) G. Binsch, *J. Amer. Chem. Soc.*, submitted for publication.

barrier—from its normal threefold behavior—due to the different nature of substituents a, b, and c (eq 2). Here the origin of the θ's is arbitrarily chosen when substituent a lies in the plane of prochirality cis to the keto group (or prochiral center). If one substituent (a) is much larger than the others, for all useful purposes the onefold potential can be simplified to

$$V_1^{\ddagger}(\theta) = (V_a/2)\cos\theta \tag{3}$$

It is assumed that the potential is, to a first approximation, affected by the reagent only to the extent that the latter determines the transition-state geometry of the substrate.[12]

By definition the two diastereoisomeric reagent positions Q and Q′ are mirror images with respect to the plane of prochirality (xy). If the position of the reagent in one diastereoisomeric transition state is defined as $Q(X,Y,Z)$, in the diastereoisomeric transition state the reagent lies at $Q'(X,Y,-Z)$. The slight change in equilibrium coordinates of Q′ at the transition state, due to a slightly different interaction energy with a, b, c, is neglected.

We assume that the interactions between Q and a, b, c are described by *central-force* potentials $W_a(R_{Qa})$, $W_b(R_{Qb})$, and $W_c(R_{Qc})$, where R_{Qa} is the distance between reagent Q and substituent a. Finally the forces between reagent and a, b, c are assumed to be *additive*. Thus the total interaction energy in any one transition state is simply the sum of W_a, W_b, and W_c. Under these conditions the differences in energies $E_Q^{\ddagger}$ and $E_{Q'}^{\ddagger}$ of the two diastereoisomeric transition states for any *single* configuration θ of C*abc is always given by

$$E_Q^{\ddagger} - E_{Q'}^{\ddagger} \equiv \Delta E(\theta) = W_a(R_{Qa}) - W_a(R_{Q'a}) + W_b(R_{Qb}) - W_b(R_{Q'b}) + W_c(R_{Qc}) - W_c(R_{Q'c}) \tag{4}$$

Average Energy Difference[13]

The manner in which the different available configurations of the chiral group are reflected in the ratio of the rates for formation of the two diastereoisomeric products depends on the relative values of the time spent by Q at the transition state and the time which C*abc takes to rotate.

If the rotation of C*abc is *fast* relative to the time spent by Q in the transition state region, the reagent at the col sees all thermally available configurations of the chiral group. The difference $\Delta E(\theta)$ must then be averaged over all possible configurations, each one being weighted according to its Boltzmann probability.

$$\overline{\Delta E} = \int_0^{2\pi} \Delta E(\theta) e^{-V^{\ddagger}(\theta)/(kT)}\,\mathrm{d}\theta \Big/ \left[\int_0^{2\pi} e^{-V^{\ddagger}(\theta)/(kT)}\mathrm{d}\theta\right] \tag{5}$$

The situation, for reagent Q or Q′, is one where the potential surface fluctuates up and down fast relative to the time spent at the col, so that eq 5 measures the average of the difference in heights between the diastereoisomeric fluctuating cols. The ratio of the reaction rates k_Q and $k_{Q'}$ for attack of Q or Q′ is then related to the average energy difference by

$$k_Q/k_{Q'} = e^{-\overline{\Delta E}/kT} \tag{6}$$

where entropy differences between the diastereoisomeric transition states are neglected.

If, on the other hand, the rotation of C*abc is *slow* relative to the time spent by Q in the transition state, in each approach of the reagent it (or its isomer) sees a precisely different configuration θ. There are then an infinite number of surfaces, each pair of which, for given θ, gives two rates k_Q and $k_{Q'}$ proportional respectively to $\exp[-(W_a + W_b + W_c)(Q,\theta)/(kT)]$ and $\exp[-(W_a + W_b + W_c)(Q',\theta)/(kT)]$. The *ratio* of the average rates is given in eq 7. One would need

$$\frac{\overline{k_Q}}{\overline{k_{Q'}}} = \frac{\int_0^{2\pi} e^{-(W_a+W_b+W_c)(Q,\theta)/(kT)} e^{-V^{\ddagger}(\theta)/(kT)}\,\mathrm{d}\theta}{\int_0^{2\pi} e^{-(W_a+W_b+W_c)(Q',\theta)/(kT)} e^{-V^{\ddagger}(\theta)/(kT)}\,\mathrm{d}\theta} \tag{7}$$

reliable potential surfaces to estimate the relative speeds of rotation (C*abc) and of translation over the col (Q). Throughout this work we have assumed that the reagent *does* have time to see the family of available configurations at the transition state, and we have used eq 5. For very large barriers $V^{\ddagger}$, with the rotation blocked and only one or several equilibrium configurations available from the rotamer, it would be more appropriate to use eq 7. However, eq 5 is used even when rotation is blocked—in which case eq 7 and 5 are identical. The results which would be derived from (7) are studied in the Appendix.

