

## CHAPTER 1

### **Barrier crossings: classical theory of rare but important events**

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## 1. – Introduction

My charge for these lectures is to describe the basic concepts associated with rare events in many body systems. I do so using the format of textbook chapters. In other words, these lectures provide reasonably self contained descriptions of ideas and principles, but they are not reviews of the large literature where these ideas and principles are applied. I append annotated bibliographies to each of the lectures. These brief listings provide reasonable starting points for the reader to learn the current literature.

“Rare events” are dynamical processes that occur so infrequently it is impractical to obtain quantitative information about them through straightforward trajectory calculations. Chemical reactions in liquids are important examples of rare events. Reactants and products tend to be long lived, and a quick molecular rearrangement that takes the system from one of these stable states to the other occurs relatively infrequently.

More generally, rare events are processes that occur infrequently due to dynamical bottlenecks that separate stable states. Once this threshold is crossed, however, a trajectory will move quickly to a new stable state. The stable states could indeed correspond to different chemical species, but they could also correspond to different phases of a condensed material or structures of a polymer. In the latter cases, the bottlenecks are located at the points where new phases or structures nucleate. The hopping of a penetrant from one interstitial site to another in a solid is another physical example of a rare event. In this case the nature of the bottleneck will depend upon the energy required to distort local lattice structure and thereby open possible pathways between interstitial sites.

Charles Bennett is one of the scientists who created the methods we now use to study these processes with computer simulations. Many years ago, he was interested in the microscopic dynamics of liquid water. The intermolecular structure and diffusion of water molecules can be thought about in terms of making and breaking of hydrogen bonds. To observe the evolution of the hydrogen bond patterns in the liquid, Charles made a computer rendered motion picture based upon a trajectory of some 200 water molecules, periodically replicated. The trajectory, one of Aneesur Rahman’s early molecular dynamics simulations, ran for a few Pico seconds (ps). A typical hydrogen bond in water lasts about 1 ps, and with 200 water molecules, there are about 400 hydrogen bonds at any point in time. So, Charles’ film had plenty of examples of making and breaking hydrogen bonds. By studying the motion picture, he gained substantial experience on how local distortions of the hydrogen bond network and librational motions lead to the switching of hydrogen bond allegiances.

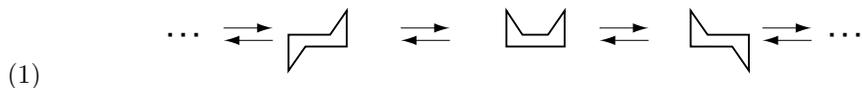
Buoyed by this success of molecular modeling, Charles imagined what would happen if he enlarged the size of his system, and added additional components so as to mimic water with a polypeptide chain dissolved in it — something like a solvated protein. A film of this system could show in great detail how water dynamics is influenced by a nearby polypeptide chain, and how the small amplitude motions of the chain are correlated to the diffusion and rotation of surrounding water molecules. If long enough, the film might

also be used to show the dynamics that leads to the folding of the chain. How long? For a polypeptide of modest length, the folding time could be, for example,  $10^{-6}$ s. At comfortable viewing speeds, it takes about one minute of film to record 1 ps of molecular dynamics. Therefore, to capture just one entire folding event, an unedited film would run for several years. To normal viewers, Charles thought, the unedited film would be tedious. They'd want to see only the good parts and skip the rest.

To the viewer interested in polypeptide folding, the “good parts” are presumably isomerizations taking the chain from one long lived conformational state to another — from one deep valley in the potential energy surface to another. In contrast to the making and breaking of hydrogen bonds in water, isomerizations of the polypeptide chain are examples of a rare events. Most of the time, trajectories move in one valley or another, and the rare passages over the barrier between them are fleeting. A well edited film showing mainly the good parts would focus on these fleeting events, and its conception is like that necessary for efficient quantitative computational studies of rare events. Imagine, for example, a computer sampling that considered only those portions of trajectories where conformational change occurs. Such sampling would focus entirely on the rare event. It would waste no computational effort on the majority of phase space where the rare event did not occur. And since each event occupies only a short period of time, the sampling could be performed over and over again, acquiring many different examples of the process, making statistical analysis possible. It is this type of importance sampling that is the focus of these lectures.

## 2. – Cyclohexane isomerization

The chair-boat interconversion of cyclohexane,



provides a concrete illustrative example. Its equilibrium constants and rate constants have been measured as illustrated in Fig.1. In liquid carbon disulfide, each cyclohexane solute molecule will undergo isomerization roughly once every 0.1s. This time is very long compared with those characterizing single molecule dynamics. For example, in that same liquid, a molecule will diffuse a distance of one molecular diameter in roughly  $10^{-11}$ s, and appreciable correlations of translational momentum of a molecule persist for less than  $10^{-12}$ s. The isomerization is therefore a rare event. A most interesting aspect of the experimental results graphed in Fig.1 is that the application of pressure causes the isomerization rate to increase. Let us imagine that it is this specific phenomenon, the pressure acceleration of this isomerization rate, that we seek to understand.

To reach an understanding, we must first know something about the potential energy function governing the torsional angles of cyclohexane. Picket and Strauss have provided such a potential,  $V(\theta, \phi)$ . It is illustrated in Fig.2. The variables  $\theta$  and  $\phi$  are collective coordinates, both of which depend upon the six vectors specifying the positions of the six carbon atoms. (Each  $\text{CH}_2$  in the  $\text{C}_6\text{H}_{12}$  molecule is pictured as an extended atom, with its center at the carbon nucleus. The distances between adjacent carbons are taken to be constant.) Integration over the secondary coordinate,  $\phi$ , gives a free energy or reversible work function in the usual way,

