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ENZYME REACTION RATES AND THE STOCHASTIC THEORY OF KINETICS

Alan M. DUNKER, Joan E. LUSK and Julian H. GIBBS ‡
Department of Chemistry, Brown University, Providence, R I 02912, USA

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The kinetics of an elementary reaction step are discussed from the viewpoint of the stochastic theory of chemical kinetics. The general form of the rate constant found in the stochastic approach is described and compared with the expression from transition state theory. Whereas the stochastic theory predicts a rate enhancement in cases which are not adiabatic (in the quantum mechanical sense), transition state theory, which is essentially an adiabatic theory of reaction rates, does not permit inclusion of the effect. This effect can be expected to be of greater importance in cases of catalysis by structures, such as enzymes, containing large numbers of vibrational degrees of freedom (particularly low frequency ones) than in cases lacking such structures. The stochastic theory is more general than the transition state theory, the rate constant expression given by the latter being obtainable from the former when restrictive assumptions, including that of adiabaticity, are made. Interpretations of enzyme catalysis based on the transition state theory must thus be viewed as speculative.

1. Introduction

The kinetics of enzymatically catalyzed reactions have been discussed by many authors [1–8]. The arguments for rate enhancement effects have generally been made [1–6] within the framework of the expression for the rate constant provided by the transition state theory (TST) [9] of chemical kinetics. As is well known, this theory can be based on either of two sets of questionable special assumptions (which will henceforth be referred to as the "equilibrium set" and the "adiabatic set").

There is, however, another approach to kinetics, the stochastic method [10–19]. When the rate constant for a reaction is formulated within the stochastic theory, one obtains an expression which is not equivalent to the usual TST result. In the present paper we discuss a feature of the general stochastic theory rate constant, which may be of importance in explaining part of the rate accelerations observed in biochemical reactions catalyzed by enzymes.

Gibbs [16] and Gibbs and Fleming [17,18] have argued that the stochastic theory rate constant is more general than the TST expression. The first section below discusses the stochastic theory rate constant and compares it with the TST result. By adopting the viewpoint that TST is an adiabatic (in the quantum mechanical sense [20] defined below) theory of chemical reactions, we are able to clarify the relationship between the two rate constants and show that the stochastic result reduces to the TST result under certain assumptions (which may be especially inappropriate in the case of enzymatically catalyzed reactions). The succeeding section discusses the general form of the frequency factor found in the stochastic theory and its relevance for enzymatically catalyzed reactions. The final section contains a brief comment on the expected range of validity of TST. It is noted that, whereas the speculations of several authors concerning an important role of certain very low frequency vibrational modes appear inconsistent with TST's underlying assumptions of adiabaticity and separability of the reaction coordinate, they are admissable within the framework of the more general stochastic theory.

‡ To whom reprint requests should be addressed. Present address: Office of the President, Amherst College, Amherst, MA 01002, USA.

2. The stochastic theory

Steady progress has been made in applying the stochastic formalism to chemical reactions [10–19]. We are particularly concerned here with the results of refs. [16–18], which describe the rate constant of a single elementary reaction step.

The stochastic theory assumes the validity of a "master" equation describing the transitions between states of the reactants and products. A stochastic master equation simply assumes that the flux of particles leaving a quantum state is proportional to the number of particles in that state. This proportionality is applied in refs. [16–18] not only to the reacting molecules but also to molecules which merely interchange energy in a given collision event with the reacting molecules. The latter are termed "reservoir" molecules. If, for example, A and B are two chemically distinct species undergoing an internal conversion from one to the other in a single transition and each is in contact with "reservoir" molecules which define the temperature, then the master equation expresses the net flux from A to B, q_{AB}, as the difference between forward and backward components [16]:

$$q_{AB} = \sum_{a,\nu,b,\mu} w(a,\nu;b,\mu) N_a N_\nu - \sum_{a,\nu,b,\mu} w(b,\mu;a,\nu) N_b N_\mu. \quad (1)$$

Here, $w(a,\nu;b,\mu)$ is the transition probability per unit time that a molecule of A in state a will proceed to state b of B upon colliding with a set of reservoir molecules which make a transition from collective state ν to collective state μ. N_a and N_b denote the number of reacting molecules in states a and b respectively; N_ν and N_μ denote the number of sets of reservoir molecules in states ν and μ respectively. In the present case the reservoir molecules may be thought of as solvent molecules primarily.

