AS.030.301 & AS.030.302
Physical Chemistry

"A theory is more impressive the greater the simplicity of its premises is, the more different kinds of things it relates, and the more extended its area of applicability. Therefore the deep impression which classical thermodynamics made upon me. It is the only physical theory of universal content concerning which I am convinced that, within the framework of the applicability of basic concepts, it will never be overthrown"
- Albert Einstein

"Quantum Mechanics quote"
- Some physicist probably

Sam Dawley

Johns Hopkins University

2021-2022

<div style="border:1px solid black; padding:20px; text-align:center;">

CONTENTS

</div>

II   Quantum Mechanics   **145**

FOREWORD

My goal here was to recreate everything a student needs to know for this class, *from the perspective of a student currently learning it.* Oftentimes there are topics Dr. Fried takes for granted cause he's been studying this stuff for years that went completely over my head during lecture and so understanding those things took a bit of extra thought. All of that extra thought I've transcribed here, in an effort to provide equally, if not more detailed explanations for the plethora of topics covered by thermodynamics.

I take no credit for any of the writing here. All of it was taken from Dr. Fried's lectures, the accompanying textbooks for the course, or other interesting books I've read. Although I didn't cite any sources *within* the text, I provided references at the end. In addition to the fact that I'm not taking credit for anything, I think I'm good as far as plagiarism goes. Also I just learned that technically the University owns all of the classes/lecture material(?) so I guess I'm just gonna hope that the University doesn't sue me.

- Sam

Part I

Thermodynamics and Kinetics

CHAPTER

1

SOME MATH

1.1 Power Series

A *power series*, a subclass of *geometric series*, is a summation with the general form

$$\sum_{k=0}^{n} ar^k = a + ar + ar^2 + ar^3 + \ldots \tag{1.1.1}$$

where a is the first term in the sequence and r is the *common ratio*.

In a closed form, the sum of an infinite power series where $n = \infty$ is given simply as

$$\sum_{k=0}^{\infty} ar^k = \frac{a}{1-r} \tag{1.1.2}$$

For finite series, however, more work is required to derive a closed form solution. Nevertheless, it can be done with only a small amount of algebra knowledge. Consider the following power series, beginning with $k = 1$[1]:

$$S = \sum_{k=1}^{N} r^k = r + r^2 + r^3 + \cdots + r^N$$

$$rS = r\sum_{k=1}^{N} r^k = r^2 + r^3 + r^4 + \cdots + r^{N+1}$$

Taking the difference between these two series affords

$$rS - S = r^2 + r^3 + r^4 + \cdots + r^{N+1} - (r + r^2 + r^3 + \cdots + +r^N)$$

$$(r-1)S = r^{N+1} - r$$

$$S = \frac{r(r^N - 1)}{r - 1}$$

---

[1] We begin with $k = 1$ here only because in a later section when I reference power series the summation begins with 1 instead of 0. Hence, doing that here will be most beneficial. The closed form solution may look slightly different for $k = 0$ as the beginning, however, who cares.

Thus, we see that a closed form solution for a finite power series can be represented as

$$\sum_{k=1}^{N} r^k = \frac{r(r^N - 1)}{r - 1} \tag{1.1.3}$$

1.2   Gaussian Integrals

A *Gaussian integral* is defined as (and equal to)

$$\int_{-\infty}^{\infty} e^{-x^2} dx = \sqrt{\pi}$$

A standard method of proving the converge of this integral to $\sqrt{\pi}$ is to first make use of the property that

$$\left(\int_{-\infty}^{\infty} e^{-x^2} dx \right)^2 = \left(\int_{-\infty}^{\infty} e^{-u^2} du \right) \left(\int_{-\infty}^{\infty} e^{-v^2} dv \right) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-(u^2+v^2)} du dv$$

After squaring both sides we've created a situation where our result could be either positive *or* negative. However, since the function we are integrating is nonnegative on all of $\mathbb{R}$, we do not need to worry about our answer being negative because our function is necessarily positive. From here, we can make a variable substitution into *polar coordinates*, allowing $r^2 = u^2 + v^2$. With this substitution, we have new constants of integration. Since r is defined to be positive, $0 \le r < \infty$. Also, since u and v can take on any value in the real numbers, θ must range from $0 \le \theta \le 2\pi$. Additionally, recall that the Jacobian for a transformation into polar coordinates is r. Thus, our new double integral becomes

$$\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-(u^2+v^2)} du dv = \int_0^{2\pi} \int_0^{\infty} e^{-r^2} r dr d\theta$$

which can be evaluated to afford a solution:

$$\int_0^{2\pi} \int_0^{\infty} e^{-r^2} r dr d\theta = \int_0^{2\pi} \left[\frac{-e^{-r^2}}{2} \right]_0^{\infty} d\theta$$
$$= \int_0^{2\pi} \left(\frac{1}{2} \right) d\theta$$
$$= \frac{2\pi}{2} = \pi$$

With this, we've shown that the square of our integral is π and therefore the integral in question evaluates to $\sqrt{\pi}$. This approach to solving the Gaussian integral can be used for any Gaussian integral, just be sure to keep track of relevant scaling factors and physical constants. Also, this isn't the only way to go about evaluating this integral: In Section **??** I illustrate a method using the Gamma function. Moreover, some interesting techniques for illustrating the convergence of this integral can be found at `https://math.stackexchange.com/questions/34767/int-infty-infty-e-x2-dx-with-complex-analysis/34776#34776`

1.3 Stirling's Approximation

1.4 Lagrange's Method of Undetermined Multipliers

1.5 Natural Variables

1.6 Ergodicity

1.7 n-Dimensional Spheres

1.8 Combinations and Permutations

1.9 Poisson Point Process

1.10 Total Partial Differentials

As a motivating example, consider the our expression for the internal energy of a system,

$$U = q + w$$

The differential form of this equation becomes

$$dU = dq + dw = TdS - PdV$$

after substituting exact differentials for dq and dw. We can express dU in terms of its *total partial differential* and relate the partial derivatives of U to physical quantities:

$$dU = \left(\frac{\partial U}{\partial S}\right)_V dS + \left(\frac{\partial U}{\partial V}\right)_S dV = TdS - PdV \tag{1.10.1}$$

Above, notice that the partial derivatives of U were chosen so that they coincided with the differential terms dS and dV. That is, for a tiny change in either entropy or volume there was a tiny change in U and so U must vary with both of these variables, in contrast to T and P which do not incite a change in U. Clearly, then, we have the relationships

$$\left(\frac{\partial U}{\partial S}\right)_V = T \quad \& \quad \left(\frac{\partial U}{\partial V}\right)_S = -P \tag{1.10.2}$$

which illustrates the usefulness of a state function's total partial differential.

More generally, we can describe the total partial differential of a function $f : \mathbb{R}^n \to \mathbb{R}$

$$df = \sum_{i=1}^{n} \left(\frac{\partial f}{\partial x_i}\right) dx_i = \left(\frac{\partial f}{\partial x_1}\right) dx_1 + \left(\frac{\partial f}{\partial x_2}\right) dx_2 + \left(\frac{\partial f}{\partial x_3}\right) dx_3 + \dots \tag{1.10.3}$$

Physically, this expression is illustrating how the function f changes with differential changes in each of its variables $x_1, \dots, x_n$, which are referred to as the *natural variables* of f.

This statement is analogous to the chain rule in calculus. Interestingly the natural variables $x_1, \dots, x_n$ were functions of some other parameter (maybe they change with time) then their differential changes would depend on the time t, that is, $dx_i/dt \neq 0$. So, the *total derivative* of f with respect to time becomes

$$df = \sum_{i=1}^{n} \left(\frac{\partial f}{\partial x_i}\right) \frac{dx_i}{dt} = \left(\frac{\partial f}{\partial x_1}\right) \frac{dx_1}{dt} + \left(\frac{\partial f}{\partial x_2}\right) \frac{dx_2}{dt} + \left(\frac{\partial f}{\partial x_3}\right) \frac{dx_3}{dt} + \dots \tag{1.10.4}$$

which looks *a lot* like the chain rule. It's almost as if we "divided" by t in the total partial differential.

1.11   State Functions

1.12   Transfer Matrices

CHAPTER

2

THE LAWS OF THERMODYNAMICS

The laws of thermodynamics put restrictions on how thermodynamic variables change when a system and its surroundings change. These restrictions include, but are not limited to, the flow of energy and the distribution of temperature in a material. In chemical reactions, the first and second laws determine the equilibrium positions of reactions.

Thermodynamics can be treated purely from a macroscopic point of view, treating its laws as being stated in terms of macroscopic variables and measurable properties. This approach is usually referred to as *classical thermodynamics*. Another approach is to derive the macroscopic behavior from a statistical treatment of the atoms and molecules composing the system, called *statistical thermodynamics*.

2.1 The First Law

One popular description of the first law is simply, *energy is conserved*. That is, energy can neither be created nor destroyed. For an isolated system, this result clearly holds. For more complicated processes, the internal energy of a system may increase or decrease but held in the context of the overall change in energy of the system and surroundings, the overall change in energy is zero. In other words, the change in energy of a system is exactly equal to the opposite change in energy of the surroundings.

The first law is sometimes represented with a statement that energy of the system can be changed either by heat or by work, and different combinations of heat and work can bring about a change of state[1].

The statement of the first law in equation can be expressed elegantly, as

$$U = q + w \tag{2.1.1}$$

with U representing the internal energy of the system, w the work done *on* the system, and q the heat *absorbed* by the system. That is, $w < 0$ when the system does work. It's also commonly expressed in its differential form.

$$dU = dq + dw \tag{2.1.2}$$

with dU as an exact differential whereas dq and dw are inexact differentials and dependent on the path. This

---

[1] In fact, it was Joule who discovered heat and work were both forms of energy. Prior to the early 1800's, heat and work were thought to be completely distinct ideas

fact that heat and work are *inexact* differentials is immensely important. A system at equilibrium possesses a uniquely determined amount of internal energy, but it makes no sense to talk about a system possessing a unique amount of heat or a certain amount of work.

2.2   The Second Law

The second law of thermodynamics establishes the concept of entropy as a state function and applies its physical properties to the direction of spontaneous change for a thermodynamic process. In particular, the second law helps us determine the spontaneity of processes, in contrast to the first law which says nothing about the direction of thermodynamically favorable change for a reaction. The importance of the second law cannot be understated. In fact, Arthur Eddington, an English physicist and mathematician, wrote the following in 1927:

> If someone points out to you that your pet theory of the universe is in disagreement with Maxwell's equations—then so much the worse for Maxwell's equations. If it is found to be contradicted by observation—well these experimentalists do bungle things sometimes. But if your theory is found to be against the second law of thermodynamics I can give you no hope; there is nothing for it but to collapse in deepest humiliation.

Analytically, the second law of thermodynamics can be expressed simply as

$$dS \geq 0 \tag{2.2.1}$$

where S is the entropy of the universe. More generally, the second law tells us that the entropy change for an isolated system must be positive [2]. Naturally, reversible processes neither increase nor decrease entropy. If one direction *decreased* entropy, then that direction would violate the second law.

As we'll come to see, the second law of thermodynamics puts a limit on the efficiency of engines that accept heat energy and output work. As a rough example, consider a power plant which accepts energy in the form of heat to be powered. In reality, only about 30% of the heat energy accepted by one of these plants is used as work and therefore 70% of it must be rejected at a lower temperature. In practice, this heat is typically absorbed by water and oftentimes taken from a natural source such as a river or lake. In this case, the resulting increase in temperature of the water reservoir has significant effects on aquatic life and has come to be known as "thermal pollution."

2.2.1   The Numerous Restatements and Corollaries of the Second Law

We know that entropy is a state function and therefore the entropy change for a reversible process is the same as the irreversible process with identical initial and final states. Thus,

$$\Delta S = \int \frac{dq_{rev}}{T} > \int \frac{dq_{irr}}{T} \tag{2.2.2}$$

since q_{rev} is strictly greater than q_{irr}. Then, we have that

$$\Delta S \geq \int \frac{dq}{T} \tag{2.2.3}$$

where the equality holds for a reversible transformation but is a strict inequality for an irreversible transformation. This is known as the *Clausius Inequality*.

The Clausius inequality is one example of a restatement of the second law. Here are a few more:

---

[2]We can think of the entire universe as an isolated system, which is why we can make the broad statement that the entropy of the universe is always increasing

In sticking with the theme of the legend himself Rudolf Clausius, we turn to the Clausius and Kelvin statements of the second law. These statements give the direction of spontaneous change for a transformation, either through heat flow or through the work done by heat engines. Although seemingly unrelated at first, these two statements imply one another. That is, if we can prove one the proof of the other is trivial. The Clausius statement of the second law is

> No process is possible where the sole result is transfer of heat from a body at lower temperature to a body at higher temperature.

The Kelvin statement of the second law is

> No process is possible where the sole result is absorption of heat from a reservoir and its complete conversion to work.

An important corollary to these statements is the following:

> Systems can spontaneously undergo processes that decrease entropy, but this must be counteracted by an increase in entropy of the surroundings.

That is, it is certainly possible for systems to spontaneously become more ordered, but only when the surroundings become less ordered to an equal or greater extent. An alternative (and potentially more useful way of phrasing this result) is that

> Any spontaneous (irreversible) process that occurs in isolation must be associated with increasing entropy.

In order to understand the Kelvin statement of the second law of thermodynamics (and therefore also the Clausius statement) and develop a connection to entropy, we'll need to understand heat engines and the Carnot cycle, which are covered in Section 4.4.1.

Another (arguably even more convoluted) restatement of the second law is *Planck's statement of the second law*, put forth as follows:

> It is impossible to devise a machine whose only effects are the removal of heat from a reservoir and the performance of work.

Okay this the last restatement of the second law I promise: Caratheodory[3] formulated the second law of thermodynamics not based on physical quantities such as heat but instead through the axiomatic principle of irreversibility in thermodynamics:

> In the neighbourhood of any initial state, there are states which cannot be approached arbitrarily close through changes of state.

In this statement he went on to coin the term *adiabatic accessibility*, the principle that two states X and Y are said to be "adiabatically accessible" if X can be transformed to Y without the system suffering from the transfer of energy as heat or matter[4]

2.2.2 Schrödinger's "Paradox"

According to the second law, all isolated systems are expected to reach a system of maximum disorder after a long enough time has passed. Since life approaches and maintains a highly ordered state some argue that this seems to violate the aforementioned law, implying a paradox. Schrödinger, however, pointed out that the biosphere is *not* an isolated system and that there is an increase in entropy in the surroundings as a result of the loss of heat to an organism's environment. By this mechanism, the second law is obeyed and life maintains a highly ordered state which is sustained by an increase in disorder of the universe.

In order to increase order on earth, as life does, organisms harness the free energy provided by the sun.

---

[3]Constantin Caratheodory was a Greek mathematician who contributed to everything from complex analysis to thermodynamics. To quote some old German book about him, "He was remembered by his colleagues as a respectable and cultured man'.'

[4]Obviously the principle is more technical than this but it's way beyond anything that we would ever need to know for this class.

2.3 The Third Law

The third law of thermodynamics concerns itself with the convergence of the entropy of a system. In particular, the behavior of substances at *absolute zero*, or zero Kelvin. In words, the third law can be written as

The entropy of a system is zero at absolute zero.

Pretty simple. Microscopically, this result agrees with our intuition about entropy. Consider the Boltzmann equation, $S = k_B \ln W$ where W is the number of microstates for a system. For a system at absolute zero, by definition there is no kinetic energy among atoms or molecules and therefore no movement. Then, the number of microstates reduces to one and entropy reduces to zero.

Interestingly, there exists a formulation of the third law which approaches the subject by postulating the behavior of energy:

If the composition of two thermodynamic systems constitutes an isolated system, then any energy exchange between the two systems is bounded.

Sometimes the third law is referred to as *Nernst's Thereom* because he was the first person to postulate a result like this. If we wanted to be as general as possible about the third law, assuming nothing about the behavior of atoms and molecules at absolute zero, then we could write alternatively that at absolute zero the entropy of a system is a well-defined constant and is determined by the degeneracy of the ground state of the system.

After the development of statistical mechanics, the third law of thermodynamics went from being a *fundamental law* to a *derived law*, as the result that substances at absolute zero have zero entropy is a consequence of the Boltzmann equation.

CHAPTER

3

STATE FUNCTIONS AND THEIR STATE VARIABLES

State functions are path independent functions, meaning that their values can be defined for a specific set of conditions. Examples of some common thermodynamic state functions include the internal energy U and the enthalpy H. An important property of state functions is that they enjoy the equality of mixed partial derivatives. This property will be of great use when we derive the Maxwell relations.

The *state variables* of a state function are those which are necessary to completely describe the value of a state function. Typically, the variables which we'll be interested in are temperature, pressure, and volume.

For reactions containing more than one chemical species, we are often interested in the *molar quantity*, denoted $\tilde{X}$, and *partial quantity*, denoted X_i of a particular species. The molar quantity is the amount of a particular extensize thermodynamic quantity contributed *per mole*, and the partial quantity is the amount of a particular thermodynamic quantity contributed by *one substance*. Using these definitions, we can define a *partial molar quantity* as $\tilde{X}_i$ which represents the amount of a particular thermodynamic quantity contributed per mole by one substance in a mixture.

3.1 Internal Energy

The internal energy of a system is conserved, forming the basis of the first law of thermodynamics. It is characterized by the heat absorbed and the work done on a system. Mathematically, it can be expressed as

$$U \equiv q + w \tag{3.1.1}$$

We could also get more technical with our expression for the internal energy and write it in a differential form,

$$dU = dq + dw \tag{3.1.2}$$

or an integrated form

$$\Delta U = \int dq + \int dw \tag{3.1.3}$$

11

Although the internal energy is the sum of two path dependent quantities (heat and work), by itself it is a state function meaning that ΔU along a closed curve (i.e., the initial and final states are the same) is equal to zero.

The natural variables of internal energy are V and S. This implies that at a constant volume and entropy, the internal energy of a system is an indicator of spontaneity.

This relationship can be shown using the differential form of the First Law:

$$
\begin{aligned}
dU &= dq + dw \\
&\leq TdS - PdV \\
&= \left(\frac{\partial U}{\partial S}\right)_V dS + \left(\frac{\partial U}{\partial V}\right)_S dV
\end{aligned}
\tag{3.1.4}
$$

Note that we'll use an equality and assume that this transformation is reversible. Here, we'll take a moment to gaze at Equation (3.1.4). Considering the inequality, dU acts as a useful potential when dS and dV are zero, that is, when S and V are fixed. When this happens, the direction of spontaneous change is the one which *decreases* internal energy (this direction is the one consistent with the Second Law of Thermodynamics). Moreover, when $dU = 0$ the system has reached equilibrium.

Here would be a good time to point out the contrast between determining spontaneity in thermodynamic systems and simple mechanical systems. Why is it that when we talk about spontaneity in thermodynamic systems we use Gibbs free energy but when we talk about spontaneity for mechanical systems we can get away with talking about just the energy?

For simple mechanical systems, we are typically interested in situations involving only a few objects: A ball rolling down a hill, an object rotating about an axis, or a projectile being launched off a cliff, to name a few. In these cases, the entropy of the system barely changes (if at all) and can therefore be treated as constant. In a similar vein, the volume of these systems doesn't change whatsoever. Then, as we've already posited, when entropy and volume are constant then the internal energy of a system will be an indicator of spontaneity.

In contrast, for thermodynamic systems the entropy of a transformation is nearly impossible to hold constant (still possible, just *nearly* impossible). For a chemical reaction, the expansion of a gas, the mixing of two substances, the entropy is always changing. Moreover, the volume changes in many of these transformations as well. Thus, we see that the internal energy of a substance is a very poor indicator of spontaneity for thermodynamic systems because of its *natural variables*.

State functions acting as potentials under certain conditions will be a common theme as we analyze different types of free energy. Alright, now we can return to our analysis of the internal energy:

In the last line after Equation (**??**) is the total partial differential of U and is there to (hopefully) clearly illustrate the relationships

$$
\left(\frac{\partial U}{\partial S}\right)_V = T \quad \& \quad \left(\frac{\partial U}{\partial V}\right)_S = -P
$$

Then, by the equality of mixed partial derivatives, we have

$$
\begin{aligned}
\frac{\partial}{\partial V}\left(\frac{\partial U}{\partial S}\right)_V &= \frac{\partial}{\partial S}\left(\frac{\partial U}{\partial V}\right)_S \\
\left(\frac{\partial T}{\partial V}\right)_S &= -\left(\frac{\partial P}{\partial S}\right)_V
\end{aligned}
\tag{3.1.5}
$$

Which is one of the four Maxwell relations.

3.2   Enthalpy

The enthalpy is defined as

$$
H \equiv U + PV
\tag{3.2.1}
$$

and was created just because we needed a state function with a differential equal $dU + PdV$ at a constant pressure. The enthalpy can be thought of as the internal energy plus the cost of pushing back the universe to make a hole in which to place (or expand) the system. Enthalpy is useful for analyzing the thermodynamics of systems *at constant pressure*. At a constant pressure, the total partial differential of H becomes

$$dH = \left(\frac{\partial H}{\partial U}\right)_{P,V} dU + \left(\frac{\partial H}{\partial P}\right)_{V,U} dU + \left(\frac{\partial H}{\partial V}\right)_{P,U} dV$$
$$= dU + PdV$$

and by the First Law of Thermodynamics we can say that $(dH)_P = (dq)_P$. Why did we go to all this trouble? Recall that we define the heat capacity at a constant pressure as $dq/T = C_p$. Thus,

$$C_p = \left(\frac{\partial H}{\partial T}\right)_P \tag{3.2.2}$$

I think I do this derivation somewhere else in these notes too.

We'll quickly jump back to the total partial differential of the enthalpy, this time deriving it from how we define H:

$$H = U + PV$$
$$dH = dU + d(PV)$$
$$= dq + dw + PdV + VdP$$
$$\leq TdS - PdV + PdV + VdP$$
$$\leq TdS + VdP \tag{3.2.3}$$
$$= \left(\frac{\partial H}{\partial S}\right)_P dS + \left(\frac{\partial H}{\partial P}\right)_S dP$$

Equation (3.2.3) indicates that under conditions with *constant entropy and pressure*, enthalpy acts as an indicator of spontaneity. In particular, if $dH < 0$ in these conditions, the transformation is spontaneous. Similar to when we talked about internal energy, this is the direction which obeys the Second Law of Thermodynamics. Moreover, if $dH = 0$ under these conditions we know that we've achieved equilibrium.

For now, however, we'll substitute an equality and assume the transformation is reversible. Thus, we see that the natural variables of enthalpy are P and S so that $H(P, S)$. Notice that

$$\left(\frac{\partial H}{\partial S}\right)_P = T \quad \& \quad \left(\frac{\partial H}{\partial P}\right)_S = V$$

so that by the equality of mixed partial derivatives,

$$\frac{\partial}{\partial P}\left(\frac{\partial H}{\partial S}\right)_P = \frac{\partial}{\partial S}\left(\frac{\partial H}{\partial P}\right)_S$$
$$\left(\frac{\partial T}{\partial P}\right)_S = \left(\frac{\partial V}{\partial S}\right)_P \tag{3.2.4}$$

which is one of the four Maxwell relations.

3.3   Entropy

Entropy is a physical property of a system that corresponds to randomness, disorder, or uncertainty. Typically, entropy is defined in the context of the second law of thermodynamics at the macroscopic level, but it can also be viewed from the microscopic level using the Boltzmann equation. Macroscopically, we define the

entropy as

$$dS \equiv \frac{dq_{rev}}{T} \tag{3.3.1}$$

where dq_{rev} is the heat absorbed by a system during a reversible transformation. Since entropy is a state function, however, we can define it for both reversible and irreversible processes:

$$\Delta S_{rev} = \Delta S_{irr} = \int \frac{dq_{rev}}{T} \tag{3.3.2}$$

Then, if asked to compute the entropy involved in an irreversible process, we can go about computing the entropy for the reversible process which has identical initial and final states.

Here, recall the important result that the heat absorbed by a system for a reversible process is always less than that for an irreversible process. That is, $q_{rev} > q_{irr}$. This implies that

$$\Delta S_{rev} = \Delta S_{irr} = \frac{dq_{rev}}{T} > \frac{dq_{irr}}{T} \tag{3.3.3}$$

and we obtain the *Clausius inequality*, a restatement of the second law of thermodynamics:

$$\Delta S \geq \int \frac{dq}{T} \tag{3.3.4}$$

This expression is an equality for a reversible process and a strict inequality for a irreversible process.

The Clausius inequality has some major implications. For an adiabatic process (or an isolated system), $dq = 0$ and therefore $\Delta S \geq 0$. This inequality forms the basis of the second law of thermodynamics. Since the universe as a whole can be considered an isolated system we can make the broad claim that *the entropy of the universe never decreases.*

A potentially more helpful way of phrasing this result is that *any spontaneous (irreversible) process that occurs in isolation must be associated with an increase in entropy.* Naturally, reversible processes neither increase nor decrease entropy. If one direction were to increase entropy the corresponding reverse reaction would be associated with a decrease in entropy and would therefore violate the second law.

Another important corollary to these statements is that *systems can spontaneously undergo processes which decrease the entropy of the system as long as the transformation increases the entropy of the surroundings to an equal or greater extent.*

As we noted above, since entropy is a state function the total change in entropy for the system remains the same for a reversible and irreversible transformation as long as the transformations have the same initial and final states. Naturally we can ask the question, how does the entropy change for the *surroundings* differ for a reversible transformation versus an irreversible one, if at all?

Recall that the heat absorbed by a system in a reversible reaction is strictly greater than the heat absorbed in the corresponding irreversible reaction. That is, $q_{rev} > q_{irr}$. Therefore, for an irreversible reaction, some of the energy of the system must be *lost* to the surroundings as heat. Then, $dq_{sur,irr} > 0$ and therefore $dS_{surr} > 0$. Thus, *the entropy change for the surroundings is greater during an irreversible reaction than it is for the corresponding reversible reaction.*

3.3.1 Entropy Change for Four Fundamental Changes of State

As we've mentioned previously, although the entropy is defined for reversible processes, we can use that definition for any sort of change of state because entropy is a state function. In fact, we can find the change in entropy for our four favorite transformations of state. Here they are without justification:

Entropy Changes for Fundamental Transformations

Reversible *Isochoric* Change of State	$\Delta S = C_V \ln\left(\frac{T_f}{T_i}\right)$
Reversible *Isobaric* Change of State	$\Delta S = C_P \ln\left(\frac{T_f}{T_i}\right)$
Reversible *Isothermal* Change of State	$\Delta S = nR \ln\left(\frac{V_f}{V_i}\right)$
Reversible *Adiabatic* Change of State	$\Delta S = 0$

Now here are their justifications:

1. *Reversible Isochoric Process.* Here, volume is fixed and reversibility is achieved by raising the temperature of the surroundings slowly, allowing heat to flow into the system to maintain thermal equilibrium.

   For an isochoric process, $w = 0$ and so all of the internal energy of a system is in the form of heat. Thus,

   $$dq_{rev} = dU = C_V dT$$

   and so we can evaluate the change in entropy as

   $$\Delta S = \int \frac{dq_{rev}}{T} = \int_{T_i}^{T_f} \frac{C_V dT}{T} = C_V \ln\left(\frac{T_f}{T_i}\right) \tag{3.3.5}$$

   (note that we can factor C_V out of the integral for ideal gasses because it will never vary with temperature).

   Notice, unlike heat flow which increases linearly as T_f increases in constant pressure expansion, entropy increases logarithmically.

2. *Reversible Isobaric Process.* Recall that reversible isobaric expansion involves substantial heat flow into the system in order to keep the pressure of the system matched with the constant pressure of the surroundings.

   To evaluate the entropy change of reversible isobaric heating we'll quickly derive a relationship between heat flow and temperature change. Recall that we define the enthalpy as $H = U + PV$. Then,

   $$dH = dU + d(PV) = dq_{rev} + dw_{rev} + PdV + VdP$$
   $$= dq_{rev} - PdV + PdV + 0$$
   $$= dq_{rev}$$

   In step 2 we made the substitution $dw = -PdV$ and also $VdP = 0$ because the transformation is isobaric. Additionally, recall that $dH = C_P dT$. So, the change in entropy can be computed as

   $$\Delta S = \int \frac{dq_{rev}}{T} = \int_{T_i}^{T_f} \frac{C_P dT}{T} = C_P \ln\left(\frac{T_f}{T_i}\right) \tag{3.3.6}$$

   For an ideal gas, we can rewrite this as

   $$\Delta S = C_P \ln\left(\frac{V_f}{V_i}\right) \tag{3.3.7}$$

   which shows how the largest entropy changes occur during expansions when the system is highly compressed. Similar to isochoric heating, whereas heat flow increases linearly with a constant pressure, entropy increases logarithmically. However, the proportionality constants differ, as $C_P > C_V$. Thus, a given temperature increase at a constant pressure results in a larger entropy increase than at a constant volume.