(2) 
$$-\beta F(\theta) = \ln \int_0^{2\pi} d\phi e^{-\beta V(\theta, \phi)},$$

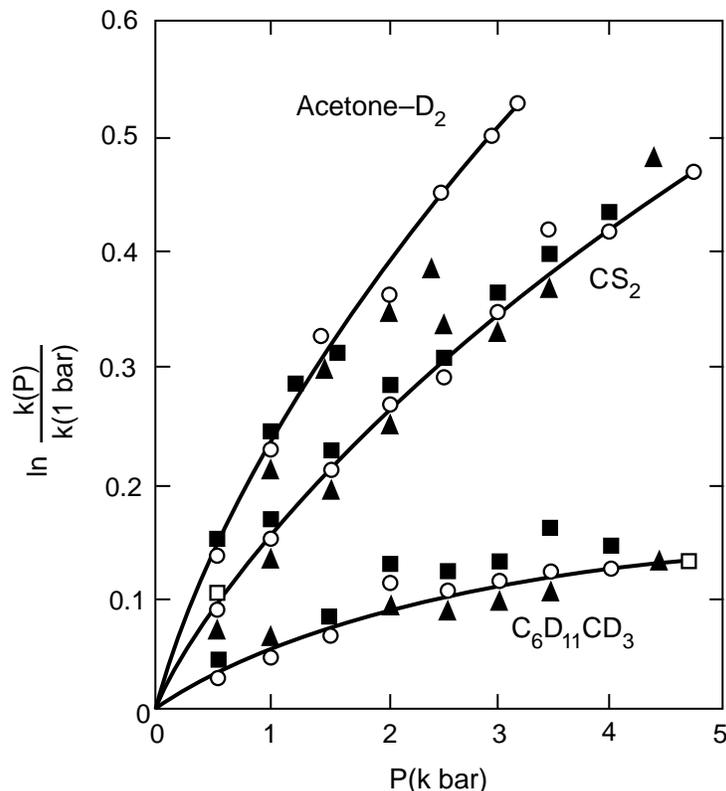


Fig. 1. – The pressure dependence of the chair-to-chair isomerization rate in cyclohexane at 225 K (circles), 218 K (triangles) and 213 K (squares). The solid lines represent a best fit to the data at 225 K. At these temperatures,  $k(1 \text{ bar}) \approx 10\text{s}^{-1}$ . Graph taken from D. L. Hasha, T. Eguchi and J. Jonas, *J. Am. Chem. Soc.* **104**, 2290 (1982).

where  $\beta$  is the reciprocal temperature in units of Boltzmann's constant, i.e.,  $\beta^{-1} = k_{\text{B}}T$ . This free energy,  $F(\theta)$ , is graphed in Fig.3.

The barrier separating chair and boat conformers is high compared to the thermal energy,  $k_{\text{B}}T$ . The probability distribution for observing a cyclohexane molecule with a specific value of  $\theta$  is proportional to  $\exp[-\beta F(\theta)]$ . In other words, the relative probability of  $\theta$  being near either  $50^\circ$  or  $130^\circ$  is small. It is because these relative probabilities are small that the isomerization is a rare event.

### 3. – High barriers, rare events

In general, transitions between stable states will be rare events because a high barrier in potential energy or free energy lies between those states. Barriers imply dynamical bottlenecks. Consider, for example, the schematic free energy function drawn in Fig.4. The point  $q = q^*$  is the transition state. Specifically, in passing from  $A$  to  $B$ , the system must pass through that point, and since  $F^* \gg k_{\text{B}}T$ , such passages must be rare or infrequent. Further, displacement by a small distance  $\ell$  from  $q = q^*$  will commit the system to one or the other stable states. As far as equilibrium statistics is concerned, the

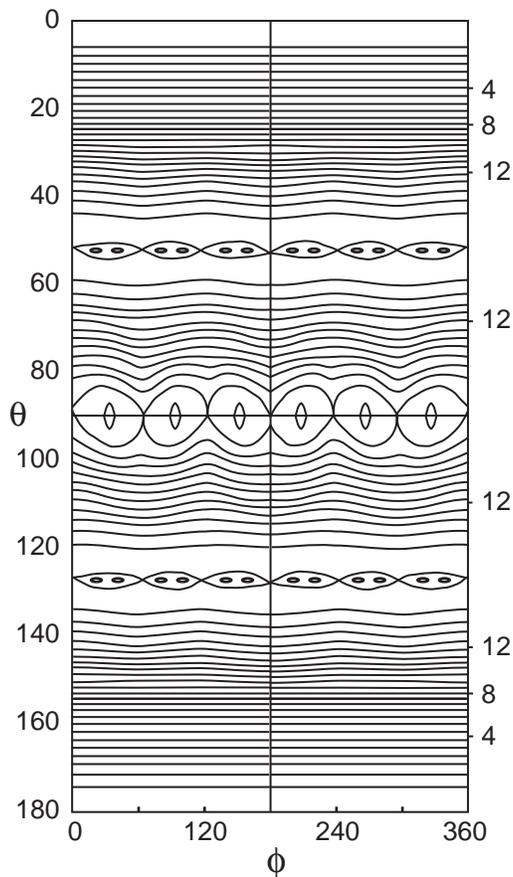


Fig. 2. – Conformation map of cyclohexane. Adapted from H.M. Pickett and H.L. Strauss, *J. Am. Chem. Soc.* **92**, 7281 (1970). Chair conformations reside near  $\theta = 0^\circ$  and  $180^\circ$ . Boat conformations reside near  $\theta = 90^\circ$ . The valleys in the conformation map coincide with these locally stable conformers. The mountain ridges near  $\theta = 50^\circ$  and  $130^\circ$  separate the chair and boat valleys.

region of configuration space near  $q = q^*$  is virtually irrelevant. For  $A \rightarrow B$  dynamics, however, this region is of utmost importance.

After passing over the barrier, the kinetic energy associated with  $q$  will be large compared to  $k_B T$ . As such, energy will flow from  $q$  to other degrees of freedom, thereby trapping the system in one of the stable states. Energy transfer to other degrees of freedom therefore plays an important role in barrier crossing dynamics. We'll have much more to say about this fact later.

While the probability of visiting a high barrier is low, once the system reaches that point, the system moves quickly across it. For example, if the motion at the barrier top were mainly inertial, the time to move across it would be

$$(3) \quad \nu^{-1} \sim \ell / \langle |\dot{q}| \rangle.$$

For typical atomic masses, and  $\ell < 1 \text{ \AA}$ , this time is a fraction of  $10^{-13} \text{ s}$ . More generally,

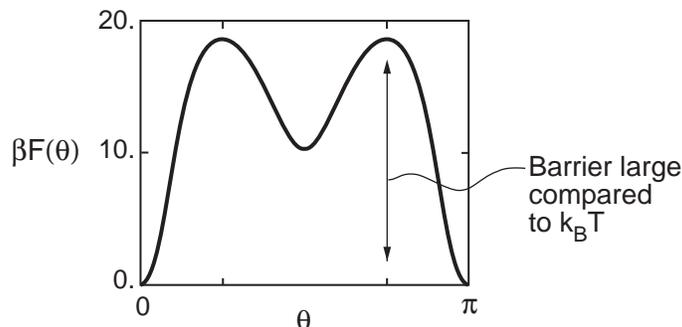


Fig. 3. – Free energy as a function of  $\theta$  for the Pickett-Strauss potential. Adapted from M.A.Wilson and D.Chandler, *Chem.Phys.***149**, 11 (1990).

