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The Sensitivity of Intramolecular Reactions to the Orientation of the Reacting Atoms[1]

G. A. DAFFORN AND D. E. KOSHLAND, JR.

Department of Biochemistry, University of California, Berkeley, California

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The contributions to rates of intramolecular and enzymatic reactions provided by proximity and correct orientation of two reacting groups are examined. It is shown that the rate enhancement arising from simple juxtaposition of two molecules or functional groups can be expressed as a statistical factor (some fraction of 55 M for aqueous solution) multiplied by a correction term for use when specific data on solution structure are available.

The effect of relative orientation of two reacting groups on their rate of reaction is expressed in terms of a simple collision theory. The angular dependence of rate is assumed to arise solely from an angle-dependent potential-energy barrier determined by the magnitude of transition state bending force constants. Crude but reasonable calculations using assumed values for bending force constants in the transition state suggest that orientation may lead to rate accelerations of up to 10^4 for a properly oriented intramolecular or enzymatic reaction compared to its bimolecular counterpart.

Although the final determination of the effect of orientation must be experimental, these calculations indicate that orientation of reacting groups may account for a substantial fraction of intramolecular and enzymatic catalysis.

It is generally assumed that chemical reactivity is a function of the orbital structure of the reacting atoms and that the velocity of the reaction is in some way related to the orbital overlap (*1–4*). The precise nature of this relationship is, of course, obscured by the difficulty of quantum mechanical calculations. One feature of reactivity, i.e., its sensitivity to angular variation, is in particular need of evaluation in view of its possible importance in enzymatic and intramolecular reactions (*5*).

The difficulty of calculating this factor definitively lies in two parts. In the first place, there is the usual uncertainty of quantum mechanical calculations on atoms or molecules appreciably more complicated than hydrogen and helium. An even further step in complexity is introduced by the uncertainty of geometry in the transition state.

A second difficulty lies in the experimental approach. When classic experiments which indicate some preferred orientation in reactions are examined, they give only very crude estimates of angular preferences. For example, the existence of a Walden inversion indicates that attack must come from one of the four quadrants on the surface of an alkyl halide molecule. The well-known experiments with cyclic systems demonstrate that epoxidation and other reactions are preferred in the *trans* conformation, i.e., with an approximately 180° angle between the attacking and leaving groups compared to the *cis* conformation with approximately 60° relative angles (*7*). Although

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these show a favored orientation for reaction, the sensitivity to smaller deviations in angle is not evaluated. Furthermore, the experiments themselves are ambiguous since contributions of ring strain, electrostatic repulsion, solvation, etc., vary for the different compounds.

Recently a series of five-membered-ring lactonizations were studied in which the contribution of factors other than orientation was controlled or made susceptible to calculation (*8*). When correction was made for these factors, an orbital orientation factor of approximately 10^4 was estimated for the increase in velocity of a favorably oriented reaction relative to a random collision. The term "orbital steering" was used to designate reactions such as intramolecular reactions or enzymatic reactions in which the angular approach of the reacting atoms is confined as compared to random bimolecular approach.

The number 10^4 is somewhat higher than might be anticipated from general pictures of the diffuseness of electron clouds, the factors observable in molecular beam experiments (*9*), and the generally accepted values in the organic literature. It seemed of importance, therefore, to see whether theoretical calculations would indicate the magnitude which various phenomena might contribute to such orientation factors.

In this paper we shall examine a calculation of the potential contribution of orbital steering to a bimolecular reaction using collision theory as the departure point. In subsequent papers a similar calculation using transition-state theory will be presented.

PROXIMITY EFFECTS

In order to evaluate the orientation factor in a bimolecular reaction relative to a unimolecular reaction, some correction must be made for changing units between these two kinetic orders. A method of carrying out such a calculation has been devised (*10*) and is shown schematically in Fig. 1.

If one assumes that the reacting atoms are the size of water molecules and there is no net attraction or net repulsion between the reacting molecules, a factor of 55 is deduced to correct the velocity observed in the usual bimolecular rate at unit activities to the first order reaction observed on the enzyme surface.