Energy Difference $\Delta E(\theta)$ for an Instantaneous Single Configuration θ of the Chiral Center C*abc

If the reagent Q, in the transition state, is at least a few bond lengths away from the chiral center C* (this will generally be the case, except possibly in certain 1,2 asymmetric inductions), the distances from Q to a, b, c are not very different from the distance R_0 between Q and C*. Thus a Taylor expansion of the form

$$W_a(R_{Qa}) = W_a(R_0) - x_a\left(\frac{\partial W_a}{\partial x}\right)_{X,Y,Z} - y_a\left(\frac{\partial W_a}{\partial y}\right)_{X,Y,Z} - z_a\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,Z} \tag{8}$$

$$W_b(R_{Qb}) = \text{etc.}$$

is justified. In (8) we have assumed that C* is at the origin of coordinates; x_a, y_a, z_a are the Cartesian coordinates of substituent a. The minus signs occur because the differentials are evaluated at the Q terminus for R_0 rather than at the origin itself. Similarly

$$W_a(R_{Q'a}) = W_a(R'_0) - x_a\left(\frac{\partial W_a}{\partial x}\right)_{X,Y,-Z} - y_a\left(\frac{\partial W_a}{\partial y}\right)_{X,Y,-Z} - z_a\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,-Z} \tag{8'}$$

Now the energy W_a depends on the dummy coordinates x, y, and z only through the distance $R_0 = (x^2 + y^2 + z^2)^{1/2}$. Thus the x and y gradients of W_a, W_b, and W_c calculated at the points $Q(X,Y,Z)$ and $Q'(X,Y,-Z)$

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[12] For low barriers in particular, this may be a relatively crude assumption. Certain models[6c] in fact assume that the nature of the potential is determined by the interactions between a, b, and c and the reagent.

[13] The author is particularly grateful to Professors Roy Gordon and Martin Karplus for illuminating discussions of the various averaging procedures.

are equal, while

$$\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,Z} = -\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,-Z} \tag{9}$$

It follows that, from eq 4

$$\Delta E = -2z_a\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,Z} - 2z_b\left(\frac{\partial W_b}{\partial z}\right)_{X,Y,Z} - 2z_c\left(\frac{\partial W_c}{\partial z}\right)_{X,Y,Z} \tag{10}$$

Equation 10 reveals that only the energy gradient or field of the chiral group C*abc in the direction perpendicular to the plane of prochirality is relevant to the energy difference between diastereoisomeric transition states. The energy gradient at Q due to a is appropriately modulated by the vertical distance z_a of a from the prochiral plane. Since W_a depends on z *via* $R_0 = (x^2 + y^2 + z^2)^{1/2}$, this field is

$$\left(\frac{\partial W_a}{\partial z}\right)_{X,Y,Z} = \frac{Z}{R_0}\left(\frac{\partial W_a}{\partial R}\right)_{R_0} \equiv -\frac{Z}{R_0}F_a \tag{11}$$

where F_a is the force on Q due to substituent a. This force is negative if W_a is attractive ($\partial W_a/\partial R > 0$), *positive if W_a is repulsive.*

The energy difference between diastereoisomeric transition states is then simply

$$\Delta E(\theta) = 2\frac{Z}{R_0}(z_aF_a + z_bF_b + z_cF_c) \tag{12}$$

In this extremely simple expression the z coordinate of each substituent of the asymmetric center is multiplied by the appropriate field which it creates at the reagent. Each term $Zz_iF_i/(R_0)$ can be thought of as the "algebraic" interaction energy between the reagent (in *one* isomeric transition state) and the field due to substituent i. For a positive (repulsive) field the interaction energy is *positive* if i lies *above* the plane, *negative* if i lies *below* the plane.

Equations 2, 5, and 12 form the basis of the following discussion.

Average Energy Difference in the Limit of a Small Onefold Potential for C*abc

The calculation of the average energy difference in the general case requires some knowledge of the relative magnitudes of $V_1^{\ddagger}$, $V_3^{\ddagger}$, and kT. Typical values of the threefold barrier V_3 in ground-state aldehydes or ketones range from 0.8 kcal/mole (acetone[14]) to 2.3 kcal/mol (propionaldehyde[15]), compared with a onefold component of approximately 1 kcal/mol.[15,16] We will make the reasonable assumption that $V_3 \geq kT$, and we will calculate the average energy difference in difference limiting cases for the onefold component $V_1^{\ddagger}$ of the barrier.