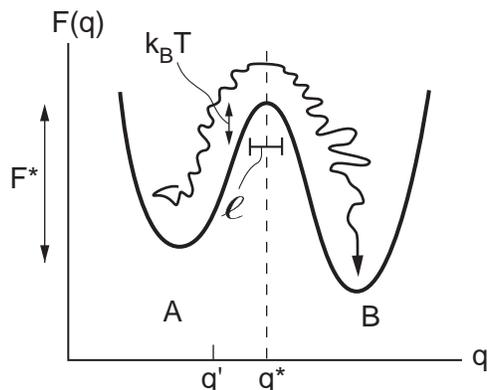


Fig. 4. – Free energy for the reaction coordinate. The transition state,  $q = q^*$ , separates stable states  $A$  and  $B$ . The wavy line depicts a trajectory from  $A$  to  $B$ . The point  $q = q'$  satisfies the condition that  $F(q')$  is several  $k_B T$  above that of the stable state  $A$  minimum, but it also several  $k_B T$  below  $F(q^*)$ .

we write

$$(4) \quad \nu^{-1} = \tau_{\text{mol}},$$

where  $\tau_{\text{mol}}$  is of the order of a typical microscopic relaxation time.

Multiplying the probability of visiting the barrier by the frequency  $\nu$  gives the overall rate of transition between  $A$  and  $B$ ,

$$(5) \quad k \sim \nu e^{-\beta F^*}.$$

Since  $F^* \gg k_B T$ , the typical time between transitions or “reactions” is exponentially long compared to  $\tau_{\text{mol}}$ ,

$$(6) \quad k^{-1} = \tau_{\text{rxn}} \sim \tau_{\text{mol}} e^{\beta F^*}.$$

A characteristic time that grows exponentially with  $F^*/k_B T$  is the hallmark of a barrier crossing. This exponential dependence is known as Arrhenius behavior. The subscripts

“rxn” denote “reaction” — in deference to the many rare events exemplified by chemical reactions.

#### 4. – Reaction coordinate, $q(t)$

Consider a trajectory for  $q$ , drawn schematically in Fig.5. The value of  $q(t)$  describes the progress of the reaction passing from one stable state to the other. It is therefore called the “reaction coordinate.” As the probability for visiting the transition state is low, passage through that state is fleeting. In the context of a trajectory of time duration  $\mathcal{T}$ , the probability distribution is the histogram

$$(7) \quad \begin{aligned} P(q) &= \langle \delta[q(t) - q] \rangle \\ &= \frac{1}{\mathcal{T}} \int_0^{\mathcal{T}} dt \delta[q(t) - q] \quad . \end{aligned}$$

This distribution will peak at the locations of the stable states. The point where it is smallest is the location of the transition state — the bottleneck between the two stable states.

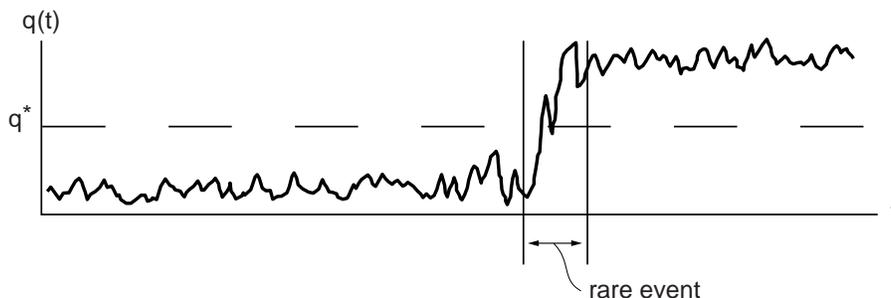


Fig. 5. – A trajectory for the reaction coordinate  $q$ . The rare fleeting transmission through the transition state,  $q \approx q^*$ , is sometimes referred to as an “instanton”.

In a straightforward computer simulation,  $n$  statistically independent samples of the transition state will require a long simulation time,

$$(8) \quad \mathcal{T} \approx n\tau_{\text{rxn}} \sim n\tau_{\text{mol}} e^{\beta F^*} .$$

One hundred independent samples, for example, would require a trajectory that runs 100 times longer than the long time between different rare events. Generally, it would correspond to a computation that is too long to be practical.

Alternatively, reasonable statistics for  $P(q)$  with  $q$  near  $q^*$  can be acquired by controlling  $q$ . In particular,  $-k_{\text{B}}T \ln P(q)$  is the reversible work function,  $F(q)$ . Thus, it can be computed by any one of a variety of free energy methods, such as umbrella sampling or thermodynamic perturbation theory.

In the case of cyclohexane, for example,  $F(\theta)$  can be computed by guiding  $\theta$  between  $0^\circ$  and  $180^\circ$  in, say,  $n$  steps. At the  $j$ th step,  $\theta$  can be confined to a limited range of values by adding

$$(9) \quad \begin{aligned} w_j(\theta) &= 0, & \frac{(j-1)\pi - \delta}{n} &\leq \theta \leq \frac{j\pi}{n} + \delta, \\ &= \infty, & \text{otherwise,} \end{aligned}$$

to the total potential energy of the system. The distribution of  $\theta$  values in a confined region,  $P_j(\theta)$ , is proportional to the full distribution in that same region. Thus, the full  $P(\theta) \propto \exp[-\beta F(\theta)]$  can be computed by splicing together the various  $P_j(\theta)$ 's, noting that the full function is continuous.

This type of calculation has been performed for a model of cyclohexane in liquid  $\text{CS}_2$ . The result is very close to that graphed in Fig.3. In other words, the solvent effect on  $F(\theta)$  is very small. (For other systems, solvent contributions to free energy changes are large, but not for the case of cyclohexane isomerization). While small, the direction of the effect is interesting. In particular, the barrier to isomerization slightly increases with increasing density (or pressure) of the solvent. From Eq.(5), therefore, one might predict that the rate of isomerization would decrease with increasing solvent pressure. The opposite occurs experimentally. The explanation must reside in the behavior of the non-Arrhenius prefactor,  $\nu$ .