Perhaps the simplest way of seeing this is to consider that molecule A in Fig. 1 is activated instantaneously by some photochemical event. Its probability of finding a neighbor, B, at the proper position for reaction will then be (B)/55. On the other hand, the probability of finding a neighbor B on the enzyme surface will be certainty when the enzyme is saturated. If the reaction mechanism is identical, the velocity on the enzyme surface would, therefore, be the same as that shown in the lower left-hand corner of the figure where the molecule of A is surrounded entirely by B molecules. In that case also, the photoactivated A would be certain of having a neighbor B for reaction. This conceptual situation is thus realized by multiplying the bimolecular constant by 55 M. (This simplified example assumes that the orientation factor discussed below is such that only one of the nearest neighbors of A can react because of the preferred orientation of the activated A molecule. The more complex situation in which more than one of the nearest neighbors could react is discussed in the previous paper (*10*)).

It should be emphasized that this proximity factor of 55 (equivalent to 8 e.u.) is the entropic factor to correct for the collisional probability of bringing two randomly colliding species together. It assumes, as stated (*10*) that there is no net attraction or net repulsion between the reacting atoms relative to the molecules of solvent. If such

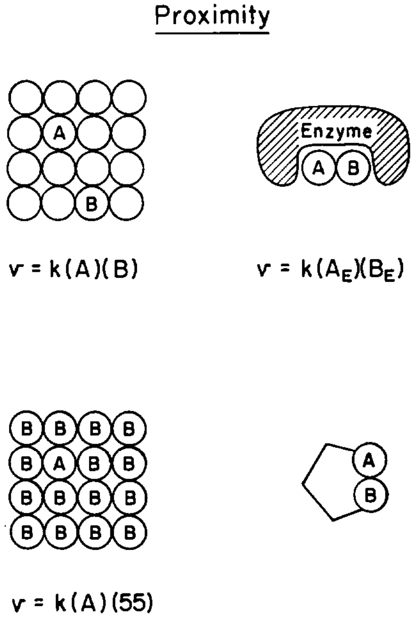

FIG. 1. Schematic illustration of proximity corrections. Upper left: The distribution of molecules A and B in a typical bimolecular process. Upper right: Model of the active site of an enzyme where B is held in juxtaposition with A. Lower left: A hypothetical bimolecular distribution of A entirely surrounded by 55 M B. Lower right: Intramolecular case in conformation in which B is juxtaposed with A.

attractions or repulsions do occur, it can easily be shown that an added factor, ψ, shown in Eq. (1) would be required to express the deviations from the idealized

$$\psi = \frac{K_d + (\mathrm{B})}{54 + (\mathrm{B})} \tag{1}$$

entropic factor because of the attractions or repulsions of the actual system under investigation. Here K_d is the dissociation constant of the AB pair. This will be 54 when there is no net attraction or repulsion between the two atoms, in which case the ψ factor is 1 and the overall proximity factor remains 55.

If there is a pronounced attraction ($K_d < 54$) or a pronounced repulsion ($K_d > 54$) between the reacting groups in the measured bimolecular reaction, the proximity correction will be correspondingly less or more. These deviations from ideality can be estimated by various physical methods such as the Debye–Hückel theory or the Westheimer–Kirkwood theory. In fact, the evaluation of similar expressions for nearest-neighbor pair formation and equilibria serves as one starting point for both the theory of diffusion-controlled reactions and the thermodynamics of strictly regular solutions (*11*). In the limit of zero specific interaction, the equilibrium expressions obtained are identical to those we have used to derive proximity corrections. It may also be possible, in certain cases, to measure actual association constants; in such cases, of course, a precise calculation of the contribution of the overall complex can be made (*12*).

