Chapter 21
Reaction coordinates and rates

21.1 Kinetics from statistical thermodynamics

For most of this course, we have discussed equilibrium properties, for which time is not a relevant variable. Indeed, thermodynamics is not concerned with time. The very notion of equilibrium invokes, in part, the concept of time-independence.

The current topic will now take a slight departure from that perspective. Here, we will consider how one might extract rates of some molecular process. In order to extract these kinetic quantities, we will have to make certain assumptions about the equilibrium behavior and molecular trajectories that take us slightly beyond the mere province of thermodynamics and into the realm of kinetics. We will find, however, that thermodynamic quantities like the free energy are strong determinants of kinetic rate coefficients.

Consider this classical picture of a chemical reaction that you may have seen in your early chemistry courses:

Here, we envision some coordinate that takes us along a reaction pathway, from start to finish. Along this coordinate we track a free energy, which in some simple cases can be just the potential energy. There is a barrier in free energy the system must overcome, $\Delta F^\ddagger$, and that barrier determines how fast the reaction can proceed. The barrier is often called the activation energy. The state of the system when it is at the height of this barrier is called the transition state, or the rate-limiting state. After reacting, if the reaction is favorable, there will be a net lowering in free energy at the product state.
In this lecture we will understand the origins of such diagrams in terms of microscopic properties. We will find that the emergence of this kind of picture really stems from many simplifications about microscopic interactions, but in many cases, it is able to give a quantitative description of the kinetic rates. This kind of analysis is called **classical transition state theory**.

### 21.2 Macroscopic considerations

For chemical reactions, reaction rates are typically written as the product of a rate coefficient times a concentration of a reactant raised to its stoichiometric coefficient. Consider the reaction $A + 2B \leftrightarrow C$. The rate of change of the components is usually written in the following form:

\[
\begin{align*}
\frac{d[A]}{dt} &= -k_f [A][B]^2 + k_r [C] \\
\frac{d[B]}{dt} &= -2k_f [A][B]^2 + 2k_r [C] \\
\frac{d[C]}{dt} &= k_f [A][B]^2 - k_r [C]
\end{align*}
\]  

(21.1)

Here, $k_f$ and $k_r$ are the **forward and reverse rate coefficients**, and the brackets indicate concentration (such as moles/molecules per volume). Each component changes concentration due to forward and reverse reactions. At equilibrium, the change of concentrations with time is zero. Setting the time derivatives equal to zero, we find:

\[
\frac{[C]}{[A][B]^2} = \frac{k_f}{k_r}
\]

(21.2)

From the previous lecture we know that this ratio of concentrations must give the equilibrium constant. Therefore, we find that the forward and reverse rate coefficients must satisfy $k_f/k_r = K_{eq}$.

What is the motivation for this particular form of the rate laws, involving concentrations raised to stoichiometric coefficients? These laws typically stem from microscopic reaction mechanisms. One can think of concentration as being related to the probability that a molecule is at a particular location in space. For the reaction above, therefore, the probability of a forward reaction occurring is the probability that an A molecule and two B molecules are simultaneously in the same location. Hence, the probability goes as $[A][B]^2$. A similar case exists for the reverse.

This recipe for writing the rate coefficients is supported by a large volume of experimental data. It is, however, not rigorous and not a general principle of reactions. There are a number of reactions that do not follow the stoichiometric coefficients in their rate laws, because they have more complicated microscopic mechanisms that cannot be
described by these simple probability considerations. However, whatever the expression for the rate equation, we must find that the concentrations in the equilibrium limit (when the derivatives are zero) satisfy the equilibrium expression, provided the system can be treated as an ideal gas or ideal solution.