### 5. – Rate constants and time correlation functions

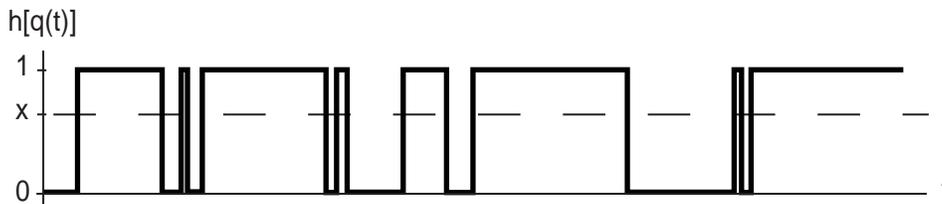


Fig. 6. – Time evolution of the product population, where  $x$  is the time average of that population.

Quantitative formulas for the rate can be written in terms of time correlation functions for the population operator,

$$(10) \quad \begin{aligned} h(q) &= 1, & q > q^*, \\ &= 0, & q < q^*. \end{aligned}$$

Figure 6 depicts how the population might evolve during a trajectory that is roughly  $15 \tau_{\text{rxn}}$  long. The fraction of time spent in state  $B$  is  $x = \langle h \rangle$ . The correlation of the instantaneous population fluctuation,

$$(11) \quad \delta h(t) = h[q(t)] - \langle h \rangle,$$

with the population at an earlier time is given by

$$(12) \quad \langle h \delta h(t) \rangle = \frac{1}{T} \int_0^T dt' h(t') \delta h(t' + t) \equiv x \overline{\delta h}(t).$$

The over-bar denotes the average of  $\delta h(t)$  for those trajectories where initially (i.e., at  $t = 0$ )  $h = 1$ . Since the system is initially constrained to state  $B$ , the over-bar average is a non-equilibrium average. In the limit of large time,  $\overline{\delta h}(t) \rightarrow 0$ . This relaxation to equilibrium occurs as the system undergoes several  $A \rightleftharpoons B$  transitions, and thereby loses memory of its initial preparation. Since their occurrence is rare, subsequent transitions

are expected to be a statistically independent events. In other words, the transition is expected to be Poissonian. Accordingly, the long time relaxation should be exponential,

$$(13) \quad \overline{\delta h}(t) \sim \overline{\delta h}(0) e^{-kt}.$$

The constant  $k$  is the average transition frequency, or equivalently,  $k^{-1}$  is the average lifetime of state  $B$ .

Equation (13) is deduced from first order kinetics. In that case,  $k$  is identified the as the sum of forward,  $A \rightarrow B$ , and backward,  $B \rightarrow A$ , rate constants,  $k = k_{A \rightarrow B} + k_{B \rightarrow A}$ . According to detailed balance,

$$(14) \quad x/(1-x) = k_{A \rightarrow B}/k_{B \rightarrow A}.$$

Within factors involving  $x$  and  $1-x$ ,  $k$  is either  $k_{A \rightarrow B}$  or  $k_{B \rightarrow A}$ . For simplicity of terminology, we call  $k$  the rate constant.

To the extent that the phenomenology is accurate, Eqs.(12) and (13) give

$$(15) \quad k(t) \equiv -\frac{d}{dt} \frac{\langle h \delta h(t) \rangle}{\langle h \delta h \rangle} \sim k e^{-kt}.$$

This connection between the rate constant and the time correlation function is valid for times longer than  $\tau_{\text{mol}}$ , as we elaborate now.

## 6. – Reactive flux correlation function

The differentiation indicated in Eq.(15) yields  $k(t) = \langle \dot{h} \delta h(t) \rangle / \langle h \delta h \rangle$ . The chain rule gives  $\dot{h} = \dot{q} \delta(q - q^*)$ , where  $\dot{q}$  is the reaction coordinate velocity. Further, since  $h^2 = h$ , it follows that  $\langle h \delta h \rangle = x(1-x)$ . Combining these observations produces

$$(16) \quad k(t) = \frac{1}{x(1-x)} \langle \dot{q} \delta(q - q^*) h[q(t)] \rangle.$$

In accord with its structure, the function  $k(t)$  is called the “reactive flux” correlation function. It can be rewritten in terms of a conditional average with the aid of Eq.(7). Specifically,

$$(17) \quad k(t) = \frac{1}{x(1-x)} P(q^*) \langle \dot{q} h[q(t)] \rangle_{q^*},$$

where  $\langle \dots \rangle_{q^*}$  denotes the average with  $q$  initially constrained to  $q^*$ .

How does this function behave? Consider the schematic trajectories drawn in Figs.4 and 5. Since  $q(0) = q^*$ , a very short time later  $h[q(t)] = 1$  if  $\dot{q} > 0$ , and  $h[q(t)] = 0$  if  $\dot{q} < 0$ . Thus,

$$(18) \quad \begin{aligned} k(0^+) &= \frac{1}{x(1-x)} P(q^*) \langle \dot{q} \theta(\dot{q}) \rangle \\ &= \frac{1}{x(1-x)} P(q^*) \frac{1}{2} \langle |\dot{q}| \rangle, \end{aligned}$$

where  $\theta(x)$  is the Heaviside function. If all trajectories were like the one drawn in Fig.4,  $k(t)$  would equal  $k(0^+)$  until such times that another activation and barrier crossing could occur. In that case,  $k \approx k(0^+)$ . This approximation is consistent with Eq.(5). It is the transition state theory approximation.

In contrast with this approximation, some percentage of trajectories may cross the transition state more than once during the fleeting transition between states  $A$  and  $B$ , as illustrated in Fig.5. In some situations, the reaction coordinate will be buffeted by other degrees of freedom, causing it to reverse direction near the barrier top. In other situations, the reaction coordinate will make an excursion across the potential well and back before other degrees of freedom cool the coordinate, trapping it in one of the wells. In either case, dynamics near the barrier ends quickly, in a transient time of the order of  $\tau_{\text{mol}}$ .

Thus, the reactive flux will generally appear similar to the function drawn in Fig.7.