The presence of a potential energy barrier between reactants and products has the effect of rendering the quantities $w(a,\nu;b,\mu)$ equal to zero for all combined states a,ν which have aggregate energy significantly less than the barrier height. Two limiting cases may be discerned. There might exist a high energy transition state that is "long-lived" in the sense described in ref. [17], undergoing many collisions with other molecules. Alternatively, the high energy transition "state" may be short-lived or transient, proceeding directly to products before undergoing collisions with any other molecules. These two limiting cases are discussed in detail in refs. [16,17].

For purposes of comparison with the TST result, we choose an example of a bimolecular reaction proceeding through a short-lived transition "state":

$$A_1 + A_2 \rightleftarrows B \rightleftarrows C_1 + C_2, \quad (2)$$

B is the high energy transition "state" and is taken to be the set of states above the potential energy barrier dividing the A_1, A_2 and C_1,C_2 species. Actually, we treat two different types of reaction simultaneously. If we take A_1 and C_1 as a reactant and product respectively, we may either take A_2 and C_2 as co-reactant and co-product, in which case we have assumed that no reservoir molecules play a role in the reaction, or we may take A_2 and C_2 as identical molecules of some species playing exclusively a reservoir role. The former viewpoint will facilitate the comparison of the stochastic result with the TST result; the latter viewpoint will provide a more realistic case for discussion of the influence of enzymes. For formal treatment of the general case involving both co-reactants and "reservoir" molecules, the reader is referred to ref. [17]. The rate constant for the forward reaction (A→C) of eq. (2) is given by [17]

$$k^f_{\underset{\sim}{AC}} = W_{\underset{\sim}{AC}}\, \Omega \exp[-\beta(F_{\underset{\sim}{B}} - F_{\underset{\sim}{A}})] = W_{\underset{\sim}{AC}}\, \Omega\, Q_{\underset{\sim}{B}}/Q_{A_1} Q_{A_2}. \quad (3)$$

Here β is $1/kT$, Q_{A_1}, Q_{A_2}, and $Q_{\underset{\sim}{B}}$ are partition functions (per unit volume), and $F_{\underset{\sim}{A}}$, $F_{\underset{\sim}{B}}$ are free energies. $W_{\underset{\sim}{AC}}\,\Omega$, termed the frequency factor, is defined by

$$W_{\underset{\sim}{AC}}\,\Omega = \sum_{\substack{a_1,a_2\\ c_1,c_2}} \{[\exp(-\beta E_{\underset{\sim}{b}})]/Q_{\underset{\sim}{B}}\} \times \delta(E_{a_1}+E_{a_2}, E_{\underset{\sim}{b}}, E_{c_1}+E_{c_2})\, w(a_1,a_2;c_1,c_2), \quad (4)$$

where $w(a_1,a_2;c_1,c_2)$ is defined similarly to the w's appearing in eq. (1). $\delta(E_{a_1}+E_{a_2}, E_{\underset{\sim}{b}}, E_{c_1}+E_{c_2})$, which arises from the requirement that energy be conserved in each reactive event, is equal to one if $E_{a_1}+E_{a_2} = E_b = E_{c_1}+E_{c_2}$ and is equal to zero otherwise. These results, eqs. (3) and (4), are obtained from eq. (1) by employing the assumption that non-reactive collisions are sufficiently more frequent than reactive ones to insure that the number of molecules of each chemical species A_1, A_2, C_1, C_2 is partitioned among the energy levels of that species in equilibrium ratio. For the simple special case described here, the derivation of the form of the rate constant (eqs. (3) and (4)) can be given without the cumbersome notation of ref. [17] and is so given in the appendix to this paper.

The right-hand side of eq. (4) contains summations over the states of both reactants and products. The quotient $[\exp(-E_b)]/Q_B$ may be taken as normalizing either the summations over reactant states a_1, a_2 or those over product states c_1, c_2 [16]. Two unnormalized summations remain, however. The entire sum may thus be viewed as an average transition rate $W_{\underset{\sim}{AC}}$ for high lying levels of A_1, A_2, C_1, C_2 times an effective number Ω of states of the products that are coupled to each state of the reactants or vice versa.