Returning to the simple picture above, the rate coefficients are generally temperature and pressure-dependent. Recall from the discussion on reaction equilibrium that the van’t Hoff relation gives the temperature dependence of the equilibrium constant:

\[
\frac{d \ln K_{eq}}{dT} = \frac{\Delta h^0}{k_B T^2}
\]

(21.3)

Based on this result, Arrhenius proposed that the general form for the rate coefficients is the same as that of the equilibrium constant:

\[
\frac{d \ln k_f}{dT} = \frac{E_f}{k_B T^2} \quad \frac{d \ln k_r}{dT} = \frac{E_r}{k_B T^2}
\]

(21.4)

where \(E_f\) and \(E_r\) are the forward and reverse activation energies. Note that the activation energies must satisfy \(\Delta h^0 = E_f - E_r\) since \(k_f/k_r = K_{eq}\) and hence \(d \ln k_f/dT = -d \ln k_r/dT = d \ln K_{eq}/dT\). This is consistent with the transition state diagram above.

For temperature-independent activation energies, one can integrate this expression directly to find:

\[
k_f = A \exp \left(-\frac{E_f}{k_B T}\right) \quad k_r = B \exp \left(-\frac{E_r}{k_B T}\right)
\]

(21.5)

where the ratio of \(A/B\) is also constrained by the equilibrium constant. These expressions embody the typical Arrhenius form of the rate dependence on temperature. Importantly, they are frequently used to extract the activation energies: a plot of the log of the measured rate coefficient versus \(1/T\) will give a slope that is related to the activation energy.

### 21.3 Microscopic origins of the rate coefficients

To begin to make a microscopic analysis of reaction rates, we need to introduce the concept of a potential energy landscape, or PEL. The PEL is just the potential energy as a function of the configurational degrees of freedom, envisioned as a surface in a highly dimensional space. If we have \(N\) spherically symmetric particles, then we have \(3N\) positional degrees of freedom. We envision the potential energy landscape as a plot of the function \(U(\mathbf{r}^N)\) in a \(3N + 1\) dimensional world, where there one axis for each position and one for the potential energy.
A potential energy landscape is the projection of the potential energy function $U(r^N)$ in high dimensional space. For a system of $N$ structureless particles, the landscape is a hypersurface in a $3N + 1$ dimensional space.

Why are we interested in examining the potential energy function as a landscape, in particular? The landscape perspective implies we are interested in the topography of the PEL: what kinds of minima, maxima, and saddle points it has, and how they are connected. It is this topography and connectivity that determines the dynamics of a system since, as we will see, the rate limiting steps typically involve hopping over saddles in the landscape.

To keep things at a manageable level in a number of dimensions that we can plot, we will consider the potential energy landscape of a simple reaction:

$$A + BC \leftrightarrow AB + C$$

(21.6)

Here, the variables $A, B,$ and $C$ indicate atoms. We will also assume that the reaction proceeds via the following molecular mechanism:

That is, the $A$ molecule approaches the $BC$ one in a co-linear form. The three molecules form a linear transition state ("activated") complex, and then dissociation occurs. We will denote the activated complex by the notation $(ABC)^\ddagger$. For the purpose of clarity in our derivation, we will assume that $A, B,$ and $C$ all have the same mass.

The PEL of this system involves nine degrees of freedom, three position components for each atom. However, if we consider only the collinear aspects of the reaction, we find that there are only two relevant degrees of freedom describing the conformation, the distances between the atoms $r_{AB}$ and $r_{BC}$. Therefore, the PEL for this system can be projected into a three dimensional space. It might look something like this:

Or, if we were to use a contour plot instead:
Here, darker colors indicate deeper (lower) energies. All numbers and units are fictitious, and just for schematic purposes.

Notice that the PEL for this system has two deep basins. One lies at small values of $r_{AB}$ and large values of $r_{BC}$, hence it is the reactant state. The other one lies at the product state, for similar considerations. In order to get from one state to another, the system must traverse this surface along a path that connects the two minima. There is a single **saddle point** separating the two minima, and this corresponds to the **transition state**.

Where do PELs come from? They derive from the microscopic energetics of the system. For reactions, we almost always must use a quantum description in order to compute the potential energies as a function of nuclear centers of the atoms, since bond breaking and formation is not well-described by simple classical energy expressions. This entails solving Schrodinger’s equation for the electrons in the system at each nuclear configuration (specified by $r_{AB}$ and $r_{BC}$) to obtain the ground-state electronic energy. Then the energies at all of the states are used to construct a continuous, smooth effectively classical energy hypersurface. This can actually be a challenging task, even for the simple reaction examined here, and the computation of PELs using numerical methods remains an active research field.