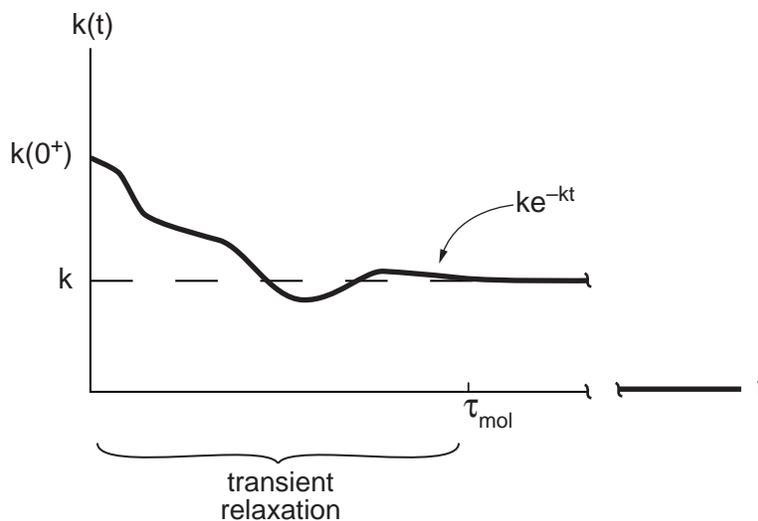


Fig. 7. – Reactive flux correlation function. After the transient relaxation,  $k(t)$  relaxes exponentially, as  $k \exp(-kt)$ , where  $k^{-1} \gg \tau_{\text{mol}}$ .

Some fraction of the trajectories initiated at the barrier top directed towards state  $B$  will be reversed and stabilized in state  $A$ . Others, initially directed towards  $A$  (i.e.,  $\dot{q} < 0$ ), will be reversed and stabilized in  $B$ . The former depletes from the positive contributions to  $k(0^+)$ , and the latter is negative. Thus, recrossing transient dynamics reduce  $k(t)$  from  $k(0^+)$ . The greater the recrossing, the greater the reduction.

For  $t \geq \tau_{\text{mol}}$ , trajectories initiated at the barrier top will be committed to one of two stable states, and a barrier crossing will not occur again until the reaction coordinate is reactivated. Thus, in this regime,  $k(t)$  behaves as indicated in Eq.(15). On the time scale of  $\tau_{\text{mol}}$ , however,  $\exp(-kt) \approx 1$ . As such,  $k(t)$  appears to reach a plateau, and the plateau value is the rate constant,  $k$ . The ratio

$$(19) \quad \kappa = k/k(0^+)$$

is essentially the fraction of trajectories that are stabilized in the state to which they were initially directed. It is called the transmission coefficient. Transition state theory assumes  $\kappa = 1$ .

In summary,

$$(20) \quad \frac{1}{\tau_{\text{rxn}}} = k = \kappa k_{\text{TST}},$$

where  $k_{\text{TST}} = k(0^+)$  and

$$(21) \quad \kappa = k(\tau_{\text{mol}}) / k(0^+).$$

The transition state theory rate constant,  $k_{\text{TST}}$ , sets the overall time scale for the rare event. It is a statistical quantity that can be computed from a free energy calculation, and it is independent of dynamics. On the other hand,  $\kappa$  does depend upon dynamics, the very quick transient relaxation dynamics.

## 7. – Choosing the transition state

The value of a rate constant of a rare event is independent of the precise choice of the population operator and transition state. For Eq.(20) to be correct, it is sufficient that the stable state be contained in the region where  $h = 1$ , and that the transition state coincides with a surface of low equilibrium concentration that must be crossed to pass from one stable state to the other. There seems to be a high degree of flexibility in choosing a surface from which to run trajectories when calculating  $k(t)$ .

Suppose, for example, some physically motivated choice of transition state has been made, and consider how Eq.(20) would be used with this choice. First, through techniques like umbrella sampling or free energy perturbation theory, one would compute the free energy difference between the stable reactant state and the transition state. In one step of that computation, the system would be constrained to equilibrate at the transition state. As such, the distribution of phase space points at the transition state would be determined. From this distribution and the free energy difference,  $k(0)$  could be evaluated, and trajectories could be initiated to compute the relative reactive flux,  $k(t)/k(0)$ , and its plateau value,  $\kappa$ . The time to reach the plateau would be relatively short. Quite a few independent trajectories could therefore be performed to compute  $\kappa$ , without exceptional computational cost. It thus appears that in the realm of classical dynamics, the problem of accessing meaningful statistics for rare events is completely solved through the implementation of Eqs.(20) and (21).

In general, however, a problem remains. A poor choice of transition state can lead to statistical uncertainties nearly as severe as those encountered when attempting to study rare events through straightforward trajectories. For example, imagine that in Fig.4, the transition state was chosen not to coincide with the barrier top, but rather to coincide with the value of  $q = q'$ . In this case, since  $F(q')$  is lower than  $F(q^*)$  by several  $k_{\text{B}}T$ , the value of  $k(0^+)$  as in Eq.(21) would be much larger than if the transition state was taken at the barrier top. Correspondingly,  $\kappa$  would be much smaller than if trajectories were initiated at the barrier top. The reason why  $\kappa$  would be much smaller is that with this choice of transition state, most trajectories will experience many recrossings of the transition state. In other words, passage over the barrier remains a rare event for the ensemble of trajectories initiated at  $q = q'$ . Only successful trajectories register contributions to  $\kappa$ . Reasonable statistics for  $\kappa$  requires a reasonable number of independent successful trajectories.

If the transmission coefficient is extremely small, something other than the assumed transition state presents a significant bottleneck to the dynamics. An optimum choice of the transition state would be one that maximizes the transmission coefficient, or equivalently, minimizes the transition state approximation to the rate. This choice optimizes the accuracy of the transition state approximation. This optimization is known as “variational transition state theory”. For a many body system, implementation of this theory

requires some well founded preconceived notions about the process. Otherwise, the search for the optimum choice would be too wide to be practical. In the third lecture of this series, I describe stochastic methods that effectively search for transition paths in complex systems, without preconceived notions. For now, however, we proceed assuming much of the underlying mechanism for a rare event is reasonably well known from the start. In other words, enough is understood about the rate determining step that a useful transition state can be identified initially, without optimization and before extensive computation is pursued.

## 8. – Lindemann-Hinshelwood and Kramers regimes

In this case, one typically conceives of the reaction coordinate in terms of only a few coordinates, as if the system undergoing the rare event was effectively low dimensional. By themselves, low dimensional systems do not relax to equilibrium. Coupling to other degrees of freedom provides the mechanism for dissipation. Figure 8 illustrates how the transmission coefficient varies with this coupling. When the coupling is zero, there is no dissipation, and therefore no net rate. As illustrated for this case, trajectories that pass once over the transition state will continue to do so over and over again, with no loss in energy, and no long lived commitment to one of the stable states. As coupling increases slightly from zero, dissipation can occur, with a rate that is proportional to the coupling. As such, for weak coupling,  $\kappa$  will be proportional to coupling. This argument focuses on dissipation from the transition state.