We will first consider the case where $V_1^{\ddagger}$ (and hence V_a, V_b, and V_c) is small compared with kT. In the exponential

$$e^{-V^{\ddagger}/(k\mathrm{T})} = e^{-V_1^{\ddagger}/(k)}e^{-V_3^{\ddagger}/(kT)} \tag{13}$$

the first factor can therefore be expanded in powers of T^{-1}.

$$e^{-V_1^{\ddagger}/(kT)} \approx 1 - \frac{1}{kT}\left\{\frac{V_a}{2}\cos\theta + \frac{V_b}{2}\cos\left(\theta + \frac{2\pi}{3}\right) + \frac{V_c}{2}\cos\left(\theta + \frac{4\pi}{3}\right)\right\} \tag{14}$$

For the second factor we use the general expansion,[17] valid for all values of the exponent

$$e^{-\beta\cos \mathrm{x}} = I_0(\beta) + 2\sum_{l=1}^{\infty} I_l(\beta)\cos(l\mathrm{x}) \tag{15}$$

where in this particular case $x = 3\theta$ and

$$\beta = V_3/(2kT) \tag{16}$$

In (15), the number $I_l(\beta)$ is the modified Bessel function of (integral) order l[17] and of argument β.

Furthermore

$$z_a = -\frac{2\sqrt{2}}{3}r_a\sin\theta$$
$$z_b = -\frac{2\sqrt{2}}{3}r_b\sin\left(\theta + \frac{2\pi}{3}\right) \tag{17}$$
$$z_c = -\frac{2\sqrt{2}}{3}r_c\sin\left(\theta + \frac{4\pi}{3}\right)$$

where r_a, r_b, and r_c are respectively the bond lengths between C* and a, b, and c and where again the origin of the θ's has been chosen when substituent a lies in the plane of prochirality cis to the prochiral center. The integration of eq 5, where $\Delta E(\theta)$ has been replaced by its value given in eq 12, is then straightforward[18] and yields

$$\overline{\Delta E} = \sqrt{\frac{2}{3}}\frac{Z}{R_0}\frac{1}{kT}\left\{\frac{V_a}{2}(r_bF_b - r_cF_c) + \frac{V_b}{2}(r_cF_c - r_aF_a) + \frac{V_c}{2}(r_aF_a - r_bF_b)\right\} \tag{18}$$

Equation 18 gives the energy differences between diastereoisomeric transition states averaged over all thermally available configurations of the chiral center. Attention should be drawn to several features of this equation:

(a) The average energy difference is inversely proportional to the temperature. It follows, if entropy differences between the diastereoisomeric transition states are neglected, that the logarithm of the diastereoisomeric ratio is (see eq 6)

$$\log\frac{c_Q}{c_{Q'}} = -\frac{\overline{\Delta E}}{kT} = \frac{\text{constant}}{(kT)^2} \tag{19}$$

The logarithm of the diastereoisomeric ratio is predicted to be inversely proportional to the *square* of the temperature.

(b) The factor $1/kT$ in the expression for $\overline{\Delta E}$ involves $(V_a/2)(r_bF_b - r_cF_c)$ and similar terms obtained by permuting a, b, and c. The term $(r_bF_b - r_cF_c)$ represents the difference in interaction energies for an approach near substituent b (field F_b) and an approach near substituent c (field F_c). This difference is ap-

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(14) R. Nelson and L. Pierce, *J. Mol. Spectrosc.*, 18, 344 (1965); D. Swalen and C. C. Costain, *J. Chem. Phys.*, 31, 1562 (1959).

(15) S. S. Butcher and E. B. Wilson, Jr., *ibid.*, 40, 1671 (1964).

(16) J. P. Guillory and L. S. Bartell, *ibid.*, 43, 654 (1965).

(17) Handbook of Mathematical Functions," 5th ed, M. Abramowitz and I. A. Stegun, Ed., Dover Publications, New York, N. Y., 1968, Sections 9.6 and 9.7 and Table 9.8.

(18) The calculation is reduced to an integration over products of elementary cosine and sine functions. The term $2\pi I_0(\beta)$ cancels between numerator and denominator.

propriately modulated by V_a, the strength of the onefold barrier term originating from substituent a. The larger V_a (>0), the more likely will C*abc adopt a configuration in which a lies in the plane of prochirality trans to the prochiral center ($\theta = 180°$), with reagent Q feeling essentially the effect of b while reagent Q′ feels essentially the effect of c. If b, for instance, exerts a steric repulsion which is large compared with that due to c ($r_bF_b > r_cF_c$ for given distance R_0), the reagent will approach more readily from *below* the plane of prochirality. So this term should give a positive contribution to ΔE ($E^{\ddagger}_Q > E^{\ddagger}_{Q'}$). This is indeed the case.