For reactions more complicated than eq. (2), such as those involving both more than one reactant molecule and also reservoir molecules which contribute energy to or receive energy from the reacting molecules, the general forms of eqs. (3) and (4) remain the same [17]. If the transition state is "long-lived" rather than "short-lived", the form of the frequency factor changes, but it still contains an overall linear dependence on an average transition rate W and an effective number of product states Ω that are coupled to a typical reactant state [16,17]. We also note that the rate constants obtained from an exact solution [19] of the stochastic master equation for a specific model reaction exhibit qualitatively the same dependence on W and Ω. For reactions proceeding through a high energy transition state it would appear, then, that the stochastic method yields a frequency factor which is a measure of both the strength of the coupling (W) between reactants and products and the effective number of (quantum mechanical) paths (Ω) to products from each reactant state (or, equivalently, from reactants to each product state).

We now consider the relationship of this stochastic theory to the familiar TST. The standard approach to the TST rate expression employs both the assumption of the existence of a long-lived "activated complex" and the assumption of an equilibrium between reactants and these activated complexes [9] (the "equilibrium set" of assumptions). A more satisfying basis for the final result has been given within the context of the "adiabatic set" of approximations [21–25]. In this a principal requirement is quantum mechanical adiabaticity [20] (as in the Born-Oppenheimer approximation). That is, the motion in the internal degrees of freedom is assumed to adjust smoothly as the system progresses along the reaction coordinate. Each initial quantum state is connected smoothly to one final state. This contrasts with the stochastic approach which allows for the possibility of multiple paths from the reactants to each product state.

Detailed discussions of TST in its setting as an adiabatic theory of reactions have been given [21–23, 25]. A brief justification has been given by Marcus [24]. This "adiabatic set" of assumptions needed to obtain the TST rate constant includes: 1. that the reactant (and product) molecules have Boltzmann populations in their internal and translational levels; 2. that the reaction progresses along a single coordinate which is separable from all other coordinates; 3. that motion along the reaction coordinate is rectilinear (as opposed to curvilinear); 4. that motion in all other coordinates is adiabatic; 5. that the probability of passing the saddle point (transmission coefficient) is a step function.

Thus the adiabatic version of the TST theory depends upon four assumptions that have not been needed in the derivation of eqs. (3) and (4), namely postulates [2–5]. We now sketch how eqs. (3) and (4) reduce to the TST results if these additional assumptions are made. For the simple case described by eq. (3) a center of mass coordinate system may be used. If there is a separable reaction coordinate x, then the energy of any state b may be written as $E_b = E_b^{K.E.}(x) + E'_b(x)$, where $E_b^{K.E.}(x)$ is the translational kinetic energy along x. (The breakdown in this approximation for reactions involving simple molecules has been discussed recently [26].) $E'_b(x)$ is the energy in the other degrees of freedom along with the potential energy in the coordinate x, and it varies smoothly as a function of x. The adiabaticity assumption implies that, as the reaction coordinate is traversed, there are no transitions among the internal states $E'_b(x)$. That is, for fixed a_1, a_2 the w of eq. (4) is nonzero for only one choice of c_1, c_2. Eq. (4) may then be regarded to contain a summation over only the initial states a_1, a_2. The transition rate w is simplified to a function only of x and of p, the momentum along x. This function is nonzero only for complexes near the top of the energy barrier which are about to pass from reactants to products. With these assumptions the rate constant of eq. (3) may be rearranged to

$$k_{\underset{\sim}{AC}} \approx \left(\sum_{\underset{\sim}{b}} [\exp(-\beta E^+_{\underset{\sim}{B}})]/Q^+_{\underset{\sim}{B}} \right) \times \left(\int_0^\infty \dot{x} \exp(-\beta E^{K.E.}) \, dp/h \right) Q^+_{\underset{\sim}{B}}/Q_{A_1} Q_{A_2}, \qquad (5)$$

where E_b^+ are the energy levels $E_b'(x)$ evaluated for x at the position of the energy barrier, and Q_B^+ is the partition function corresponding to the states E_b^+. $E^{K.E.}$ is the kinetic energy along x at the top of the barrier, $\dot{x}$, the velocity, arises from the transition rate w, and $1/h$ is included as the appropriate density of states [27] in classical phase space. The first factor in eq. (5) is simply unity. Utilizing $dE^{K.E.} = \dot{x}dp$, one obtains kT/h for the integral, and the rate constant of eq. (5) is then identical to the TST result [9]:

$$k_{AC} = (kT/h)\, Q_B^+/Q_{A_1} Q_{A_2}$$

$$= (kT/h) \exp[(\Delta S^+/k) - (\Delta E^+/kT)], \qquad (6)$$

where ΔS^+ and ΔE^+ are the usual entropy and energy of activation, respectively.