The logic in the derivation of this factor can be used to obtain a maximum proximity factor for intramolecular reactions relative to their intermolecular counterparts. Thus in Fig. 1, γ-hydroxybutyric acid is shown with the hydroxyl group juxtaposed with the carbon atom of the carboxylic acid group. If γ-hydroxybutyric acid existed in this conformation at all times, its velocity should be 55 times the intermolecular rate based on proximity arguments alone (assuming, of course, that only one of the nearest neighbors would react). If γ-hydroxybutyric acid exists in many other conformations (as is generally supposed), the intra–inter rate ratio would have to be less than 55 if proximity alone were important. In fact it is 79. The discrepancy is even greater for other intramolecular reactions. Detailed comparisons in intramolecular cases will be made elsewhere. This calculation illustrates that the proximity factor in intramolecular and neighboring group reactions is moderate relative to the 1 *M* reaction and thus other factors must be responsible for the high velocities one usually observes in neighboring group effects. It is suggested that one of these factors is the orbital steering of the reacting atoms generated by the limited angular approach in a constrained intramolecular system.

CALCULATION OF ORIENTATION FACTORS IN COLLISION THEORY

One possible description of orientation effects could be introduced by assuming that only a small fraction $1/\theta_A$ of the surface of A and $1/\theta_B$ of B are reactive. Then a bimolecular reaction on an enzyme surface which required juxtaposition of the reactive area of A and B would be faster than a random collision of the same two atoms by a factor $\theta_A\theta_B$. In the collision theory expression, $k = pZe^{-E_a/RT}$, the steric factor p is usually interpreted as a reduction of the rate due to improperly oriented collisions (*13*); thus we might expect that reactions in which orbital steering is important would show effects in the value p. This does not mean that orbital steering effects could not affect E_a as well, but only that a simple model in which the effects are concentrated in p is possible.

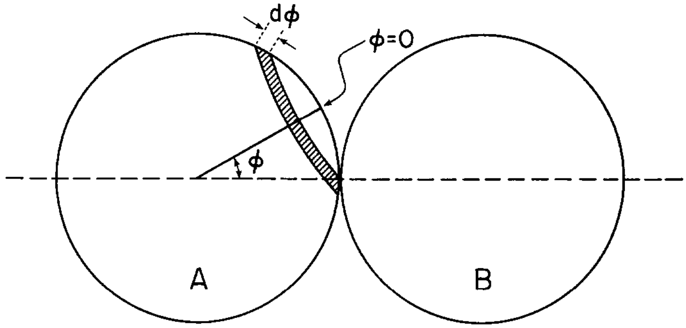

FIG. 2. A simple coordinate system for describing the orientation of Group A relative to B. The shaded ring (partially hidden) represents the area on sphere A which could be in contact with B for an orientation between ϕ and $\phi + d\phi$.

A very simple semiquantitative treatment of orientation effects can be derived on the assumption that the angular component of the height of the potential barrier to reaction can be obtained from transition-state bending force constants alone. A pair of nearest neighbors A and B are considered as spheres. For convenience, B is first considered as fixed in orientation (or, alternatively, as reactive over its entire surface). The optimum orientation of A is specified by some point on its surface and the deviation of this point from the AB line of centers by some set of spherical coordinates. To a good first approximation, deviations in any direction will have the same effect on reactivity and may be represented by a single deviation coordinate ϕ. This coordinate system is illustrated in Fig. 2. The mathematical formalism for description of a collision is then similar to that presented by Wigner for the reaction of H· and H_2 (*14*) and by Kacser for S_N2 reactions (*15*).

The total probability P_t that a given collision on the surface of A leads to reaction can be written as

$$P_t = \int_0^{\pi} P_1(\phi) P_2(\phi)\,\mathrm{d}\phi, \tag{2}$$

with $P_1(\phi)$ = probability that collision at ϕ leads to reaction; $P_1(0)$ = probability that collision at $\phi = 0°$ leads to reaction; $P_2(\phi)\,\mathrm{d}\phi$ = probability that a given collision occurs between ϕ and $\phi + \mathrm{d}\phi$

$$\left(\text{The total probability is always normalized; i.e. } - \int_0^{\pi} P_2(\phi)\,\mathrm{d}\phi = 1\right). \tag{3}$$