For nonreactive systems, such as a peptide binding to a protein—where association involves only nonbonded forces like van der Waals interactions and electrostatics—analytical expressions for the potential energy from classical considerations can be sufficient to produce an accurate PEL, and so no quantum electronic structure calculations are needed. Still, such cases can also be extremely challenging due to the numbers of degrees of freedom that need to be considered.
We will now make a number of approximations that describe the system’s trajectory over the PEL. These ideas constitute **classical transition state theory**, a field originated by **Henry Eyring** in the 1930s. The approximations this theory makes are the following:

- In going from reactants to products, the system takes the lowest energy trajectory on its PEL. This involves it passing through the **saddle point** on the energy surface. In reality, there is no physical constraint that dictates the system must follow this specific pathway. However, at constant temperature, the Boltzmann factor, $\exp(-\beta E)$, says that lower energy states have exponentially higher probability. Therefore the assumption of lowest energy trajectory is roughly equivalent to examining the most likely trajectory.

- We will use the variable $\xi$ to indicate a **reaction coordinate** that traces the current position along this trajectory. $\xi$ takes on a specific value $\xi^\ddagger$ at the saddle.

- We can consider the **transition state** as effectively one “component” in the system. We consider this component to correspond to all of the configurations that lie within a small region of $r_{AB}$ and $r_{BC}$ around the saddle point. Similarly, the reactant and product “components” correspond to the states of the system when it is in those respective basins.

- The transition state is in equilibrium with the reactant state. That means that the relative populations of each are given by partition functions and Boltzmann factors.

- Once the system reaches the transition state, regardless of how it arrived there, it is 50% likely to convert to a product and 50% likely to convert back to a reactant.

If we project the energy landscape along the minimum energy reaction pathway into a two-dimensional plot, it will look something like the figure at the beginning of the lecture:
In order to define the parts of the PEL that correspond to the transition state, we have to look at a differential range of the reaction coordinate $d\xi^\pm$ around the transition state value $\xi^\pm$. This is shown in the figure above.

The most important assumption stated above is the equilibrium condition between reactants and the transition state. Considering the different components to be independent, this statement dictates that:

$$\frac{\rho_{(ABC)^\pm}}{\rho_A \rho_{BC}} = \left(\frac{q_{(ABC)^\pm}}{V}\right) \left(\frac{q_A}{V}\right) \left(\frac{q_{BC}}{V}\right)$$

(21.7)

where each $\rho$ is a density in molecules per volume, and the $q$'s are the single-molecule partition functions of each component. To calculate each $q$, one simply performs the integral over positions and momenta of each component restricting to the conformations that define those states (in the basins for the products and reactants, and around the saddle point for the transition state). Even though we haven’t included more detail in the PEL, the $q$'s can actually include other degrees of freedom due to electronic and nuclear states as well.

There is a subtlety with the expression above. The transition state represents an \textbf{unstable} state, since it is at a saddle point. Small perturbations along the reaction coordinate $\xi$ will lower the energy and lead to configurations of increased probability, according to the Boltzmann factor. In contrast, states of lower probability are found for any perturbation to the reactants and products, or for perturbations to the transition state in directions that are perpendicular to $\xi$.

The partition function for the transition state might be written as:

$$q_{(ABC)^\pm} = \frac{1}{\Lambda(T)^9} \int \exp[-\beta U] d\mathbf{r}^3$$

(21.8)

where $\mathbf{r}^3$ contains all of the coordinates of the three atoms, and the integral is restricted to only those conformations in the volume $V$ which lie close to the saddle point on the PEL, i.e., which have $\xi$ in the range $\xi^\pm \pm d\xi^\pm/2$. That is, the integral is performed for configurations of specified $r_{AB}$ and $r_{BC}$ values. Note that if the atoms had different masses, we would incur three different de Broglie wavelengths in the expression above, rather than a single one.