In summary, TST makes specific simplifying assumptions about the form of the w's in eq. (1) and is thereby able to evaluate the frequency factor in eq. (3) (within those assumptions). However, since TST is essentially an adiabatic theory of reactions, each initial state is assumed to be connected to a final state in one-to-one correspondence, and the Ω of eq. (3) is then effectively unity. The frequency factor kT/h in eq. (6) is the TST estimate for W in eq. (3). The stochastic theory, on the other hand, makes no assumptions about the transition rates and obtains the more general form $W\Omega$ for the frequency factor. Because the master equation (eq. (1)) allows for the possibility that reactant molecules in different initial states may have nonzero probabilities of proceeding to the same final state of the products, Ω is not approximated as unity in the stochastic theory.

3. Enzymatic reactions

When discussing the ability of an enzyme to catalyze a reaction, one is comparing the overall rate of a series of elementary steps catalyzed by the enzyme to the rate of the same overall reaction in the absence of the enzyme. The intermediates and the elementary steps between them in the two observed overall reactions may not, however, be chemically analogous. Nevertheless, an elementary step of the enzymatic pathway can be compared to a hypothetical chemically analogous step involving only small molecules. Thus any elementary step,

$$EX_i \rightleftarrows E'Y_i \qquad (7a)$$

of an enzymatic reaction can be compared (theoretically) with its corresponding, possibly hypothetical, non-enzymatic step

$$A_i \rightleftarrows B_i, \qquad (7b)$$

where the transformation of the sets of molecules A_i to B_i is chemically analogous to that of EX_i to $E'Y_i$.

Suppose one step $A_j \rightarrow B_j$ to be rate-controlling in the hypothetical non-enzymatic pathway. The corresponding step $EX_j \rightarrow E'Y_j$ in the enzymatic pathway must have been accelerated by a factor at least as great as the ratio of the rate of the overall enzymatic pathway to that of the hypothetical non-enzymatic one. If the real non-enzymatic pathway does not proceed through the series of hypothetical steps (7a), it must proceed through a faster route. Therefore the experimental measurement of overall enzymatic and non-enzymatic rates underestimates the enzymatic rate enhancement of the slowest hypothetical elementary step. The same conclusion applies when the overall enzymatic rate is limited by processes that have no analogy in a non-enzymatic process, such as binding or release of substrate or product, or a conformational change in the enzyme.

The stochastic theory may be invoked to interpret the enzymatic acceleration of an elementary reaction step. However, in contrast to the comparison between rates of similar non-enzymatic reactions, the comparison of enzymatic with non-enzymatic reaction rates does not allow the assumption that the product $W\Omega$ of eq. (3) is nearly constant. When the substrate binds to the enzyme, the potential energy surface for the reaction is greatly altered. In particular, the internal vibrational states of the substrate are coupled to those of the enzyme. The density of states (number per energy interval) in the EX and E'Y complexes is much larger than in the A and B molecules, and the EX and E'Y complexes include many low frequency vibrations which are expected to be non-adiabatic in reactive events [5,20, and below]. Of course, the transition probabilities connecting many of the states of EX and E'Y are zero. Nevertheless, one may expect an increase in the effective number of initial states, Ω, coupled to each state of the products. The very large density of states in the enzyme implies that this effect has the potential of altering by several orders of magnitude the frequency factor, and thus yielding a significant acceleration of the elementary step [17].

Unfortunately, orthodox kinetic experiments gen-

erally measure only two parameters, which describe the magnitude of the reaction rate and its temperature dependence. It is therefore impossible in such experiments to separate the effects described above from the often discussed [1–3,5] entropy of activation, ΔS^{+} in eq. (6), even when the rates of elementary steps can be measured. By the same token it should be clear from the preceding analysis that comparisons of observed temperature independent factors between reactions as different as eqs. (7a) and (7b) may be thoroughly deceptive if used as measures of the corresponding ΔS^{+} values. In addition to differences between the reactants and activated complexes influencing the ΔS^{+} values, one may be comparing hidden differences (which may be very large) in the frequency factors attributable to variations in either the transition probabilities W or the effective number of coupled states Ω. Perhaps future experiments employing lasers to activate enzyme states may be able at least to detect coupling between the states of the enzyme and those of the substrate.