Equivalently, the weak coupling regime can be understood in terms of excitation from a stable state. In a stable state at a low energy, the reaction coordinate requires a boost in energy if it is to surmount the transition state and move to another stable state. This boost must come from coupling to other degrees of freedom. For example, rates of unimolecular process in the gas phase are proportional to the frequency of collisions between the reacting molecule and neighboring molecules. It is in this context that F.A.Lindemann and C.N.Hinshelwood understood the weak coupling regime long ago. The constant of proportionality constant between the rate constant and the collision frequency is usually estimated from a microcanonical transition state theory of independent molecules (so-called “RRKM” theory, after Rice, Ramsperger, Kassel and Marcus).

Unlike the Lindemann-Hinshelwood regime, when the reaction coordinate is strongly coupled to other degrees of freedom, it progresses only a short distance from the transition state before being committed to one of the stable states. In this case, the coupling causes a buffeting of the trajectory in the vicinity of the transition state. The reaction coordinate undergoes something like a random walk at the barrier top. In the limit of infinitely strong coupling, the trajectory’s outcome will be uncorrelated with its initial direction, and  $\kappa$  will be zero, vanishing as the diffusion constant vanishes with increasing friction. In the high coupling regime,  $\kappa$  will therefore be proportional to the inverse of the coupling. This behavior was first understood by Hendrick Kramers.

At some intermediate coupling, there will be a crossover between the Lindemann-Hinshelwood regime, dominated by inertial dynamics and energy diffusion, to the Kramers regime, dominated by spatial diffusion. The location of the crossover regime, known as the Kramers turnover, is highly system dependent. It manifests the detailed mechanisms for coupling and energy flow between the reaction coordinate and its surroundings, both intramolecular and intermolecular. Cyclohexane isomerization illustrates this system specificity, as we discuss now.

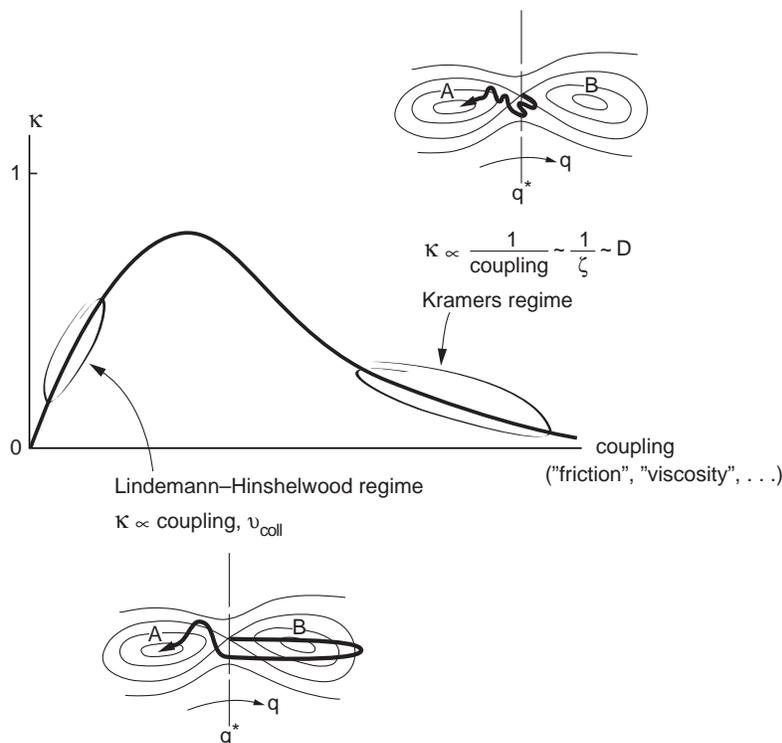


Fig. 8. – Variation of the transmission coefficient,  $\kappa$ , as a function of the coupling between a reaction coordinate and a bath. “Coupling” refers to the rate at which energy can flow from the reaction coordinate to other degrees of freedom. Depending upon the physical situation, it could be proportional to “collision frequency”, “friction” or “viscosity”,  $\zeta$ , or the reciprocal of the spatial diffusion constant,  $D^{-1}$ . Figure adapted from D.Chandler, *J.Stat.Phys.***42**,49(1986).

## 9. – Cyclohexane reactive flux

Molecular dynamics trajectory calculations have been performed for a model of cyclohexane in liquid carbon disulfide, employing  $\theta$  as the reaction coordinate and identifying the transition state with the point of maximum in  $F(\theta)$ . Figure 9 shows the reactive flux computed in this way for two different liquid densities. The figure shows that the transmission coefficient, given by the plateau value of  $k(t)/k(0)$ , increases with increasing density. On the other hand, as we noted earlier, the transition state approximation for the rate, given by  $k(0)$ , exhibits negligible variation with density. The simulated model therefore exhibits pressure acceleration of the chair-boat isomerization rate. This behavior is in agreement with the experimental observations cited at the beginning of this lecture. Indeed, trajectory calculations of the cyclohexane transmission coefficients carried out over a wide range of solvent viscosity successfully interpret the thermodynamic state dependence of the chair-boat isomerization rate.

Evidently, the liquid phase isomerization of cyclohexane lies in the inertial region of Fig.8, at smaller couplings than those of the Kramers turnover region. This fact sheds light on the nature of intramolecular energy flow. The usual conception of the transition state for isomerization of a hypothetical polyatomic molecule is that of a saddle point