3. *Reversible Isothermal Process.* For ideal gasses, $\Delta U = 0$ which implies that $dq_{rev} = -dw_{rev}$. Fortunately, we have an expression for dw_{rev}, allowing us to compute the change in entropy with relative ease:

$$\Delta S = \int \frac{dq_{rev}}{T} = \int \frac{-dw_{rev}}{T} = \int \frac{PdV}{T}$$
$$= \int \frac{nRTdV}{VT}$$
$$= nR \int_{V_i}^{V_f} \frac{dV}{V}$$
$$= nR \ln\left(\frac{V_f}{V_i}\right) \tag{3.3.8}$$

4. *Reversible Adiabatic Heating.* As long as adiabatic expansion is reversible, Equation (3.3.2) requires that there is no change in entropy since $dq_{rev} = 0$ along the entire adiabat. Because entropy remains constant, reversible adiabatic transformations can be regarded as *isentropic*.

What about the entropy change for irreversible transformations? Let's consider the irreversible expansion of a gas against a vacuum. Above we identified that entropy change for the reversible isothermal expansion of a gas to be

$$\Delta S = nR \ln\left(\frac{V_f}{V_i}\right)$$

What is different in the irreversible case where the external pressure is zero (the vacuum)? Firstly, there can be no work done on the surroundings because there is no external pressure. Secondly, there is no heat absorbed or emitted by the system because the surroundings are a vacuum. Hence, $\Delta U = 0$ (which is consistent with the isothermal reaction of an ideal gas) and the system must remain along an isotherm during this transformation, implying that PV is constant. Thus, for this irreversible expansion, we have that

$$\Delta S = nR \ln\left(\frac{V_f}{V_i}\right) = nR \ln\left(\frac{P_i}{P_f}\right)$$

Another important thing to note about this scenario which contrasts its reversible counterpart is the entropy change of the surroundings. For the reversible expansion, $\Delta S_{univ} = 0$ (as for any reversible process) because although the system absorbs heat as it expands ($\Delta S > 0$), it simultaneously does work on its surroundings ($\Delta S < 0$) and we're in accordance with the second law of thermodynamics.

For the irreversible transformation, however, the expansion against a vacuum can be though of as an isolated system (a vacuum is nothing, after all). Thus, there are no surroundings to counteract the positive change in entropy of the system and therefore

$$\Delta S_{sys} = \Delta S_{univ} > 0$$

which is consistent with the process being spontaneous.

3.3.2   The Microscopic View of Entropy

So far we've dealt with entropy from a macroscopic level, considering heat flow through a system. A far more profound definition for entropy comes from statistical mechanics in the form of the Boltzmann equation. Mathematically, it can be expressed as

$$S = k_B \ln \Omega \tag{3.3.9}$$

where $k_B = R/N_A \approx 1.381 \times 10^{-23}$ J/K is the Boltzmann constant and Ω is the number of microstates for a system. Interestingly, this equation is engraved on Ludwig Boltzmann's tombstone in Vienna, Austria.

Let's consider the simplified example of the expansion of a gas in a lattice: For a lattice with L spaces available to occupy and N total molecules within the lattice, there are

$$\binom{L}{N} = \frac{L!}{N!(L-N)!}$$

total ways to arrange the (indistinguishable) molecules. Considering the expansion of a gas, we can think of the initial volume containing L_1 lattice cells and the final volume containing L_2 lattice cells. The change in entropy can be computed using the Boltzmann equation:

$$\Delta S = S_f - S_i = k_B \ln \binom{L_2}{N} - k_B \ln \binom{L_1}{N}$$
$$= k_B \left[\ln \left(\frac{L_2! N! (L_1 - N)!}{N! L_1! (L_2 - N)!} \right) \right]$$
$$= k_B \ln \left(\frac{L_2!(L_1 - N)!}{L_1!(L_2 - N)!} \right)$$

This expression is not very computationally friendly. We can simplify this result using *Stirling's Approximation*,

$$\ln(x)! = x \ln x - x$$

which becomes more accurate as x becomes larger. There is a more technical version of this approximation but I'm not really concerned with that. Approximations are lame to begin with.

Let's apply this formula to our expression above (I'm gonna omit some of the algebra because I trust myself to be able to do it any other time):

$$\frac{\Delta S}{k_B} = \ln \left(\frac{L_2!(L_1 - N)!}{L_1!(L_2 - N)!} \right)$$
$$= \ln(L_2)! + \ln(L_1 - N)! - \ln(L_1)! - \ln(L_2 - N)!$$
$$\approx L_2 \ln(L_2) + (L_1 - N)\ln(L_1 - N) - L_1 \ln(L_1) - (L_2 - N)\ln(L_2 - N)$$
$$= L_2 \ln \left(\frac{L_2}{L_2 - N} \right) + L_1 \ln \left(\frac{L_1 - N}{L_1} \right) - N \ln \left(\frac{L_1 - N}{L_2 - N} \right)$$

In the majority of physical systems, a container of gas will be mostly empty so that $L_1, L_2 \gg N$ and we can simplify our approximation as

$$\frac{\Delta S}{k_B} \approx L_2 \ln \left(\frac{L_2}{L_2} \right) + L_1 \ln \left(\frac{L_1}{L_1} \right) - N \ln \left(\frac{L_1}{L_2} \right)$$
$$\Rightarrow \Delta S = k_B N \ln \left(\frac{L_2}{L_1} \right)$$

If we say that each lattice cell has volume V_L then $V_2 = L_2 V_L$ and $V_1 = L_1 V_L$ so that

$$\Delta S = k_B N \ln \left(\frac{V_2}{V_1} \right) = nR \ln \left(\frac{V_2}{V_1} \right) \tag{3.3.10}$$

which agrees exactly with our formulation for the entropy change at the macroscopic level. To make the final substitution above note that $N_A k_B = R$ and that $N_A = N/n$ where N is the number of molucules and n is the number of moles.

3.4   Free Energy

Free energy can be defined as the maximum amount of work a thermodynamic process can do at a constant temperature and its sign indicates whether or not the process is spontaneous (this is true for both the

Helmholtz and Gibbs free energy; both have temperature as a natural variable and are tied to the work done during a reaction).

The basic definition of free energy is a measure of a system's ability to cause change. Free energy, in slight contrast, is the measure of a system's ability to do work at a constant temperature, i.e., the "useful" energy.

3.4.1   Helmholtz Free Energy

The Helmholtz free energy [1] , defined before the Gibbs free energy, is defined as

$$A \equiv U - TS \tag{3.4.1}$$

and is an indicator of spontaneity for processes which occur at a constant volume and temperature, as indicated by the total partial differential of A:

$$dA = \left(\frac{\partial A}{\partial V}\right)_T dV + \left(\frac{\partial A}{\partial T}\right)_V dT \tag{3.4.2}$$

The Helmholtz free energy is useful for gas-phase reactions or for isolated systems kept at a constant volume. This is the main distinction between the Helmholtz and Gibbs free energies: While Helmholtz energy is useful for reactions at a constant volume, say, a transformation within a bomb calorimeter, the Gibbs energy is useful for transformations at a constant pressure where $\Delta H = q$.

3.4.2   Gibbs Free Energy

Gibbs free energy is defined as

$$G \equiv H - TS \tag{3.4.3}$$

and is an indicator of spontaneity for processes which occur at a constant pressure and temperature, as indicated by the total partial differential of G:

$$dG = \left(\frac{\partial G}{\partial P}\right)_T dP + \left(\frac{\partial G}{\partial T}\right)_P dT \tag{3.4.4}$$

The Gibbs free energy is an invaluable measure for thermodynamic processes, as most take place at a constant P and T. In fact, G is independent of the PdV work needed to "make space for additional molecules" and therefore equals the work *not* associated with system expansion or compression *at a constant temperature*. Hence, it has immense utility for solution-phase chemistry.

The quantities for each partial derivative of G can be found as follows:

$$
\begin{aligned}
dG = dH - d(TS) &= d(U + PV) - d(TS) \\
&= dU + d(PV) - d(TS) \\
&= dq + dw + PdV + VdP - TdS - SdT \\
&= TdS - PdV + PdV + VdP - TdS - SdT \\
&= VdP - SdT
\end{aligned}
$$

Thus, we find

$$\left(\frac{\partial G}{\partial P}\right)_T = V \quad \& \quad \left(\frac{\partial G}{\partial T}\right)_P = -S$$

---

[1]The designation A for the Helmholtz free energy comes from the German word for work, *arbeit*. This makes sense with the context that free energy is the maximum amount of work a process can do at a constant temperature.

3.5 Spontaneity

Any system that does not evolve over time is said to be at equilibrium. Otherwise, the direction of evolution is the *spontaneous direction. A spontaneous process will occur without additional work being done on the system.* Most spontaneous processes are irreversible, and the processes that are spontaneous and reversible must be spontaneous in both directions, in accordance with the second law of thermodynamics.

Spontaneity does not imply that the process occurs immediately. Rather, that it will occur with a very high probability once the barrier of change is overcome. Take the combustion of wood into carbon dioxide and water as an example. The process can only begin at very high temperatures but once it does it will proceed until all of the wood is used.

One of the driving forces behind a spontaneous process is the spreading out of energy as heat rather than through work. In developing a new state function that allows us to predict the direction of this energy dispersion, we can utilize the first law of thermodynamics. Because heat flow is a key factor in the spontaneous direction, we can write the first law as follows, for an ideal gas undergoing reversible changes to volume and temperature:

$$
\begin{aligned}
dq_{rev} &= dU - dw_{rev} \\
&= C_V(T)dT + PdV \\
&= C_V(T)dT + \frac{nRT}{V}dV
\end{aligned}
\tag{3.5.1}
$$

Recall that in order for a function to be a state function its mixed partial derivatives must be equal. So, let's test that:

$$
\left(\frac{\partial C_V(T)}{\partial V}\right)_T \neq \left(\frac{\partial(nRT/V)}{\partial T}\right)_T
$$

So close! Notice, however, that if we divide both sides of the equation by T we can make it so these partials are equal:

$$
\left(\frac{\partial C_V(T)/T}{\partial V}\right)_T = \left(\frac{\partial(nRT/VT)}{\partial T}\right)_T = 0
$$

Thus, dq_{rev}/T is a state function that we define as *entropy*:

$$
dS = \frac{dq_{rev}}{T}
\tag{3.5.2}
$$

In contrast to the macroscopic view of spontaneity mentioned above we can also discuss and analyze the *microscopic* view of spontaneity and see how the two approaches are connected.

As an example, consider a mixture of 1 mole of a unique molecule and 1 mole of a different molecule in a lattice where the members of each species are indistinguishable. If we distributed the molecules such that one species occupied one half of the box and the other species occupied the other half of the box then there would only be one microstate for the system. In contrast, if we allowed each species to occupy anywhere on the lattice (affording more of a "mixed" state), there are many more possible arrangements of molecules in space.

The microstates consistent with a description of "mixed" are not necessarily more likely to occur, however, there are vastly more arrangements that can be described as mixed than those that cannot. From a probability standpoint, then, the likelihood of being in the "mixed" state is much greater because of the number of arrangements that are mixed.

Thus, given enough time to explore all such microstates which are mixed or nonmixed, at equilibrium a system will be mixed because it is much more likely to occupy that state.

3.5.1 Criteria for Spontaneity

There are numerous criteria for spontaneity depending on the conditions of the system and which properties of a substance are being held constant, if any. Below is a table illustrating the different conditions and system

could be under and the corresponding indicator of spontaneity:

Criteria for Spontaneity

Indicator	Condition
$dS \geq 0$	Isolated system ($dq = dw = 0$)
$dU \leq 0$	Constant entropy S and volume V
$dH \leq 0$	Constant entropy S and pressure P
$dF \leq 0$	Constant volume V and temperature T
$dG \leq 0$	Constant pressure P and temperature T

As we can see from above, entropy is an indicator of spontaneity when the system is isolated, that is, when neither matter nor energy is exchanged between the system and its surroundings. This agrees with our intuition behind the second law of thermodynamics because the universe itself can be considered an isolated system. In reality, however, the reactions we deal with are not often isolated. So, we need a better indicator of spontaneity for most thermodynamic processes: Enter Gibbs free energy.

Okay I lied about Gibbs free energy entering I'm gonna make a quick aside first. Notice that under a constant *temperature* we should immediately focus on the free energy of a system. Meanwhile, under a constant entropy (which will pretty much only ever happen when considering mechanical systems) we'll shift our focus away from free energy and instead focus on the internal energy and enthalpy. These are easy rules to keep in mind, not as easy as when to use the entropy as an indicator of spontaneity though, which can be considered in nearly every case as having some effect on the spontaneity of a reaction. Now, enter Gibbs free energy.

As we can see from the table above, the Gibbs free energy is an indicator of spontaneity at a constant pressure and temperature, 2 variables which can be held constant for a thermodynamic system with relative ease. In fact, this is the case because the pressure and temperature are oftentimes interacting with the pressure and temperature of the surroundings which are more or less constant over the course of a reaction. Although we could use any of the other state functions to indicate spontaneity for *any* sort of process, there is oftentimes a clear choice as to which will be the best.

With this idea in mind, consider what might make a good indicator for a simple mechanical system, composed of a few moving parts. If you've taken an introductory physics class you'll know that we use the internal energy of a system U to indicate spontaneity in this case. Why? For a simple mechanical system, the entropy virtually does not change since the number of microstates are limited with so few "particles" ("particles" in this case being the macroscopic objects). Moreover, the volume of the system will likely not change (consider the example of rolling a ball down a hill; theres no volume change whatsoever here). Thus, the internal energy of the system will be a great indicator of spontaneity.

The relationships described above will be illustrated whilst deriving the Maxwell relations in the following section.

3.5.2 Some Spontaneity Questions

I've begun studying for finals. Here are some questions regarding spontaneity. For each scenario, state whether it is certainly, not necessarily, or certainly not spontaneous and provide a brief justification.

1. *Under constant temperature and pressure, an ideal polymer expands to its maximal extension.*   At a constant temperature and pressure we'll want to consider the Gibbs free energy associated with this process. Recall that we define the change in Gibbs free energy as

$$\Delta G = \Delta H - T\Delta S$$

   In the case of extension, we can assume that $\Delta H \ll \Delta S$ because although there might be some change in enthalpy due to changing intermolecular reactions, it is nowhere near the change in entropy.

Moreover, we know that the entropy change will large and negative since extension is associated with fewer arrangements and microstates. Then, by Boltzmann's equation, the entropy change will be negative. Hence, ΔG will be (potentially very) large and positive and this reaction will *certainly not be spontaneous.*

2. *Under a constant temperature, an ideal gas expands to its maximal volume.* This reaction is *certainly spontaneous.* First, just by using the example of what we observe in everyday life, we know that gasses expand to fill their containers (spontaneously). So, if I were to go into a Macy's and get sprayed by those people who spray the perfume, the perfume wouldn't just idly in the place I was standing, it would diffuse throughout the store! Figure 3.1 is provided for any visual learners.

Figure 3.1: Me running through a Macy's.

Now, a more thermodynamic approach. Notice that with the *expansion* of a gas, there will be a greater number of microstates associated with the final (larger) volume than with the initial (smaller) volume. Hence, by Boltzmann's equation we have that the change in entropy must be positive and therefore this reaction is always spontaneous.

Now, another more thermodynamic approach. Notice that this system is isolated so that we can use the entropy of the isothermal expansion to predict spontaneity. Then,

$$dS = \frac{dq}{T} = \frac{-dw}{T} = \frac{P_{ext}dV}{T} = \frac{nR}{V}dV$$
$$\Delta S = nR \int_{V_i}^{V_f} \frac{dV}{V}$$
$$= nR \ln\left(\frac{V_f}{V_i}\right)$$

Hence, the change in entropy is positive since $V_f > V_i$ and the reaction is certainly spontaneous.

3. *Under a constant temperature and pressure, a chemical reaction proceeds in which the products are more "ordered" than the reactants.* Constant temperature and pressure should immediately sound the alarm for using Gibbs free energy. Similar to the first question, recall that

$$\Delta G = \Delta H - T\Delta S$$

so that the Gibbs energy is dependent on two quantities, enthalpy and entropy. Now, for just a moment

consider the following two reactions:

$$2\text{Al}_{(s)} + \frac{3}{2}\text{O}_{2\,(g)} \longrightarrow \text{Al}_2\text{O}_{3\,(s)}, \quad \Delta\tilde{G}_f = -1.528 \text{ kJ/mol}$$

$$\text{Ag}_{(s)} + \frac{1}{2}\text{N}_{2\,(g)} + \frac{3}{2}\text{O}_{2\,(g)} \longrightarrow \text{AgNO}_{3\,(s)}, \quad \Delta\tilde{G}_f = 19.8 \text{ kJ/mol}$$
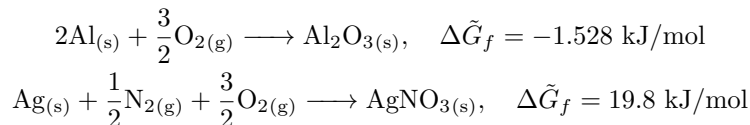
Clearly, both of these reactions have a decrease in entropy, based off of the number of products and their phases. However, the signs of the Gibbs free energies of formation are different! That is all to say, there can be a decrease in entropy for a chemical reaction which is spontaneous. Hence, this is *not necessarily spontaneous*.

4. *Under constant temperature and pressure, a chemical system where the species are at their equilibrium concentrations returns to the standard state conditions.* I mean I feel like this one is obvious. Clearly, work must be done on the system in order for it to progress *away* from equilibrium. In fact, if movement in one direction away from equilibrium were spontaneous and therefore movement in the other direction were not spontaneous, we'd be violating the second order of thermodynamics. Thus, this is *certainly not spontaneous*.

5. *At $T = 273.15$ K, water transforms entirely from liquid to solid.*

3.6   Maxwell Relations

The Maxwell relations are a system of partial differential equations which relate thermodynamic quantities which would typically be very difficult to measure. They can be derived from the equality of mixed partial derivatives and come from the definitions of the familiar thermodynamic potentials, U, H, F, and G.

It is important to note that these relations hold *for all reversible and irreversible processes*.

The four most common Maxwell relations utilize the definitions of the state functions named above. Here they are:

$$\frac{\partial^2 U}{\partial S \partial V} = \left(\frac{\partial T}{\partial V}\right)_S = -\left(\frac{\partial P}{\partial S}\right)_V \tag{3.6.1}$$

$$\frac{\partial^2 H}{\partial S \partial P} = \left(\frac{\partial T}{\partial P}\right)_S = \left(\frac{\partial V}{\partial S}\right)_P \tag{3.6.2}$$

$$\frac{\partial^2 F}{\partial T \partial V} = \left(\frac{\partial S}{\partial V}\right)_T = \left(\frac{\partial P}{\partial T}\right)_V \tag{3.6.3}$$

$$\frac{\partial^2 G}{\partial T \partial P} = \left(\frac{\partial S}{\partial P}\right)_T = -\left(\frac{\partial V}{\partial T}\right)_P \tag{3.6.4}$$

CHAPTER

4

HEAT AND WORK

4.1 Work

There are tons of ways work can be performed:

Work!

Type of Work	Intensive Variable	Extensive Variable	Differential Work, dw
Hydrostatic	Pressure, P	Volume, V	$-P_{ext}dV$
Surface	Surface Tension, γ	Area, A	γdA
Elongation	Force, F	Length, L	FdL
Electrical	Potential Difference, φ	Electrical Charge, Q	φdQ
Gravitational	Gravitational Potential, gh	Mass, m	$mgdh$

Most of the time we're interested in pressure-volume (PV) work. Looking at this one in the table, why is there a negative for the differential work, $dw = -P_{ext}dV$? Well, consider the cases in which volume could change: If $\Delta V < 0$ then work is done *on* the gas and $w > 0$. Conversely, if $\Delta V > 0$ the gas does work on the surroundings and so $w < 0$.

Aside from most of the time, the numerous other types of work show up often. Consider a mechanical example, involving the stretching of a spring. By Hookes' Law we have $F = kx$ where k is some proportionality constant and x is the displacement from equilibrium for the spring (this scenario is represented as "Elongation" in the table above). Then, the work done is given by $w = Fx$, or $dw = Fdx$ for some differential change in distance.

Another, I think more interesting example/problem, can come from considering the surface tension of a lipid vesicle and how it affects the surface area of the vesicle: Consider a lipid molecule which self-assembles into a sphere whose shape is determined predominantly by the surface area and surface tension of the vesicle. Then, we're interested in the differential work $dw = \gamma dA$.

For a process carried out at a constant temperature and constant area, let's write down a condition for

spontaneity in terms of free energy. To do this we'll consider the Helmholtz free energy:

$$F = U - TS$$
$$dF = dU - d(TS)$$
$$= dq + dw - TdS - SdT$$
$$\leq TdS + \gamma dA - TdS - SdT$$
$$dF \leq \gamma dA - SdT$$

Thus, at a constant area and temperature, we see that the condition for spontaneity is simply $dF \leq 0$.

Now, suppose that the internal energy and entropy of the vesicle are given by the following expressions:

$$U(A, \gamma) = \frac{\gamma}{A_0}(A - A_0)^2$$
$$S(A) = k_B \ln(A/a)$$

for some initial area A_0 and a real number a. Write down an expression for F, the Helmholtz free energy of the system: To do this, all we have to consider is the functional form of the Helmholtz free energy we already wrote above. Thus,

$$F = U - TS$$
$$F(A, \gamma) = \frac{\gamma}{A_0}(A - A_0)^2 - T[k_B \ln(A/a)]$$

which is the final answer. Notice that we've expressed the Helmholtz free energy as a function of *only* A and γ.

Now, suppose that I'm interested in how to measure

$$\left(\frac{\partial \gamma}{\partial T}\right)_A$$

but that I'm incapable of varying the temperature for some reason. Is there an alternate expression we could use to compute this partial derivative? Yes.

Recognize that we can use the Maxwell relation for the Helmholtz free energy,

$$\left(\frac{\partial^2 F}{\partial A \partial T}\right) = \left(\frac{\partial^2 F}{\partial T \partial A}\right)$$

by recognizing that $(\partial F/\partial A)_T = \gamma$ and $(\partial F/\partial T)_A = -S$. Thus, we have that

$$\left(\frac{\partial \gamma}{\partial T}\right)_A = -\left(\frac{\partial S}{\partial A}\right)_T$$

We can take the derivative of S with respect to A at a constant temperature in the expression above to afford the simple expression

$$\left(\frac{\partial \gamma}{\partial T}\right)_A = -\frac{k_B}{A}$$

4.1.1   Irreversible Expansion of an Ideal Gas

4.2   Heat

4.2.1   Heat Capacities

Heat capacity is defined as the amount of heat necessary to cause a unit change in the temperature of the substance. Symbolically, this can be written as

$$C \equiv \frac{dq}{dT} \tag{4.2.1}$$

Since C is a function of heat (an inexact differential), the heat capacity of a substance depends on the path of a transformation.

Note that for an ideal gas, we can take the heat capacity of a substance to be constant. In contrast, the heat capacity of a real gas will be a function of temperature.

The heat capacity of a system heated at a constant volume, C_V differs from that at a constant pressure, C_P. Both are state functions, but they represent two *different* state functions. Thus, it is important to specify between the two:

$$C_V = \left(\frac{dq}{dT} \right)_V \quad \& \quad C_P = \left(\frac{dq}{dT} \right)_P$$

Note that $C_P > C_V$ for any substance. Why? To rephrase the question, we're interested in why it takes more heat to raise the temperature of a gas under a constant pressure than it does under a constant volume. The difference is that at a constant volume, the gas can't do work so that all of the heat goes into kinetic energy, i.e., raising the temperature. In contrast, at a constant pressure, the gas can do work on the surroundings and so some heat will also cause the gas to expand.

The importance and relevance of heat capacity cannot be stressed enough. The flow of heat appears explicitly in the first law of thermodynamics and therefore the heat capacity, a quantity which directly relates the flow of heat to the temperature at which a process is occurring, warrants particular attention.

Since dq is an inexact differential we'd like an alternative definition for C_V and C_P based on something that is more easily calculable, such as a state function. Let's begin by trying to rewrite C_V in terms of a state function: Notice that at a constant volume we can rewrite the first law as

$$(dU)_V = dq + dw = dq$$

since there can be no work done due to the fact that the volume is unchanging ($dV = 0$). Thus, we can express the internal energy as

$$(dU)_V = dq = CdT$$
$$\left(\frac{\partial U}{\partial T} \right)_V = C_V(T) \tag{4.2.2}$$

which gives us a relationship between the internal energy and the heat capacity at a constant volume. Notice that this result is *general*. That is, for *any* transformation of an ideal gas we can use this relationship since U is path independent. This idea wrinkled my brain for a while, but I recommend looking at some example problems regarding transformations of an ideal gas, drawing the transformations on a PV diagram, and finding a path where we can definitively say that this equality holds no matter what. In fact, here's an example:

PV shenanigans

Let's return to heat capacities. In particular, let's try to find an analogous expression for C_P as we did with C_V above. Whenever we think about constant pressures, enthalpy should be the first thing that pops into our

minds. So, let's run with that. Consider a differential change in enthalpy:

$$dH = dU + d(PV)$$
$$= dq + dw + d(PV)$$
$$= dq - PdV + PdV + VdP$$
$$= dq + VdP$$

at a constant pressure, we have that

$$(dH)_P = dq = CdT$$
$$\left(\frac{\partial H}{\partial T}\right)_P = C_P(T) \tag{4.2.3}$$

which affords the relationship between heat capacity at a constant pressure and enthalpy that we were looking for. Similar to the Equation (4.2.2), this result is *general*. In a manner similar to how we "proved" it above, try to convince yourself that we can use this result for the transformation of *any* ideal gas.

4.2.2   The Heat Capacity Ratio

For an ideal gas, the heat capacity of a substance is constant with temperature. In fact, we can relate the heat capacity at a constant pressure to that at a constant volume with the *Mayer's relation*:

$$C_P - C_V = nR \tag{4.2.4}$$

using molar heat capacities this takes the form $\tilde{C}_P - \tilde{C}_V = R$. As a result, if we know the heat capacity at a constant pressure for an ideal gas we can immediately determine its heat capacity at a constant volume.

Another relationship we are often interested in is the ratio of these heat capacities, namely

$$\gamma = \frac{\tilde{C}_P}{\tilde{C}_V} = \frac{C_P}{C_V} \tag{4.2.5}$$

(I believe I hint at this relation in Section ?? on adiabatic transformations. Refer to that section for this relations utility I guess). Two values of γ that come up often are those for a monatomic and diatomic ideal gas and are worth remembering:

$$\text{For a monatomic gas,} \quad \gamma = 5/3$$
$$\text{For a diatomic gas,} \quad \gamma = 7/5$$

Both of these relations stem from the following facts about ideal gasses:

	Monatomic Gas	Diatomic Gas
C_P	$3nR/2$	$5nR/2$
C_V	$5nR/2$	$7nR/2$

I already mentioned this but its worth repeating: *The heat capacity at a constant pressure is always greater than the heat capacity at a constant volume for all substances.* That is, $C_P > C_V$ always. This guarantees that $\gamma > 1$ for all substances.

Interestingly, we can alternatively compute γ for an ideal gas using the degrees of freedom f of a monatomic or diatomic gas:

$$\gamma = 1 + \frac{2}{f} \tag{4.2.6}$$

For a monatomic gas, an atom has 3 degrees of freedom: It can translate in any of the x, y, or z directions. Thus, $\gamma = 5/3$ for a monatomic gas as written above. For a diatomic gas, the molecule has all of the

translational freedom as does a monatomic gas, however, it has the added ability to stretch in the direction of either atom, affording 5 degrees of freedom. Then, $\gamma = 7/5$ for a diatomic gas as posited above.

Now, what about real gasses? For real gasses, the main difference is that the heat capacity is a function of temperature, as noted above. However, as the temperature increases (or decreases) both C_P and C_V increase (or decrease) at a similar rate so that Mayer's relationship *becomes a good guess*, that is, $C_P - C_V \approx nR$. This constant difference reflects the relatively constant PV work done during a transformation at a constant pressure versus at a constant volume.