Several ways in which the frequency factor might remain constant between reactions (7a) and (7b) should be noted. If both reactions are truly adiabatic, then, as we have seen, $\Omega = 1$, which removes one possibility for variation. If, for example, the motion of all coordinates of each species is completely classical, $\Omega = 1$, because the initial conditions in any classical system completely determine the final state. Also, the conditions for a significant change in the frequency factor assume that, at least in reaction (7b), reactive events are rare compared to non-reactive events. There is an overall limit to the size of the $W\Omega$ product in eq. (3), which is determined by the case in which every collision between reactants (with sufficient energy) produces products. In the TST description, for example, it is clear that the rate of appearance of products is limited by the initial velocity along the reaction coordinate. If reactive events in eq. (7b) were very frequent, then the frequency factor would be nearly at its limiting value (saturated) and no further increase would be possible in eq. (7a).

4. Discussion

Many catalytic effects of enzymes which have traditionally been discussed within the TST framework, such as lowering of the potential barrier and favorable positioning of reactants, are of undoubted importance in understanding the observed rate accelerations. These have been discussed many times elsewhere in relation to their effects on the energies and entropies of activation, constructs which arise in the stochastic theory as well as in TST.

We have discussed in the above the fact that the frequency factor in the stochastic theory is profitably viewed as dependent on two effects, an average probability of transition from reactants to products and an effective number of reactant states coupled to each state of the products. Only the former effect is apparent in the TST result, owing to the assumption of adiabaticity for all internal quantum states in that theory. Insight into the nature of the frequency factor has suggested that it may vary greatly when the rate constants of uncatalyzed and enzymatically catalyzed reactions are compared. This possibility has apparently not been appreciated before and indicates that one should exercise caution when comparing the entropies of activation (eqs. (3) and (6)) of catalyzed and uncatalyzed reactions.

Viewing TST as an adiabatic theory of kinetics is useful in discussing its expected range of validity. In particular, the assumptions of separability of a reaction coordinate and adiabaticity for the internal states require a large difference between the average speed of the motion along the reaction coordinate and that normal to it. More precisely, given that the vibrational frequencies for motions normal to the reaction coordinate are altered between the reactants and the transition state, the frequency separations between these vibrational levels must remain large relative to the rate at which the frequencies change during a reactive event [20]. The details of the potential energy surface for the reaction determine, of course, whether the assumptions of separability and adiabaticity are good approximations. However, as a rough rule we cannot expect the TST theory to describe adequately vibrational modes for which $h\nu_{\mathrm{vib}} \leqslant kT$. Cook and McKenna [5] have suggested that alterations in such low frequency vibrational modes may result in a rate acceleration in enzymatically catalyzed reactions. It would appear from the above comments, however, that the treatment within TST of low frequency vibrational modes which are altered during the course of the reaction is inconsistent with the assumptions of that theory. Con-

clusions reached by such a procedure are questionable.

The considerations presented in this paper in no way vitiate the precepts of reaction mechanism (as the term is understood in physical organic chemistry) that have been applied to the problem of reaction rate enhancement by enzymes. "Reaction mechanism" in the latter sense deals with a succession of states (e.g., the transition state) pictured essentially statically. Appropriately, then, these mechanism considerations have been based solely on the free energy of activation, a factor present in the final result of the stochastic theory as well as that of TST. In TST, however, only these conventional considerations of mechanism can be brought to bear on the problem of enzyme catalysis, inasmuch as TST presents a universal factor kT/h for the frequency factor. The factor $W\Omega$ of the stochastic theory admits other considerations in addition to those of TST-based physical organic chemistry.