(c) It is interesting to compare the term in braces in eq 18 with the Ruch–Ugi formula (eq 1). The right-hand side of (1) can be rewritten as

$$\rho[\lambda_a(\lambda_b^2 - \lambda_c^2) + \lambda_b(\lambda_c^2 - \lambda_a^2) + \lambda_c(\lambda_a^2 - \lambda_b^2)] \qquad (20a)$$

which should be compared with

$$\frac{\text{constant}}{(kT)^2}\left[\frac{V_a}{2}(r_bF_b - r_cF_c) + \frac{V_b}{2}(r_cF_c - r_aF_a) + \frac{V_c}{2}(r_aF_a - r_bF_b)\right] \qquad (20b)$$

It is clear that both expressions possess the proper symmetry of the problem and vanish when any two substituents a, b, or c are identical. They also have the same functional dependence on the subscripts a, b, and c, but the resemblance is limited to these features. Whereas for each substituent (20b) involves three physical observables—a potential barrier, a bond length, a force—eq 20a involves only one parameter λ. We do, however, gain some insight into the various factors which are "buried" in λ by this comparison.

It should be noted, furthermore, that if the chirality product can be expanded into a form which resembles the correct expression (20b), the reverse is not true. Equation 20b is not readily amenable to the form of a chirality product (unless one imposes the unreasonable constraint $V_i^2 = 4r_iF_i$).

(d) In the extreme limit where the onefold potential vanishes ($V_a \equiv V_b \equiv V_c \equiv 0$), the average energy difference between diastereoisomeric transition states vanishes. *There is no contribution to the asymmetric induction from a chiral center whose rotation is governed solely by a threefold potential.* This is true whatever the threefold barrier height.

Yet, "once chiral, always chiral";[19] the presence of the chiral center (even with $V_1^{\ddagger} = 0$) should lead to different amounts, however minute the difference, of diastereoisomers. The answer to the dilemma is that $\overline{\Delta E}$ would be nonzero if we had allowed for nonadditivity in the interaction energy between reagent and chiral group by introducing *three-center forces*. Indeed, with only two-center forces, the total energy of interaction between the reagent and the various substituents in some configuration θ was the sum of *two-center* terms

$$E(\theta) = W_a(R_{Qa}) + W_b(R_{Qb}) + W_c(R_{Qc})$$

Now each term of this expression appears *once* in a similar expression for the energy of the diastereoisomer. For instance, $W_a(R_{Qa})$ appears in the energy of interaction between Q′ and the configuration in which substituent a has turned until it has reached its mirror image a′. Since, for a cos 3θ potential (but not for a cos θ potential!) the three configurations which include a′, b′, and c′ all have the same rotational energy as the initial configuration abc, the average energies of the two diastereoisomeric transition states are equal. In the presence of *three-center* forces, however, an energy term such as $W_{ab}(R_{Qa}, R_{Qb}, R_{ab})$ will appear for a configuration θ. The corresponding term in the diastereoisomer is $W_{ab}(R_{Q'a'}, R_{Q'b''}, R_{a'b''})$, where b″ is the position of b when a reaches a′. Since b″ is distinct from b′ (image of b), the second set of three internal coordinates can *never* be made identical with the first set. Thus E_Q and $E_{Q'}$ will contain *different* three-center terms. Even if the two configurations are weighted equally, the average energies of the diastereoisomeric transition states will be different.

Energy Difference in the Limit of a Large Onefold Potential ($V_a \gg V_b$, V_c, kT)

Let us consider the case where one substituent, "a" say, is very large, so that its interactions with the center d dominate those of b and c.

$$V_a \gg V_b, V_c \qquad (21)$$

If furthermore

$$V_a \gg kT \qquad (22)$$

the rotation can be considered to be blocked (whatever the value of V_3) in the configuration $\theta = 180°$. The "average" energy is simply the energy for this configuration

$$\overline{\Delta E} = \Delta E(180°) = 2\sqrt{\frac{2}{3}}\frac{Z}{R_0}(r_bF_b - r_cF_c) \qquad (23)$$

where we have used (12) and (17). We have already given the interpretation of the term ($r_bF_b - r_cF_c$) (previous section b). We shall see further that (23) is actually the *maximum value* of the energy difference for the case where the onefold potential is dominated by a single substituent. In this case the logarithm of the diastereoisomer ratio varies as the inverse first power of the temperature.

General Expression for the Energy Difference ($V_a \gg V_b$, V_c)

We now calculate the general formula for the energy difference as a function of temperature in the case where the onefold potential energy is dominated by one substituent (eq 3). If we use the general expansion 15 for both factors of eq 13, the integral in the numerator of (5) becomes

$$\int_0^{2\pi}\Delta E(\theta)\left[I_0(\alpha) + 2\sum_{n=1}^{\infty}I_n(\alpha)\cos(n\theta)\right]\times\left[I_0(\beta) + 2\sum_{l=1}^{\infty}I_l(\beta)\cos(3l\theta)\right]\mathrm{d}\theta$$

where β is defined in eq 16 and

$$\alpha = V_a/(2kT) \qquad (24)$$

A very similar expression holds for the denominator of eq 5, except that $\Delta E(\theta)$ is replaced by unity. Again,[18] since $\Delta E(\theta)$ involves only terms in cos θ and sin θ (see eq 12 and 17), the numerator and denominator reduce to sums of integrals over products of elementary trig-

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(19) The author is indebted to V. Prelog for this proverb.