Unlike their difference, the ratio between C_P and C_V *decreases* with an increasing temperature. Since both heat capacities increase as the temperature increases,

$$\gamma = \frac{C_P}{C_V} \to 1 \text{ as } T \to \infty$$

Using Equation (4.2.6), this result should make some intuitive sense because as the temperature increases the number of degrees of freedom a substance has increases as well.

Importantly, keep in mind that this limit *does not hold* for ideal gasses because the heat capacities of an ideal gas are unchanging. Then, the ratio of C_P/C_V will remain the same always for an ideal gas.

4.3 Fundamental Changes of State

Without any explanation, here are expressions for work and heat for the four most common fundamental changes of state we'll encounter *for an ideal gas*:

Work and Heat for Different Changes of State

Condition	Work Done on System	Heat Absorbed by System	ΔU
Isobaric	$-P\Delta V$	$\int_{T_i}^{T_f} C_P dT = C_P \Delta T$	$\int_{T_i}^{T_f} C_P dT - P\Delta V$
Isochoric	0	$\int_{T_i}^{T_f} C_V dT = C_V \Delta T$	$\int_{T_i}^{T_f} C_V dT$
Isothermal	$-nRT \ln(V_f/V_i)$	$nRT \ln(V_f/V_i) = -w$	0
Adiabatic	$C_V \Delta T$	0	$C_V \Delta T$

4.3.1 Reversible Isobaric Transformations

A reversible isobaric transformation is a constant pressure process that can occur spontaneously in either direction without additional work being done on the system.

We'll first consider the work done during one of these processes: Reversible constant pressure-volume change results in a very simple work calculation when the external pressure is constant:

$$w = -\int P_{ext} dV = -P_{ext} \int dV = -P_{ext} \Delta V$$

For a quasistatic process we can assume $P_{sys} = P_{ext}$ and simplify this result as

$$w = -P\Delta V \tag{4.3.1}$$

Expansion involves $\Delta V > 0$ which agress with our intuition that the expansion of an ideal gas does work on the surroundings.

Comparing reversible isobaric expansion to reversible isothermal expansion, it should make intuitive sense that $\Delta T > 0$ in the former, since isobars move through higher temperature isotherms during expansion. To understand this temperature increase we'll consider the expansion of a gas on a molecular level. Because the number of moles of gas is constant, at a larger volume the gas density is lower and therefore to maintain a constant pressure the gas molecules must be imbued with more energy to maintain the sam frequency of collisions. In order to give these molecules more energy their must be a temperature increase.

Now we'll consider the heat flow during one of these processes: When an ideal gas expands at a constant pressure, the appropriate heat capacity is C_P. Moreover, it cuts upward through isotherms on the PV diagram and is therefore associated with an increase in temperature. We'll start by rearranging Equation (4.2.1) and using C_P:

$$dq = C_P dT$$
$$q = \int_{T_i}^{T_f} C_P dT$$

The solution to this integral will depend on how the heat capacity changes with temperature. For most systems, C_P can very greatly even across large temperature ranges. However, over small temperature ranges (those often encountered in a laboratory) the heat capacity can be treated as independent of the temperature so that we can evaluate the integral with ease:

$$q = C_P \int_{T_i}^{T_f} dT = C_P(T_f - T_i) \tag{4.3.2}$$

Additionally, it's important to note that for ideal gasses, C_P (and C_V, for that matter) is constant[1]. We can also rewrite the change in internal energy of the system using this expression for heat and our expression for work during a reversible isobaric transformation, Equation (4.3.1):

$$\Delta U = q + w = C_P \Delta T - P \Delta V \tag{4.3.3}$$

4.3.2   Reversible Isochoric Transformations

A reversible isochoric transformation is a constant volume process that can occur spontaneously in either direction without additional work being done on the system.

First we'll consider the work done during one of these processes: When the pressure of a gas is increased at a constant volume, no work is done. If we try to evaluate the work integral,

$$w = -\int P_{ext} dV = 0 \tag{4.3.4}$$

because $dV = 0$ for an isochoric process.

Now we'll consider the heat flow during one of these processes: The heat flow for a constant volume process can be analyzed in the same way as the constant pressure transformation, using C_V instead of C_P:

$$q = \int_{T_i}^{T_f} C_V dT = C_V \Delta T \tag{4.3.5}$$

Similar to above, the second equality holds only when C_V is not a function of temperature. In a constant volume process (and also dealing with an ideal gas), since there is no work done on the surroundings the change in internal energy of the system can be written as

$$\Delta U = \int dq = C_V \Delta T$$

Once again, we see that the internal energy of an ideal gas is a function of only the temperature. This fact holds in general and is worth remembering.

---

[1]For monatomic gasses, $C_P = 5nR/2$ and $C_V = 3nR/2$. For diatomic gasses, $C_P = 7nR/2$ and $C_V = 5nR/2$. In both cases $C_P - C_V = nR$. This is a fact that will come in handy whenever we deal with ideal gasses.

4.3.3 Reversible Isothermal Transformations

A reversible isothermal transformation is a constant temperature process that can occur spontaneously in either direction without additional work being done on the system.

First we'll consider the work done during one of these processes: When a gas expands isothermally, there is an associated change in pressure and therefore pressure is not constant like it was in the isobaric case. To get around this, we can use the ideal gas law to evaluate the work integral:

$$w = -\int P_{ext}dV = -\int_{V_i}^{V_f} \frac{nRT}{V}dV = -nRT\int_{V_i}^{V_f} \frac{dV}{V} = -nRT\ln(V)|_{V_i}^{V_f} = -nRT\ln\left(\frac{V_f}{V_i}\right)$$

Thus,

$$w = -nRT\ln\left(\frac{V_f}{V_i}\right) \tag{4.3.6}$$

for the isothermal expansion of an ideal gas.

Expansion of a system causes $V_f > V_i$ so that the logarithm in the final step is positive which is associated with negative work done on the system and positive work done on the surroundings which agrees with our intuition about work associated with the expansion of a gas.

For isotherms, heat must flow into the system during reversible expansion in order to keep the temperature constant. This is somewhat clear when comparing the curves in the PV diagram for isothermal expansion and adiabatic expansion. From a molecular perspective, the work done on the surroundings causes a loss in energy for the gas molecules, thereby decreasing the energy and temperature of the gas. Thus, to maintain temperature, heat must flow into the system.

Comparing reversible isobaric expansion to reversible isothermal expansion, it should make intuitive sense that $\Delta T > 0$ in the former, since isobars move through higher temperature isotherms during expansion. To understand this temperature increase we'll consider the expansion of a gas on a molecular level. Because the number of moles of gas is constant, at a larger volume the gas density is lower and therefore to maintain a constant pressure the gas molecules must be imbued with more energy to maintain the sam frequency of collisions. In order to give these molecules more energy their must be a temperature increase.

We could also make this argument using the First Law, $dU = dq + dw$. Since the internal energy of an ideal gas is dependent only on temperature, during an isothermal expansions we'd expect $dU = 0$. Since $dw < 0$ we require that $dq > 0$ in order to not break any fundamental laws of physics.

Now we'll consider the heat flow during one of these processes: For an isothermal expansion, there is no temperature change (as the name implies) and therefore $dT = 0$. So, we cannot employ the same method as above. Instead, recognize that for an ideal gas, $\Delta U = 0$ (since $U(T)$ is a function of temperature for an ideal gas) and so we have the equality

$$q = -w = nRT\ln\left(\frac{V_f}{V_i}\right) \tag{4.3.7}$$

which comes from the calculation done in Equation (4.3.6) for the work done during reversible isothermal expansion.

4.3.4 Reversible Adiabatic Transformations

A reversible adiabatic transformation is a process in which no heat is exchanged with the system's surroundings (that is, $dq = 0$) that can occur spontaneously in either direction without additional work being done on the system.

First we'll consider the work done during one of these processes: Unlike any of the other state changes, an adiabatic transformation is more difficult to analyze because there is an associated change in pressure, volume, and temperature. For an adiabatic expansion, the heat flow is zero ($dq = 0$) and so the change in internal energy is due to only the work performed during the transformation. So, in order to evaluate the

work we need an expression $P = P(V)$, that is, a functional expression for the pressure of the system in terms of only the volume.

The decrease in pressure for an adiabatic expansion of an ideal gas is similar to that of an isothermal expansion, however, the decrease is much sharper because the heat flow that is required to maintain constant temperature is prevented by the adiabatic boundary. This dependance suggests a decay of the form

$$P = \frac{\lambda}{V^\gamma}$$

for some proportionality constants λ and and $\gamma > 1$.

From here, recognize that for a particular adiabat, the constant λ must remain unchanged at all points (P, V) on the PV diagram. Thus,

$$PV^\gamma = P_i V_i^\gamma$$

which affords an expression for the pressure as a function of the volume,

$$P = \frac{P_i V_i^\gamma}{V^\gamma} \tag{4.3.8}$$

Now we can plug this into the work integral:

$$w = -\int P dV = -\int_{V_i}^{V_f} \frac{P_i V_i^\gamma}{V^\gamma} dV$$

$$= -P_i V_i^\gamma \int_{V_i}^{V_f} \frac{dV}{V^\gamma}$$

$$= -P_i V_i^\gamma \left[-\frac{1}{(\gamma - 1)V^{\gamma-1}} \right]_{V_i}^{V_f}$$

$$= \frac{P_i V_i^\gamma}{\gamma - 1} \left(\frac{1}{V_f^{\gamma-1}} - \frac{1}{V_i^{\gamma-1}} \right)$$

This form can be used directly to compute the work done in an adiabatic process, but it's not super friendly. However, for an ideal gas we can take advantage of the fact that $C_P - C_V = nR$ to simplify the expression above: Recall that $\gamma = C_P/C_V$ so that

$$\frac{C_P - C_V}{C_V} = \frac{nR}{C_V}$$

$$\gamma - 1 = \frac{nR}{C_V}$$

and we can substitute this result into our expression for the work:

$$w = \frac{P_i V_i^{\frac{nR}{C_V}+1}}{\frac{nR}{C_V}} \left(\frac{1}{V_f^{\frac{nR}{C_V}}} - \frac{1}{V_i^{\frac{nR}{C_V}}} \right)$$

$$= \frac{P_i V_i C_V}{nR} \left[\left(\frac{V_i}{V_f} \right)^{\frac{nR}{C_V}} - 1 \right]$$

From here we'll utilize the ideal gas law and replace pressure with temperature and volume, giving

$$w = \frac{nRT_iC_V}{nR}\left[\left(\frac{V_i}{V_f}\right)^{\frac{nR}{C_V}} - 1\right]$$

$$= T_iC_V\left[\left(\frac{V_i}{V_f}\right)^{\frac{nR}{C_V}} - 1\right]$$

$$= C_V\left[T_i\left(\frac{V_i}{V_f}\right)^{\frac{nR}{C_V}} - T_i\right]$$

Now for a little algebraic gymnastics. We've already shown why $PV^\gamma = P_iV_i^\gamma$ for an adiabatic process, so briefly consider the adiabatic expansion of an ideal gas from (P_i, V_i) to (P_f, V_f): Using the ideal gas law, we can express this relationship as

$$P_iV_i^\gamma = P_fV_f^\gamma$$

$$\frac{nRT_i}{V_i}V_i^\gamma = \frac{nRT_f}{V_f}V_f^\gamma$$

$$T_iV_i^{\gamma-1} = T_fV_f^{\gamma-1}$$

$$T_f = \left(\frac{V_i}{V_f}\right)^{\gamma-1}T_i$$

Now we'll mess around with the exponent, $\gamma - 1$ a little bit:

$$\gamma - 1 = \frac{C_P}{C_V} - 1 = \frac{C_P - C_V}{C_V} + \frac{C_V}{C_V} - 1 = \frac{nR}{C_V}$$

Why go about all this trouble? Well, we've just shown that

$$T_f = \left(\frac{V_i}{V_f}\right)^{\frac{nR}{C_V}}T_i$$

and so our equation for the work done in an adiabatic process simplifies to

$$w = C_V(T_f - T_i) = C_V\Delta T \tag{4.3.9}$$

Now we'll consider the heat flow during one of these processes: For an adiabatic process, $dq = 0$ and so there is no heat flow! Then, the change in internal energy is given solely by the work done during the transformation:

$$\Delta U = w = C_V\Delta T \tag{4.3.10}$$

4.4 Heat Engines

An engine is simply a device that uses a cycle to convert energy from one form to another and always returns to its original state once the process is complete. In particular, a heat engine is one that receives heat (q_{in}) from a hot thermal reservoir and converts some of it into mechanical work. As we'll see, in reality it is impossible to convert all of this heat into mechanical work (this is the Kelvin Statement). Since not all of this heat is transformed into work, some of it must be lost to the surroundings (q_{out}).

4.4.1 The Carnot Engine

The Carnot engine is a theoretical ideal thermodynamic cycle and provides an upper limit on the efficiency of any classical thermodynamic heat engine. A *major* consideration to make about the Carnot cycle is that it is purely theoretical. Not only do we assume perfectly reversible reactions but also ideal gasses.

With this in mind (and the first law of thermodynamics, as always), when considering a heat engine we see that all of the heat received by an engine (q_{in}) cannot be converted into work (w_{out}) while some of it is lost as heat.

In an analysis of engines it is useful to define the *efficiency* of an engine, ε

$$\varepsilon = \frac{w_{out}}{q_{in}} = \frac{q_{in} - q_{out}}{q_{in}} = 1 - \frac{q_{out}}{q_{in}} \tag{4.4.1}$$

The Carnot cycle is defined by 4 particular transformations of an ideal gas:

1. Reversible *isothermal* expansion at a hot temperature (T_h)

2. Reversible *adiabatic* expansion to a cold temperature (T_c)

3. Reversible *isothermal* compression to a hot temperature (T_h)

4. Reversible *adiabatic* compression to a cold temperature (T_c)

The fourth step completes the cycle, returning the engine to its initial state. We'll analyze the heat and work flow in each of these steps. Note that for all of these steps, q_{in} refers to the heat absorbed by the engine from the thermal reservoir and q_{out} refers to the heat extracted from the engine and released into the surroundings (typically this is a cooling rod or some other very cold substance). Similarly, w_{in} refers to the work done on the engine and w_{out} refers to the work the engine does on its surroundings. Additionally, I'll refer to the hot temperature of the thermal reservoir as T_h and the colder temperature as T_c.

1. *Reversible Isothermal Expansion from Hot to Hot*

   For an isothermal expansion we can compute the work easily:

   $$w_{in} = -w_{out} = -\int PdV = -\int_{V_i}^{V_f} \frac{nRT_h}{V} dV = -nRT_h \ln\left(\frac{V_f}{V_i}\right)$$

   Thus, we see that the work output by the engine in the first step is

   $$w_{out} = nRT_h \ln\left(\frac{V_f}{V_i}\right)$$

   In the isothermal expansion of an ideal gas $\Delta U = 0$ so by the First Law of Thermodynamics we have $q_{out} = -w_{out}$ so that $q_{in} = w_{out}$ and we can express the heat absorbed by the system as

   $$q_{in} = w_{out} = nRT_h \ln\left(\frac{V_f}{V_i}\right)$$

2. *Reversible Adiabatic Expansion from Hot to Cold*

   In an adiabatic expansion we have $dq = 0$ and so by the First Law of Thermodynamics we have $dU = dw$ and we can compute the work done by the engine as

   $$w_{out} = -w_{in} = -\int_{T_i}^{T_f} C_V dT = -C_V(T_c - T_h) = C_V(T_h - T_c)$$

   Notice that we assume there is no dependence on temperature for the heat capacity because the Carnot cycle is interested in ideal gasses.

3. *Reversible Isothermal Compression from Cold to Cold*

   Similar to above, we can compute the work performed by the engine on the surroundings in an isothermal expansion as

   $$w_{out} = -w_{in} = \int PdV = -\int_{V_i}^{V_f} \frac{nRT_c}{V} dV = -nRT_c \ln\left(\frac{V_f}{V_i}\right)$$

Morevoer, since this is an isothermal process we have that $\Delta U = 0$ and so $q_{in} = w_{out}$.

4. *Reversible Adiabatic Compression from Cold to Hot*

Again, a pretty straightforward calculation considering we did it a second ago

$$w_{out} = -\int dU = -\int_{T_i}^{T_f} C_V dT = -C_V(T_c - T_h) = C_V(T_h - T_c)$$

Make sure to remember that for any adiabatic process, $dq = 0$.

We can now summarize our results in the following table, using the preceding diagram as reference points for the processes as well as the initial and final volumes for each process:
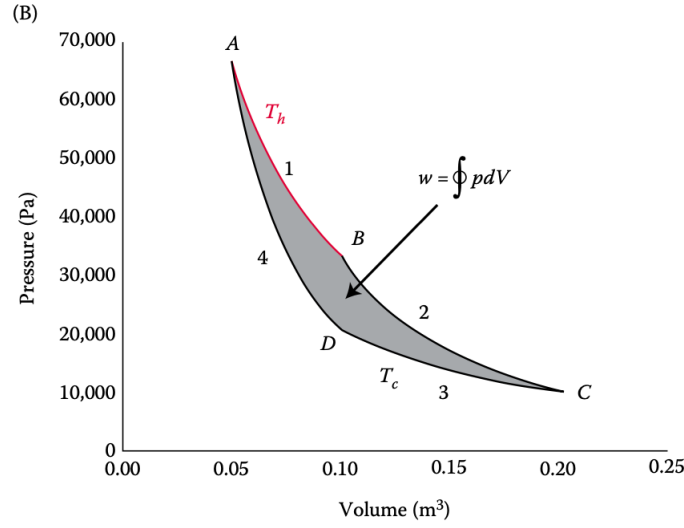
Figure 4.1: The Carnot Cycle. The shaded region represents the total work done on the surroundings during the transformation

Heat and Work for each Process of the Carnot Cycle

Process	Heat Flow into Engine	Work Done by Engine
Isothermal Expansion	$q_1 = q_{in} = nRT_h \ln\left(\frac{V_B}{V_A}\right)$	$nRT_h \ln\left(\frac{V_B}{V_A}\right)$
Adiabatic Expansion	0	$C_V(T_c - T_h)$
Isothermal Compression	$q_3 = -q_{out} = nRT_c \ln\left(\frac{V_D}{V_C}\right)$	$nRT_c \ln\left(\frac{V_D}{V_C}\right)$
Adiabatic Compression	0	$C_V(T_h - T_c)$

Recall our expression for the efficiency of a heat engine, Equation (4.4.1). Using this, we can express q_{out} and q_{in} in terms of the quantities above, i.e., the initial and final temperatures and volumes:

$$\varepsilon = 1 - \frac{-nRT_c \ln(V_D/V_C)}{nRT_h \ln(V_B/V_A)} = 1 - \frac{nRT_c \ln(V_C/V_D)}{nRT_h \ln(V_B/V_A)} \tag{4.4.2}$$

In order to simplify this expression recall that for adiabatic processes, $PV^\gamma = $ constant and so

$$P_B V_B^\gamma = P_C V_C^\gamma$$
$$\frac{nRT_h}{V_B}V_B^\gamma = \frac{nRT_c}{V_C}V_C^\gamma$$
$$T_h V_B^{\gamma-1} = T_c V_C^{\gamma-1}$$
$$\frac{T_h}{T_c} = \left(\frac{V_C}{V_B}\right)^{\gamma-1}$$

for the isothermal compression of the gas, and

$$P_D V_D^\gamma = P_A V_A^\gamma$$
$$\frac{nRT_c}{V_D} V_D^\gamma = \frac{nRT_h}{V_A} V_A^\gamma$$
$$T_c V_D^{\gamma-1} = T_h V_A^{\gamma-1}$$
$$\frac{T_h}{T_c} = \left(\frac{V_D}{V_A}\right)^{\gamma-1}$$

which implies that

$$\left(\frac{V_D}{V_A}\right)^{\gamma-1} = \left(\frac{V_C}{V_B}\right)^{\gamma-1}$$
$$\frac{V_B}{V_A} = \frac{V_C}{V_D}$$

Consequently, we can substitute into Equation (4.4.2) to afford

$$\varepsilon = 1 - \frac{nRT_c \ln(V_B/V_A)}{nRT_h \ln(V_B/V_A)} = 1 - \frac{T_c}{T_h} \tag{4.4.3}$$

Eureka! This short equation implies that the primary constraint on an engine's efficiency is how cold the cold reservoir is. Moreover, the only point at which an engine could be 100% efficient is at *absolute zero*.

Another way of looking at the maximum work output of a Carnot engine is to consider the processes which do the work, that is, the isotherms. Ideally, the isothermal expansion is at a high temperature, thereby maximizing the area under the curve in the PV diagram. Additionally we would want the adiabatic expansion to reach the largest volume possible, thereby increasing the area under the curve in the PV diagram again. A large as possible volume increase during the adiabatic expansion also minimizes the area under the curve during the isothermal compression, which *decreases* the area under the curve in the PV diagram but since it is a compression this would be favorable. The below diagram illustrates these "optimized" transformations.

The following table summarizes everything we would ever really need to know about the Carnot cycle. Make sure to note the use of q_{in} and w_{out} for the engine instead of the typical q and w used to represent the heat absorbed by and work done on the system, respectively.

Heat, Work, and ΔU for the Reversible Carnot Cycle

Segment	Initial State	Final State	q_{in}	w_{out}	ΔU
$A \to B$	P_A, V_A, T_{hot}	P_B, V_B, T_{hot}	$q_{in,AB} > 0$	$w_{out,AB} > 0$	0
$B \to C$	P_B, V_B, T_{hot}	P_C, V_C, T_{cold}	0	$w_{out,BC} > 0$	w_{out}
$C \to D$	P_C, V_C, T_{cold}	P_D, V_D, T_{cold}	$q_{in,CD} < 0$	$w_{out,CD} < 0$	0
$D \to A$	P_D, V_D, T_{cold}	P_A, V_A, T_{hot}	0	$w_{out,DA} < 0$	w_{out}
Cycle	P_A, V_A, T_{hot}	P_A, V_A, T_{hot}	$\sum q_{in}$	$\sum w_{out}$	0

Ultimately, the reversible Carnot engine acts as an upper limit on efficiency, as stated in the "*Carnot Theorem*":

> No heat engine operating between two temperatures can be more efficient than a reversible Carnot engine operating between the same two temperatures.

Expressing the Carnot Theorem in terms of efficiencies,

$$\varepsilon_{rev} > \varepsilon_{irr}$$

$$1 - \frac{T_{rev}}{T_h} > 1 - \frac{q_{out,irr}}{q_{in,irr}}$$

$$\frac{T_{rev}}{T_h} < \frac{q_{out,irr}}{q_{in,irr}} \qquad (4.4.4)$$

The subscripts rev and irr refer to reversible and irreversible cycles, respectively. Note that the left-hand side of the inequality can be used because the temperature of a reversible Carnot engine is well defined throughout the cycle. Although this is not the case for irreversible cycles, the heat flow is still well defined and can be used on the right-hand side of the inequality. Rearranging Equation (4.4.4) gives

$$\frac{q_{in,irr}}{T_h} - \frac{q_{out,irr}}{T_c} < 0$$

where $q_{out} = -q_{in}$ for the Carnot engine. Then, if we use this idealized limit of $q_{out} = -q_{in}$, we have

$$\frac{q_{in,irr}}{T_h} + \frac{q_{in,irr}}{T_c} \leq 0$$

for an irreversible process. In approximating an irreversible heat engine, we can use a collection of reversible Carnot cycles so that the above inequality can be rewritten as

$$\sum_{i=1}^{n} \frac{q_i}{T_i} < 0$$

and in the limit as $n \to \infty$,

$$\oint_{irr} \frac{dq_{irr}}{T} < 0 \qquad (4.4.5)$$

Here, it is worth remembering that dq_{irr} represents the heat *absorbed* by the engine. Since this quantity is less than zero we observe that for an irreversible heat engine, some of the heat must be lost and therefore not all of it can be converted to work (which agrees with everything we've said up until this point).

Regardless of whether or not the cycle is reversible, if the engine is returned to its original state then all of the state functions must remain unchanged (i.e., $\Delta S = 0$).

How can we relate the macroscopic, idealized example of the Carnot engine back to a microscopic model? Well, we already know that heat and work are both ways to change the internal energy of a gas. In contrast to heat, work can be thought of as *organized* energy, e.g., for a gas to do work on a piston the molecules must all move in the same direction (against the piston). On the other hand, heat is much more like *random* energy, that is, there is no requirement for what direction the molecules must move or behave in order to absorb heat. All that is required when heat is absorbed is for the kinetic energy of the particles to increase (for idealized gasses, all of the internal energy is in the form of kinetic energy). Hence, there are fewer arrangements of particles in a gas that "look" like work, thereby favoring heat.

Let's return to the Carnot cycle. Notice that if we sum q across all of the processes in the cycle, $\sum q \neq 0$ (this makes sense because heat is not a state function). However, recall from above that

$$\frac{V_B}{V_A} = \frac{V_C}{V_D}$$

Using a little bit of algebraic gymnastics we can rewrite this as

$$\ln\left(\frac{V_B}{V_A}\right) = -\ln\left(\frac{V_D}{V_C}\right) \qquad (4.4.6)$$
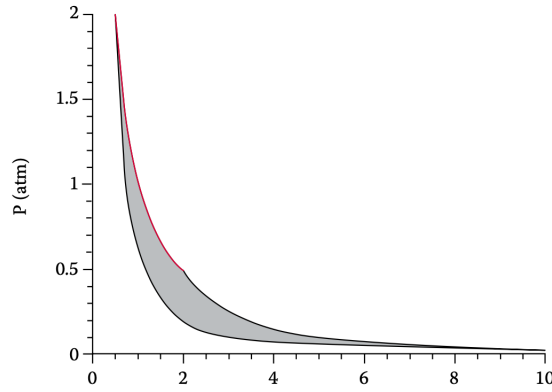
Figure 4.2: In the first isothermal expansion step, the initial hot temperature is maximized and in the succeeding adiabatic expansion the final volume reached is also maximized. Both of these conditions maximize the area under the curve, thereby maximizing the work done by the engine on the surroundings.

and take the sum of the heat across the entire cycle to afford the following result:

$$q_{in} + q_{out} = nRT_h \ln \left(\frac{V_B}{V_A} \right) + nRT_c \ln \left(\frac{V_D}{V_C} \right)$$
$$= nRT_h \ln \left(\frac{V_B}{V_A} \right) - nRT_c \ln \left(\frac{V_B}{V_A} \right)$$
$$= (T_h - T_c)nR \ln \left(\frac{V_B}{V_A} \right)$$

Thus, we see that if we define a new quantity q/T *it would be zero over the entire cycle*. In other words, the quantity q/T acts like a *state function*[2]. Thus,

$$\oint \frac{dq_{rev}}{T} = 0 \tag{4.4.7}$$

which implies that dq_{rev}/T acts like an exact differential. We refer to this state function as the *entropy*,

$$dS = \frac{dq_{rev}}{T} \tag{4.4.8}$$

This is another way of coming across an expression for the entropy as its defined in Sections **??** and **??**

---

[2]It's important to note that this result holds *only if the cycle is reversible*. Had any step been irreversible we cannot define this state function. Recall that $q_{rev} > q_{irrev}$.

CHAPTER

5

CHEMICAL POTENTIAL

In developing a robust analysis of thermodynamic systems we need to begin to consider the concentrations of different chemical components involved in a reaction. In particular, elucidating the thermodynamic contributions from each species, that is, how chemical i effects the enthalpy, entropy, and Gibbs free energy change of a reaction, for example. This foundational approach will offer a basis for analyzing simple reactions and phase transitions, as well as additional Maxwell relations that offer a framework for energetic coupling.

Firstly, we'll consider the idea of *partial molar quantities*, an approach to separating thermodynamic contributions from each species that does not require detailed structural knowledge of the chemical species or their modes of interaction. Next, the idea of a *chemical potential* will be developed as a means of predicting the phase of a species which will prevail at equilibrium for different thermodynamic systems. The chemical potential will be applied to systems with phase transitions and chemical reactions and ultimately afford the foundation for which we can analyze phase transitions using the *Clausius-Clapeyron equation.*

5.1   Partial Molar Quantities

A partial molar quantity is the amount of a particular extensive thermodynamic quantity contributed per mole of a substance. Such a quantity is represented as $\tilde{X}_i$ where the bar refers to "per mole" and the subscript i denotes the particular species in question.