To compute this partition function, we first perform a change of coordinates. That is, we swap the usual Cartesian axes and the coordinates $\mathbf{r}^N$ for a different set of axes in which one of the axes is along $\xi$ and the remaining 8 are conjugate to it, denoted by $s_1, s_2, \ldots, s_8$. This enables us to write the integral as:

$$q_{(ABC)^\pm} = \frac{1}{\Lambda(T)^9} \int \exp[-\beta U] d\xi ds_1 ds_2 \ldots ds_8$$

(21.9)
This representation assumes the coordinate transform was linear. In general, the differentials can incur a Jacobian due to the change of variables. Either way, it will not affect the results here, since the Jacobian would be absorbed into a variable later on.

Since this integral is performed over the transition state conformations, the $\xi$ integral varies over a differential slice $d\xi^\mp$ surrounding $\xi^\mp$. We can thus factor the partition function as:

$$q_{(ABC)}^\mp = \left[ \frac{1}{\Lambda(T)^8} \int \exp[-\beta (U - U^\mp)] ds_1 ds_2 \ldots ds_8 \right] \frac{\exp[-\beta U^\mp] d\xi^\mp}{\Lambda(T)}$$

(21.10)

where $q^\mp$ includes the integrals over all of the other degrees of freedom perpendicular to $\xi$, normalized to the energy at the saddle point.

We would now like to find the speed with which the system moves along the reaction coordinate. The average value of the absolute velocity along any one degree of freedom is just given by the Maxwell-Boltzmann distribution; here the velocity of interest is that corresponding to the degree of freedom $\xi$:

$$\langle v_\xi \rangle = \int |v_\xi| \varrho(v_\xi) dv_\xi$$

$$= \left( \frac{2k_B T}{\pi m} \right)^{1/2}$$

(21.11)

The amount of time it takes a molecule, on average, to leave the transition state region is given by the length of the region $d\xi^\mp$ divided by the speed it moves along $\xi$:

$$dt = d\xi^\mp / \langle v_\xi \rangle$$

$$= d\xi^\mp \left( \frac{2k_B T}{\pi m} \right)^{-1/2}$$

(21.12)

Finally, the net rate of molecules moving to the product state is given by the number of molecules that sit at the transition state times the average rate at which they cross it, times the 50% probability that they go to the reactant versus product:

$$\frac{\text{molecules reacted}}{\text{time \cdot volume}} = \rho_{(ABC)}^\mp \times \frac{1}{dt} \times \frac{1}{2}$$

$$= \rho_A \rho_{BC} \left( \frac{q_{(ABC)}^\mp}{V} \right) \times \frac{\langle v_\xi \rangle}{d\xi^\mp} \times \frac{1}{2}$$

(21.13)

$$= \rho_A \rho_{BC} \left( \frac{q^\mp}{V} \right) \times \frac{\exp[-\beta U^\mp] d\xi^\mp}{\Lambda(T)} \times \left( \frac{2k_B T}{\pi m} \right)^{1/2} \frac{1}{d\xi^\mp} \times \frac{1}{2}$$

After expanding the de Broglie wavelength and simplifying:
\[
\frac{\text{molecules reacted}}{\text{time} \cdot \text{volume}} = \rho_A \rho_{BC} \left( \frac{q^\dagger}{V} \right) \left( \frac{k_B T}{h} \right) \exp\left[ -\beta U^\dagger \right] \tag{21.14}
\]

Therefore we can write the rate constant for this reaction as:

\[
\text{reaction rate} = k_f \rho_A \rho_{BC} \quad \text{where} \quad k_f \equiv \frac{(q^\dagger / V)}{(q_A / V)(q_{BC} / V)} \left( \frac{k_B T}{h} \right) \exp\left[ -\beta U^\dagger \right] \tag{21.15}
\]

As can be seen, we are able to develop an expression for the reaction rate constant in terms of the molecular partition functions. Note that we can consider the quantity \( U^\dagger \) as the potential energy of the transition state above that of the reactants, since we can shift the energy surface so that the energy of at the minimum of the reactant basin sits at \( U = 0 \) (note that shifts of the PEL do not affect the thermodynamic properties).