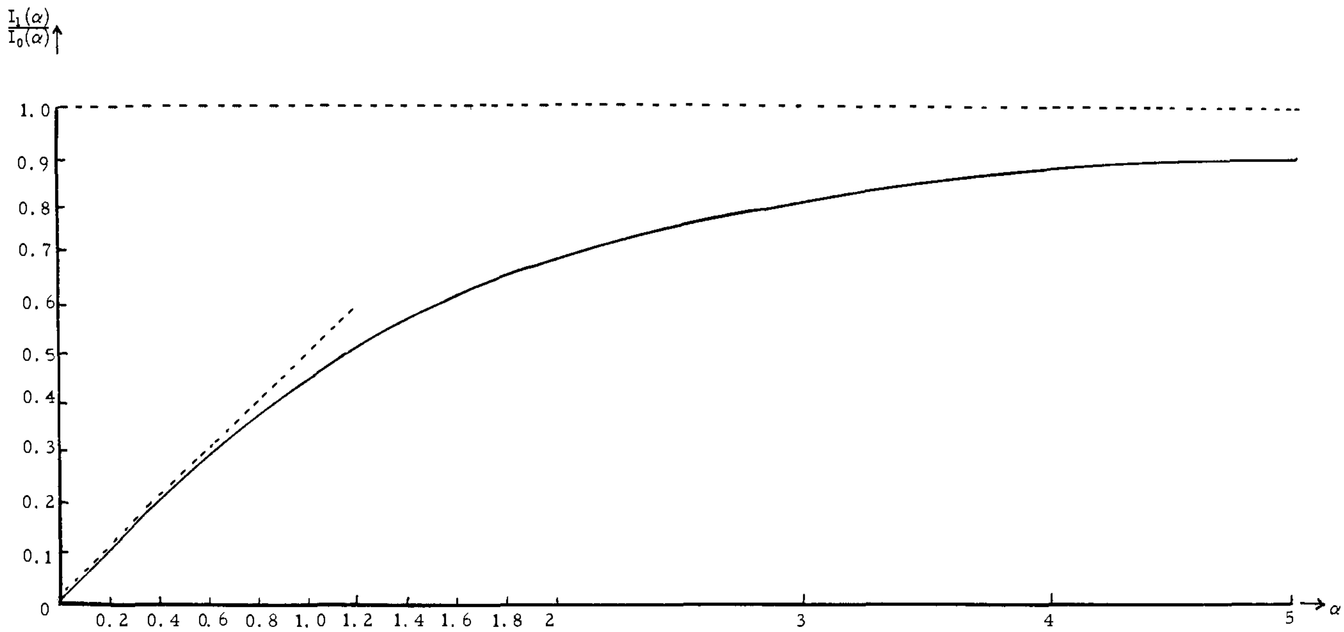

Figure 2. Behavior of ratio $I_1(\alpha)/I_0(\alpha)$.

onometric functions. The final result is

$$\overline{\Delta E} = -2\sqrt{\frac{2}{3}}\frac{Z}{R_0}(r_bF_b - r_cF_c)[I_0(\beta)I_1(\alpha) + I_1(\beta)\{I_2(\alpha) + I_4(\alpha)\} + \ldots]/[I_0(\beta)I_0(\alpha) + I_1(\beta)I_3(\alpha) + \ldots] \quad (25)$$

Now for arguments α of order unity, $I_m(\alpha)$ is a rapidly decreasing function of its argument.[20] It is therefore legitimate to keep only the leading term in both numerator and denominator, whence[21]

$$\overline{\Delta E} = 2\sqrt{\frac{2}{3}}\frac{Z}{R_0}(r_bF_b - r_cF_c)\frac{I_1(\alpha)}{I_0(\alpha)}$$
$$\alpha = V_a/(2kT)\,(V_a \gg V_b,\ V_c) \quad (26)$$

The average energy difference depends on the temperature *via* the ratio of the modified Bessel function of order 1 to that of order zero, both with argument $V_a/(2kT)$. We can check immediately that (26) has the proper behavior both in the large V_a limit and in the small V_a limit. First for large α[17]

$$I_m(\alpha) \sim e^{\alpha}/\sqrt{2\pi\alpha} \quad (27)$$

and the ratio $I_1(\alpha)/I_0(\alpha)$ tends toward 1. Equation 26 reduces immediately to (23). On the other hand, in the limit of small α[17,22]

$$I_0(\alpha) \sim 1 + \frac{\alpha^2}{2^2(1!)^2} + \ldots$$
$$I_1(\alpha) \sim \frac{\alpha}{2} + \frac{\alpha^3}{2^3 1!2!} + \ldots \quad (28)$$

so that $I_1(\alpha)/I_0(\alpha)$ can be approximated by $\alpha/2$. Thus

$$\overline{\Delta E} = \sqrt{\frac{2}{3}}\frac{Z}{R_0}\frac{1}{kT}\left[\frac{V_a}{2}(r_bF_b - r_cF_c)\right] \quad (29)$$

which is identical with the first term of (18).