An important distinction that's made when converting to partial molar quantities is that whereas X_i is extensive, $\tilde{X}_i$ is intensive. Intensive properties of a system typically provide a more fundamental description of a thermodynamic system than do their extensive counterparts (for example, consider the enthalpy of a reaction versus the molar enthalpy. Clearly, one is more illustrative of the chemistry going on than the other).

We'll begin our analysis of partial molar quantities by considering the partial molar volume(s) of a system because it closely parallels the behavior and intuition behind the partial molar Gibbs energy, a measurement that will be of immense use to us.

5.1.1 Partial Molar Volume

The partial molar volume of a system is defined as

$$\tilde{V}_i = \frac{V_i}{n_i} \tag{5.1.1}$$

where n_i is the number of moles of chemical i and V_i is the volume assumed by the same chemical. For single-species systems, this equation simplifies as $\tilde{V}_i^* = V/n_i$ where $\tilde{V}_i^*$ is used to denote the fact that the system is composed of only one species (we'll be interested in single-species systems for the majority of this beginning part). Rearranging Equation (5.1.1) affords

$$V = \tilde{V}_i^* n_i$$

This simple rearrangement better illustrates the fact that $\tilde{V}$ acts as a proportionality constant, relating how the volume contributed by a particular species in a reaction changes with the number of moles of the species. In particular, if we consider incredibly small incremental changes in n_i we see that the partial molar volume is in fact a partial derivative:

$$\tilde{V}_i = \left(\frac{\partial V_i}{\partial n_i}\right)_{P,T,n_{i\neq j}} \tag{5.1.2}$$

The subscripts of the partial derivative indicate that pressure and temperature are being held constant, in addition to the number of moles of the other species involved in the reaction. Finally, we see that the total volume differential can be expressed in the following form for a chemical reaction with a single species:

$$dV = \tilde{V}_i^* n_i = \left(\frac{\partial V}{\partial n_i}\right) dn_i \tag{5.1.3}$$

Now we'll move on to multiple component systems. Consider a 1:1 mixture of water and ethanol so that the mole fractions are $x_{H_2O} = x_{EtOH} = 0.5$. In mixing 50 mL of water with 50 mL of ethanol, we afford a mixed solution totaling 97 mL, in contrast to the case using *just* pure water. I don't yet know why this happens, it's known as "mixing volume ideality", but I'm dying to find a physical explanation. Nevertheless, this discrepancy reflects the dependence of partial molar volumes on composition. In fact, we can represent the total molar volume of an ideal solution (for two components water and ethanol, this case) as

$$\tilde{V} = x_{H_2O}\tilde{V}_{H_2O}^* + x_{EtOH}\tilde{V}_{EtOH}^* \tag{5.1.4}$$

The use of the star in this equation illustrates the fact that in order for this equality to hold we assume ideality. In fact, multiplying this equation by the total number of moles in solution affords the sensible result,

$$V = n_{H_2O}\tilde{V}_{H_2O} + n_{EtOH}\tilde{V}_{EtOH} \tag{5.1.5}$$

Unsurprisingly, this equation generalizes to any number of species with ease. More generally, we can also express the total partial derivative of the volume of this sort of solution as

$$dV = \left(\frac{\partial V}{\partial n_A}\right)_{n_B} dn_A + \left(\frac{\partial V}{\partial n_B}\right)_{n_A} dn_B \tag{5.1.6}$$

which generalizes similarly.

5.1.2 Partial Molar Gibbs Energy

The partial molar Gibbs free energy is defined exactly as we'd expect. Because of its importance, however, its given the special denomination of "chemical potential":

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{n_{i \neq j}} \tag{5.1.7}$$

The chemical potential can be thought of as an analogue to potentials in physics, such as the electric potential or gravitational potential; particles of a substance tend to move from high chemical potential to low potential. The chemical potential has applications in a nearly inappropriate amount of disciplines. An understanding in everything from chromatography to electrochemistry[1] benefits from having a foundational understanding of the chemical potential. Something I recently just learned about are *theoretical plates,* the hypothetical stage in a chromatographic process in which the liquid and vapor phases of a substance are in equilibrium. The performance of a separation process such as chromatography depends on having a series of these theoretical plates. Alright that was only a small tangent back to the things that we'll be tested on at one point.

Before diving into a derivation and analysis of the relationships between some thermodynamic quantities and the chemical potential, it would behoove us not to mention the close (and ideally helpful) analogies between the chemical potential, temperature, and pressure, three intensive variables which may determine the equilibrium of a system:

1. *Temperature* determines equilibrium with respect to heat flow. Heat flows from higher temperatures to lower ones (a restatement of the second law). When flow stops, equilibrium is attained and the temperature is uniform.

2. *Pressure* determines the equilibrium of a system with respect to volume change. When a higher-pressure part of the system expands at the expense of one at a lower pressure, this can be considered a "flow" of volume from low pressure to high pressure. When flow stops, equilibrium is attained and pressure is uniform[2].

3. *Chemical potential* determines the equilibrium with respect to the flow of matter. Each species of matter flows from high chemical potential to low chemical potential. When the flow stops, equilibrium is attained and the chemical potential of each species is uniform.

If variations in temperature and pressure are considered alongside variations in the number of moles of each species, the chemical potentials combine nicely to afford the total partial differential of Gibbs free energy as

$$dG = VdP - SdT + \sum_{i=1} \mu_i dn_i \tag{5.1.8}$$

where the summation on the right iterates through every chemical species involved in the reaction. This variation equation offers a number of additional Maxwell relations. Moreover, this new equation for the Gibbs free energy will be paramount for systems with phase transitions, chemical reactions, or that are open and can exchange matter with the surroundings (all of these types of transformations can lead to changes in n).

This affords a new expression for the total partial differential of dG:

$$dG = \left(\frac{\partial G}{\partial T}\right)_{P,n_i,n_j} dT + \left(\frac{\partial G}{\partial P}\right)_{T,n_i,n_j} dP + \left(\frac{\partial G}{\partial n_i}\right)_{T,P,n_i} dn_i + \left(\frac{\partial G}{\partial n_j}\right)_{T,P,n_j} dn_j \tag{5.1.9}$$

Note that we've already named all of these quantities:

$$dG = -SdT + VdP + \mu_i dn_i + \mu_j dn_j \tag{5.1.10}$$

---

[1] Depending on how much chemistry you're familiar with that may or may not be a large breadth of knowledge.
[2] This realization of the pressure for a system must be modified if such effects as gravity are significant.

Hold on a minute! Above we just defined the molar Gibbs free energy *as the sum of the chemical potential* so it can be expressed as

$$\tilde{G} = \mu_i + \mu_j \;\Leftrightarrow\; G = n_i\mu_i + n_j\mu_j \tag{5.1.11}$$

which means we should also be able to express the differential Gibbs free energy as

$$dG = d\mu_i n_i + \mu_i dn_i + d\mu_j n_j + \mu_j dn_j \tag{5.1.12}$$

At this point, we're left with two equations expressing the same quantity:

$$dG = -SdT + VdP + \mu_i dn_i + \mu_j dn_j$$
$$dG = d\mu_i n_i + \mu_i dn_i + d\mu_j n_j + \mu_j dn_j$$

Putting these together affords the following relationship:

$$d\mu_i n_i + d\mu_j n_j = SdT + VdP$$

We can generalize this equation to any number of chemical species nicely, affording what's known as the *Gibbs-Duhem equation*:

$$\sum_{i=1}^{n} n_i d\mu_i = -SdT + VdP \tag{5.1.13}$$

Essentially, this equation is telling us that the chemical potentials for each species in a reaction *are dependent on one another*. For a single species this equation simplifies as

$$nd\mu = -SdT + VdP \;\Leftrightarrow\; d\mu = -\tilde{S}dT + \tilde{V}dP$$

Up until this point we've talked all about Gibbs free energy. How might chemical potential be expressed in terms of other state functions such as the Helmholtz free energy of a system or the internal energy? (An excellent question, might I add). Well, let's consider the Helmholtz free energy as an example: We can express the Helmholtz free energy as

$$A = U - TS + \sum_{i=1}^{n} \mu_i n_i$$

for a reaction with n chemical species present. Then, the total partial differential of A can be computed as

$$dA = PdV - SdT + \sum_{i=1}^{n} \mu_i dn_i$$

recalling the derivation for the total partial differential of the Helmholtz free energy from Section **??** and adding in the term(s) for the influence of the chemical potential. Using the same equation for the total partial differential of the Helmholtz energy, we see that

$$\mu_i = \left(\frac{\partial A}{\partial n_i}\right)_{T,V\,n_{i\neq j}} \tag{5.1.14}$$

Hopefully it's clear that a similar relationship will appear for the internal energy of a system as well as the enthalpy. I'll leave those derivations to you because I don't wanna do it. Here they all are:

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{P,T,n_{i\neq j}} = \left(\frac{\partial A}{\partial n_i}\right)_{T,V,n_{i\neq j}} = \left(\frac{\partial H}{\partial n_i}\right)_{T,V,n_{i\neq j}} = \left(\frac{\partial U}{\partial n_i}\right)_{S,V,n_{i\neq j}}$$

One important aspect of these relationships is that the partial derivatives are all taken while the respective

natural variables are held constant.

Let's keep in mind the intuition behind defining a chemical potential in the first place: The notion of μ helps us predict the spontaneity of a process that involves adding or taking away molecular components of a transformation. This includes both chemical transformations where multiple species are present and phase transitions where only a single chemical is present but in different phases. This statement begs an important question: How do we define a phase? Typically we define three phases of matter, solid, liquid, and gas. However, phases and phase transitions encompass a much broader range of physical phenomena. A quick example might be *magnetism,* the uniform orientation of electron spins within a material. Another example might be the *mesophase* of a substance, a state of matter in between a liquid and a solid. Some examples of mesophases include the lipid bilayers of cell membranes and gelatin. In the next section we'll take a more rigorous approach to defining the properties of a thermodynamic phase.

One thing that sometimes peeves me in this class is the lack of formalized math and statistics that's applied to some of these complicated systems. Old whites dudes have been grinding for years to provide rigorous definitions for everything we've talked about and will talk about, but for the sake of "simplicity" they're just ignored for the most part. That's my short preface into trying to reintroduce the use of partial derivatives for important thermodynamic relationships.

Recall that through the use of the total partial differential for Gibbs free energy we have the relationship

$$-S = \left(\frac{\partial G}{\partial T}\right)_{P,n_{i\neq j}}$$

so that we can rewrite our definition for the Gibbs free energy as

$$G = H + T\left(\frac{\partial G}{\partial T}\right)_{P,n_{i\neq j}}$$

Differentiating with respect to an infinitesimal change in amount of substance i, we have that

$$\left(\frac{\partial G}{\partial n_i}\right)_{P,n_{i\neq j}} = \left(\frac{\partial H}{\partial n_i}\right)_{P,n_{i\neq j}} + T\left(\frac{\partial^2 G}{\partial n_i \partial T}\right)_{P,n_{i\neq j}} \tag{5.1.15}$$

As a result of Clairaut's theorem we can change the order of differentiation to afford an equivalent expression for the right-most partial derivative in the expression above,

$$\left(\frac{\partial^2 G}{\partial n_i \partial T}\right)_{P,n_{i\neq j}} = \left(\frac{\partial^2 G}{\partial T \partial n_i}\right)_{P,n_{i\neq j}} = \left(\frac{\partial \mu_i}{\partial T}\right)_{P,n_{i\neq j}}$$

ultimately lending itself to the expression

$$\mu_i = h_i + T\left(\frac{\partial \mu_i}{\partial T}\right)_{P,n_{i\neq j}} \tag{5.1.16}$$

where h_i is the partial molar enthalpy. This equation for the chemical potential will prove useful later when we consider ideal mixtures.

5.1.3 Consequences of an Ideal Solution

Just as the treatment of gasses can be simplified by starting with an idealized kind of gas, so can mixtures be simplified. However, this range of usefulness will prove much more restricted than the tried-and-true $PV = nRT$.

There are several equivalent ways of defining an ideal mixture. A common analytical definition is given by

$$\mu_i = \mu_i^* + RT\ln x_i \tag{5.1.17}$$

where μ_i^* is the chemical potential of the pure liquid and x_i is the mole fraction of the compound in solution. As we'll come to realize, this equation affords an easy way of showing why the enthalpy of mixing for an ideal solution is necessarily zero (that time of realization is now, by the way). By the chain rule, we have that

$$\frac{\partial(\mu_i/T)}{\partial T} = \frac{T\frac{\partial \mu_i}{\partial T} - \mu_i \frac{\partial T}{\partial T}}{T^2}$$
$$= -\frac{1}{T}\frac{\partial \mu_i}{\partial T} - \frac{\mu_i}{T^2}$$

so that we can make the substitution

$$-T^2\frac{\partial(\mu_i/T)}{\partial T} = -T\frac{\partial \mu_i}{\partial T} + \mu_i$$

into Equation (5.1.16) to afford the following relationship:

$$h_i = -T^2\left(\frac{\partial(\mu_i/T)}{\partial T}\right)_{P,n_{i \neq j}} \tag{5.1.18}$$

To prove the utility of our expression for the partial molar enthalpy above, we'll first rewrite Equation (5.1.17) by dividing through by temperature,

$$\frac{\mu_i}{T} = \frac{\mu_i^*}{T} + R\ln x_i \tag{5.1.19}$$

and differentiating this equation with respect to temperature (following the same logic using the chain rule a moment ago), followed by multiplying through by $-T^2$, we find that

$$h_i = h_i^* \tag{5.1.20}$$

That is to say, *the change in enthalpy of mixing for an ideal solution is zero.*

Using Equation (5.1.17) as a template, we could also define the chemical potential of a pure *vapor* as

$$\mu_i = \mu_i^\circ + RT\ln\left(\frac{P_i}{P^\circ}\right) \tag{5.1.21}$$

where the fraction P_i/P can be thought of as a "pressure fraction," analogous to mole fractions in the case of the solution[3]. If the vapor is in equilibrium with its solution, the chemical potential of species i in either phase must be the same, so that

$$\mu_i^* = \mu_i^\circ + RT\ln\left(\frac{P_i^*}{P^\circ}\right)$$

Taking the difference between this equation and Equation (5.1.21), we find

$$\mu_i - \mu_i^* = \mu_i^\circ + RT\ln\left(\frac{P_i}{P^\circ}\right) - \left[\mu_i^\circ + RT\ln\left(\frac{P_i^*}{P^\circ}\right)\right]$$
$$= RT\ln\left(\frac{P_i}{P^*}\right)$$
$$= RT\ln x_i$$

from which we see that $P_i = x_i P_i^*$ also known as *Raoult's law*.

---

[3]A more common expression for μ_i of an ideal vapor defines the quantity of terms of *fugacity*, a property of a real gas which, when substituted for the partial pressure P_i of an ideal gas, gives equations applicable to a real gas. The fugacity is related to the real pressure of the gas through the relationship $f = \varphi P$, where φ is the *fugacity coefficient*.

5.1.4   Consequences of a Nonideal Solution

Solutions that behave truly ideal are few and far between and the relatively simple relationships derived in the preceding section are not nearly as applicable as we may like. Just as in the case of the nonideal gas, however, using these equations as a template for defining relationships between the real quantities of a substance will prove beneficial. For a solution, we introduce the *activity*, a_i, that satisfies

$$\mu_i = \mu_i^\circ + RT \ln a_i \tag{5.1.22}$$

for each chemical in a solution. In order to define the standard chemical potential for a solution we'll need to first specify which substance will assume the role of our solvent. Then, μ_i° is the chemical potential of the pure solvent. For the other chemicals in solution, the reference state is defined such that $[i] = 0$ M, i.e., the concentration is zero[4]. Then, the standard chemical potential is such that

$$\lim_{x_i \to 1} \frac{a_i}{x_i} = 1 \tag{5.1.23}$$

The ratio a_i/x_i is the *activity coefficient*, symbolized by γ_i.

5.2   Phases and Phase Transitions

Finally we'll determine the major incentive for defining the chemical potential: *At equilibrium, the phase of a substance with the lower chemical potential prevails.*

Familiar phases typically differ in the type and quantity of *non-covalent interactions between molecules*; Van der Walls forces and induced dipoles are good examples of these. Gasses often have the fewest intermolecular interactions, then liquids, then solids. Compared to gasses, liquids and solids have vastly more intermolecular interactions, however, the molecules in a liquid are *isotropically* (randomly) oriented so that there is no long-range order. Solids on the other hand do have long-range order, i.e., *crystallinity*.

Not all phases are distinguished by non-covalent interactions, though. Some differ in their covalent bonding pattern. For example take C(s). Carbon can exist as graphene, an sp^2 hybridized form which exhibits aromaticity, and diamond, an sp^3 hybridized form which forms a strong covalent network where each carbon is bound to four other carbons.

Usually we can distinguish between which phase of a substance is favored at or around standard conditions. At room temperature water will be liquid and we can freeze or it boil it by dropping it below 0°C or brining it above 100°C, respectively. However, which phase of water will be favored at 75°C and 15 atm? Here we can invoke the chemical potential.

Let α and β represent different phases of a component (for example, the liquid and vapor phases of water). We can write down a change in Gibbs free energy in response to the change in the number of moles of each phase:

$$dG = \mu^\alpha dn^\alpha + \mu^\beta dn^\beta$$

By the conservation of matter it must be the case that $dn^\alpha = -dn^\beta$ so that we can rewrite this as

$$dG = (\mu^\alpha - \mu^\beta)dn^\alpha$$

The above expression makes the following claim clear: Under conditions where $\mu^\alpha < \mu^\beta$, at equilibrium the system will consist entirely of the α phase because the partial molar Gibbs free energy with respect to the α phase will be negative, indicating the direction of the reaction which minimizes G.

In contrast, the point where $\mu^\alpha = \mu^\beta$, i.e., $dG = 0$, the equilibrium condition is maintained regardless of the change in moles of phase α and so both phases can exist in equilibrium. We call this point *phase coexistence*.

---

[4]This condition is sometimes also referred to as the *state of infinite dilution*.

Another way of thinking about phase coexistence is that the material can change reversibly between phases.

Thus, we're left with the result that if we can compute the chemical potential of different phases at any condition we will know which phase prevails at that condition (at equilibrium). So, let's try and do that

Starting from Equation (5.1.11) for a single species we have that

$$\mu^{\alpha} = \tilde{G}^{\alpha} = \tilde{H}^{\alpha} - T\tilde{S}^{\alpha} \tag{5.2.1}$$

for some phase α. As a minor aside, notice that this equation explains the two familiar phase changes of water. Consider the differential chemical potential:

$$d\mu^{\alpha} = d\tilde{G}^{\alpha} = -\tilde{S}^{\alpha}dT + \tilde{V}^{\alpha}dP \tag{5.2.2}$$

As the temperature of the sample increases, the Gibbs free energy will decrease (because of the negative sign associated with that term) and so the phase with a greater entropy will be favored (explaining the transition from solid to liquid to gas as temperature increases). Returning to Equation (5.2.1), our goal now is to try and express μ^{α} in terms of manipulable thermodynamic properties, e.g. temperature and pressure.

Recall that our key expressions for enthalpy and entropy in terms of pressure and temperature are in terms of the heat capacity,

$$dH = C_P dT \iff H(T) = \int_{T_0}^{T_f} C_P(T)dT + H_r$$
$$dS = \frac{C_P}{T}dT \iff S(T) = \int_{T_0}^{T_f} \frac{C_P(T)}{T}dT + S_r \tag{5.2.3}$$

where H_r and S_r are reference states for the enthalpy and entropy, respectively. With these expression we can evaluate the enthalpy and entropy changes over a temperature range with no phase change. *During* a phase change, however, none of the heat goes into changing the temperature of a substance and therefore the heat capacity is no good. Hence, we need a new quantity to define the energy change associated with phase change.

This new quantity is the *enthalpy of melting/vaporization/fusion etc.,*, denoted $\Delta\tilde{H}_m$. Intuitively, the enthalpy of vaporization represents the heat being put into breaking up intermolecular reactions (thereby increasing potential energy) as opposed to speeding up molecules (which would have increased the kinetic energy of a sample). The *entropy of melting/vaporization/fusion etc.,* is defined how we might expect, as $\Delta\tilde{S}_m = \Delta\tilde{H}_m/T_m$ where T_m represents the temperature at which the phase change occurs.

The last thing we need to define the chemical potential of a phase at a particular thermodynamic state is *reference states for enthalpy and entropy*, to define an absolute scale (recall from Equations (5.2.3) that when integrating we are left with reference enthalpies and entropies).

For enthalpy, this is an intrinsically arbitrary question: Which energy are we counting? We could be referencing the bond enthalpies of a compound, the energies of the intermolecular interactions between molecules of a compound, or even the electronic energy associated with the energies of electrons. Hence, we define the arbitrary reference point of 0 (enthalpy units, I suppose) to quantify the partial molar enthalpy of a phase transition as follows:

$$\tilde{H}(T) = 0 + \int_0^{T_m} \tilde{C}_P(T)dT + \Delta\tilde{H}_m + \int_{T_m}^{T_v} \tilde{C}_P(T)dT + \Delta\tilde{H}_v + \int_{T_v}^{T_f} \tilde{C}_P(T)dT \tag{5.2.4}$$

In contrast to enthalpy we do in fact have the ability to create an absolute reference point for the entropy. Because of its microscopic definition, $S = k_B \ln W$, at absolute zero a substance will have only one microstate[5], that is, a perfectly crystalline structure. Hence, $W = 1$ and therefore $S = 0$. This is known as the

---

[5]At absolute zero the number of *degenerate ground states* for a substance is incredibly small such that the *residual entropy* can be safely approximated as 0.

third law of thermodynamics. Now, we can define the partial molar entropy for a phase transition absolutely:

$$\tilde{S}(T) = 0 + \int_0^{T_m} \frac{\tilde{C}_P(T)}{T} dT + \Delta\tilde{S}_m + \int_{T_m}^{T_v} \frac{\tilde{C}_P(T)}{T} dT + \Delta\tilde{S}_v + \int_{T_v}^{T_f} \frac{\tilde{C}_P(T)}{T} dT \tag{5.2.5}$$

Ultimately, these equations will help us to do is derive a pressure-dependence for the chemical potential.

Recall Equation (5.2.2), relating the change in chemical potential of a phase to the natural variables of the Gibbs free energy,

$$d\mu^\alpha = -\tilde{S}^\alpha dT + \tilde{V}^\alpha dP \tag{5.2.6}$$

As discussed previously, the temperature dependence of this equation makes sense; as temperature increases the phase which maximizes entropy will be favored. What about the pressure dependence on the thermodynamic favorability of a phase? Funny you should ask because that's what I was just about to talk about.

As we can see from the Equation (5.2.6), phases with *large molar volumes* will have chemical potentials which vary (potentially significantly) with pressure. For all intents and purposes, the chemical potential of the condensed phases don't vary significantly with the pressure[6] and so we'll only consider the pressure-dependence of the chemical potential on the gaseous state. Suppose we consider a constant-temperature gas phase α with chemical potential given by

$$d\mu^\alpha = \tilde{V} dP = \frac{RT}{P} dP$$

where we estimate the gas to be ideal and the n term drops out because the chemical potential is a molar quantity (by definition). Proceeding with integration:

$$\int_{P_r}^P d\mu^\alpha = RT \int_{P_r}^P \frac{dP}{P}$$
$$\mu^\alpha(P) - \mu^\alpha(P_r) = RT \ln\left(\frac{P}{P_r}\right)$$
$$\mu^\alpha(P) = RT \ln\left(\frac{P}{P_r}\right) + \mu^\alpha(P_r) \tag{5.2.7}$$

In the lecture slides Dr. Fried likes to use units of atm to simplify the logarithm in the final line. I will not do that. I refuse to be a slave to atm.

Now we're left with an expression for the chemical potential as a function of the pressure and temperature of the sample. Notice that $\mu^\alpha(P_r)$ is a function of only temperature so that we can express it in terms of the enthalpy and entropy of the sample, with them as functions of temperature as well. Then, starting from Equation (5.2.7),[7]

$$\mu^\alpha(P, T) = RT \ln\left(\frac{P}{P_r}\right) + \mu^\alpha(T; P_r)$$
$$= RT \ln\left(\frac{P}{P_r}\right) + \tilde{H}^\alpha(T; P_r) - T\tilde{S}^\alpha(T; P_r)$$
$$= RT \ln\left(\frac{P}{P_r}\right) + \tilde{H}_v^\alpha(; T_v, P_r) + \tilde{C}_P^\alpha(T - T_v) - T\left(\tilde{S}^\alpha(; T_v, P_r) + \tilde{C}_P^\alpha \ln(T/T_v)\right)$$
$$= \tilde{H}_v^\alpha(; T_v, P_r) - T\tilde{S}^\alpha(; T_v, P_r) - \tilde{C}_P^\alpha T_v - T\left(R \ln\left(P/P_r\right) - \tilde{C}_P^\alpha + \tilde{C}_P^\alpha \ln(T/T_v)\right)$$
$$= \mu^\alpha(; T_v, P_r) - \tilde{C}_P^\alpha T_v - T\left(R \ln\left(P/P_r\right) - \tilde{C}_P^\alpha(1 - \ln(T/T_v))\right)$$

In the second line above I utilized Equations (5.2.4) and (5.2.5) to rewrite the enthalpies and entropies as

---

[6] At extreme pressures (we're talking on the order of gigapascals) solids undergo interesting pressure-dependent phase transitions. I think Dr. McQueen's lab might deal with pressures great enough to observe this.

[7] In the following expressions I've adopted the notation $T(x; y)$ where T is a variable which varies with x with some constant parameter y.

they varied with temperature as the sum of reference enthalpies and entropies and their respective changes over a temperature range according to their dependence on the heat capacity. I colored them to try and make it more clear what was being substituted and moved around because I feel like the derivation provided in the slides does a poor job of this. Also in the last line I substituted

$$\mu^{\alpha}(;T_v, P_r) = \tilde{H}_v^{\alpha}(;T_v, P_r) - T\tilde{S}^{\alpha}(;T_v, P_r)$$

by definition of the chemical potential for a phase.

At this point, I'm gonna stop doing math. We could try and simplify this further, however, we've reached a point where we can already draw some meaningful conclusions. Notice that everything on the right-hand side of the equation *varies only with pressure* for a fixed temperature. So, doing a tiny bit of analysis we find that *the chemical potential of the gaseous state increases as the pressure of the gas pressure increases so that the gaseous state becomes less thermodynamically favorable.* I know, it was an annoying set of mathematical manipulations to get to an arguably underwhelming result. I agree.

So we've derived some sort of pressure dependence of the chemical potential for a sample and now we're left to determine how the pressure dependence changes with temperature and vice versa. Recall from looking at thermodynamic potentials that we utilized PV diagrams to visualize the properties of a thermodynamic system. Here, we'll follow a similar procedure to visualize phase changes, instead utilizing a PT diagram. Below is the PT diagram of water. There a few labeled points: The *triple point* are the pressure and temperature conditions at which all three phases of matter exist in equilibrium. The *critical point* is the minimum pressure and temperature at which a substance can be distinguished between a gas and a liquid. In other words, beyond the critical point a substance can no longer be distinguished between the liquid and gas phases. Additionally, the triple point pressure corresponds to the minimum pressure at which the liquid phase of a substance can exist and the triple point temperature is *typically* the minimum temperature at which the liquid phase can exist[8].
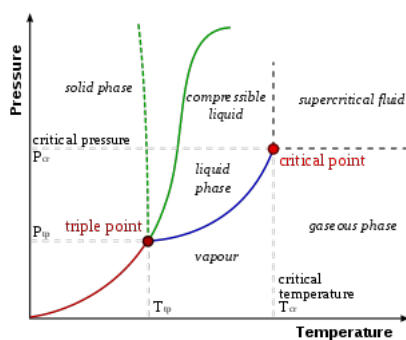
Figure 5.1: Phase diagram of water

Another major part of a phase diagram are the *coexistence curves,* the lines of the diagram on which neighboring phases can exist in equilibrium. The slopes of the coexistence curves are given by the *Clausius-Clapeyron equation.*

5.3   The Clausius-Clapeyron Equation

Although it's usually applied to liquid-vapor equilibrium, the Clausius-Clapeyron equation can be applied to a wide variety of circumstances: The conditions for validity are (1) it must involve equilibrium with respect to change that can take place reversibly at a constant temperature and pressure and (2) the equilibrium pressure must depend only on temperature.

---

[8]One of the exceptions to this is water which has a coexistence curve between the gaseous and liquid phase with a negative slope.