Appendix:

Derivation of the stochastic theory equation for the rate constant in a simple case

For the elementary reaction step [2] involving 2 reactant molecules A_1 and A_2 reacting to form 2 product molecules C_1 and C_2 via a "transition state" B of such "short-lived" [17] existence that the reaction is to be viewed as a single quantum-mechanical transition, the appropriate master equation is

$$q_{\underset{\sim}{\underset{\sim}{AC}}} = \sum_{\substack{a_1,a_2\\c_1,c_2}} W(a_1,a_2;c_1,c_2)N_{a_1}N_{a_2} - \sum_{\substack{a_1,a_2\\c_1,c_2}} W(c_1,c_2;a_1,a_2)N_{c_1}N_{c_2}. \quad (A.1)$$

We now assume that the partitioning of the N_{A_1} molecules of A_1 and of the N_{A_2} of A_2 among their quantum states a_1 and a_2 is equilibrated and that the partitioning of N_{C_1} and N_{C_2} is similarly equilibrated among their state c_1 and c_2 and thereby write

$$N_{a_1} = P_{a_1}N_{A_1} = \frac{\exp(-E_{a_1}/kT)}{Q_{A_1}}N_{A_1} = [\exp(-E_{a_1}/kT)\exp(+F_{A_1}/kT)]N_{A_1}, \quad (A.2)$$

and similar expressions for N_{a_2}, N_{c_1} and N_{c_2}. Here P_{a_1} is the equilibrium fraction of A_1 in state a_1, Q_{A_1} is the partition function of reactant A_1 and F_{A_1} is its free energy.

We also introduce the law of microscopic reversibility,

$$W(a_1,a_2;c_1,c_2) = W(c_1,c_2;a_1,a_2) \quad (A.3)$$

which is legitimate because the transition probabilities, $W(a_1,a_2;c_1,c_2)$ used here refer to total events including the changes occurring in reservoir molecules (here represented by a_2,c_2), in cases involving these, as well as those among the reactants. As such these total events conserve energy, so we have

$$E_{a_1} + E_{a_2} = E_{c_1} + E_{c_2}, \quad (A.4)$$

for every aggregate choice of a_1,a_2,c_1,c_2 that yields a non-zero $W(a_1,a_2;c_1,c_2)$.

Introducing (A.2), (A.3) and (A.4) into (A.1) yields, after quantities independent of a_1,a_2,c_1,c_2 have been factored out of the summations,

$$q_{\underset{\sim}{\underset{\sim}{AC}}} = \{N_{A_1}N_{A_2}\exp[(F_{A_1}+F_{A_2})/kT] - N_{C_1}N_{C_2}\exp[(F_{C_1}+F_{C_2})/kT]\} \times \sum_{\substack{a_1,a_2\\c_1,c_2}} W(a_1,a_2;c_1,c_2)\exp[-(E_{a_1}+E_{a_2})/kT]. \quad (A.5)$$

We note in passing that eq. (A.5) only gives $q_{\underset{\sim}{\underset{\sim}{AC}}} = 0$ when

$$N_{C_1}N_{C_2}/N_{A_1}N_{A_2} = \exp\{-[(F_{C_1}+F_{C_2}) - (F_{A_1}+F_{A_2})]/kT\} = K_{eq},$$

the thermodynamic equation for the equilibrium constant K_{eq}. This result was, of course, not guaranteed by the narrower equilibrium assumptions that we have made, namely that the reactant and product systems are each internally equilibrated (but not equilibrated with each other); it is a consequence of the consistency of the stochastic master equation with the Boltzmann distribution of equilibrium.

According to (A.5) the rate constants $k^f_{\underset{\sim}{\underset{\sim}{AC}}}$ and $k^b_{\underset{\sim}{\underset{\sim}{AC}}}$ for forward and backward reactions are

$$k^{f}_{\underset{\sim}{A}\underset{\sim}{C}} = \exp[(F_{A_1}+F_{A_2})/kT]$$

$$\times \sum_{\substack{a_1,a_2\\ c_1,c_2}} W(a_1,a_2;c_1,c_2)\exp[-(E_{a_1}+E_{a_2})/kT] \qquad (A.5a)$$

and a similar expression for $k^{b}_{\underset{\sim}{A}\underset{\sim}{C}}$.