In the intermediate case where V_a is of the order of $2kT$, one must resort to numerical tables[17] of the functions I_0 and I_1. Table I shows the ratio $I_1(\alpha)/I_0(\alpha)$

Table I. Values of Modified Bessel Functions[17]

$\alpha = V_a/(2kT)$	$I_0(\alpha)$	$I_1(\alpha)$	$I_1(\alpha)/I_0(\alpha)$
0	1.0000	0.0000	0.0000
0.1	1.0025	0.0501	0.0500
0.2	1.0100	0.1005	0.0995
0.4	1.0404	0.2040	0.1961
0.6	1.0921	0.3137	0.2872
0.8	1.1665	0.4329	0.3711
1	1.2661	0.5652	0.4464
1.2	1.3937	0.7147	0.5128
1.4	1.5534	0.8861	0.5704
1.6	1.7500	1.0848	0.6199
1.8	1.9895	1.3172	0.6621
2	2.2796	1.5906	0.6978
3	4.8808	3.9534	0.8100
4	11.302	9.7594	0.8635
5	27.240	24.335	0.8934

for values of α ranging from 0–5. The behavior of the ratio is also shown in Figure 2.

Since $I_1(\alpha)/I_0(\alpha)$ never exceeds 1, it is clear that the energy difference (eq 23) calculated for large onefold barriers is the *maximum value* of the energy difference between the diastereoisomeric transition states. Thus eq 26 can be reduced to the simple form

$$\Delta E = \Delta E_{\max}(I_1(\alpha)/I_0(\alpha))$$
$$\alpha = V_a/(2kT)\,(V_a \gg V_b,\ V_c) \quad (30)$$

or, in an equivalent manner

$$\log \frac{c_Q}{c_{Q'}} = -\frac{\Delta E_{\max}}{kT}\frac{I_1(\alpha)}{I_0(\alpha)} \quad (31)$$

Comparison with Experiment

The comparison of the theoretical results with experimental data can be approached from three

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[20] For instance $I_0(1) = 1.2661$, $I_1(1) = 0.5652$, $I_2(1) = 0.1357$, $I_3(1) = 0.0222$. More generally $I_{m+1}(\alpha) = -(2m/\alpha)I_m(\alpha) + I_{m-1}(\alpha)$.

[21] Note here that $I_0(-\alpha) = I_0(\alpha)$ but $I_1(-\alpha) = -I_1(\alpha)$.

[22] I. S. Gradshteyn and I. W. Ryzhik, "Tables of Integrals, Series and Products," Academic Press, New York, N. Y., 1965, Section 8.44.

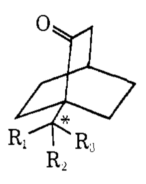
different angles: variation of product ratio with temperature, influence of the onefold potential $V_1^{\ddagger}(\theta)$, and information on intermolecular forces.

(1) The manner in which the logarithm of the diastereoisomeric ratio is predicted to vary with temperature is summarized in eq 31. For small $V_1^{\ddagger}$ we predict a T^{-2} dependence; for large $V_1^{\ddagger}$, the conventional T^{-1} dependence. At "intermediate" values a complex dependence of the form

$$\frac{1}{T}\frac{I_1(V_a/(2kT))}{I_0(V_a/(2kT))}$$

(see Figure 2) is predicted. The novel prediction concerns the *inverse square temperature dependence for small onefold barrier* components. Unfortunately existing temperature-dependent studies are not extensive enough (generally three or four points alone have been measured on the product ratio *vs.* T curve) to distinguish between a T^{-2} behavior and, say, a T^{-1} behavior. Furthermore the accuracy of the experimental results is relatively low.[23]

Synthesis of **1** and **2** is presently being carried out by Kagan and his collaborators in order to make a careful study of the temperature dependence of the diastereoisomer ratio in the reduction. In both cases the asymmetric carbon atom lies nicely in the plane of the prochiral keto group, so that the present model should be applicable.