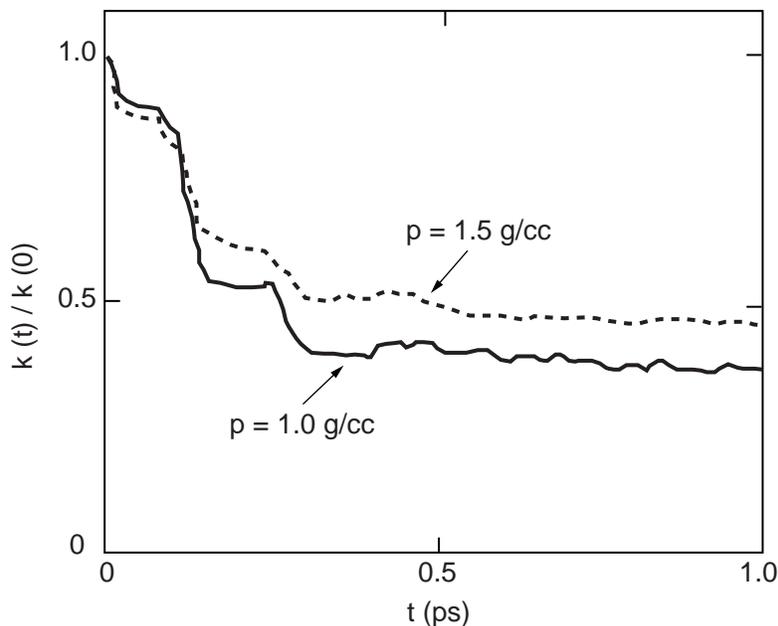


Fig. 9. – Reactive flux correlation functions for cyclohexane in liquid carbon disulfide at two different liquid densities. Each function was computed from 1000 independent trajectories initiated at the transition state surface of the Pickett-Strauss potential for cyclohexane. The trajectories employed the Pickett-Strauss intramolecular potential and standard intermolecular interaction site potentials for  $\text{CS}_2$  and  $\text{C}_6\text{H}_{12}$ . This figure is adapted from the paper describing these calculations: M.A.Wilson, D.Chandler, *Chem.Phys.***149**,11(1990)

lying on a dividing surface in a high dimensional potential energy surface. Due to the high dimensionality, one imagines that the configuration space of the product (or reactant) region is very large. Accordingly, after crossing the dividing surface, trajectories would likely be lost in the product space, not finding a way back to the transition state until after a relatively long time. In other words, energy will leave the reaction coordinate and dissipate into other intramolecular modes so quickly that recrossing trajectories are irrelevant.

This idea is the essential statement of the RRKM theory of unimolecular kinetics. As noted earlier, it is a transition state approximation for independent polyatomic molecules. In this picture, the solvent is not needed to cool the molecule and stabilize the product. The molecule provides its own sink for energy flow. Thus, according to this picture, the only possible dynamical role for the solvent is one that might reverse trajectories at the barrier top, before commitment to a stable state. If correct, the solvent could only lower the rate, not accelerate it. But for cyclohexane isomerization in the liquid phase, this prediction is in discord with the facts. The error in RRKM theory for this case is due to neglecting the time scale for intramolecular energy flow. This time scale is short compared to  $1/k$ , but it is not so short to be negligible compared to that for energy to move from the reaction coordinate to the solvent.

To illustrate the importance of this short time scale, let us characterize the reactive

flux of a gas phase cyclohexane molecule in terms of two relaxation times,

$$(22) \quad k_0(t)/k_0(0^+) \approx f e^{-t/\tau_s} + (1-f)e^{-t/\tau_1}.$$

Here,  $\tau_s$  denotes a short time transient relaxation time, and  $\tau_1$  denotes the long plateau decay time. The subscript “0” indicates that the reactive flux in this formula is for the case where “zero” solvent (i.e., nothing) interacts with the molecule. The entire time dependence in this case is due to intramolecular relaxation. In the transition state approximation, there is no transient relaxation. In other words, if trajectories never recrossed the transition state, the onset of long time relaxation would be instantaneous. The parameter  $f$  is the fraction of trajectories that do recross. Gas phase experiments and theoretical estimates give a measure of  $\tau_1$ , and trajectory calculations provide estimates of  $f$  and  $\tau_s$ . The results are

$$(23) \quad \begin{aligned} \tau_1 &\sim 1/k_0(0^+) \sim 0.1 \text{ s}, \\ \tau_s &\approx 0.5 \text{ ps}, \\ f &\approx 0.6. \end{aligned}$$

In actuality, the transient relaxation of the gas phase molecule is more complicated than the single exponential embodied in the caricature (22). Trajectory calculations show that decay occurs in three pronounced steps, much like the solvated molecule transient behavior graphed in Fig.9. This behavior is due to trajectories that ride for some period of time on one of the ridges of the potential energy surface, near either  $\theta = 50^\circ$  or  $\theta = 130^\circ$ . See Fig.2. During such trajectories, most of the velocity is in the direction of  $\phi$ , while  $\theta$  exhibits small oscillations with a period of about 0.1 to 0.2 ps. Due to coupling to other intramolecular degrees of freedom, some of these trajectories are forced off the ridge into a stable state after one oscillation of  $\theta$ , others after two oscillations, and so on. Typically, all of this interesting behavior is completed within 0.5 ps.

On the same time scale, coupling to a dense fluid solvent can also affect stabilization of these transient trajectories. Let  $\alpha$  denote the average frequency with which intermolecular coupling will randomize the state of the reaction coordinate. Then, to the extent that subsequent randomizations can be approximated as uncorrelated,  $\exp(-\alpha t)$  is the probability that no randomization has occurred, and

$$(24) \quad k_{\text{cm}}(t) \approx e^{-\alpha t} k_0(t) + \alpha \int_0^t k_0(t') dt'$$

provides an estimate of the effects of intermolecular coupling on the reactive flux. The first term on the right hand side of Eq.(24) is the contribution to  $k(t)$  from trajectories where no randomization has yet occurred during the time  $t$ . The second term is the sum of all contributions for which a randomization has occurred. Namely,  $\alpha \exp(-\alpha t') dt'$  is the probability that a randomization event occurs between  $t'$  and  $t' + dt'$ , and with Eq.(24), we imagine that such an event immediately stabilizes the reaction.  $k_0(t')$ , with  $t' \leq t$ , is the contribution to  $k(t)$  for trajectories where the randomization event occurred at time  $t'$ . The second term on the right hand side adds up all such contributions.

The subscript “cm” stands for “collision model” because each randomization event is viewed as instantaneous, like a “collision” between the reaction coordinate and the solvent. In reality, molecules in a liquid are in continuous contact with their neighbors. The concept of a collision is an abstraction. Many sorts of fluctuating forces couple to the reaction coordinate, most of which have small effects on the reaction coordinate

path. Equation (24) neglects the small effects, and treats those fluctuations that have strong effects as if they occur very quickly, each one uncorrelated from its predecessor. This equation can successfully fit the trajectory results graphed in Fig.9 when  $\alpha$  is in the neighborhood of  $10^{11} s^{-1}$ .