In the idealized case where all collisions occur at $\phi = 0°$, no integration is necessary and $P_t = P_1(0)$. For a random bimolecular collision, it can easily be shown that

$$P_2(\phi)\,\mathrm{d}\phi = \tfrac{1}{2}\sin\phi\,\mathrm{d}\phi. \tag{4}$$

Even in a perfectly oriented intramolecular reaction, A and B will be undergoing oscillation about their equilibrium positions of a magnitude determined by the ground-state force constants of the bonds maintaining their orientation. Such oscillation will introduce a distribution of angles of attack about the optimum angle $\phi = 0°$. If we collect these force constants into a single constant F describing the oscillation of spherical A about its center (essentially a geometrical operation), the potential energy $V(\phi)$ of any ground-state orientation can be described in the harmonic oscillator approximation as $V(\phi) = \frac{1}{2}F\phi^2$. Classically, the "Boltzmann-weighted" statistical probability that a one-dimensional harmonic oscillator is at displacement x is $P = (1/Q')e^{-V(x)/kT}$ or, in one polar coordinate, $P = (1/Q)e^{-V(\phi)/kT} = (1/Q)e^{-F\phi^2/2kT}$. Q is the configurational integral and essentially serves here to normalize the probability (*16*). Since the purely statistical probability of an orientation ϕ is $\frac{1}{2}\sin\phi$ in our coordinate system, $P_2(\phi)$ can be obtained by incorporating this factor and adjusting the normalization constant. Then

$$P_2(\phi)\,\mathrm{d}\phi = \tfrac{1}{2}A\sin\phi\,e^{-F\phi^2/2kT}\,\mathrm{d}\phi, \tag{5}$$

where A is the normalizing constant. If we substitute f for $F/2kT$ and ϕ (in radians) for $\sin\phi$ and normalize, then

$$\tfrac{1}{2}A\int_0^{\pi} \sin\phi\,e^{-f\phi^2}\,\mathrm{d}\phi \simeq \frac{A}{2}\int_0^{\pi} \phi\,e^{-f\phi^2}\,\mathrm{d}\phi = -\frac{A}{4f}e^{-f\phi^2}\Big|_0^{\pi} \simeq \frac{A}{4f} = 1 \text{ or } A = 4f; \tag{6}$$

f will normally be at least 10 rad^{-2} for strongly oriented systems; thus only small angles will actually contribute to the integral.

The probability that collision at angle ϕ leads to reaction ($P_1(\phi)$) must now be evaluated. If we make the assumption that the orientation of A and B remains unchanged during the course of a collision and if the optimum ground-state orientation is defined as that which leads to an undistorted transition state, then an orientation ϕ will lead to a transition state distorted by an angle ϕ. This point is illustrated in Fig. 3 for possible distorted transition states resulting from (a) collision of methyl bromide with a nucleophile and (b) from collision of an ester function with a nucleophile N.

The increased energy $V^*(\phi)$ of a transition state is, as in the ground state, related to its configuration by a force constant F^* such that $V^*(\phi) = \frac{1}{2}F^*\phi^2$. Effects other than orientation may be cancelled out by relating the probability $P_1(\phi)$ to the probability