As mentioned above, the slopes of the coexistence curves on a phase diagram are expressed by the *Clausius-Clapeyron equation.* So, consider the equilibrium of two phases, an α and a β phase:

$$\mu^\alpha = \mu^\beta$$

Along a coexistence curve the chemical potential of a species will certainly change. Recall from the Gibbs-Duhem Equation (5.1.13) that the chemical potentials of the species in a thermodynamic system exhibit some dependence on the thermodynamic properties of that system. Hence, when the pressure and temperature of a sample change so will the chemical potentials. Along the coexistence curve, however, the change in potential will remain the same so that $d\mu^\alpha = d\mu^\beta$ and we can express

$$- \tilde{S}^\alpha dT + \tilde{V}^\alpha dP = -\tilde{S}^\beta dT + \tilde{V}^\beta dP \tag{5.3.1}$$

by Gibbs-Duhem. A little bit of algebraic gymnastics gets us to the desired expression:

$$-\tilde{S}^\alpha dT + \tilde{V}^\alpha dP = -\tilde{S}^\beta dT + \tilde{V}^\beta dP$$
$$(\tilde{V}^\beta - \tilde{V}^\alpha)dP = (\tilde{S}^\beta - \tilde{S}^\alpha)dT$$
$$\frac{dP}{dT} = \frac{\tilde{S}^\beta - \tilde{S}^\alpha}{\tilde{V}^\beta - \tilde{V}^\alpha}$$

Which affords the Clausius-Clapeyron equation, defined as

$$\left(\frac{dP}{dT}\right)_{\alpha \to \beta} = \frac{\Delta \tilde{S}^{\alpha \to \beta}}{\Delta \tilde{V}^{\alpha \to \beta}} \tag{5.3.2}$$

where a substance is transitioning from the α to the β phase. Clearly, since the entropy and volume change of a transition are not constant this slope will not be constant and we'd never expect the coexistence curve to be necessarily linear.

For most substances, we expect that the phase with a higher molar entropy ($\tilde{S}_{gas} > \tilde{S}_{liquid} > \tilde{S}_{solid}$) will also have a higher molar volume ($\tilde{V}_{gas} > \tilde{V}_{liquid} > \tilde{S}_{solid}$). Consequently, the slope of the coexistence curve is positive for almost all substances[9]

5.3.1 The Clapeyron Equation

The Clapeyron equation aims to approximate the thermodynamics of the liquid to gas phase transition for a substance. Beginning from Equation (5.3.2), we can approximate

$$\left(\frac{dP}{dT}\right)_{\alpha \to \beta} = \frac{\Delta \tilde{S}^{l \to g}}{\Delta \tilde{V}^{l \to g}} = \frac{\Delta \tilde{S}^{l \to g}}{\tilde{V}^g}$$

since the molar volume of the gaseous state will be far greater than that of the liquid phase. By the ideal gas law we can rewrite this as

$$\frac{\Delta \tilde{S}^{l \to g}}{\tilde{V}^g} = \frac{P \Delta \tilde{S}^{l \to g}}{RT}$$

and we can express the Clausius-Clapeyron equation as

$$\frac{dP}{P} = \left(\frac{\Delta \tilde{S}^{l \to g}}{R}\right)\frac{dT}{T} = \left(\frac{\Delta \tilde{H}_v}{R}\right)\frac{dT}{T^2}$$

---

[9]Water is an excellent example of a substance with a negative slope for the coexistence curve for the liquid and solid phases. This is because the density of ice is *less than* the density of water, hence why ice floats on water! Ultimately this property is due in part to the strong hydrogen bonding water exhibits.

where we took advantage of the fact that $\Delta \tilde{S}^{l \to g} = \Delta \tilde{H}_v / T$. Integrating this expression affords

$$\int_{P_r}^{P} \frac{dP}{P} = \frac{\Delta \tilde{H}_v}{R} \int_{T_r}^{T} \frac{dT}{T^2}$$

$$\ln \left(\frac{P}{P_r} \right) = \frac{-\Delta \tilde{H}_v}{R} \left(\frac{1}{T} - \frac{1}{T_r} \right) \tag{5.3.3}$$

which is the *Clapeyron equation*.

The utility of the Clapeyron equation is in its ability to determine any point on a coexistence curve, *given we know at least one other point and the enthalpy of vaporization*, $\Delta \tilde{H}_v$. But why the enthalpy of vaporization and not the enthalpy of fusion? Recall that the Clapeyron equation is an estimate for the liquid to gas phase transition. Thus, we're only interested in the enthalpy of vaporization.

Below is a birds-eye-view of what's been covered on phases so far:

1. A *phase* of a substance refers to a uniform macroscopic state characterized by certain types of interactions (enthalpy) and the substance's level of order (entropy). As a consequence, it will also be characterized by certain macroscopic properties (e.g., density, magnetism).

2. Phases can be characterized by an *order parameter*. Higher temperatures will favor the phase with lower order (gasses are favored over liquids, for example). The lower order phase typically has a lower enthalpy and higher entropy.

Now, here's an example problem utilizing (most) of what we talked about: The normal boiling point of benzene is 353.24 K and the vapor pressure of liquid benzene is 11.9 kPa at 298.15 K. The enthalpy of fusion is 9.95 kJ/mol and the vapor pressure of solid benzene is 137 Pa at 228.85 K. Firstly, compute $\Delta \tilde{H}_v$.

Notice that we have the following (P, T) pairs:

Phase	P (kPa)	T (K)
Liquid $\to$ Gas	101.325	353.24
Liquid	11.9	293.15
Solid	0.137	228.85

where the first coordinate was attained from the normal boiling point (normal implies atmospheric pressure), the second was given for the *liquid phase*, and the third was given for the *solid phase*. Then, the enthalpy of vaporization can be computed by the Clapeyron equation and the two (P, T) coordinates in the liquid phase:

$$\ln \left(\frac{101.325 \text{ kPa}}{11.9 \text{ kPa}} \right) = \frac{-\Delta \tilde{H}_v}{R} \left(\frac{1}{353.24 \text{ K}} - \frac{1}{293.15 \text{ K}} \right)$$

$$\Delta \tilde{H}_v = -R \ln \left(\frac{101.325 \text{ kPa}}{11.9 \text{ kPa}} \right) \left(\frac{1}{353.24 \text{ K}} - \frac{1}{293.15 \text{ K}} \right)^{-1}$$

$$= 30.69 \text{ kJ/mol}$$

Awesome!

Now compute $\Delta \tilde{S}_v$. This is far easier than above; all we have to do is divide the enthalpy of vaporization by the temperature of vaporization (which is given):

$$\Delta \tilde{S}_v = \frac{\Delta \tilde{H}_v}{T_v} = \frac{30.69 \text{ kJ/mol}}{353.24 \text{ K}} = 86.88 \text{ J/K/mol}$$

Amazing!

Lastly, find the triple point temperature and pressure for benzene. To compute the triple point we'll need to establish a system of 2 equations in 2 variables, those being the triple point temperature and triple point pressure. The two equations we'll use will consider as reference the points we're given on the coexistence

curves and use the triple point parameters as the unknowns. The naive chemist may set this system up as follows:

$$\ln\left(\frac{P_{tp}}{11.9 \text{ kPa}}\right) = -\frac{30.69 \text{ kJ/mol}}{R}\left(\frac{1}{T_{tp}} - \frac{1}{293.15 \text{ K}}\right)$$

$$\ln\left(\frac{P_{tp}}{0.137 \text{ kPa}}\right) = -\frac{9.95 \text{ kJ/mol}}{R}\left(\frac{1}{T_{tp}} - \frac{1}{228.85 \text{ K}}\right)$$

Why is this incorrect? Recall that the Clapeyron equation *is a model for transitions to the gaseous phase.* Hence, all of our equations should represent phase changes that evolve a gas. Notice that in the second equation which utilizes the enthalpy of *fusion* is illustrative of a transition from the solid to liquid phase. Instead of using the enthalpy of fusion we need to find the enthalpy of sublimation which is representative of a phase transition from the solid to gaseous state. Since enthalpy is a state function this can be computed with ease:

$$\Delta\tilde{H}_{sub} = \Delta\tilde{H}_{vap} + \Delta\tilde{H}_{fus} = 40.64 \text{ kJ/mol}$$

Then, our system becomes

$$\ln\left(\frac{P_{tp}}{11.9 \text{ kPa}}\right) = -\frac{30.69 \text{ kJ/mol}}{R}\left(\frac{1}{T_{tp}} - \frac{1}{293.15 \text{ K}}\right)$$

$$\ln\left(\frac{P_{tp}}{0.137 \text{ kPa}}\right) = -\frac{40.64 \text{ kJ/mol}}{R}\left(\frac{1}{T_{tp}} - \frac{1}{228.85 \text{ K}}\right)$$

which, following a little bit of algebraic gymnastics, affords the triple point temperature and pressures as $P_{tp} = 5.97$ kPa and $T_{tp} = 278$ K.

5.4 Gibbs Rule of Phase

Gibbs rule of phase, or just *the phase rule*, is a general principle governing PVT systems, that is, systems whose states are defined completely by pressure, volume, and temperature. The basis for this rule is that at equilibrium, the number of phases present places a constraint on the intensive variables. More rigorously, since the phases are in equilibrium with one another, the chemical potentials of the phases must be equal. Hence, a restriction is placed on one of P, V, or T by the Gibbs-Duhem equation.

Let's motivate a mathematical definition by working up from a 1-component system. For a system of one phase, say, solid, assuming we do not allow for any phase transitions, we are free to vary any one of P or T without affecting the identity of the solid. By introducing a second phase, say, liquid, we've restricted our system to the coexistence curve between the solid and liquid phases so that if we choose to vary T, P must also vary as to maintain the existence of both phases in equilibrium. Hence, we have one fewer *degree of freedom.* Naturally, at the triple point for a substance there are 0 degrees of freedom since the triple point is exactly that—a point. We could summarize the number of degrees of freedom F for this simple experiment as

$$F = 3 - \pi$$

where π is the number of phases of the substance present.

We could generalize our results to a system of multiple components with relative ease to afford the *Gibbs rule of phase*:

$$F = C - \pi + 2 \tag{5.4.1}$$

where F is the number of degrees of freedom a system has, π is the number of phases present, and C is the number of unique chemical species.[10]

---

[10]Materials scientists oftentimes deal with phase changes between solid structures and therefore imagine pressure as being constant. This convention affords what is commonly referred to as the *condensed phase rule*, and is expressed as $F = C - \pi + 1$.

6

CHEMICAL REACTIONS AND EQUILIBRIUM

Thermodynamics of mixing, connecting the macroscopic to the microscopic. Develop a theory of chemical equilibrium using potentials. Define some stuff.

The topic of "chemical reactions" is certainly a broad one: Everything ranging from why your apple rots when left out for too long to stars exploding in space can be considered a chemical reaction. Clearly, these two things are vastly different. One is the tragic destruction of something beautiful, the other has like a 0.000001% chance of affecting us cause stars are really far away. So, it's important we define *standard states* for different chemical processes[1].

A standard state is an *experimentally accessible reference state* for a thermodynamic quantity. Standard states are important because a multitude of thermodynamic quantities are easier to define *relative* to a standard state rather than being defined absolutely (consider the idea of trying to defining an absolute state for enthalpy as discussed in Section 5.2). We tackled this idea already a little bit with chemical potentials. Equation (5.2.7), for example, defines the chemical potential as a function of pressure given some reference pressure. Using the same equation as a motivating example, we can express the chemical potential for mixing two liquids together as

$$\mu_i^{soln} = \mu_i^* + RT \ln x_i \tag{6.0.1}$$

where μ_i^{soln} is the chemical potential of species i in the mixture, μ_i^* is the chemical potential of the pure liquid i with a mol fraction of 1, and x_i is the mole fraction of species i. We can express the potential for adding a solute to a solution analogously,

$$\mu_i^{soln} = \mu_i^\circ + RT \ln[i] \tag{6.0.2}$$

where μ_i° is the chemical potential of a solution with species i having a concentration of 1 M, and $[i]$ is the concentration of species i.

---

[1]One might think about how the standard states for the oxidation of an apple and a supernova differ.

6.1   The Thermodynamics of Mixing

As a simple model based off of the mixing discussed a moment ago, let's suppose we have a container of N lattice cells and we have N_p particles of species p and N_q particles of species q such that $N_p + N_q = N$. The maximum number of microstates associated with this system is given by the multinomial coefficient

$$W = \binom{N}{N_p, N_q} = \frac{N!}{N_p! N_q!}$$

and the minimum number of microstates would be 1, in the case where no mixing has occurred whatsoever. We can compute the change in entropy of this system, going from unmixed to completely mixed, using the Boltzmann equation:

$$\begin{aligned}
\Delta S_{mix} &= k_B \left(\ln W_f - \ln W_i \right) \\
&= k_B \ln \left(\frac{N!}{N_p! N_q!} \right) \\
&= k_B \left(N \ln N - N - (N_p \ln N_p - N_p) - (N_q \ln N_q - N_q) \right) \\
&= k_B \left((N_p + N_q) \ln N - N_p \ln N_p - N_q \ln N_q \right) \\
&= k_B \left[N_p \ln \left(\frac{N}{N_p} \right) + N_q \ln \left(\frac{N}{N_q} \right) \right] \\
&= -k_B(N) \left[\frac{N_p}{N} \ln \left(\frac{N_p}{N} \right) + \frac{N_q}{N} \ln \left(\frac{N_q}{N} \right) \right] \\
&= -k_B N (x_p \ln x_p + x_q \ln \ x_q)
\end{aligned} \tag{6.1.1}$$

Which gives us an expression for the entropy of mixing in terms of the mole fraction of each species. Notice that both x_p and x_q are less then zero, since they're mole fractions, and so $\Delta S_{mix} > 0$ as expected. What's reassuring is that we could have derived an equivalent expression from a macroscopic description of the system instead of a microscopic one:

$$\begin{aligned}
\Delta G_{mix} &= G_{mixed} - G_{unmixed} \\
&= (n_p \mu_p + n_q \mu_q)_{mixed} - (n_p \mu_p + n_q \mu_q)_{unmixed} \\
&= n_p (\mu_p^* + RT \ln x_p) + n_q (\mu_q^* + RT \ln x_q) - (n_p \mu_p^* + n_q \mu_q^*) \\
&= n_p RT \ln x_p + n_q RT \ln x_q \\
&= nRT \left(\frac{n_p}{n} \ln x_p + \frac{n_q}{n} \ln x_q \right) \\
&= nRT (x_p \ln x_p + x_q \ln x_q)
\end{aligned} \tag{6.1.2}$$

At this point, recall from Equation (3.4.4) that $S = -(\partial G / \partial T)_P$ which recovers the desired expression for the entropy in Equation (6.1.1). In the second line of the derivation above we made use of the definition of Gibbs free energy in terms of the chemical potential, Equation (5.1.7), and in the third line we utilized the reference state definitions defined in this section, in particular Equation (6.0.1). Lastly, notice that our expressions for ΔG_{mix} and ΔS_{mix} imply that $\Delta H_{mix} = 0$. Does this result make any sense?

Yes! When mixing there is no bond breaking or forming going on. Hence, there is no enthalpy change going on.

6.2   The Thermodynamics of a Chemical Reaction

In the analysis of mixtures above, we treated all components in the system as unreactive and although unreactive mixtures can exhibit interesting behaviors such as phase transitions, the complexity of a thermodynamic system cannot be described without chemical reactions.

Recall from our study of phase transitions that we could compute the free energy of a phase transition from the chemical potentials as $G = n^\alpha \mu^\alpha + n^\beta \mu^\beta$. Significantly, this equation implies that *the transition will proceed to completion*. That is, if we suppose $\mu^\beta < \mu^\alpha$ at a particular set of conditions, zero moles of phase α will exist at equilibrium because that would be the state which minimizes the free energy of the system. From the perspective of mixing, the reason why phase transitions proceed to completion is because it involves no unmixing. In contrast, the progression of a chemical reaction is associated with the breaking down and building up of different reactants and products, respectively. So, a reaction which proceeds to completion is associated with *complete unmixing*, which is clearly entropically unfavorable. Hopefully this point provides some intuition behind why we study equilibrium in the first place. The distribution of products and reactants for a chemical reaction in equilibrium gives us vital information about the thermodynamic favorabilities of each species and, as we'll see later, are crucial for calculating some of these thermodynamic quantities[2].

To begin our discussion on chemical reactions let's first establish some notation:

$$aA + bB \rightleftharpoons gG + hH$$
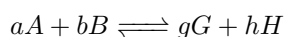
Here, A, B, G, and H are chemical species with respective reaction numbers a, b, g, and h. Additionally we'll define *reaction coefficients* ν_A, ν_B, ν_G, and ν_H as the reaction numbers for products and the opposite of the reaction numbers for the reactants. So, for a reaction like $2H_2 + O_2 \rightleftharpoons 2\,H_2O$,

$$\nu_{H_2O} = 2, \quad \nu_{H_2} = -2, \quad \nu_{O_2} = -1$$

This formalism allows us to describe a chemical reaction similar to a mathematical equation, using the reaction coefficients suh that

$$\sum_{i=1}^{n} \nu_i I_i = 0$$

where we sum over all species I_i in a reaction composed of n components.

Using the defined notation we'll approach defining a reaction energy in two ways. Firstly, we'll consider the difference between the chemical potentials of the products and reactants to deduce the free energy of reaction and secondly, we'll evaluate the differential free energy change with respect to the moles of reaction.

6.2.1   Free Energy of Reaction from Finite Differences

Here we'll consider a very direct approach of determining the free energy of a reaction, by representing it as the difference between the free energy of the products and of the reactants. Each of these moles of reaction are connected by the total number of moles involved in the reaction such that

$$\eta_i = \nu_i \eta_{rxn} \tag{6.2.1}$$

---

[2]Here I'll also mention the *Curtin-Hammett principle*, which concerns the distribution of products for a reaction as well, a more particular set of conditions. I mention this principle mainly caused I learned about it recently and still don't completely understand.

where ν_i is the reaction coefficient, defined above. This allows us to define the change in Gibbs free energy of reaction as

$$\begin{aligned}
\Delta G_{rxn} &= \eta_{react}\tilde{G}_{react} + \eta_{prod}\tilde{G}_{prod} \\
&= \nu_A \eta_{rxn}\tilde{G}_A + \nu_B \eta_{rxn}\tilde{G}_B + \nu_G \eta_{rxn}\tilde{G}_G + \nu_H \eta_{rxn}\tilde{G}_H \\
&= \eta_{rxn}(\nu_A \mu_A + \nu_B \mu_B + \nu_G \mu_G + \nu_H \mu_H)
\end{aligned} \tag{6.2.2}$$

and dividing both sides by the total number of moles involved in the reaction affords

$$\Delta \tilde{G}_{rxn} = \nu_A \mu_A + \nu_B \mu_B + \nu_G \mu_G + \nu_H \mu_H \tag{6.2.3}$$

Let's stop for a moment and consider the result above. Since an initially prepared chemical system will continue reacting spontaneously until reaching equilibrium we can deduce that $\Delta \tilde{G}_{rxn}$ is the amount of molar free energy evolved in this process. Naturally, this free energy change will depend on concentrations; if a system starts near equilibrium not much free energy will be evolved whereas if it starts far away from equilibrium there will a much more significant free energy change. Let's try and determine this dependence on concentration.

Recall from Equation (6.0.2) that we can express the chemical potentials of each species in terms of reference potentials and the concentration of the respective species. Hence, we can rewrite Equation (6.2.3) as

$$\begin{aligned}
\Delta \tilde{G}_{rxn} &= \nu_A(\mu_A^\circ + RT\ln[A]) + \nu_B(\mu_B^\circ + RT\ln[B]) \\
&\quad + \nu_G(\mu_G^\circ + RT\ln[G]) + \nu_H(\mu_H^\circ + RT\ln[H]) \\
&= \nu_A \mu_A^\circ + \nu_B \mu_B^\circ + \nu_G \mu_G^\circ + \nu_H \mu_H^\circ + RT\ln\left([A]^{\nu_A}[B]^{\nu_B}[G]^{\nu_G}[H]^{\nu_H}\right)
\end{aligned} \tag{6.2.4}$$

where the right-side terms are representative of the standard state and are *independent of initial concentrations* whereas the left-side terms within the logarithm are *entirely dependent on concentrations*. Notice that if we choose to evaluate $\Delta \tilde{G}_{rxn}$ at the standard state so that $\Delta \tilde{G}_{rxn} = \Delta \tilde{G}_{rxn}^\circ$ then by definition the right-most term of Equation (6.2.4) must be zero.

In other words, the left-side terms of the equation express the amount of free energy released in a reaction if the reaction commenced at standard state and the righ-side terms correct for the energy release in the event that species do not start at their standard state concentrations.

Unless this is the first chemistry class you've ever taken, you'll have seen the equation above already just with some different variable names. Suppose we define

$$\Delta \tilde{G}_{rxn}^\circ = \nu_A \mu_A^\circ + \nu_B \mu_B^\circ + \nu_G \mu_G^\circ + \nu_H \mu_H^\circ$$

as the *amount of free energy released in a chemical reaction that is initially prepared at its standard state* and

$$Q = [A]^{\nu_A}[B]^{\nu_B}[G]^{\nu_G}[H]^{\nu_H} = \frac{[G]^g[H]^h}{[A]^a[B]^b}$$

as the *reaction quotient*. Then, we're left with

$$\Delta \tilde{G}_{rxn} = \Delta \tilde{G}_{rxn}^\circ + RT\ln Q \tag{6.2.5}$$

as the *amount of free energy released in a chemical reaction that is prepared at some arbitrary conditions and allowed to reach equilibrium*.

The two unique terms in Equation (6.2.5) play very different roles in reaction thermodynamics and therefore warrant additional discussion. The first term imparts a *uniqueness* to the reaction and determines the specificity and cooperativity. Suppose we are developing a drug that must maintain a high affinity for a

molecular target. Then, it is $\Delta \tilde{G}^\circ_{rxn}$ which must be optimized. Although the second term affects the standard Gibbs free energy change in response to product and reactant concentrations it does so in a *predetermined way*. That is, once initial conditions are determined than Q is fixed. Now that we have an intuitive understanding of this equation we'll consider how it might change at equilibrium conditions.

As mentioned previously, we know that a chemical reaction will proceed to equilibrium at which point no more energy will be released and there is no more work the system can do on its surroundings[3]. In this case, $\Delta \tilde{G}_{rxn} = 0$ and so we can rewrite Equation (6.2.5) as

$$\Delta \tilde{G}^\circ_{rxn} = -RT \ln K_{eq} \tag{6.2.6}$$

where

$$K_{eq} = \frac{[G]^g_{eq}[H]^h_{eq}}{[A]^a_{eq}[B]^b_{eq}} \tag{6.2.7}$$

is the *equilibrium constant* which denotes the relationship between reactant and product concentrations once the equilibrium state is reached.

Here's a example problem illustrating the utility of some of the equations we derived: The acid dissociation constant, denoted K_a, is a measure of the distribution of free protons and conjugate base in solution for some acid. Recall that the pK_a of a molecule is an important measure of its acidity and is useful in comparing the acidities of different organic compounds. The pK_a of acetic acid is 4.76. Calculate the free energy change when 1 M acetic acid, initially placed in neutral water with 1 mM acetate, reaches equilibrium.

Equation (6.2.5) will be of great use to us here. First, we can compute the standard molar Gibbs free energy change of reaction using Equation (6.2.6):

$$\Delta \tilde{G}^\circ_{rxn} = -RT \ln K_a = -(8.3145)(298) \ln(10^{-4.76}) = 27.16 \text{ kJ/mol}$$

Before we can compute the molar Gibbs free energy change of reaction we need the reaction quotient, Q. Luckily we're given everything we need to compute that as well,

$$Q = \frac{[H^+][A^-]}{[HA]} = \frac{(10^{-7})(10^{-3})}{1} = 10^{-10}$$

and we can compute the molar Gibbs free energy change as,

$$\Delta \tilde{G}_{rxn} = \Delta \tilde{G}^\circ_{rxn} + RT \ln Q = 27.16 + (8.3145)(298) \ln 10^{-10} = -29.89 \text{ kJ.mol}$$

which is our final answer.

6.2.2   The van't Hoff Equation

Recall from Equation (**??**) that, by definition, we can express the Gibbs free energy as $\Delta G = \Delta H - T\Delta S$ so that Equation (6.2.6) can be rewritten to afford

$$\Delta \tilde{H}^\circ_{rxn} - T\Delta \tilde{S}^\circ_{rxn} = -RT \ln K_{eq}$$

$$\ln K_{eq} = \frac{-\Delta \tilde{H}^\circ_{rxn}}{R}\left(\frac{1}{T}\right) + \frac{\Delta \tilde{S}^\circ_{rxn}}{R} \tag{6.2.8}$$

Equation (6.2.8) is known as the *van't Hoff equation* and has exceptional utility because it allows us to disentangle the enthalpic and entropic contributions of the free energy by measuring the temperature depdendence of the equilibrium constant. There are a few key takeaways from this equation that are worth noting:

---

[3]Recall that one definition of free energy is that it is the amount of work available the system has to do work on its surroundings.

1. At very high temperatures, the *entropic* contribution dominates and at very low temperatures, the *enthalpic* contribution dominates.

2. If a reaction has a large *enthalpic* contribution, we would expect it to have a high temperature-dependence.

3. For exothermic reactions, increasing the temperature will shift the equilibrium *toward the reactants* since the right-hand side of the equation will become less positive and therefore $\ln K_{eq}$ will become less positive implying K_{eq} has shrunk. This is the basis for le Châtelier's principle.

As we know from, well... life... physical processes don't typically proceed at discrete time increments. That is, using a chemical transformation as an example, the species involved in a reaction are continuously being transformed instead of reactants being spontaneously converted into products, waiting a sec, and then being spontaneously converted again. Thus, the "finite differences" approach we took to determining the Gibbs free energy change of reaction above may be an alarm for some concern. Although Q allows us to compute $\Delta \tilde{G}^{\circ}_{rxn}$ at any set of reactant and product concentrations, Equation (6.2.5) is evaluated for a *fixed* set of these conditions. However, we know from physical intuition that as a reaction proceeds, reactants will be converted to products and therefore the concentrations of each species will be constantly changing. So what is the usefulness of Equation (6.2.5)? If you're a biochemist, fear not, since the "chemostatic" approach is actually quite common in cells because reactant and product concentrations are controlled by a network of biochemical reactions.

However, if you're like me and don't care for cells, this reassurance is anything but reassuring. In the next section we'll consider an approach which accounts for these differential changes in reactant and product concentrations.

6.2.3 Free Energy of Reaction from Differentials

In contrast to the method of finite differences, now we will consider a differential change in the chemical potentials which results in a more mathematical yet hopefully less conceptually-exhausting method of deriving the free energy change for a reaction. Recall Equation (5.1.12) that we can express the differential change in molar Gibbs free energy as a sum of chemical potentials,

$$d\tilde{G} = \sum_{i=1}^{n} \mu_i$$

and using the reaction defined above in Section 6.2.1 we can express a differential change in Gibbs free energy as

$$dG = \mu_A dn_A + \mu_B dn_B + \mu_G dn_G + \mu_H dn_H \tag{6.2.9}$$

An advantage we gain when studying the free energy of reaction from a differential approach is that we can concern ourselves with the total amount of reactant and product present (defined earlier as η_i for each species i) as opposed to the total amount of species *involved* in the reaction (defined earlier as η_{rxn}) which was necessary when handling the free energy of reaction from the perspective of finite differences. Hence, we can define the *extent of reaction*[4], denoted ξ, to describe how the number of moles of each species involved in a reaction changes as the reaction progresses. Intuitively, value of ξ represents how much the reactant has converted to product[5].

Because the variations of reaction we'll consider are infinitesimal, thereby leaving the chemical potential of each species effectively unchanged, we can express a differential change in moles for each species as

$$dn_i = \nu_i d\xi$$

---

[4]ξ can sometimes also be referred to as the "reaction coordinate."

[5]Relating this back to the finite differences approach, since we did not take into account any changes in reactant and product concentrations we could think of our method in Section **??** as taking place at a fixed value of ξ.

where ν_i is the reaction coefficient as defined earlier. Substituting this result into Equation (6.2.9) affords an expression for a differential change in Gibbs free energy:

$$dG = \mu_A \nu_A d\xi + \mu_B \nu_B d\xi + \mu_G \nu_G d\xi + \mu_H \nu_H d\xi$$

Notice that we can rewrite this expression as the differential equation

$$\left(\frac{\partial G}{\partial \xi} \right)_{T,P} = \mu_A \nu_A + \mu_B \nu_B + \mu_G \nu_G + \mu_H \nu_H = \Delta \tilde{G}_{rxn} \tag{6.2.10}$$

where the equality with $\Delta \tilde{G}_{rxn}$ comes by definition (and also Equation (6.2.3)). Notice that we define the partial derivative at a constant temperature and pressure because otherwise the chemical potentials of each species would be changing. In this instance, we don't want that.