Therefore, this expression shows that the rate constant depends on the elevation in potential energy of the saddle point. However, it also depends on the partition functions for all of the species involved, which correspond to integrals over the PEL. These partition functions depend not only on the energy of the reactant basin and saddle point, but also on the curvature of the energy surface around it. They are also dependent on the temperature. All of these contributions mean that the general expression for the rate constant is:

\[
k_f = \left( \frac{k_B T}{h} \right) \exp(-\beta \Delta F^\dagger) \quad \text{where} \quad \Delta F^\dagger \equiv -k_B T \ln \left[ \frac{(q^\dagger / V)}{(q_A / V)(q_{BC} / V)} \right] + U^\dagger \tag{21.16}
\]

Thus, in general, the forward rate constant depends on the relative free energy of the transition state complex.

In some cases, the assumption that half of the molecules at the transition state make it to the product state turns out to be poor, with fewer molecules passing over the saddle point than this ideal case. For such instances, a correction factor is usually introduced called a \textbf{transmission coefficient}, \( \kappa \). The transmission coefficient simply corrects for deviations from this 50% probability. As such, the rate coefficient is then defined:

\[
\text{reaction rate} = k_f \rho_A \rho_{BC} \quad \text{where} \quad k_f \equiv \kappa \frac{(q^\dagger / V)}{(q_A / V)(q_{BC} / V)} \left( \frac{k_B T}{h} \right) \exp\left[ -\beta U^\dagger \right] \tag{21.17}
\]

### 21.4 General considerations for rates of rare event molecular processes

The above considerations were applied to a specific chemical reaction, in order to determine its reaction rate. However, the ideas that were used to find the rate—involving the PEL and hopping over a saddle point—can be applied to many rate problems, including non-reactive ones. For example, transition state theory can be applied to the rate at which molecules hop from one adsorption site on a surface to another, the rate of propagation of crystal defects, or the rate of noncovalent binding.
The general idea of transition state theory is to find a reaction coordinate $\xi$ for the process of interest that takes the system along the most likely kinetic trajectory. The coordinate must be well-defined so that it has a definite value for any given microscopic configuration, or equivalently, any location on the PEL. It is usually defined so that it varies between 0 and 1 as the system moves from “reactants” to “products”. Typically this coordinate follows the trajectory of lowest potential energy on the PEL. In general, however, determining the appropriate reaction coordinate for a molecular process is a challenging task and is the subject of much modern research.

If a particular form of $\xi$ in the landscape can be identified, it becomes possible to construct a free energy along $\xi$. Essentially, one divides up the total partition function (and hence the free energy) into contributions from parts of the landscape that correspond to different values of $\xi$. In a conceptual sense, we write:

$$Q(T, V, N, \xi) = \sum_{\text{all } n} \exp(-\beta E_n) \delta_{\xi_n = \xi}$$

Here, the sum extends over all microstates of the system—all locations on the PEL. The delta function, however, selects out and only includes those points on the PEL where the reaction coordinate takes on a specified value. Summing this coordinate partition function over all possible values of $\xi$ gives back the usual canonical partition function:

$$\sum_{\xi} Q(T, V, N, \xi) = \sum_{\xi} \sum_{\text{all } n} \exp(-\beta E_n) \delta_{\xi_n = \xi}$$

$$= \sum_{\text{all } n} \exp(-\beta E_n) \sum_{\xi} \delta_{\xi_n = \xi}$$

$$= \sum_{\text{all } n} \exp(-\beta E_n)$$

$$= Q(T, V, N)$$

Thus we can define a free energy along $\xi$ as follows:

$$A(T, V, N, \xi) = -k_B T \ln Q(T, V, N, \xi)$$

This free energy corresponds to a partition sum over all degrees of freedom orthogonal to the coordinate $\xi$.