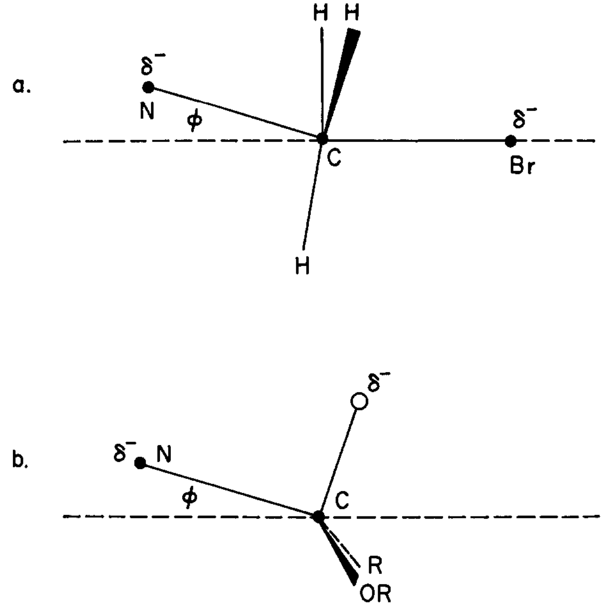

FIG. 3. Possible representations of distorted transition states resulting from reaction of a nucleophile N with (a) methyl bromide and (b) an ester function. In (a), the H–C–H plane is taken as bisecting the Br–C–N angle. In (b), all bond angles except for C–N are tetrahedral. ϕ is measured from the threefold axis of symmetry of tetrahedral carbon.

$P_1(0)$ for a transition state with no angle strain. $P_1(0)$ may be written as $P_1(0) = Ce^{-V^*(0)/kT}$ since, for a perfectly oriented collision, the probability of reaction is at least proportional to the probability that a collision is energetic enough to pass over a barrier of height $V^*(0)$. (If multiplied by the number of collisions Z and converted to a mole basis, this expression gives the collision theory rate constant with the steric factor and the constant C both = 1.) Strain in the transition state will increase the barrier height by an amount $V^*(\phi)$, so that

$$\frac{P_1(\phi)}{P_1(0)} = \frac{Ce^{-(V^*(0)+V^*(\phi))/kT}}{Ce^{-V^*(0)/kT}} = e^{-V^*(\phi)/kT},$$

or

$$P_1(\phi) = P_1(0)\, e^{-F^*\phi^2/2kT}.$$

If $f^* = F^*/2kT$, then

$$P_1(\phi) = P_1(0)\, e^{-f^*\phi^2}. \qquad (7)$$

These expressions may now be collected and integrated (using methods and approximations already described) to give relative rates per reacting group.

$$\text{Optimum } P_t = P_1(0) = C e^{-V^*(0)/kT}.$$

$$\text{Intramolecular } P_t = P_i = \int_0^{\pi} P_1(0)\, e^{-f^*\phi^2} \frac{4f}{2} \sin\phi\, e^{-f\phi^2}\, \mathrm{d}\phi$$

$$\simeq 2f P_1(0) \int_0^{\pi} \phi\, e^{-(f^*+f)\phi^2}\, \mathrm{d}\phi \simeq 2f P_1(0) \left(\frac{1}{2(f^*+f)}\right)$$

$$P_i = \frac{f}{f^*+f} P_1(0). \tag{8}$$

$$\text{Bimolecular } P_t = P_b = \int_0^{\pi} \tfrac{1}{2} P_1(0) \sin\phi\, e^{-f^*\phi^2}\, \mathrm{d}\phi \simeq \int_0^{\pi} \tfrac{1}{2} P_1(0)\, \phi\, e^{-f^*\phi^2}\, \mathrm{d}\phi$$

$$\simeq \frac{P_1(0)}{4f^*}. \tag{9}$$

The rate ratio of interest is

$$P_i/P_b = \frac{f}{f^*+f} P_1(0) \Big/ \frac{P_1(0)}{4f^*} = \frac{4ff^*}{f^*+f}. \tag{10}$$

The rate enhancement obtained is the θ factor, originally described (*8*, *10*) in terms of a potential well with a square cross section. The behavior of this function is most easily visualized for the hypothetical case of groups A and B with identical force constants, giving a rate enhancement of $\theta_A \theta_B$. This quantity is plotted in Fig. 4 as a function of the transition state bending constant F^* for several reasonable values of the ground state constant F. The shaded area represents a likely range of force constants for reactions such as nucleophilic attack in which the species are fairly strongly bound in the transition state (as opposed, e.g., to a diffusion-controlled protonation). Examination of this graph indicates that the magnitude of the orbital steering factor is strongly dependent on transition-state force constants, but only weakly so on ground-state force constants except for those classes of reactions in which the ground states are only weakly oriented ($F < F^*$).