The significance of Equation (6.2.10) is clear once we recall that the Gibbs free energy acts as an indicator of spontaneity at a constant temperature and pressure. If we observe G increasing as ξ increases (i.e., $(\partial G/\partial \xi)_{T,P} > 0$) then we'd expect the reaction to proceed in the direction that converts products back into reactants, that is, we'd expect ξ to decrease. Thus, when plotted against the extent of a reaction, the total Gibbs free energy serves as a reaction potential.

To illustrate some of these key principles, let's consider a simple chemical reaction $A \rightleftharpoons B$ with μ_A° and μ_B° as the standard chemical potentials for A and B, respectively. Additionally, assume that there are n_A moles of A and n_B moles of B such that $n_A + n_B = n$ where n is the total number of moles present. Then, the number of moles of reactant and product (n_A and n_B, respectively) can be expressed as $n_A = n(1 - \xi)$ and $n_B = n\xi$ where the initial solution is composed of entirely species A. Lastly, suppose that the molar volume of A is $\tilde{V}_A$ and that of B is $\tilde{V}_B$ and for the sake of simplicity assume that $\tilde{V}_A = \tilde{V}_B = V$. By Equations (5.1.12) and (6.0.2) we can express the Gibbs free energy with our new notation as

$$G = \sum_{i=1}^{\#\ \text{species}} \mu_i n_i = \mu_A n_A + \mu_B n_B$$

$$= (\mu_A^\circ + RT \ln[A]) n_A + (\mu_B^\circ + RT \ln[B]) n_B$$

$$= n(1 - \xi) \left[\mu_A^\circ + RT \ln \left(\frac{n(1 - \xi)}{V} \right) \right] + n\xi \left[\mu_B^\circ + RT \ln \left(\frac{n\xi}{V} \right) \right]$$

Recall from Equation (6.2.10) that we can compute the change in molar Gibbs free energy of reaction as the partial derivative of G with respect to ξ. Moreover, suppose we "standardize" the reaction and let $n_A + n_B = n = 1$. Thus,

$$\Delta \tilde{G}_{rxn} = \left(\frac{\partial G}{\partial \xi} \right)_{T,P} = \frac{\partial}{\partial \xi} \left\{ (1 - \xi) \left[\mu_A^\circ + RT \ln \left(\frac{1 - \xi}{V} \right) \right] + \xi \left[\mu_B^\circ + RT \ln \left(\frac{\xi}{V} \right) \right] \right\}$$

$$= -\mu_A^\circ - RT \left[1 + \ln \left(\frac{1 - \xi}{V} \right) \right] + \mu_B^\circ + RT \left[1 + \ln \left(\frac{\xi}{V} \right) \right]$$

$$= \mu_B^\circ - \mu_A^\circ + RT \left[-1 - \ln \left(\frac{1 - \xi}{V} \right) + 1 + \ln \left(\frac{\xi}{V} \right) \right]$$

$$= \mu_B^\circ - \mu_A^\circ + RT \ln \left(\frac{\xi}{1 - \xi} \right)$$

$$= \Delta \tilde{G}_{rxn}^\circ + RT \ln \left(\frac{\xi}{1 - \xi} \right) \tag{6.2.11}$$

Hopefully it's clear how this equation is the same as Equation (6.2.5). If not, I'll try to make it so. Recall that we defined $n_A = n(1 - \xi)$ and $n_B = \xi$ so that the expression in the logarithm becomes n_B/n_A. These are concentrations though! Nice catch! Recall that we let $\tilde{V}_A = \tilde{V}_B = V$ so that the volumes cancel out in the expression, hence why we're left with moles instead of concentrations.

The whole ξ thing get's pretty weird I'd say, so here's an example problem illustrating how we might use it to analyze a system: Assume that a sealed vessel at a constant pressure of 1 bar initially contains 2 moles of $NO_{2(g)}$. The system is allowed to equilibriate with respect to the reaction

$$2\,NO_{2(g)} \rightleftharpoons N_2O_{4(g)}$$
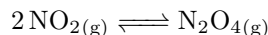
The number of moles of $NO_{2(g)}$ and $N_2O_{4(g)}$ at equilibrium are $2 - 2\xi$ and ξ, respectively, where ξ is the extent of reaction. Derive an expression for the entropy of mixing as a function of ξ.

Okay! We'll start from the change in Gibbs free energy of mixing:

$$\Delta G_{mix} = G_{\text{mixed}} - G_{\text{unmixed}}$$
$$= (n_1\mu_1)_{\text{mixed}} - (n_2\mu_2)_{\text{unmixed}}$$

where n_1 and n_2 represent the number of moles of $NO_{2(g)}$ and $N_2O_{4(g)}$, respectively, and μ_1 and μ_2 represent their respective chemical potentials. Continuing, and using Equation (6.0.1) to substitute for the chemical potentials which aren't in their standard state in the equation above, we have

$$(n_1\mu_1)_{\text{mixed}} - (n_2\mu_2)_{\text{unmixed}} = n_1(\mu_1^* + RT\ln x_1) + n_2(\mu_2^* + RT\ln x_2) - (n_1\mu_1^* + n_2\mu_2^*)$$

where x_1 and x_2 represent the respective mole fractions of $NO_{2(g)}$ and $N_2O_{4(g)}$. Hence,

$$\Delta G_{mix} = n_1(\mu_1^* + RT\ln x_1) + n_2(\mu_2^* + RT\ln x_2) - (n_1\mu_1^* + n_2\mu_2^*)$$
$$= n_1 RT\ln x_1 + n_2 RT\ln x_2$$
$$= (n_1 + n_2)RT\left[\left(\frac{n_1}{n_1+n_2}\right)\ln x_2 + \left(\frac{n_2}{n_1+n_2}\right)\ln x_2\right]$$
$$= nRT(x_1\ln x_1 + x_2\ln x_2)$$

where n represents the total number of moles in solution. You may recognize this expression from Equation (6.1.2). That's because they're the same thing. Noting that the enthalpy change associated with mixing is zero, we can determine the entropy change by the relationship $\Delta G = -T\Delta S$ to afford the entropy as a function of mole fractions:

$$\Delta S_{mix} = -nR(x_1\ln x_1 + x_2\ln x_2)$$

Now to express the mole fractions of each species as a function of ξ. Notice that the vessel initially contains 2 moles of reactant so that when $\xi = 0$, the number of moles is 2. As ξ increases, the moles of reactant will decrease by 2ξ (according to the reaction coefficient) and the moles of product will increase by ξ (again, according to the reaction coefficient). Hence, the mole fractions can be expressed as

$$x_1 = \frac{2 - 2\xi}{2 - \xi}, \quad \& \quad x_2 = \frac{\xi}{2 - \xi}$$

which affords an expression for the entropy of mixing in terms of the extent of reaction:

$$\Delta S_{\text{mix}} = -nR\left[\frac{2-2\xi}{2-\xi}\ln\left(\frac{2-2\xi}{2-\xi}\right) + \frac{\xi}{2-\xi}\ln\left(\frac{\xi}{2-\xi}\right)\right]$$

6.3   Conformational Equilibrium

In this section we'll apply everything we've learned about the thermodynamics of equilibrium and apply it to the conformational change of a protein. Surprisingly, a useful model for conformational equilibrium is a *two-state system* where a protein exists in either a folded (native) or unfolded state. While this seems like an

over-simplified model, we're already familiar with plenty of physical processes which exhibit this behavior: The conformational equilibrium between the two chair conformers of cyclohexane and the keto-enol tautomerization of a hydrocarbon are two great examples.

When dealing with conformational changes there are a few common aspects among every reaction of this type: They are reversible reactions, no atoms are (net) added or removed from the molecule, and no covalent bonds are "broken," only rearranged.

The conformational change we'll consider now is the unfolded and folded conformers of a protein in equilibrium with one another, modeled by $U \rightleftharpoons N$ where U and N represent the unfolded and native forms of the protein, respectively. This transformation has an equilibrium constant afforded by

$$K_{eq} = \frac{[N]}{[U]} \tag{6.3.1}$$

Already the beauty of this model is becoming clear: By knowing only the relative concentrations of the native and unfolded states we can determine some thermodynamic quantities that describe the system, namely, K_{eq} and $\Delta \tilde{G}^\circ$.

In practice, determining the concentrations of the native and unfolded states of the protein can be quite complex. One method has proven useful for studying proteins in conformational equilibrium is *circular dichroism spectroscopy*[6], or just CD spectroscopy. Circular dichroism relies on the difference in the absorption of left and right circularly polarized light, typically in the range of 200-230 nm. At these wavelengths, both α-helices and β-sheets display strong negative "ellipticity"[7] due to the regular and repetitive geometry of the structures. In contrast, unfolded coils consist of primarily random coils and don't display any sort of particular ellipticity. Hence, the CD spectra of folded and unfolded proteins will look very different.

Unsurprisingly, the experimental spectrum will be a *superposition* of the basis spectra, that is, the experimental spectrum will be a linear combination of the spectra for the unfolded and native proteins. The presence of an *isosbestic point* on the spectra supports this theory. Below is a CD spectra.
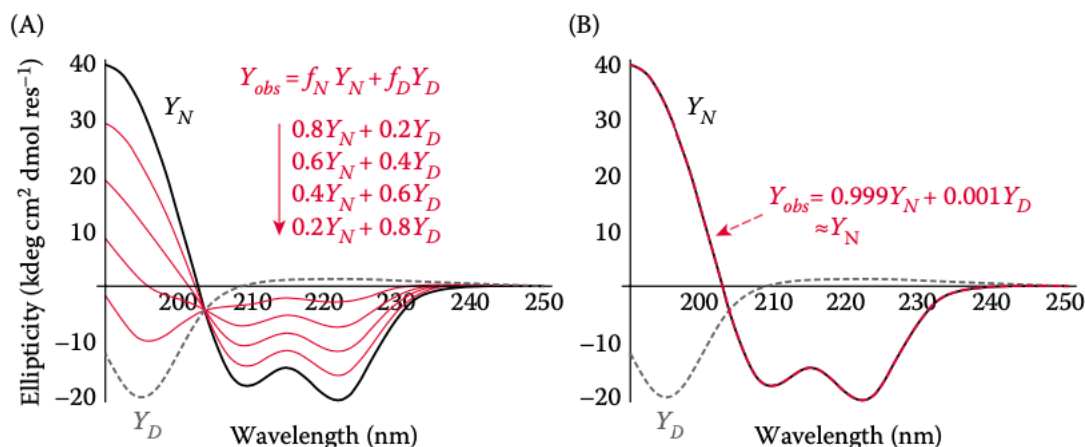
Figure 6.1: Circular dichroism spectrum, illustrating superposition of basis spectra. The *isobestic point* is the point at which all curves intersect. (A) Spectra of mixtures from the measurable equilibrium range. (B) Spectrum for a mostly folded mixture.

Now we will introduce the simplest, both experimentally and conceptually, model for conformational change, the *thermal unfolding transition*. Below is a theoretical graphic illustrating the distribution of conformers for the two-state system during thermal unfolding. Note that Dr. Barrick uses Y_D to denote the protein in a "denatured" state. I've been using Y_U to denote the same quantity.

---

[6]"Circular" refers to the polarization of light being measured and "dichroism" refers to the two types of light we can measure
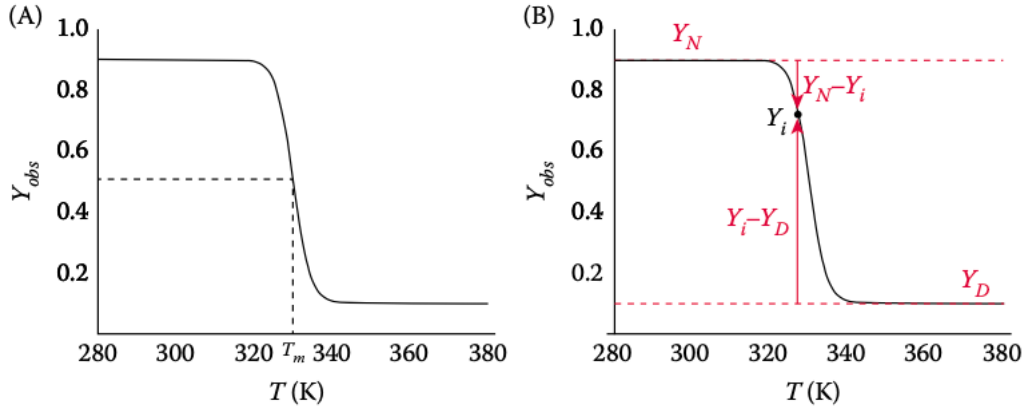
Figure 6.2: (A) The observed signal, the solid black line, shows a sharp transition between the native and denatured baselines. The value T_m is fixed at the arbitrarily fixed conditions in the graph. (B) The baselines play a key role in determining the value of fractional populations and equilibrium constants. The fractional populations f_N and f_U can be described geometrically with red arrows connecting the baseline to the observed signal.

Above, we see that by increasing the temperature of a system we can shift the equilibrium constant for most proteins toward the unfolded state. In the "baseline" regions of the native and unfolded states of the protein, the observed signal Y_{obs} is insensitive to changes in temperature. However, when the equilibrium constant shifts to the measurable range, the spectroscopic signal changes sharply with changes in temperature. The center of this transition, where the sample is such that $[N] = [U]$, is referred to as the *midpoint temperature*, oftentimes denoted as T_m. Suppose that we could measure the observable Y_{obs}. Then how could we determine K_{eq} from a set of Y_{obs} values?

The key idea lies in Figure 6.1, where we see that the signal Y_{obs} is linearly proportional to the amount of each state present. If we let f_N and f_U represent the *fractional populations*[8] of the native and unfolded states, respectively, we can represent the observed signal Y_{obs} as

$$Y_{obs} = f_U Y_U + f_N Y_N \tag{6.3.2}$$

Since $f_U + f_N = 1$ by the conservation of mass, we can rewrite the expression for Y_{obs} to afford

$$Y_{obs} = f_N Y_N + (1 - f_N)Y_U$$
$$= f_N Y_N + Y_U - f_N Y_U$$
$$= f_N(Y_N - Y_U) + Y_U$$
$$f_N = \frac{Y_{obs} - Y_U}{Y_N - Y_U} \tag{6.3.3}$$

A similar expression can be derived for the fractional population of Y_U:

$$f_U = \frac{Y_N - Y_{obs}}{Y_N - Y_U} \tag{6.3.4}$$

With Equations (6.3.3) and (6.3.4) we can give a description of the equilibrium constant, after some algebraic

---

using this method.

[7]Ellipticity is a measure of CD strength and is proportional to the amount of structured molecules present.

[8]The fractional populations f_U and f_N, which range from zero to 1, can be thought of as probabilities, as long as the sample is large enough for good averaging (by the law of large numbers).

manipulation. Start by noticing

$$\frac{f_N}{f_U} = \left(\frac{Y_{obs} - Y_U}{Y_N - Y_U}\right)\left(\frac{Y_N - Y_U}{Y_N - Y_{obs}}\right) = \frac{Y_{obs} - Y_U}{Y_N - Y_{obs}}$$

and that we could have also expressed the fractional populations as $f_U = [U]/([U] + [N])$ and $f_N = [N]/([U] + [N])$ so that the ratio above could be alternatively expressed as

$$\frac{f_N}{f_U} = \left(\frac{[N]}{[U] + [N]}\right)\left(\frac{[U] + [N]}{[U]}\right) = \frac{[N]}{[U]} = K_{eq} \tag{6.3.5}$$

Geometrically, we can think of K_{eq} as the ratio of the two red arrows in Figure 6.2. For this reason, we need enough sample points in the "baseline" regions to know where to start these arrows when trying to analyze CD spectroscopy data. With this in mind, we can think of the conformational transition as containing three distinct regions: The native conformer baseline, the transition region, and the unfolded conformer baseline.

Referring back to Equation (6.3.5), we have that

$$K_{eq} = \frac{Y_{obs} - Y_U}{Y_N - Y_{obs}} \tag{6.3.6}$$

which allows us to (finally) rewrite the observable quantity Y_{obs} as

$$Y_{obs} = \frac{Y_U + Y_N K_{eq}}{1 + K_{eq}} = \frac{Y_U + Y_N e^{-(\Delta \tilde{H}^\circ - T\Delta \tilde{S}^\circ)/RT}}{1 + e^{-(\Delta \tilde{H}^\circ - T\Delta \tilde{S}^\circ)/RT}} = \frac{Y_U + Y_N e^{-(\Delta \tilde{H}^\circ/RT)}e^{(\Delta \tilde{S}^\circ/R)}}{1 + e^{-(\Delta \tilde{H}^\circ/RT)}e^{(\Delta \tilde{S}^\circ/R)}} \tag{6.3.7}$$

Equation (6.3.7) illustrates the enthalpy and entropy dependence of the observable Y_{obs}. Moreover, we see that Y_{obs} varies with temperature. Naturally, the next question we might ask is whether or not $\Delta \tilde{H}^\circ$ and $\Delta \tilde{S}^\circ$ depend on temperature as well (the answer is that they do).

You may recsall that we have numerous definitions and expressions for the heat capacity. In this instance, while we're trying to determine the temperature dependence of the enthalpy and entropy, we'll mainly be concerned with the relationship $d\tilde{H} = \tilde{C}_P dT$. Similarly, we have that $d\tilde{S} = (\tilde{C}_P/T)dT$. UNFINISHED

CHAPTER

7

CALORIMETRY AND THERMOCHEMISTRY

As the name(s) imply, calorimetry and thermochemistry rest on the analysis of heat energy and exchange with a system's surroundings. As such, the enthalpy of reaction will be of primary consideration constantly, in (slight) contrast to the discussion on thermodynamics previously. This contrast poses a question: Why is it that the entropy of a reaction is emphasized so heavily in our formal development of thermodynamics, whereas when we begin to analyze chemical reactions and processes everything seems to be dominated by enthalpy?

The answer to this question lies in *how we define a system*. Oftentimes, the thermodynamic system of interest in calorimetry and thermochemistry is defined as the reacting molecules and is typically closed (the system is exchanging heat with the surroundings but not matter). In this system, the bonds of each molecule are broken and reformed to create a lower energy ensemble of particles. This results in the *enthalpy of reaction*.

When this heat is released (or absorbed) from a reaction it goes into heating up (or cooling down) the surroundings, by the second law of thermodynamics. If we alter our POV of the system from the collection of particles to the collection of particles *and* the surroundings, we can imagine that the system is isolated. Then, since the energy of an isolated system must be conserved, the latent energy[1] in the "energy-rich" bonds of the molecules that go into heating up the surroundings don't actually change the energy of the system.

The hotter surroundings will be associated with a greater entropy since

$$\Delta S_{surr} = \int_{T_{low}}^{T_{high}} \frac{C_{P,surr}(T)}{T} dT > 0$$

where the change in temperature of the surroundings can be determined by

$$-\Delta H_{rxn} = \int_{T_{low}}^{T_{high}} C_{P,surr}(T) dT$$

Thus, if we consider the system as including both the reacting molecules and the immediate surroundings, we would say that reactions occur because they are *entropically favored*—there are not as many configurations

---

[1]latent energy

associated with the energy "trapped" in bonds as compared to the energy liberated into thermal motion.

7.1 Calorimetry

Calorimetry is the process of measuring the amount of heat released or absorbed during a chemical reaction. There are numerous different types of calorimetry to consider: Constant-pressure, constant-volume, and differential scanning calorimetry are all tools which have proven their use in many fields of physical chemistry.

No matter the method by which heat exchange is measured, calorimetry is useful in the succeeding section on *thermochemistry*, the study of heat energy. As we'll see, calorimetry provides a much more direct measurement of various equilibria, including conformational equilibria discussed previously.

7.1.1 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) is a technique in which the difference in amount of heat required to increase the temperature of a sample, i.e., the heat capacity, is measured as a function of temperature. This "differential" heat capacity is denoted $\delta \tilde{C}_P$. As the name implies, our goal is to make the differences in temperature at each step we measure the difference in heat as small as possible in order to accurately measure the heat capacity of a substance.

Since unfolded and folded proteins have different heat capacities, DSC is useful in elucidating the structures of different conformers for the protein. As we saw earlier in Section 6.3 on conformational equilibrium, the fastest rate of change between the native and unfolded state occurs at T_m, the midpoint temperature. This is where the spike occurs in Figure 7.1A.
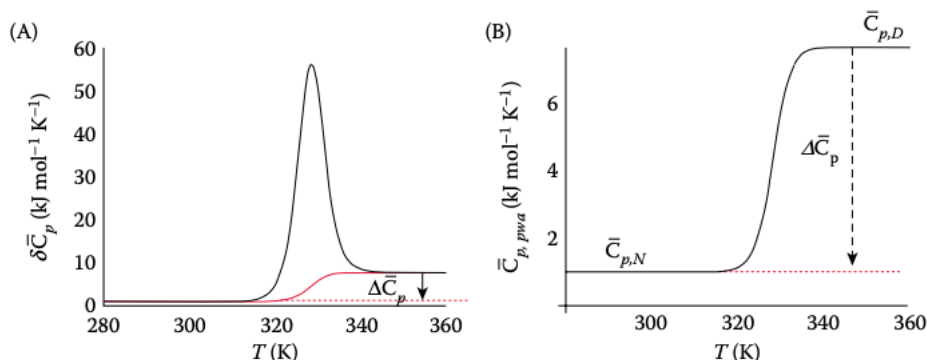
Figure 7.1: (A) A DSC folding transition (black line) super imposed on the population-weighted average heat capacity (red line denoted by $\tilde{C}_{P,pwa}$, shown in (B) as black line). The area between the black and red lines is the enthalpy of unfolding for the reaction. (B) An expanded view of the population-weighted average heat capacity. Note that the difference between the two baselines is the change in molar heat capacity.

Wait a minute... does the sharp peak we see at T_m even make sense? An increase in heat capacity certainly makes sense; after all, the heat capacity of the unfolded state is greater than that of the native state. However, if that were the only explanation, we'd expect a step function rather than a peak.

To rationalize this result we'll have to do some math. We can express the measured differential heat capacity as

$$\delta \tilde{C}_P = \tilde{C}_{P,pwa} + \tilde{C}_{P,ex} \tag{7.1.1}$$

where $\tilde{C}_{P,pwa}$ represents the population-weighted average heat capacity of the sample[2], and $\tilde{C}_{P,ex}$ represents the "excess" heat capacity which must be added to $\tilde{C}_{P,pwa}$ to afford the measured $\delta \tilde{C}_P$. We can rewrite

---

[2]The "population-weighted average" can be thought of as the sum of the heat capacities of native and unfolded proteins multiplied by their respective fractional populations. I'm trying to find a way to rephrase the term "weighted average" but I feel the name itself is already pretty self-explanatory.

$\tilde{C}_{P,pwa}$ in terms of the heat capacities for the native and unfolded states to afford a new expression for $\delta\tilde{C}_P$:

$$\begin{aligned}
\delta\tilde{C}_P &= f_N\tilde{C}_{P,N} + f_U\tilde{C}_{P,U} + \tilde{C}_{P,ex} \\
&= f_N\tilde{C}_{P,N} + (1 - f_N)\tilde{C}_{P,U} + \tilde{C}_{P,ex} \\
&= \tilde{C}_{P,U} + f_N\Delta\tilde{C}_{P,N} + \tilde{C}_{P,ex}
\end{aligned} \tag{7.1.2}$$

To secure a better understanding of the shape of the DSC curve we need an analytical expression for $\tilde{C}_{P,ex}$. This can be determined from analyzing the differential enthalpy, δH. Unlike the heat capacity, dH is simply a linear combination of the weighted averages for the native and unfolded state since enthalpy is a state function:

$$\begin{aligned}
\delta\tilde{H} &= f_N\tilde{H}_N + f_U\tilde{H}_U \\
&= \tilde{H}_U + f_N\Delta\tilde{H}
\end{aligned} \tag{7.1.3}$$

Equation (7.1.3) can be obtained by following a similar algebraic approach as was taken to afford Equation (7.1.2). Because DSC measures heat capacity, we must find a way to relate these enthalpies to the heat capacity of a protein. Lucky for us the heat capacity at a constant pressure is equal to the partial derivative of the enthalpy with respect to temperature:

$$\begin{aligned}
\delta\tilde{C}_P &= \left(\frac{\partial\delta\tilde{H}}{\partial T}\right)_P \\
&= \left(\frac{\partial(\tilde{H}_U + f_N\Delta\tilde{H})}{\partial T}\right)_P \\
&= \left(\frac{\partial\tilde{H}_U}{\partial T}\right)_P + f_N\left(\frac{\partial\Delta\tilde{H}}{\partial T}\right)_P + \Delta\tilde{H}\left(\frac{\partial f_N}{\partial T}\right)_P
\end{aligned} \tag{7.1.4}$$

The first two derivatives are simply expressions for heat capacity which sum to afford $\tilde{C}_{P,pwa}$ by Equation (7.1.2). Therefore, we are left with

$$\tilde{C}_{P,ex} = \Delta\tilde{H}\left(\frac{\partial f_N}{\partial T}\right)_P \tag{7.1.5}$$

which explains where the "extra" heat capacity comes from.

How can we interpret Equation (7.1.5)? Firstly, it should be clear that the large amplitude of the peak comes from the derivative term, since the derivative of the transition is so large. At the baseline values, where there is no change in the fractional populations of the native and unfolded states, the derivative term goes to zero and we see the plots in Figure 7.1A superimposed on one another.

Alternatively we could relate this unexpected behavior to what we already know about phase transitions: Just as how in a phase transitions all energy being put into the system goes into breaking interactions rather than raising the temperature, in protein folding the energy being put into the system goes into altering the conformation of the protein rather than raising the temperature of the system.

Our goal now is to fit DSC folding transitions. To do this, we'll start by expressing the derivative in Equation (7.1.5) in terms of some protein folding parameters. Note that

$$\begin{aligned}
f_N &= K_{eq}f_U \\
&= K_{eq}(1 - f_N) \\
&= K_{eq} - f_N K_{eq} \\
f_N(1 + K_{eq}) &= K_{eq} \\
f_N &= \frac{K_{eq}}{K_{eq} + 1}
\end{aligned}$$

and so we can compute the derivative as

$$
\begin{aligned}
\left(\frac{\partial f_N}{\partial T}\right)_P &= \frac{\partial}{\partial T}\left(\frac{K_{eq}}{K_{eq}+1}\right)_P \\
&= \frac{(K_{eq}+1) - K_{eq}}{(K_{eq}+1)^2}\frac{\partial K_{eq}}{\partial T} \\
&= \frac{1}{(K_{eq}+1)^2}\frac{\partial K_{eq}}{\partial T}
\end{aligned}
$$
(7.1.6)

At this point both Dr. Barrick and Dr. Fried make a substitution that I don't think either of them ever explain once which, understandably, is confusing. So, let me make it more clear. Notice that

$$
\frac{\partial \ln K_{eq}}{\partial T} = \frac{1}{K_{eq}}\frac{\partial K_{eq}}{\partial T} \;\; \Rightarrow \;\; K_{eq}\frac{\partial \ln K_{eq}}{\partial T} = \frac{\partial K_{eq}}{\partial T}
$$

Thus, we can rewrite Equation (7.1.6) as

$$
\left(\frac{\partial f_N}{\partial T}\right)_P = \frac{1}{(K_{eq}+1)^2}\frac{\partial K_{eq}}{\partial T} = \frac{K_{eq}}{(K_{eq}+1)^2}\frac{\partial \ln K_{eq}}{\partial T}
$$
(7.1.7)

Why even bother making our lives more difficult in this way? Recall Equation (6.2.8), namely, the van't Hoff equation, which relates the natural logarithm of the equilibrium constant to relevant thermodynamic quantities. Taking the derivative of the van't Hoff equation with respect to temperature affords

$$
\left(\frac{\partial f_N}{\partial T}\right)_P = \frac{K_{eq}}{(K_{eq}+1)^2}\frac{\Delta \tilde{H}}{RT^2}
$$

The left-most term of the right hand side in the equation above is known as the "spread over states" term, alternatively expressed as

$$
\frac{K_{eq}}{(K_{eq}+1)^2} = \frac{K_{eq}}{K_{eq}+1} \times \frac{1}{K_{eq}+1} = f_N f_U
$$
(7.1.8)

In addition to the fact that this expression *peaks at T_m*, the spread over states term appears in a variety of conformational equilibria such as ligand-binding interactions. For two-state systems, such as the one we're currently interested in, it represents the extent to which the population is spread out over N and U.