Combining Eqs.(22) and (24) gives an estimate of the plateau value of  $k(t)$  in terms of inter and intra molecular time scales. Its transmission coefficient is

$$(25) \quad \kappa_{\text{cm}} \approx \frac{f\alpha}{\alpha + \tau_s^{-1}} + \frac{(1-f)\alpha}{\alpha + \tau_1^{-1}} \quad .$$

When  $\alpha \ll \tau_1^{-1}$ , this formula predicts that  $\kappa$  is proportional to  $\alpha$ , with proportionality constant  $(1-f)\tau_1$ . It coincides with the Lindemann and Hinshelwood's formula for the pressure dependence of the rate constant for a gas phase unimolecular reaction. (In that case,  $\alpha$  is truly a collision frequency, and this collision frequency is proportional to gas pressure.) In a liquid, however,  $\alpha \ll \tau_1^{-1}$ . For that case, but when  $\alpha$  is still smaller than  $\tau_s^{-1}$ , Eq.(8.4) predicts that  $\kappa$  grows linearly with  $\alpha$ , but with slope  $\tau_s$ .

When  $\alpha$  is large compared to both  $\tau_1^{-1}$  and  $\tau_s^{-1}$ , Eq.(25) tends to a limiting value of 1. It is unrealistic to imagine that a liquid environment can produce strong randomization at such high frequencies. In this regime, it is more realistic to imagine that coupling to the solvent will lead to diffusive motion of the reaction coordinate. In that case, Kramers' limiting behavior,  $\kappa \sim 1/\alpha$ , is the correct result. The interpolation formula,

$$(26) \quad \kappa^{-1} \approx (1 + \alpha\tau_s) + \kappa_{\text{cm}}^{-1},$$

connects small and large  $\alpha$  regimes by, in effect, adding the time to diffuse across a barrier top to the time to equilibrate in a stable state. When  $f = 0$ , Eq.(26) predicts that  $\kappa$  reaches its maximum (the Kramers turn-over) when  $1 = \tau_1\tau_s\alpha^2$ .  $\tau_1$  is a relatively long time. If for the isolated molecule, the fraction of recrossing trajectories were indeed negligible (i.e., if  $f = 0$ ), the liquid phase rate process (where  $\alpha \sim 10^{11} s^{-1}$  or greater) would therefore occur in the Kramers diffusive regime. On the other hand, if  $f$  is not negligible, Eq.(26) predicts that  $\kappa$  can reach its maximum when  $\tau_s\alpha \sim 1$ . In this case, the Kramers turnover will be within or beyond the range of liquid state conditions. Hence, the rate process should occur in the inertial regime. This prediction is in accord with both the trajectory results illustrated in Fig.9 and the experimental results illustrated in Fig.1.

A short but not negligible time is required to commit a molecule to a stable state. Within this time, transient trajectories can recross the transition state. Since coupling to a solvent can accelerate the equilibration, the coupling will lower the number of recrossing trajectories and thus increase the net rate. This point is the essence of the analysis given above.

## 10. – Summary

The case study of cyclohexane isomerization is interesting in its own right, demonstrating the significance of intramolecular energy flow, and the sensitivity of condensed phase chemical dynamics to the application of pressure. Traditionally, the effect of pressure on kinetics has been interpreted from the perspective of statistics, namely transition state theory. In this approximation, pressure dependence of a rate constant is associated with pressure variation of the activation free energy (i.e., the partial molar volumes of

transition states relative to stable state). Calculations of the type illustrated in this lecture, however, demonstrate that dynamics rather than statistics, can dominate the pressure dependence. Indeed, the partial molar volume of the transition state of cyclohexane in liquid carbon disulfide is slightly larger than that of either of the stable states. Yet the application of pressure in this case causes the rate to increase.

More generally, for the purposes of this lecture, the cyclohexane case study also illustrates the most important ideas used in carrying out calculations concerning rare events. The first step is the identification of a reaction coordinate, presupposing some understanding of the mechanism of the transition between stable states. The next step is the calculation of the free energy change or reversible work incurred through changing the reaction coordinate. It gives us the probability of visiting the transition state, and it provides an ensemble of transition state configurations. From this ensemble, many short trajectories can be initiated to compute the reactive flux and thus the rate constant for transitions between stable states. The initiation point for each trajectory corresponds to a midpoint on a representative transition pathway.

What is the computational advantage of taking these steps? In a straightforward trajectory,  $N$  independent examples of transition paths would require a computation time of  $N \cdot t_{\text{rxn}}$ , where  $t_{\text{rxn}}$  is the computing time required for a trajectory of length  $\tau_{\text{rxn}}$ . Due to the low probability for visiting the transition state,  $t_{\text{rxn}}$  itself is very large, and  $N \cdot t_{\text{rxn}}$  is  $N$  times larger. On the other hand, following the series of steps designed specifically for rare events requires first  $n \cdot t_{\text{eq}}$ , where  $t_{\text{eq}}$  is the computation time to equilibrate at one of  $n$  points used in sampling the free energy of the reaction coordinate. Then,  $\kappa^{-1} \cdot N$  trajectories can be initiated from the transition state. The factor  $\kappa^{-1}$  is included because only the fraction  $\kappa$  of attempted trajectories will contribute to the reactive flux. Each attempted trajectory will require  $t_{\text{mol}}$ , the computation time corresponding to a trajectory of length  $\tau_{\text{mol}}$ . Thus, comparing the relative times for sampling leads us to predict that the advantage over straightforward simulation is roughly the factor

$$\frac{N t_{\text{rxn}}}{n t_{\text{eq}} + \kappa N t_{\text{mol}}} \approx \kappa^{-1} t_{\text{rxn}} / t_{\text{mol}}.$$

Since the ratio  $t_{\text{rxn}}/t_{\text{mol}}$  grows exponentially with the free energy barrier height, the computational advantage can be substantial indeed.

If the analysis begins with a poor assignment of the transition state, however,  $\kappa$  will be very small. Much, if not all, the advantage will then be lost. This observation stresses the need to begin the calculation with a reasonable qualitative understanding of the reaction pathways. What might we do if we did not already have such an understanding? This question is addressed in the third lecture of this series. Before getting there, in the next lecture, we leave the realm of purely classical dynamics and consider rare events involving electrons — electron transfer reactions.

\* \* \*

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Background to much of what is said in this lecture can be found in the elementary review, D.Chandler, *J. Stat. Phys.* **42**, 49 (1986), and the elementary text, D. Chandler, *Introduction to Modern Statistical Mechanics*(Oxford University Press, New York, 1987), especially Chapters 6 and 8.

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There are a handful of analytically tractable models that can be used to interpret the results of detailed numerical calculations. Our use of the strong collision model closely follows developments due to Bruce Berne and his co-workers. This and other pertinent material is discussed in their review, B.J.Berne, M.Borkovec and J.E.Straub, *J. Phys. Chem.* **92**, 3711 (1988).

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