Ingold et al. have described the transition states for S_N2 reactions of a number of alkyl halides with halide ions on the basis of a simple semiclassical treatment employing vibrational frequencies, Morse functions, van der Waals interactions, etc. (*17*). Their results are in qualitative agreement with experimental relative rates and provide apparently reasonable estimates of transition-state force constants.

One possible interpretation of the distorted transition state for methyl bromide + Br^- is shown in Fig. 3a. Another possible representation in which the H–C–H plane remains perpendicular to the departing Br^- would have a slightly higher energy. The distortion shown is a normal mode to which Ingold assigns 2.24 e.u. (*17a*). This entropy can be reconverted to a force constant through Ingold's equations

$$S = -R \ln(1 - e^{-h\nu/kT}) + R(h\nu/kT)\, e^{-h\nu/kT}(1 - e^{-h\nu/kT})$$

and

$$4\pi^2 \nu^2 = 2F^* MN/10^{-16} M_h M_a r_t^2,$$

where the M's are masses, r_t is the C–Br bond distance, and N = Avogadro's number (*17a*). The result is roughly $F^* = 0.4 \times 10^{-11}$ erg/rad^2 (10^{-11} erg/rad^2 = 0.0438 kcal/mole degree^2).

One suitable way of attaching methyl bromide to a rigid structure would be as a secondary alkyl structure with the β-carbons incorporated in a rigid system. The ground state oscillation would then be governed by a C–C–C bending force constant, taken as 1.1×10^{-11} erg/rad^2 (*18*).

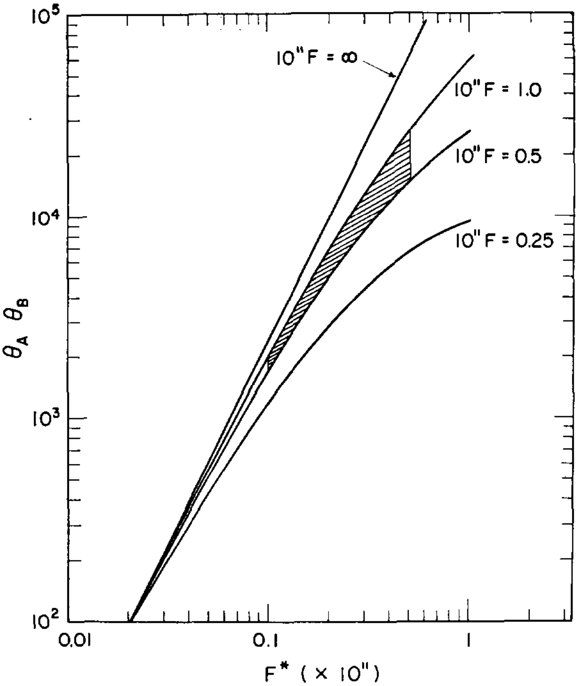

FIG. 4. Rate enhancements expected on the basis of a simple collision theory when reacting groups A and B are properly oriented (if the potential wells of A and B can be described by identical force constants). $\theta_A\theta_B$, the ratio of rates of oriented reactions to bimolecular reactions, is given as a function of the transition-state bending force constant F^* (in erg rad^{-2}) for several values of the ground-state force constant F. F describes the stiffness of the bonds maintaining the orientation. The shaded area encloses force constants for reactions in which the transition state is fairly tightly bound. $F = \infty$ represents the case of an optimally oriented reaction with $P_t = P_1(0)$.

Since Ingold finds isopropyl and methyl bending motions to be very similar in the transition state, the constants above may be directly substituted into Eq. (10). The resulting rate enhancement at 25° is about 1.4×10^2 in spite of the fact that the bromide ion is spherically symmetrical.