Putting everything we have together finally, our expression to fit the DSC curve is given as

$$
\delta \tilde{C}_P = \tilde{C}_{P,U} + f_N \Delta \tilde{C}_{P,N} + \frac{K_{eq}}{(K_{eq}+1)^2}\frac{\Delta \tilde{H}^2}{RT^2}
$$
(7.1.9)

7.1.2 Bomb Calorimetry (Constant Volume Calorimetry)

To measure the heat associated with a chemical transformation (most commonly combustion) we can use bomb calorimetry. In a bomb calorimetry experiment, we ignite a (typically highly exothermic) chemical reaction in a container of a fixed volume and record the change in temperature of the water reservoir surrounding the calorimeter. Because $dV = 0$, there is no work done by the system and by the first law of thermodynamics we have that $q = \Delta U$. This heat will go into warming up the vessel and water bath. If we define our thermodynamic system as being the reaction, vessel, and water bath, all of which are encased in a thick diathermal container,[3] no heat is lost to the surroundings.

The tricky part of this sort of experiment is determining the heat capacity of the calorimeter which will be some weighted average of the heat capacity of the steel vessel and the water:

$$
C_{V,\text{calorimeter}} = n_{\text{water}}\tilde{C}_{V,\text{water}} + n_{\text{vessel}}\tilde{C}_{V,\text{vessel}}
$$

---

[3]This is a fancy way of saying no heat can be exchanged through the container.

In practice, we can evaluate the heat capacity of the calorimeter (often referred to as the *calorimeter constant*) by performing a reaction with a known ΔU_{rxn} and working backwards:

$$\Delta U_{rxn} = \Delta T(n\tilde{C}_{V,water} + C_{cal})$$

As we've seen before, at a constant pressure $q = \Delta H$ so that the calorimeter constant can be used to measure ΔH_{rxn}:

$$\Delta H_{rxn} = C_{P,cal}\Delta T \qquad (7.1.10)$$

If we performed this reaction at 298 K and 1 atm we will have measured ΔH_{rxn}°, by definition.

7.2 Thermochemistry

Thermochemistry is the study of heat energy associated with chemical reactions and physical transformations. Chemical reactions may absorb or release heat, those being endothermic and exothermic reactions, respectively. In combination with entropic calculations, the spontaneity of a chemical reaction may be determined from the Gibbs free energy change.
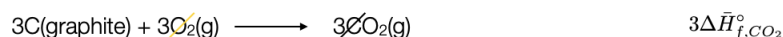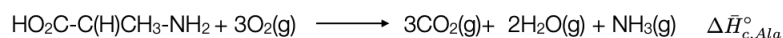
7.2.1 Heats of Formation

The *standard enthalpy of formation*, or just *standard heat of formation* is the change in enthalpy during the formation of 1 mole of a substance from its constituent elements with all substances in their standard states. An example reaction which satisfies these conditions might be the formation of carbon dioxide:

$$C_{(s,graphite)} + O_{2(g)} \longrightarrow CO_{2(g)} \quad \Delta\tilde{H}_f^{\circ} = -393.5 \text{ kJ/mol}$$
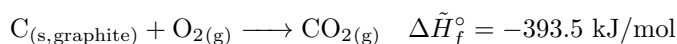
The true utility of heats of formation rest on the fact that enthalpy is a state function which permits the use of *Hess's law*, stating that the heat of any reaction is equal to the sum of the heats of reaction which in sum are equivalent to the overall reaction. Here is an entire example I've stolen from the lecture slides because (i) it's a good example of using Hess's law and (ii) as if I'm gonna type all that out for a concept that I already understand very well.

Example: What is $\Delta\bar{H}_f^{\circ}$ of alanine:

$$3\text{ C(graphite)} + 3.5\text{H}_2(g) + \text{O}_2(g) + 0.5\text{N}_2(g) \longrightarrow \text{HO}_2\text{C-C(H)CH}_3\text{-NH}_2$$

$$\text{HO}_2\text{C-C(H)CH}_3\text{-NH}_2 + 3\text{O}_2(g) \longrightarrow 3\text{CO}_2(g) + 2\text{H}_2\text{O}(g) + \text{NH}_3(g) \quad \Delta\bar{H}_{c,Ala}^{\circ}$$

$$3\text{CO}_2(g) + 2\text{H}_2\text{O}(g) + \text{NH}_3(g) \longrightarrow \text{HO}_2\text{C-C(H)CH}_3\text{-NH}_2 + 3\text{O}_2(g) \quad -\Delta\bar{H}_{c,Ala}^{\circ}$$

$$3\text{C(graphite)} + 3\text{O}_2(g) \longrightarrow 3\text{CO}_2(g) \quad 3\Delta\bar{H}_{f,CO_2}^{\circ}$$

$$2\text{H}_2(g) + \text{O}_2(g) \longrightarrow 2\text{H}_2\text{O}(g) \quad 2\Delta\bar{H}_{f,H_2O}^{\circ}$$

$$0.5\text{N}_2(g) + 1.5\text{H}_2(g) \longrightarrow \text{NH}_3(g) \quad \Delta\bar{H}_{f,NH_3}^{\circ}$$

$$\Delta\bar{H}_{f,Ala}^{\circ} = -\Delta\bar{H}_{c,Ala}^{\circ} + 3\Delta\bar{H}_{f,CO_2}^{\circ} + 2\Delta\bar{H}_{f,H_2O}^{\circ} + \Delta\bar{H}_{f,NH_3}^{\circ}$$

Figure 7.2: Using Hess's law to determine the heat of formation of the amino acid alanine.

As a consequence of our definition, ΔH_f° will be zero for pure elements in their most stable states. However, this is quite alright because "absolute enthalpy" is already something we've determined is arbitrary.

Entropy, however, is different. We can define *absolute molar entropies* for each substance by the third law of thermodynamics. Moreover, it is necessarily nonzero for all substances in their pure forms.

What would a discussion on thermodynamics be without the Gibbs free energy? Since ΔG_f° depends on the enthalpy of formation it is also not possible to define this quantity on an absolute scale. Hence, the common

convention is to define ΔG_f° to be zero for elements in their most stable states. In principle, this ignores the absolute entropy of an element, however, when computing ΔG_{rxn}°, this contribution goes away and we have nothing to fear. That is to say, we can define entropy on an absolute scale but it is not necessary to do so to determine ΔS_{rxn}°.

Here is an example illustrating the use of heats of formation and thermodynamic cycles: Suppose I'm interested in developing a catalyst to perform the following chemical reaction:

$$\text{Benzene}_{(l)} + 3\,\text{H}_{2(g)} \rightleftharpoons \text{Cyclohexane}_{(l)} \quad \Delta H_{rxn} = -202 \text{ kJ/mol}$$
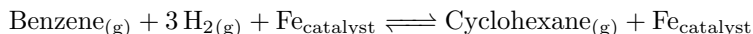
In a constant pressure calorimeter I combust benzene at STP and find that the temperature of 10 kg of water in the calorimeter increases by 6°C. My friend Sai runs the same experiment, this time using only 1 kg of water in his calorimeter, and finds that the temperature of the water reservoir increases by 58.5°C. Why was the temperature increase of Sai's experiment not simply ten times greater than that of my experiment?

Instead of doing math I'll offer a conceptual answer to this question. Obviously with less water in the calorimeter, the temperature of the water will increase by more because the specific heat capacity is the amount of heat required to raise the temperature of a kilogram of a substance by a unit celsius. Hence, with more mass and the same heat afforded to the system there will be a smaller change in temperature. However, note that the heat capacity is *not constant*, and *can vary significantly over large temperature ranges.* In Sai's experiment there was a large increase in temperature and so the heat capacity of the water increased enough to illustrate an experimental difference in the expected temperature change of the reservoir.

Ultimately, the discrepancy we see is due to the fact that the heat capacity of all substances is a function of the temperature, and in particular, increases with temperature.

With a year of committed research I've finally discovered a catalyst that can hydrogenate benzene, with the caveat that it works only at 400 K, where the following reaction takes place:

$$\text{Benzene}_{(g)} + 3\,\text{H}_{2(g)} + \text{Fe}_{\text{catalyst}} \rightleftharpoons \text{Cyclohexane}_{(g)} + \text{Fe}_{\text{catalyst}}$$

Our work isn't done, however, because now I am interested in determining the standard enthalpy of reaction for this synthesis. Describe the relevant thermodynamic quantities I'll need to compute ΔH_{rxn}° at 400K, and write a mathematical expression with these quantities to explicitly show how ΔH_{rxn}° at 400 K can be found. You don't have to evaluate the expression but I'm not your mom I'm not gonna tell you what to do.

To compute the enthalpy of reaction at 400 k we'll need the enthalpies of formation of everything involved in the reaction, heats of vaporization for benzene and cyclohexane, the heat capacities of benzene and cyclohexane in both the liquid and gaseous states for each compound, and the heat capacity of $\text{H}_{2(g)}$. Notice that I omitted the catalyst from the necessary quantities we'll need. This is because the catalyst appears in the same phase on both sides and therefore won't affect the enthalpy of reaction at all. Also, notice that we're given the enthalpy of reaction for the hydrogenation of benzene to cyclohexane in their liquid states above. So, instead of requiring the heats of formation for each compound we can base our analysis off of the enthalpy of reaction for the liquid phase transformation which affords us no need for knowing the heats of formation for any of the reactants or products.

Figure 7.3 hopefully summarizes what I just said. Thus, an expression for ΔH_{rxn}° at 400K is given by

$$\Delta \tilde{H}_{rxn}(400 \text{ K}) = \Delta \tilde{H}_{rxn}^\circ$$
$$+ \left\{ \int_{298}^{T_{v,benz}} \left(\tilde{C}_{P,benz} + 3\tilde{C}_{P,\text{H}_2} dT \right) + \Delta \tilde{H}_{vap,benz} + \int_{T_{v,benz}}^{400} \left(\tilde{C}_{P,benz} + 3\tilde{C}_{P,\text{H}_2} dT \right) \right\}$$
$$+ \left\{ \int_{298}^{T_{v,cxh}} \tilde{C}_{P,cxh} dT + \Delta \tilde{H}_{vap,cxh} + \int_{T_{v,cxh}}^{400} \tilde{C}_{P,cxh} dT \right\}$$

where the first term is the heat of reaction for the hydrogenation in the liquid phase, the second term

$benzene_{(298K, liq)} + 3\ H_{2(298K, g)} \rightleftharpoons CxH_{(298K, liq)}$

heating up, $C_{P,benz(l)}$ & $C_{P,H2(g)}$ | heating up, $C_{P,CxH(l)}$

$benzene_{(353.2K, liq)} + 3\ H_{2(353.2K, g)}$ | $CxH_{(354.2K, liq)}$

vaporize benzene, $\Delta H_{vap,benz}$ | vaporize, $\Delta H_{vap,CxH}$

$benzene_{(353.2K, g)} + 3\ H_{2(353.2K, g)}$ | $CxH_{(354.2K, g)}$

heating up, $C_{P,benz(g)}$ & $C_{P,H2(g)}$ | heating up, $C_{P,CxH(g)}$

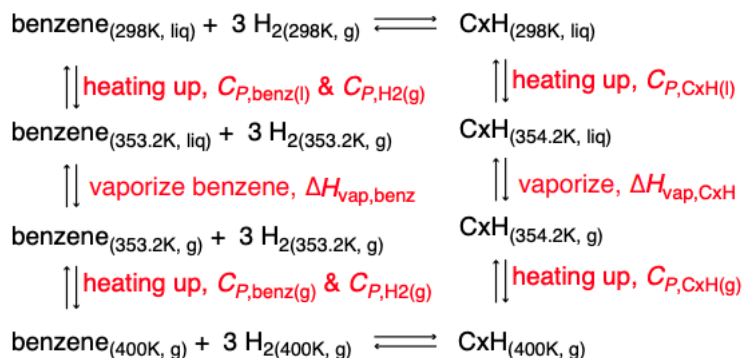$benzene_{(400K, g)} + 3\ H_{2(400K, g)} \rightleftharpoons CxH_{(400K, g)}$

Figure 7.3: Thermodynamic cycle for the proposed hydrogenation of benzene to cyclohexane. Shoutout Dr. Fried for making this graphic.

represents the contribution from the heating up and vaporization of the reactants, and the third term represents the heating up and vaporization of the product. Also note that I used $T_{v,X}$ to represent the temperature of vaporization for a species X cause they weren't given to us.

7.2.2 Bond Dissociation Enthalpy

The *bond dissociation enthalpy*[4] (BDE) is the energy needed to break one mole of a bond between atoms to give separated atoms whilst the compound is in a gaseous state. Organic chemists tend to focus more attention on the breaking of specific bonds in a molecule as opposed to creating one from its constituent elements.

BDEs are necessarily positive since breaking bonds requires an input of energy. Interestingly, BDEs are measured using spectroscopic models of bond vibrations, since the reactions are oftentimes too difficult to execute experimentally.[5]

Bond dissociation energies have proven useful in predicting whether a chemical reaction will be enthalpically favorable or not. This is all fine and dandy, however, using BDEs is not always exact because the energy of one sort of bond in a particular molecule will not always be the same as the same type of bond in a different molecule. Why? This is the question that Sidney Benson sought to answer (in the next section, in fact).

Here is a question regarding bond dissociation energies from one of the homeworks that I thought was cool: Consider the possibility that the Cope rearrangement proceeds through a biradical intermediate. We could imagine two such possible pathways, illustrated in Figure 7.4. Evaluate the feasibility of the two mechanisms, based on the following data:

Quantity	kcal/mol
ΔH_f°(1,5-hexadiene)	20.1
ΔH_f°(propene)	4.8
ΔH_f°(cyclohexane)	-29.5
BDE(H$-$H)	104
BDE(H$-$propyl)	86.5
BDE(H$-$cyclohexyl)	95.5

To evaluate the feasibility of each mechanism we can start by computing the enthalpy of formation for the two intermediates. For the top intermediate in Figure 7.4, the heat of formation is going to be a linear combination of the heat of formation for two propene groups, the BDE(H$-$propyl), and the BDE(H$-$H) since the H atoms we liberate will react to form H_2 gas.

---

[4]The bond dissociation enthalpy can also be referred to as the bond dissociation energy and even just the bond strength. For all intents and purposes, these phrases are interchangeable.

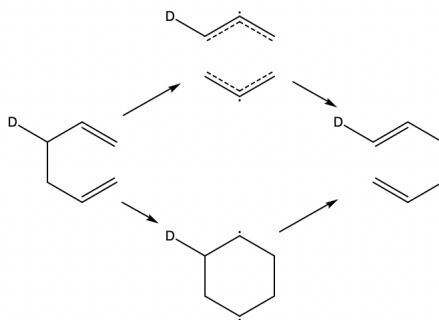[5]These types of reactions are known as "homolytic cleavages."

Figure 7.4: Two possible biradical pathways for the Cope rearrangement

Thus, this heat of formation is given by

$$\Delta H^{\circ}_{f,propenes} = 2\Delta H^{\circ}_{f,propene} + 2\mathrm{BDE(H-propyl)} - \mathrm{BDE(H-H)}$$
$$= 2(4.8) + 2(86.5) - (104)$$
$$= 78.6 \text{ kcal/mol}$$

We can follow a similar procedure to find the heat of formation for the lower intermediate. In this case, the heat of formation will be a linear combination of the heat of formation for a molecule of cyclohexane, the BDE(H−cyclohexyl), and the BDE(H−H) for the same reason as above. Thus,

$$\Delta H^{\circ}_{f,cyclohexane} = \Delta H^{\circ}_{f,cyclohexyl} + 2\mathrm{BDE(H-cyclohexyl)} - \mathrm{BDE(H-H)}$$
$$= (-29.5) + 2(95.5) - (104)$$
$$= 57.5 \text{ kcal/mol}$$

Clearly the formation enthalpies for each of these are very high with respect to the enthalpy of formation for 1,5-hexadiene, coming in at only 20.1 kcal/mol. Thus, we can say with confidence that the biradical intermediate is implausible and the more likely mechanism is the *concerted sigmatropic rearrangement*, which we know to be the case.

Here's another example, this one being slightly more disconnected from what we just discussed but important nonetheless[6]: A remarkable property of NaCl is that its solubility is essentially constant in temperatures from 0°C to 100°C, going from 370 g/L to 380 g/L over the interval. Explain what this implies about relevant thermodynamic properties for the dissolution of sodium chloride in water and rationalize the result with a molecular-level explanation.

Recall Equation (6.2.8), the van't Hoff equation, which relates the equilibrium constant of a reaction to some relevant thermodynamic quantities:

$$\ln K_{eq} = \frac{-\Delta \tilde{H}^{\circ}_{rxn}}{R}\left(\frac{1}{T}\right) + \frac{\Delta \tilde{S}^{\circ}_{rxn}}{R}$$

We're given that the solubility is unchanging over a temperature range and therefore the equilibrium constant, which can be thought of as a *dissociation constant* in this context, must be unchanging. Hence, the enthalpy of reaction must be zero for the dissolution of sodium chloride in water.

Now, how can we rationalize this result using molecular interactions? First, let's illustrate the transformation that is taking place:

$$\mathrm{NaCl_{(s)} \rightleftharpoons Na^+_{(aq)} + Cl^-_{(aq)}}$$

---
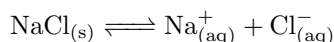
[6]Also I just wasn't really sure where to put this example but I really like the question so I wanted to include it somewhere.

With the enthalpy of reaction being zero we can think of the heats of formation of the reactants and products being equal. Note that crystalline $NaCl_{(s)}$ has a very high bond enthalpy associated with the ionic bonds in the lattice and to match this large heat of formation there must be an equally strong enthalpic contribution from solvent-ion interactions in the products. Thus, the solvation energy associated with dissolving the sodium and chloride ions must be equally as strong as the bond enthalpy of the ionic bonds in the lattice of $NaCl_{(s)}$. With all of this in mind it makes sense intuitively that the dissolution of sodium chloride is a primary entropy driven reaction.

7.2.3 Benson Group Additivity

Benson group additivity uses the experimentally calculated heats of formation for individual groups of atoms to calculate the entire heat of formation for a molecule under investigation[7]. Moreover, using Benson increments can quickly afford an estimate for whether a reaction is endo- or exothermic.

I think the best way to illustrate Benson increments is using an example. Here's one from the homework: Use Benson increments to calculate ΔH°_{rxn} for the retro Diels-Alder reaction below, with the values given by the NIST at this link. Also, use the following strain values:

$$\text{Strain for bicyclo-(4,1,0)-heptane} \quad \Delta H^{\circ} = 28.9 \text{ kcal/mol}$$
$$\text{Strain for } cis \text{ double bond} \quad \Delta H^{\circ} = 1.0 \text{ kcal/mol}$$
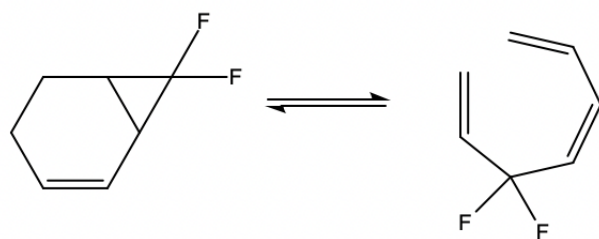

Figure 7.5: Retro Diels Alder Reaction

Note that with the link given we don't have values for $C-C_2F_2$ or $F-C$. However, notice that we have bond of the former type and two of the latter type in each structure so that these values would cancel anyways. With this in mind, I won't include any of these terms in the calculation for the heats of formation. Figure 7.6 illustrates the Benson increments for each group on both the reactant and product.
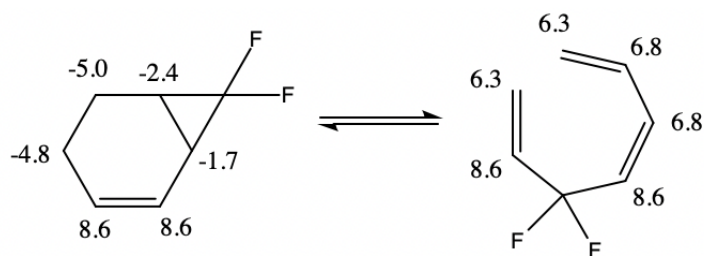
Figure 7.6: Benson increments labeled for each group

Then, proceeding with the calculation, the heat of formation for the reactants is given by (making sure to

---

[7]Benson increments fall under the umbrella category of *heat of formation group additivity*, a topic which includes all of the methods for calculating the heat of formation of an organic compound based on additivity. Other methods include the Gronert model which is based on not breaking molecules into fragments but instead considering the 1,2- and 1,3- interactions of groups

include the terms for ring strain and *cis* double bonding)

$$\Delta H^{\circ}_{f,reactant} = (-4.8) + (-5.0) + (-2.4) + (-1.7) + 2(8.6) + 28.9 + 1 = 33.2 \text{ kcal/mol}$$

and the heat of formation for the product is given by

$$\Delta H^{\circ}_{f,product} = 2(6.3) + 2(8.6) + 2(6.8) + 1 = 44.4 \text{ kcal/mol}$$

so that the heat of reaction can be computed as

$$\Delta H^{\circ}_{rxn} = 44.4 - 33.2 = 11.2 \text{ kcal/mol}$$

CHAPTER

8

STATISTICAL MECHANICS

Statistical mechanics spans a much broader, intellectually challenging, and mathematically rigorous field than I cover here. I'll try to talk about things that I find cool that are even somewhat related to what Dr. Fried asks of his students but not covered in class but I implore anyone who's interested to read more on the subject.

An infamous quote regarding statistical mechanics from Goodstein's *States of Matter* reads as follows:

> Ludwig Boltzmann who spent much of his life studying statistical mechanics, died in 1906, by his own hand. Paul Ehrenfest, carrying on the work, died similarly in 1933. Now it is our turn to study statistical mechanics.

I thought it was pretty funny. For now, this will have to stand as our introduction to the subject.

The science of statistical mechanics has the special function of providing reasoning for treating the behavior of mechanical systems under circumstances such that our knowledge of the condition of the system is less than the theoretically possible maximum. That is, it allows us to make good guesses. Since our knowledge of the physical world and thermodynamic systems is such that we can never know *everything* about the system, statistical mechanics provides significant supplementation to ordinary mechanics, which is abstract at best when it comes to *real* systems. Stated in another way, the transition from knowing exactly what is going on to knowing only the probability of exactly what is going on is the same transition from mechanics to statistical mechanics. With these key ideas lurking in the background we'll begin to analyze the general structure of statistical mechanics, beginning with the *ensemble approach*.

An ensemble is a large collection of trajectories of a system, considered all at once, each of which represents a possible state the system might be in. A *thermodynamic ensemble* is a specific variety of ensemble that is in statistical equilibrium and is used to derive the properties of thermodynamic systems from the laws of classic and/or quantum mechanics.

For our purposes, the ensemble method will provide a means of accessing bulk thermodynamic properties from molecular models. On their own, molecular models tells us nothing about the equilibrium distribution of thermodynamic properties and instead provide a comprehensive list of allowed microstates of a system.

The beauty of using ensembles instead of computation-intensive simulations[1] is in our ability to calculate

---

[1]Running simulations for a system involves determining (arbitrary) initial conditions, defining potential functions, evaluating the instantaneous forces on each particle at the system at all times in the interval, and generating new conditions from these forces. With modern technology simulations can be very intuitive and visualized with relative ease. However, they require many calculations and were not possible until very recently. Hence the creation of the ensemble method.

the average thermodynamic properties of a system by averaging across the different trajectories (mentioned above) within our ensemble. This "convergence" to the time averages is made possible by the *Ergodic hypothesis*,[2] which formally states that ensemble averages are equal to time averages,

$$\langle A \rangle \equiv \frac{1}{N} \sum_{i=1}^{N} A_i = \lim_{t \to \infty} \int A(t) dt \qquad (8.0.1)$$

where A_i is some measure of the system, and N is the number of trajectories we consider in the system. Phrased slightly differently, the Ergodic hypothesis posits that the average of microstates taken at different times from a single system can be replaced with the average of microstates taken from many trajectories of the same system, taken at an arbitrary time.

The central idea behind Ergodic theory is that any single trajectory within an ensemble will eventually pass through all accessible trajectories possible in the system. For example, this would imply that if we looked at a gas particle restricted to a box of a finite volume then the particle would eventually occupy every single accessible point in space within the box. Unfortunately, not many systems are strictly ergodic, hence the "Ergodic hypothesis".

There are two important differences that make dealing with ensembles easier than simulations:

1. The ensemble has no concept of time.

2. We can *predict* many properties about an ensemble (in the form of ensemble-averaged properties) starting from a potential function (for thermodynamic systems these are states and energies) and without necessarily simulating the dynamics.

Based on what we've read so far, ensembles seem like the clear winner when choosing a method of trying to connect the microscopic properties of a system to the macroscopic ones through statistical mechanics. However, there are some aspects of our assumptions about ensembles that we need to keep in mind when choosing the trajectories of the system to represent the ensemble.

Firstly, for ensemble-averages to accurately reflect real, observed properties, the number of times a given microstate appears in the ensemble (i.e., its *weight*) must be directly proportional to the amount of time the system would spend in that microstate. Then, the challenge is to ensure we include each microstate *the right number of times*. How then can we populate an ensemble without explicitly looking at the simulation? That's a good question.

8.1   Extensive and Intensive Properties

`https://scholar.harvard.edu/files/schwartz/files/8-freeenergy_0.pdf`

8.2   The Microcanonical (NVE) Ensemble

We'll now consider the simplest case of an isolated system. Then, we have a well-defined number of molecules (N) in the system as well as a constant volume (V) and energy (E). In creating the ensemble we'll choose m trajectories of the system so that each trajectory corresponds to one of m different microstates. Logic insists that if all m microstates have equal energy then in theory they should be equiprobable (or in the words of Dr. Fried, they're *a priori equally likely*). Let $\mathbb{N}_i$ represent the ith microstate and let $\mathbb{A}$ represent the total

---

[2]The Ergodic hypothesis is part of *Ergodic theory*, which is the study of systems possessing the property that given enough time, all points within a system will eventually visit all parts of the space that the system exists in. This theory implies that the average behavior of a system can be deduced from the "trajectory" of a normal point, exactly as we've postulated above. This property is known as *ergodicity* and is pretty cool.

number of microstates in our ensemble so that

$$\sum_{i=1}^{m} \mathbb{N}_i = \mathbb{A} \tag{8.2.1}$$

where the probability of being in a particular microstate p_i is given by,

$$p_i = \frac{\mathbb{N}_i}{\mathbb{A}} \tag{8.2.2}$$

(sometimes referred to as the "case of equally likely outcomes").

Now let's shift our attention to the ways of assigning trajectories to this system, i.e., choosing the total number of ways we could have selected $\mathbb{N}_1, \ldots, \mathbb{N}_m$ from the $\mathbb{A}$ total number of microstates. This is given by the multinomial coefficient:

$$\binom{\mathbb{A}}{\mathbb{N}_1, \ldots, \mathbb{N}_m} = \frac{\mathbb{A}!}{\mathbb{N}_1! \ldots \mathbb{N}_m!}$$

Now that we have a representation of the number of microstates W of the system, the most probable state of the system is the one which maximizes W. This is tantamount to asking, which value of W maximizes $S = k_B \ln W$?[3] Recall that for an isolated system, entropy is an indicator of spontaneity. So, the intuition behind maximizing entropy should make sense in the context of trying to find the most probable state of the system at equilibrium. In the above representation for W, apply Stirling's approximation:

$$\ln W = \mathbb{A} \ln \mathbb{A} - \sum_{i=1}^{m} \mathbb{N}_i \ln \mathbb{N}_i$$

The algebra is omitted here because a) it's lame and b) it's pretty simple.