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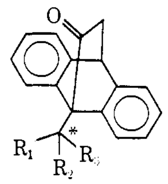

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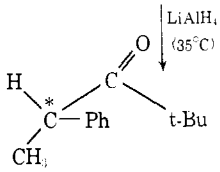
(2) In the case where one substituent at the chiral center is much larger than the two others (for example, a = phenyl, b = methyl, c = H) it is possible to obtain from eq 31 estimates of the contribution V_a to the rotational barrier (eq 3) in various transition states. We can compare, for instance, the onefold component V_a in the transition states of **3**, **4**, **5**, and **6**, which differ only by the nature of the substituent at the prochiral center. For compound **3** we can be assured that rotation of the chiral center is blocked. From the measured[6c] diastereoisomeric ratio of 49 we deduce

$$|\Delta E_{\max}| = kT\log 49 = 0.61 \times 3.9 = 2.4 \text{ kcal/mol} \quad (32)$$

We can now use this value of $|\Delta E_{\max}|$ in (31) to write

$$\frac{I_1(\alpha)}{I_0(\alpha)} = 0.25 \log \frac{c_Q}{c_{Q'}} \quad (33)$$



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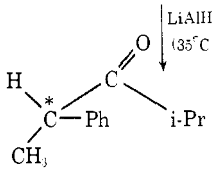

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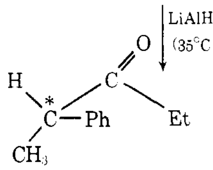

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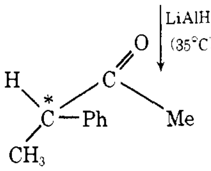


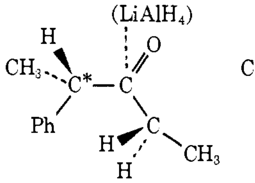
6

Measurement of the diastereoisomeric ratio in **4**, **5**, or **6** then leads directly[24] to $I_1(\alpha)/I_0(\alpha)$—whence to V_a—for these compounds. The results are summarized below in Table II. The calculated onefold terms do not have unreasonable values and can be rationalized in terms of similar optimal "transition state" configurations **5′** and **6′** for **5** and **6**, but a more hindered one (**4′**) for **4**. In **4′**, **5′**, and **6′**, the keto group and phenyl group are trans to each other.[25] In **4′**, the phenyl group is eclipsed by a hydrogen atom, whereas in **5′** and **6′** there is staggering of the phenyl group with a pair of hydrogen atoms.

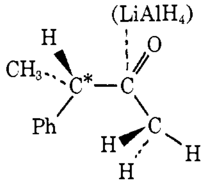
Table II. Values of the Onefold Barrier V_a in Various Transition States

Compd	$c_Q/c_{Q'}$	$I_1(\alpha)/I_0(\alpha)$	α	V_a[a]
4	5.0	0.41	0.90	1.1
5	3.2	0.29	0.60	0.73
6	2.8	0.25	0.51	0.62

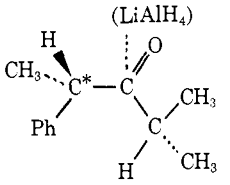
[a] $V_a = 2kT\alpha$ kcal/mol.



5′



6′



4′

(3) For blocked rotation of the chiral group (large substituent a) eq 23 relates the diastereoisomeric energy difference $\Delta E_{\max}$ to the difference $(r_bF_b - r_cF_c)$ in interaction energies between the reagent and the other two substituents. Measurement of $\Delta E_{\max}$ for a "1,2," "1,3," and "1,4," asymmetric induction series should give some information on the interaction energies W_b and W_c between reagent and substituents b and c.

For instance, in **7**, in spite of the small size of the CH_3 group the rotation of the chiral center is most probably blocked, owing to its proximity to the prochiral center. Our model can be applied to this system if C* is assumed to be in the prochiral plane. The measured diastereoisomeric ratio[26] is 1.4, leading to

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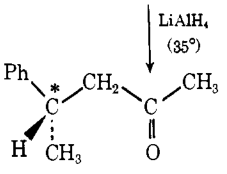
[23] See, for example, Table 3-1, ref 4a, where the reduction of 3-phenyl-2-butanone by $LiAlH_4$ at 35° yields a diastereoisomer ratio of 2.5, 2.6, and 2.8 in three different experiments.

[24] It is convenient to use Table I or Figure 2.

[25] This corresponds essentially to Cram's open-chain model.[3d,5] Other possibilities have C*—CH_3 eclipsed with C═O,[6b,15,16] or the phenyl group trans to the incoming reagent.[6c] The first of these also leads to the instability of 4 relative to 5 and 6.

[26] M. Brienne, C. Ouannès, and J. Jacques, *Bull. Soc. Chem. Fr.*, 1036 (1968).



7

$|\Delta E_{\mathrm{max}}| = 0.20$ kcal/mol. Assuming the vertical coordinate Z of the incoming hydrogen atom to be the same in the transition states of **3** and **7**, we have

$$\frac{[(1/R_0)(r_bF_b - r_cF_c)]_{1,2\ \mathrm{induction}}}{[(1/R_0)(r_bF_b - r_cF_c)]_{1,3\ \mathrm{induction}}} \approx 12 \qquad (34)$$

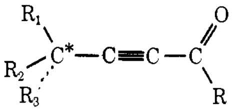
The strong variation with distance is indicative of exponential repulsive forces.