An even cruder estimate can be obtained for the reaction of an alkoxide ion and an ester function (Fig. 3b). Since C–O–C, C–C–O, and O–C–O bonds all have about the same bending frequency (*19*), their force constants will differ only by slightly different reduced masses. For our purposes, they may all be taken equal to 0.98×10^{-11} erg/rad^2 for C–C–O (*18*). In the absence of information about the transition state, the generalization that the transition state is halfway between reactants and products is described by reducing F^* to 0.5×10^{-11} erg/rad^2. Since all of the bonds involved in the transition state for transesterification are of one of these types, the force constants may be inserted into Eq. (10) (squared since two groups are involved) to give a rate enhancement of 2.5×10^4. (Actually, substitution into the type of valence force equation for which these constants are derived (*20*) will give a higher potential energy for distortion somewhat moderated by the geometrical relationship between ground-state oscillation in our coordinate system and actual bending of the bonds involved. We have chosen to ignore both factors in these rough calculations.) In this case, reduction of the enhancement by statistical factors of 2 for RCOOR and 3 for MeO^- to allow for the vacant *p* orbitals brings the final result down to about 4×10^3.

Since most bending force constants are of the same order of magnitude (*18*), there is little point in enumerating further examples. The theory presented above suggests that orbital steering factors of the order of 10^4 for a bimolecular reaction can be obtained from bending motions and the statistical effects which derive from them.

DISCUSSION AND CONCLUSIONS

An assessment of the results obtained so far first requires some understanding of the assumptions and limitations involved in applying such treatments to real systems.

One fundamental problem of interpretation is that these calculations are valid only in the gas phase. Although this fact has some utility in that it allows a separation of solvation from structural effects, we are ultimately interested in reactions in which only relative solvation effects have been evaluated or cancelled out. While individual reactions will not behave identically to their (usually unknown) gas-phase counterparts, it is possible that relative rates will show similar qualitative effects.

Most of the assumptions used to develop the collision theory were made for the sake of simplicity and would not affect the order of magnitude of the results. In general, they may be easily removed in cases where they are obviously inapplicable or where accurate potential functions warrant a more sophisticated treatment. The major exception appears to be the assumption that orientation remains unchanged during the course of a reactive collision. There is no simple way to evaluate the error caused by this assumption; at present it must be considered a basic limitation of the theory. It may prove possible to overcome some of these problems in the framework of transition state theory, and we are presently considering this approach. Nevertheless, this simple collision theory has the considerable advantage of allowing a separation of the effect of orientation from essentially all other factors influencing a reaction.

It should be stressed that there are a number of factors which might lead to orientational phenomena such as specific nonbonded interactions, variation with angle of the barrier-crossing frequency, or ion–dipole or hydrogen bonding interactions leading to unfavorable angles of approach in bimolecular reactions. Orbital orientation preferences will include all of these influences but, of course, one of the factors will be the transition state bending discussed here.

Given the ambiguities discussed above and the highly approximate nature of quantum-mechanical calculations for organic molecules, it is clear that the final evaluation of the contribution of orbital steering must be experimental. In principle, the simplest test arises from the fact that orbital steering can be formulated in terms of activation parameters. Though measured steric factors in solution can be quite large—e.g. about 10^{-4}–10^{-8} for the Menschutkin and similar reactions (*21*)—it is well known that the interpretation of steric factors or ΔS^* is very difficult because of their high sensitivity to solvation effects (*22*) and of the necessity for many model reactions of separating the overall measured ΔS^* into contributions from each elementary step. For these reasons, previous work has been concentrated on relative rates utilizing molecular structures designed to minimize competing effects (*8*).

At present, the arguments given above suggest that rate accelerations of the order of 10^4 can reasonably be expected when bimolecular reactions are suitably oriented. If orientation of catalytic groups is taken into account, rate effects of this order could obviously provide a substantial contribution to observed rate enhancements in intramolecular and enzymatic processes.

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    Actually, this portion of the treatment depends on the assumption that the bending modes are in thermal equilibrium even for a reactive collision. Even if the bending modes and the reaction coordinate are of different symmetry, the strongly anharmonic vibration along the reaction coordinate may well be able to exchange energy with the bending motion (Johnston, p. 87). The point that normal ground state vibrations introduce only a second-order correction in the calculated rate ratios will not be affected by any of these uncertainties.
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systems. We can see no reason to expect this equation to fit our systems and thus have retained the harmonic oscillator approximation.

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