Most PELs are continuous, and so the sums in these expressions really entail integrals, and the Kronecker delta functions become Dirac delta functions. Conceptually, the properties of the coordinate partition function are no different. The general expression is:

$$Q(T, V, N, \xi) = \frac{1}{N(T)^{3N} N!} \int \delta[\xi(\mathbf{r}^N) - \xi] e^{-\beta U(\mathbf{r}^N)} d\mathbf{r}^N$$
\[ Q(T, V, N) = \int Q(T, V, N, \xi) d\xi \]

where the function \( \tilde{\xi}(r^N) \) returns the value of the reaction coordinate for any particular configuration \( r^N \).

The probability that the system is at a particular value of the reaction coordinate is given by a ratio of the partition functions:

\[
\varphi(\xi) = \frac{Q(T, V, N, \xi)}{Q(T, V, N)} = \exp[-\beta A(\xi)] \tag{21.22}
\]

In the second line, we have just suppressed the dependence on all variables but the reaction coordinate. Usually, we will find that this probability has a minimum value (due to a maximum in \( A(\xi) \)) at some value \( \xi^\ddagger \). This is the transition state. It is a bottleneck in the probability of the system in going from \( \xi = 0 \) to \( \xi = 1 \).

The major assumption of the previous derivation was that the transition state is in equilibrium with the reactant state. We can invoke a similar argument here, in terms of probabilities:

\[
\frac{\varphi(\xi = \xi^\ddagger)}{\varphi(\xi = 0)} = \exp[-\beta A(\xi^\ddagger) + \beta A(0)] \tag{21.23}
\]

This just says that we have the equilibrium probabilities at each state, given by the ratio of the partition functions.

The next assumption is that the bottleneck probability at the transition state is the key factor that determines the rate at which the system can pass from \( \xi = 0 \) to \( \xi = 1 \). We assume that the rate of the molecular process is given by the probability the system is at the transition state times the rate at which it leaves it to go to the products. Typically, this latter quantity depends linearly on the temperature, since \( T \) determines the average velocities of all the particles, and hence the average speed with which the system traverses the PEL. Therefore, we write a general expression,

\[
\text{rate} = f(T) \exp[-\beta \Delta A^\ddagger] \tag{21.24}
\]

where \( \Delta A^\ddagger \equiv A(\xi^\ddagger) - A(0) \) and \( f(T) \) is a function of temperature, typically linear in \( T \). In this way, we see how the free energies of the system can dominate the rate of the molecular process, since they appear in the exponential. The prefactor of \( f(T) \) is usually needed to give quantitative agreement, but it is the difference in free energy between the transition state and the reactants that dominates the magnitude of the rate.

Free energies play a strong role in determining the kinetics of molecular processes because they determine the bottleneck probabilities of
When does this simple transition state picture break down? This occurs when the assumption of equilibrium at the transition state cannot be made, and the probability that the system will cross it is strongly correlated with the specific trajectory it is on. Moreover, there are molecular processes which proceed, not by crossing a single barrier with high energy, but by crossing a very large number of small barriers. Similarly, some processes do not take a single trajectory from reactant to product, but can follow one of a highly degenerate number of trajectories.

One case of a system that is not well described by classical transition state theory is that of protein folding. Starting from a “denatured” state corresponding to one of many disorganized conformations, a protein will spontaneously fold to a single, native structure that is the conformation of lowest free energy. Much research has focused on understanding the factors that determine the rate at which proteins fold. In contrast to the previous considerations, the folding process corresponds to moving from a large number of conformations (a broad space in the PEL) to a single conformation. This is because the denatured state includes many possible conformations. Because of this degeneracy, the starting point and ultimate folding pathway can vary each time a protein folds. Therefore, an approach different from classical transition state theory is needed to treat the many possible pathways.

One way of representing the folding process for a protein is to draw a “funnel” diagram. This diagram replaces the simple two-dimensional reaction coordinate diagram for simple chemical reactions. It shows that as the protein folds, it goes from a high free energy state that is highly degenerate (the wide part of the funnel) to a low free energy state that is a single conformation (the native state). The ruggedness of the funnel represents free energy barriers along the way, which ultimately determine the folding rate.