Up to this point our equations apply to reactions that may or may not involve significant potential energy barriers to be surmounted. In the usual case, for which such a barrier exists, its effect is contained in the dependence of the transition probabilities $W(a_1,a_2;c_1,c_2)$ on the energies $E_{a_1}+E_{a_2}$ $(=E_{c_1}+E_{c_2})$ of the aggregate state of the reactant system (or product system for the back reaction). The simplest assumption we can make to allow for the effect of a barrier is simply that $W(a_1,a_2;c_1,c_2)=0$ for all aggregate states a_1,a_2 (or c_1,c_2) for which $E_{a_1}+E_{a_2}<E_0$ (or equivalently $E_{c_1}+E_{c_2}<E_0$), where E_0 is a "threshold" energy approximately equal to the height of the potential barrier. With this assumption we can easily cast (A.5) in a more illuminating form by the following devices. Among the set of aggregate states a_1,a_2 of the reactant system (or the set c_1,c_2 of the product system) we consider the subset of states that lie above E_0 and designate these by $\underset{\sim}{b}$ and their energies $E_{a_1}+E_{a_2}$ by $E_{\underset{\sim}{b}}$. We also define a "free energy" $F_{\underset{\sim}{B}}$ and a partition function $Q_{\underset{\sim}{B}}$ associated with this (sub) set of "activated" states by

$$F_{\underset{\sim}{B}} = -kT\ln Q_{\underset{\sim}{B}} = -kT\ln\left(\sum_{\underset{\sim}{b}}\exp(-E_{\underset{\sim}{b}}/kT)\right). \qquad (A.6)$$

and a free energy of the initial state by

$$F_{\underset{\sim}{A}} \equiv F_{A_1}+F_{A_2}.$$

Introducing this new notation, multiplying and dividing (A.5) by $\exp(-F_{\underset{\sim}{B}}/kT)$, and making explicit the dual condition $E_{a_1}+E_{a_2}=E_{c_1}+E_{c_2}=E_{\underset{\sim}{b}}$ for non-zero $W(a_1,a_2;c_1,c_2)$, we have

$$k^{f}_{\underset{\sim}{A}\underset{\sim}{C}} = \exp[-(F_{\underset{\sim}{B}}-F_{\underset{\sim}{A}})/kT]$$

$$\times \sum_{\substack{a_1,a_2\\ c_1,c_2}} W(a_1,a_2;c_1,c_2)\,[\exp(-E_{\underset{\sim}{b}}/kT)]/Q_{\underset{\sim}{B}}$$

$$\times \delta(E_{a_1}+E_{a_2}, E_{\underset{\sim}{b}}, E_{c_1}+E_{c_2}), \qquad (A.7)$$

as cited in the main text.

With this procedure we have clearly forced the first factor into a form which by itself carries the sort of temperature dependence observed experimentally for the whole rate constant. The obvious question to be faced now is whether this procedure has also removed most of the temperature dependence from the remaining factor (the summation). This summation can be seen to be of the form of an average of the quantity $W(a_1,a_2;c_1,c_2)$ over the states for which $E_{a_1}+E_{a_2}=E_{\underset{\sim}{b}}=E_{c_1}+E_{c_2}$. Such temperature dependence as the sum may contain is attributable solely to that in the statistical weight factors $[\exp(-E_{\underset{\sim}{b}}/kT)]/Q_{\underset{\sim}{B}} \equiv P_{\underset{\sim}{b}}$. Inasmuch as $P_{\underset{\sim}{b}}$ is normalized over the manifold of states $\underset{\sim}{b}$ alone (not over all the states a_1,a_2!) the sum will be temperature-independent if the quantity $W(a_1,a_2;c_1,c_2)$ is independent of energy in the range of states $\underset{\sim}{b}$ (i.e., above E_0).

That the temperature dependence of our whole final result for $k^{f}_{\underset{\sim}{A}\underset{\sim}{C}}$ is approximately an exponential dependence on $(-1/T)$ can be seen in another way. If, instead of multiplying and dividing by $Q_{\underset{\sim}{B}} \equiv \exp(-F_{\underset{\sim}{B}}/kT)$ to obtain our result in the form (A.7), we had multiplied and divided by the quantity $Q_{\underset{\sim}{A}} \equiv Q_{A_1}Q_{A_2} \equiv \exp(-F_{\underset{\sim}{A}}/kT)$, and had thereby removed the temperature dependence from the factor outside the summation, the statistical weight factor in the summation would have been normalized over the whole set of states a_1,a_2, including the non-reacting states below E_0; the presence in the summation of this band of non-reacting states would have given this sum the same sort of temperature dependence that the non-conducting band of states gives to semiconductors, i.e., the exponential dependence in question.

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