If we think of the fraction $(1/R_0)(r_bF_b - r_cF_c)$ as some function g *characteristic of the substituents* (*b and c*) *and of the reagent*, we have $g(R_{12})/g(R_{13}) \approx 12$. Assuming $R_{12} = 2.5$ Å and $R_{13} = 3.2$ Å (values calculated for $Z = 2$ Å at the transition state), we can derive the numerical exponent in an assumed exponential form of g.

$$g_{\mathrm{H,CH_3(LiAlH_4)}} = A \exp(-3.6R_{\text{Å}}) \qquad (35)$$

A similar 1,4-asymmetric induction experiment would yield the value of the constant A. In principle, therefor, the proper number of experimental results and their proper interpretation could lead to tables of g functions which would be typical of given pairs of substituents in a chosen reaction. Of course each g function will also depend on temperature, solvent, etc.

A final remark concerns the case where $V_1^{\ddagger} \equiv 0$. As mentioned and explained previously, our model gives no asymmetric induction for a chiral center whose rotation is governed solely by a threefold potential. If, for instance, a sizable V_3 term ensures that only three configurations (60, 180, 300°) are populated, the asymmetric induction due to these three configurations compensates exactly (add eq 23 with its two cyclic permutational analogs). The role of the onefold potential is to discriminate between these configurations by making their populations slightly unequal, thereby leading to a nonvanishing asymmetric induction. However, as also mentioned previously there is an "intrinsic" asymmetric induction due to nonadditive intermolecular forces. For instance, a careful analysis of all the energy terms in **8** together with a measurement of typical diastereoisomeric ratios could, in principle, lead to information on the nature of three-center forces between reagent and pairs of substituents.



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Acknowledgments. The author is extremely grateful to Professors Roy Gordon, Martin Karplus, Vlado Prelog, and Dr. Xavier Chapuisat for many stimulating discussions. Professors John Pople and Paul von Ragué Schleyer were instrumental in drawing the author's attention to the relative roles of the onefold and threefold barrier terms. Last, but not least, I thank Professor Henri Kagan for having stimulated my interest in this problem and for his patience in our innumerable discussions.

Appendix

Equation 7 can be transformed by using (8), (8′), and equations similar to (11) for the various energy gradients. The result is

$$\frac{\overline{k_{\mathrm{Q}}}}{\overline{k_{\mathrm{Q'}}}} = \frac{\displaystyle\int_0^{2\pi} \exp\{-[(X\Sigma x_iF_i + Y\Sigma y_iF_i + Z\Sigma z_iF_i)/R_0 + V^{\ddagger}]/(kT)\}\mathrm{d}\theta}{\displaystyle\int_0^{2\pi} \exp\{-[(X\Sigma x_iF_i + Y\Sigma y_iF_i - Z\Sigma z_iF_i)/R_0 + V^{\ddagger}]/(kT)\}\mathrm{d}\theta} \qquad \text{(A-1)}$$

where the subscript i = a, b, or c and the summations cover all three substituents. The x, y, z coordinate axes are shown in Figure 1. The coordinates z_i depend on θ *via* eq 17 while clearly the coordinates x_i are independent of θ. Finally

$$\begin{aligned} y_a &= r_a \cos\theta \\ y_b &= r_b \cos(\theta + (2\pi/3)) \\ y_c &= r_c \cos(\theta + (4\pi/3)) \end{aligned} \qquad \text{(A-2)}$$

If the potential is written as in (2) or (3), the integrals in both numerator and denominator have the general form

$$J = \int_0^{2\pi} e^{p\sin\theta} e^{q\cos\theta} e^{-V_1^{\ddagger}/(kT)} e^{-V_3^{\ddagger}/(kT)}\, \mathrm{d}\theta \qquad \text{(A-3)}$$

where the p and q in the numerator differ from those (p' and q') in the denominator. The expansion 15 can be used for the second, third, and fourth exponentials. An alternate expansion[17] is required for the first exponential

$$e^{p\sin\theta} = I_0(p) + 2\sum_{k=0}^{\infty}(-1)^k I_{2k+1}(p)\sin\{(2k+1)\theta\} + 2\sum_{k=1}^{\infty}(-1)^k I_{2k}(p)\cos(2k\theta) \qquad \text{(A-4)}$$

Thus (A-1) can be expressed as a ratio of series of modified Bessel functions. We will not make explicit this ratio any further. The leading term, however, is equal to

$$\frac{I_0(p)I_0(q)}{I_0(p')I_0(q')}$$

In the large barrier limit, when the rotation is blocked, there is no need for the averaging process implied by the integration over θ, and the ratio of the average rates is equal to that of the rates for the single configuration $\theta = 180°$

$$\frac{\overline{k_{\mathrm{Q}}}}{\overline{k_{\mathrm{Q'}}}} = \frac{k_{\mathrm{Q}}(\theta = 180°)}{k_{\mathrm{Q'}}(\theta = 180°)} = e^{-\Delta E(180°)} \qquad \text{(A-5)}$$

which is identical with (23).