Now for the fun part: Notice that we could increase W with ease by simply having a larger ensemble. So, let's assume that we have a fixed number of microstates in the ensemble so that $\mathbb{A}$ is constant. Furthermore, notice that W is a function of m variables, all of the $\mathbb{N}_i$'s (the $\mathbb{A}$ is fixed number, as mentioned literally 2 seconds ago how did you already forget smh) constrained to the condition that $\mathbb{A} = \sum_{i=1}^{m} \mathbb{N}_i = \text{const}$. Hence, we invoke (enter stage left) *the Lagrangian*:

$$\mathcal{L}(\vec{x}, \vec{\lambda}) = f(\vec{x}) - \sum_{i=1}^{c} \lambda_i g_i(\vec{x}) \tag{8.2.3}$$

If you've taken Calc III, skip this paragraph. The method of Lagrange multipliers utilizes the fact that for the level sets of a n-dimensional function, the gradient (a fancy word for the vector of partial derivatives for a function of more than one variable) of the function is *always perpendicular* to the level sets. Hence, when the function we are trying to optimize ($f(\vec{x})$ above) is along the constraint function ($g(\vec{x})$ above) their gradients will be parallel. But Sam, I don't see any gradients above, what's up with that? Not only is that a fantastic observation, but also it segways greatly into the following point: We're trying to *optimize* the function f above, so let's find the gradient and set it equal to zero (just as we would in single-variable calc):

$$0 = \nabla f(\vec{x}) - \nabla \left(\sum_{i=1}^{c} \lambda_i g_i(\vec{x}) \right)$$

$$\nabla f(\vec{x}) = \nabla \left(\sum_{i=1}^{c} \lambda_i g_i(\vec{x}) \right)$$

$$\nabla f = \lambda \nabla g$$

The last equation (hopefully) looks familiar if you've taken Calc III. Thus, for a system of m variables (like

---

[3]Note that we have this relationship between maximizing W and S because the natural logarithm is a monotonically increasing function.

the one we began with), we're left with a *system* of equations of the form

$$\frac{\partial f}{\partial x_1}(\vec{x}) = \lambda_1\left(\frac{\partial g}{\partial x_1}(\vec{x})\right)$$

$$\frac{\partial f}{\partial x_2}(\vec{x}) = \lambda_2\left(\frac{\partial g}{\partial x_2}(\vec{x})\right)$$

$$\vdots$$

$$\frac{\partial f}{\partial x_m}(\vec{x}) = \lambda_m\left(\frac{\partial \vec{g}}{\partial x_m}(\vec{x})\right)$$

alongside the initial constraint function (which I didn't rewrite above)[4].

Now, how can we apply the Lagrangian to the microcanonical ensemble? Notice that the function we are trying to optimize (in particular, maximize) is $\ln W$ while we're constrained to the fact that $\mathbb{A} = $ const. So, in the example above we have $f \sim \ln W$ and $g \sim \mathbb{A}$. Then, we are left with

$$\mathcal{L}(\vec{x}, \vec{\lambda}) = \ln W - \lambda \sum_{i=1}^{m} \mathbb{N}_i$$

$$= \nabla\left(\mathbb{A}\ln\mathbb{A} - \sum_{i=1}^{m} \mathbb{N}_i\ln\mathbb{N}_i\right) - \lambda\nabla\left(\sum_{i=1}^{m}\mathbb{N}_i\right)$$

$$\nabla\left(\mathbb{A}\ln\mathbb{A} - \sum_{i=1}^{m} \mathbb{N}_i\ln\mathbb{N}_i\right) = \lambda\nabla\left(\sum_{i=1}^{m}\mathbb{N}_i\right)$$

To simplify our lives let's first differentiate only one of these elements on the left-hand side with respect to some $\mathbb{N}_i$ and determine what the partial derivatives look like:

$$\frac{\partial}{\partial\mathbb{N}_i}\left(\mathbb{A}\ln\mathbb{A} - \mathbb{N}_i\ln\mathbb{N}_i\right) = \left(\frac{\partial\mathbb{A}}{\partial\mathbb{N}_i}\ln\mathbb{A} + \mathbb{A}\frac{\partial\ln\mathbb{A}}{\partial\mathbb{N}_i}\right) - \left(\frac{\partial\mathbb{N}_i}{\partial\mathbb{N}_i}\ln\mathbb{N}_i + \mathbb{N}_i\frac{\partial\ln\mathbb{N}_i}{\partial\mathbb{N}_i}\right)$$

$$= \ln\mathbb{A} + \mathbb{A}\frac{1}{\mathbb{A}} - \ln\mathbb{N}_i + \mathbb{N}_i\frac{1}{\mathbb{N}_i}$$

$$= \ln\mathbb{A}_i - \ln\mathbb{N}_i$$

$$= \ln\left(\frac{\mathbb{A}}{\mathbb{N}_i}\right)$$

For the derivation above, recall that $\mathbb{A} = \sum_{i=1}^{m}\mathbb{N}_i$ so that $\partial\mathbb{A}/\partial\mathbb{N}_i = 1$. Now, let's relate this to our Lagrange equation above:

$$\nabla\left(\mathbb{A}\ln\mathbb{A} - \sum_{i=1}^{m}\mathbb{N}_i\ln\mathbb{N}_i\right) = \lambda\nabla\left(\sum_{i=1}^{m}\mathbb{N}_i\right)$$

$$\ln\left(\frac{\mathbb{A}}{\mathbb{N}_i}\right) = \lambda\frac{\partial}{\partial\mathbb{N}_i}\left(\mathbb{N}_i\right)$$

$$\ln\left(\frac{\mathbb{A}}{\mathbb{N}_i^*}\right) = \lambda$$

$$\frac{\mathbb{N}_i^*}{\mathbb{A}} = \frac{1}{e^\lambda} \tag{8.2.4}$$

Here, $\mathbb{N}_i^*$ denotes the set of $\mathbb{N}_i$ which maximize W. Awesome! Recall two things: 1) We have m equations of this form for each $\mathbb{N}_i$ and 2) each of the m equations will look the exact same because we derived this result

---

[4]More generally, optimizing a nonlinear function with a set of constraints which are *inequalities* instead of *equalities* requires satisfying the *Karush-Kuhn-Tucker* conditions, a set of optimality conditions which are useful in finding the minima of such systems. This could not be less related to this class, however, I just took my intro to optimization final and the KKT conditions are all I can think about.

using an arbitrary $\mathbb{N}_i$. Then, summing each of these equations affords

$$\frac{\mathbb{N}_1^*}{\mathbb{A}} + \frac{\mathbb{N}_2^*}{\mathbb{A}} + \cdots + \frac{\mathbb{N}_m^*}{\mathbb{A}} = \frac{\mathbb{A}}{\mathbb{A}} = 1 = me^{-\lambda}$$
$$m = e^{\lambda}$$

Now, returning to our m equations, recall that $p_i = \mathbb{N}_i/\mathbb{A}$ for any given i so that $p_i = 1/m$ by Equation (8.2.4). This result is uber important: *In the beginning of this derivation we postulated that each the microstates was equiprobable; here we proved it.* Not only is this the most probable ensemble, but later we'll come to realize that this is the *only possible* ensemble.

An interesting connection between this derivation and the macroscopic world is in the limit as $\mathbb{A}$ tends to infinity. As the number of possible trajectories increases (that is, m increases; this is the quantity we constrained to a constant earlier), the probability that a particular microstate effectively decreases so that the distributions of each particular $\mathbb{N}_i$ becomes more tightly peaked. Hence, we view macroscopic systems as "ordered," even when their underlying molecular descriptions are immensely chaotic.

With this critical fact derived, let's derive some terms and organize our results:

- $p_i = \dfrac{1}{e^{\lambda}} = \dfrac{1}{m}$ is the *population* of the ith microstate, which is equivalent to the probability of occupying a particular microstate in this ensemble.

- $\Omega = e^{\lambda} = m$ is the *Microcanonical partition function*. It illustrates all of the possible microstates possible in the system.

- $S = k_B \ln \Omega$ is the entropy of the microcanonical ensemble.

8.2.1 The Microcanonical Ensemble for an Ideal Gas

So far we've considered an ensemble for a discrete number particles. Now, we'll analyze the mechanics of an ideal gas.

Consider a collection of N gas particles, each of which has 3 degrees of freedom (movement in the x, y, and z directions). Then, we can express the total energy of the system as,

$$E = \text{PE} + \text{KE} = 0 + \sum_{i=1}^{3N} \frac{1}{2} m_i v_i^2 = \sum_{i=1}^{3N} \frac{p_i^2}{2m_i} \tag{8.2.5}$$

that is, all of the energy is in the form of kinetic energy. Furthermore, suppose that this gas is isolated so that the energy of the system can be considered constant and all microstates have the same energy.

How can we express the number of microstates of the system? Firstly, consider a single atom of ideal gas: The energy of this atom is given by

$$E = \frac{p^2}{2m} = \frac{1}{2m}(p_x^2 + p_y^2 + p_z^2)$$
$$p_x^2 + p_y^2 + p_z^2 = 2mE \tag{8.2.6}$$

Notice that this equation is in the form of a 3-dimensional sphere with radius $\sqrt{2mE}$. Thus, each point on the "surface" of this sphere ("surface" is in quotes here because it's not technically a sphere, but it makes our life easier thinking about this situation in terms of a sphere) has an equal weight in the ensemble and all points off the surface have zero weight in the ensemble.

Above we considered a single atom of an ideal gas with 3 translational degrees of freedom which afforded momentum in the x, y, and z directions, p_x, p_y, and p_z, respectively. However, we also must specify the *coordinates* of that atom, x, y, and z. Then, each microstate is defined by 6 points and therefore lives in 6-dimensional space, as opposed to 3-dimensions. Additionally, recall that each microstate of this system that

has weight in the ensemble must lie on the "shell" corresponding to a specific amount of energy E. Then, if we integrate over each coordinate of the system over the entire phase space,

$$\Omega(E) = \int_E dx_1 dy_1 dz_1 \ldots dz_N dp_{x_1} dp_{y_1} \ldots dp_{z_N} \tag{8.2.7}$$

Above we considered the phase space Ω as being a shell of energy, in particular an n-dimensional sphere. Most of the time we're interested in an infinitesimally small section of the sphere, one that represents only a specific amount of energy E. We can restrict atoms to this particular energy value by assigning some E^* and $E^* + \delta E^*$ to bound the specific energy E that we're interested in. Then,

$$\Omega(E)\delta E = \int_{E^* < E < E^* + \delta E} dx_1 dy_1 dz_1 \ldots dz_N dp_{x_1} dp_{y_1} \ldots dp_{z_N} \tag{8.2.8}$$

represents the shell of energy corresponding to a *specific* energy level.

Notice that part of the integral in Equations (8.2.7) and (8.2.8) returns the volume of a $3N$-dimensional sphere (there are N sets of 3 positional coordinates x, y, and z. This convention temporarily ignores the momenta terms). Lucky for us, people smarter than us already computed an explicit formula for an n-dimensional sphere:

$$V_n(R) = \frac{\pi^{n/2} R^n}{\left(\frac{n}{2}\right)!}$$

Here, R is the radius of the sphere. Recall that above we already defined the radius of our sphere as $\sqrt{2mE}$. This formula will allow us to calculate the volume of a thin shell of momenta space that corresponds to the total energy at the specific point on the sphere E that we're interested in.

To begin that calculation let's break up the integral above (in the manner that I've already hinted at):

$$\Omega(E)dE = \left(\int_{E^* < E < E^* + dE} dx_1 dy_1 dz_1 \ldots dz_N \right) \left(\int_{E^* < E < E^* + dE} dp_{x_1} dp_{y_1} dp_{z_1} \ldots dp_{z_N} \right)$$
$$= dV_{3N} + \int_{E^* < E < E^* + dE^*} dp_{x_1} dp_{y_1} dp_{z_1} \ldots dp_{z_N}$$

The dV_{3N} term is in fact a change because we are looking at the integral on $E^* < E < E^* + \delta E$ which has an inherent change. Thus, we can compute the total energy at on the particular shell of energy E in momenta space as

$$\begin{aligned}
\Omega(E) &= \frac{dV_{3N}(\sqrt{2mE})}{dE} \\
&= \frac{d}{dE}\left(\frac{\pi^{3N/2}(\sqrt{2mE})^{3N}}{\left(\frac{3N}{2}\right)!} \right) \\
&= \frac{\pi^{3N/2}[3Nm(2mE)^{\frac{3N}{2}-1}]}{\left(\frac{3N}{2}\right)!} \\
&= \frac{3Nm\pi^{3N/2}R^{3N-2}}{\left(\frac{3N}{2}\right)!}
\end{aligned} \tag{8.2.9}$$

where $R = \sqrt{2mE}$ is the radius of the sphere.

At this point we shift our attention and ask an interesting question about the collection of particles we've been studying: What is the probability that a particular atom will have a given amount of momentum, p_1, in the z direction? For a single atom system, this probability is proportional to the area of the circular annulus elevated p_1 along the z-axis from the center of the sphere. To compute this we'll be interested in the area bounded by two circles which lie along arbitrarily close to one another on the sphere, one of radius $R = \sqrt{2mE}$ and the other of radius $r = \sqrt{2m(E + dE)}$. Notice that this new radius r can be equivalently expressed as $r = \sqrt{2mE - p_1^2}$ using the fact that the probability is proportional to the area of the annulus

mentioned above and the Pythagorean Theorem. Now, we'll compute the area of this annulus in a similar fashion as the volume of the sphere itself. Note that since the sphere lived in $3N$-dimensional space, the annulus lives in $(3N-1)$-dimensional space (which I think is intuitive enough).

$$
\begin{aligned}
\frac{\text{area of annulus}}{dE} &= \frac{dV_{3N-1}(\sqrt{2mE - p_1^2})}{dE} \\
&= \frac{d}{dE}\left(\frac{\pi^{(3N-1)/2}(\sqrt{2mE - p_1^2})^{3N-1}}{(\frac{3N-1}{2})!}\right) \\
&= \frac{\pi^{(3N-1)/2}[(3N-1)m(2mE - p_1^2)^{\frac{3N-1}{2}-1}]}{(\frac{3N-1}{2})!} \\
&= \frac{(3N-1)m\pi^{(3N-1)/2}r^{3N-3}}{(\frac{3N-1}{2})!}
\end{aligned}
\tag{8.2.10}
$$

The probability density of being in the particular annulus (above) is the area of said annulus, Equation (8.2.10), divided by the total volume of the shell, Equation (8.2.9). Thus,

$$
\begin{aligned}
f(p_1) &= \frac{\text{area of annulus}}{\text{volume of sphere}} \\
&= \frac{(3N-1)m\pi^{(3N-1)/2}r^{3N-3}}{(\frac{3N-1}{2})!}\left(\frac{3Nm\pi^{3N/2}R^{3N-2}}{(\frac{3N}{2})!}\right)^{-1} \\
&\vdots \\
&= \frac{R^2}{r^3}\left(1 - \frac{p_1^2}{2mE}\right)^{3N/2}
\end{aligned}
\tag{8.2.11}
$$

Briefly, let's considering the feasibility of our result. The factor inside the parentheses is taken to an enormous power, on the order of N. Thus,

$$
1 - \frac{p_1^2}{2mE} \approx 1
$$

otherwise, the entire expression in (8.2.11) would vanish. Moreover, notice that

$$
1 \approx 1 - \frac{p_1^2}{2mE} = \frac{2mE - p_1^2}{2mE} = \left(\frac{\sqrt{2mE - p_1^2}}{\sqrt{2mE}}\right)^2 = \frac{r^2}{R^2} \implies r \approx R
$$

and that we can approximate

$$
1 - \frac{p_1^2}{2mE} \approx \exp\left\{-\frac{p_1^2}{2mE}\right\}
$$

for small enough values in the exponent (check for yourself that this is true). Thus, we can make the following approximation:

$$
\begin{aligned}
\frac{R^2}{r^3}\left(1 - \frac{p_1^2}{2mE}\right)^{3N/2} &\approx \frac{1}{r}\left(\exp\left\{-\frac{p_1^2}{2mE}\right\}\right)^{3N/2} \\
&= \frac{1}{\sqrt{2mE}}\left(\exp\left\{-\frac{1}{2}\left(\frac{3Np_1^2}{2mE}\right)\right\}\right)
\end{aligned}
$$

Notice that this is (nearly) a Gaussian distribution with mean zero and standard deviation $\sqrt{2mE/3N}$. The only thing left to do to afford our probability density for p_1 is to normalize this expression:

$$
f(p_1; E, N, m) = \frac{1}{\sqrt{2\pi m(2E/3N)}}\exp\left\{-\frac{p_1^2}{2m}\frac{3N}{2E}\right\}
\tag{8.2.12}
$$

Alright that was a lot of math, even for me. Let's take a quick H_2O break, maybe grab a snack, and regroup in 5.

We're back. Let's consider the implications of our derivation above:

1. We were able to solve the momentum distribution for any particle without solving any equations of motion.

2. We've found that the momentum distribution is extremely tightly peaked. In fact, most of the momenta will be found within one standard deviation of the center of the distribution, that is, within $\sqrt{2mE/3N}$ which is tiny compared to the total possible values of momenta, $\sqrt{2mE}$. Intuitively, this result makes sense: As we increase the number of particles in our system, by the law of large numbers, the average momentum limits towards a fixed value.

A major implication of our derivation that is deserved of more than just a bullet point is that it *affords the internal energy for an ideal gas*. Suppose that we choose to substitute $3N/2E = 1/k_BT$ (do these quantities have the same physical meaning? i.e., do they have the same units?) to afford an expression for the energy E,

$$\frac{3N}{2E} = \frac{1}{k_BT} \;\Rightarrow\; E = \frac{3}{2}Nk_BT = \frac{3}{2}RT$$

which is exactly the familiar representation for the internal energy of an ideal gas.

Another major implication of our derivation is that it *affords the ideal gas law*. Suppose we want to find the average amount of (kinetic) energy of the particles in this collection. This is equivalent to calculating the weighted average of the kinetic energies over all possible momenta (i.e., using the function we just defined):

$$KE_{avg} = \int_{-\infty}^{\infty} \left(\frac{p_1^2}{2m}\right) f(p_1)dp_1$$

$$= \int_{-\infty}^{\infty} \left(\frac{p_1^2}{2m}\right) \frac{\exp\{\frac{-p_1^2}{2m}\frac{3N}{2E}\}}{\sqrt{2\pi m(2E/3N)}}dp_1$$

$$= \frac{1}{2m\sqrt{2\pi mk_BT}} \int_{-\infty}^{\infty} p_1^2 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}dp_1$$

This integral is not at all trivial and in the lecture slides Dr. Fried omits the entire evaluation because this is a physical chemistry class and not a vector calculus class. I, however, think the derivation is more than worthy enough of being shown off in all its glory. Moreover, I'll integrate the function in more than one way: Firstly, let's rearrange the integral above (omitting the constants, for brevity) as follows:

$$\int_{-\infty}^{\infty} p_1 \left(p_1 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}\right)dp_1$$

Now, allow $u = p$ and $dv = p_1\exp\{\frac{-p_1^2}{2mk_BT}\}$ so that we can integrate by parts with $du = dp$ and $v = -mk_BT\exp\{\frac{-p_1^2}{2mk_BT}\}$:

$$\int_{-\infty}^{\infty} p_1 \left(p_1 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}\right)dp_1 = \left[-p_1 mk_BT\exp\left\{\frac{-p_1^2}{2mk_BT}\right\}\right]_{-\infty}^{\infty} - \int_{-\infty}^{\infty} -mk_BT\exp\left\{\frac{-p_1^2}{2mk_BT}\right\}dp$$

$$= 0 + mk_BT \int_{-\infty}^{\infty} \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}dp_1$$

The integral that remains is a *Gaussian integral* and has a known value. The derivation is really cool, involving a change of variables and some cheeky intuition. I'm not gonna derive it here, but I provide the derivation in Section **??** if you're interested. Using this known value, we find

$$mk_BT \int_{-\infty}^{\infty} \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}dp_1 = mk_BT\sqrt{2\pi mk_BT} = \sqrt{2\pi}(mk_BT)^{3/2}$$

and remembering that I omitted the constants in front of this integral in the first place for brevity, we have

that

$$KE_{avg} = \frac{1}{2m\sqrt{2\pi mk_BT}}\sqrt{2\pi}(mk_BT)^{3/2} = \frac{1}{2}k_BT \tag{8.2.13}$$

which represents the *average amount of energy carried by a translational degree of freedom for a particle*. This result is known as *equipartition*. Additionally, it agrees with what we know already about the internal energy for an ideal gas: First, recall that $N_Ak_B = R$ for a single particle. Then, notice that each particle of an ideal gas has three translational degrees of freedom (in accordance with the three dimensions of motion) so that the internal energy of a *single* particle is given as

$$U = \frac{3}{2}RT$$

and the internal energy for n moles of an ideal gas is given by

$$U = \frac{3}{2}nRT$$

Awesome!

Before utilizing this result, here's another way of evaluating the integral that gave us some trouble: Let's start by rearranging, this time in a slightly different way:

$$\int_{-\infty}^{\infty} p_1^2 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}dp_1 = \int_{0}^{\infty} p_1 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}2p_1 dp_1$$

Above we shifted the lower limit of integration up to 0 since the function is completely nonnegative. At the same time, we doubled the value of the integral to account for negative momenta which are lost when we begin integration at 0. This factor of 2 was brought inside the integral, affording the $2p_1 dp_1$ term. At this point, we can make the variable substitution $u = p_1^2/(2mk_BT)$ so that $du = 2p_1 dp_1/(2mk_BT)$ which simplifies our integral as

$$\int_{0}^{\infty} p_1 \exp\left\{\frac{-p_1^2}{2mk_BT}\right\}2p_1 dp_1 = \int_{0}^{\infty} (2mk_BTu)^{1/2}e^{-u}(2mk_BTdu)$$

which can be evaluated with the Gamma function:

$$\int_{0}^{\infty} (2mk_BTu)^{1/2}e^{-u}(2mk_BTdu) = \sqrt{2}(mk_BT)^{3/2}\Gamma\left(\frac{3}{2}\right)$$

$$= (2mk_BT)^{3/2}\frac{\sqrt{\pi}}{2}$$

$$= \sqrt{2\pi}(mk_BT)^{3/2}$$

Plugging this result back into our original expression:

$$KE_{avg} = \frac{1}{2m\sqrt{2\pi mk_BT}}\sqrt{2\pi}(mk_BT)^{3/2} = \frac{1}{2}k_BT$$

which agrees exactly with our result from before.

Now, onto deriving the ideal gas law. Somehow we need to relate the average amount of energy we considered above to the pressure and volume of a container holding an ideal gas. Let's consider the momentum of a particle particle in this collection: Pressure is a result of molecules colliding with a surface (in this case the wall of the container). For an ideal gas, the collisions will be entirely elastic so that the change in momentum will be given by:

$$\Delta\vec{p} = \vec{p}_f - \vec{p}_i = 2\vec{p}$$

Since collisions are elastic and the components of $\vec{p}_f$ are directed antiparallel to the components of $\vec{p}_i$, $\vec{p}_f = -\vec{p}_i$ which explains the result above. Considering a short time interval where we measure the number of

particles which collide with the wall, only those particles which are within

$$\Delta \vec{x} = \vec{v}\Delta t = \frac{\vec{p}}{m}\Delta t$$

will hit the container and be transfer momentum. Then, the total momentum transfer to the wall is given by

$$\Delta \vec{p}_{tot} = \int_0^\infty f(p)\left(\frac{N}{V}\right)\left(\frac{\vec{p}}{m}\Delta t\right)(\text{Area})2\vec{p}d\vec{p}$$

where $f(p)$ is the probability distribution of the momentum we derived above, N/V accounts for the total number of particles per volume of the container (as to not scale our answer by an unnecessary factor), Area is the area of the container which particles are colliding with, $2\vec{p}$ is the change in momentum we illustrated above, and we're integrating over all particles with momenta in the direction of the wall (hence only positive values. We could have elected to include "negative" momenta which aren't directed toward the wall and range from negative to positive infinity. This point is remedied later). Before evaluating this integral recall that

$$\text{Pressure} = \frac{\text{Force}}{\text{Area}} = \frac{\Delta \vec{p}}{\Delta t \times \text{Area}}$$

so that our integral and can be rearranged and evaluated as follows:

$$\frac{\Delta \vec{p}_{tot}}{\Delta t \times \text{Area}} = \frac{2N}{V}\int_0^\infty f(p)\frac{(\vec{p})^2}{m}d\vec{p}$$
$$P = \frac{2N}{V}\left(\frac{1}{2}k_B T\right) = \frac{Nk_B T}{V}$$
$$PV = RT$$

In the second step we obtain the same result as we did in the prior derivation. Note that although there isn't a factor of one-half in the integral above, we're only integrating over half of the support as we did in the derivation for Equation (8.2.13) hence the factor of one-half in the answer.

Sam! This isn't the ideal gas law! Might I say that that is an apt observation. Recall that the momentum distribution we've been considering up until this point was for *a single particle*. So, for a mole of particles, we have that $PV = nRT$ as desired.

8.3   The Canonical (NVT) Ensemble

The canonical ensemble describes a system that can exchange heat with a thermal reservoir (in other words, the ensemble is in thermal equilibrium with the reservoir) and therefore energy is *not* conserved in the system. Therefore, microstates will differ in energy. We can justify this observation by saying that lower energy microstates have "donated" their energy to the reservoir while high energy states have "borrowed" energy instead. Moreover, each replica in the ensemble has a fixed number of particles and fixed volume. As before, our goal in constructing an ensemble is to determine the appropriate weight (or contribution) that each microstate plays in the particular macrostate of the system.

Similar to the microcanonical ensemble we'll be interested in finding the weights of each microstate which maximize $S \sim \ln W$ given

$$W(\mathbb{N}_i; \mathbb{A}) = \binom{\mathbb{A}}{\mathbb{N}_1, \ldots, \mathbb{N}_m} = \frac{\mathbb{A}!}{\mathbb{N}_1! \ldots \mathbb{N}_m!}, \quad \ln W = \mathbb{A}\ln\mathbb{A} - \sum_{i=1}^m \mathbb{N}_i \ln\mathbb{N}_i$$

with $\sum_{i=1}^n \mathbb{N}_i =$ constaint. This time, however, instead of maximizing $\ln W$ we'll explicitly maximize $S = k_B \ln W$ and instead of solving for the extensize variables $\mathbb{N}_i$ (which sum to $\mathbb{A}$) we will solve for the intensive microstate probabilities, p_i (which sum to 1).

In addition, since the energy is not being conserved within the ensemble, we have a new constraint,

$$U \equiv \sum_{i=1}^{m} p_i E_i \tag{8.3.1}$$

where U is the total internal energy of the system, E_i is the ith energy of the particle in the ensemble, and p_i is the probability particle i obtains that energy. By the first law of thermodynamics, all of the energies in the system must sum to a constant, in particular the total internal energy of the system. If we were to express this energy constraint as an extensive variable, that is, representing the extensive energy of the entire ensemble[5], we have

$$\mathbb{A} E = \sum_{i=1}^{m} \mathbb{A} p_i E_i \;\Rightarrow\; E_T = \sum_{i=1}^{m} \mathbb{N}_i E_i$$

as our second constraint.

With these two constraints defined and keeping in mind that we are trying to maximize $S = k_B \ln W$, our system of Lagrange multipliers becomes

$$\nabla \left(k_B \ln W \right) = \lambda \left(\sum_{i=1}^{m} p_i \right) + \beta \left(\sum_{i=1}^{m} p_i E_i \right)$$

where the right-hand side is the entropy (which we are trying to maximize), the left hand side contains those terms which constrain the function, defined above, and we are differentiating all terms with respect to the ith probability, p_i. Before continuing recall that we can express the entropy as *Gibbs entropy*, given as

$$S = -k_B \sum_{i=1}^{m} p_i \ln p_i$$

so that we can evaluate the Lagrangian equation above, considering just a single p_i at first and generalizing after:

$$\nabla \left(-k_B p_i \ln p_i \right) = \nabla \left(\lambda p_i \right) + \nabla \left(\beta p_i E_i \right)$$

$$-k_B \left(\ln p_i + \frac{p_i}{p_i} \right) = \lambda + \beta E_i$$

$$\ln p_i + 1 = \frac{\lambda + \beta E_i}{k_B}$$

$$p_i = \exp \left\{ \frac{-k_B + \lambda + \beta E_i}{k_B} \right\} \tag{8.3.2}$$

Here we can use on of our constraints. We know that the sum of all the probabilities must be 1 (otherwise we wouldn't have a probability space) and therefore

$$1 = \sum_{i=1}^{m} \exp \left\{ \frac{-k_B + \lambda + \beta E_i}{k_B} \right\}$$

$$= \exp \left\{ \frac{-k_B + \lambda}{k_B} \right\} \sum_{i=1}^{m} \exp \left\{ \frac{\beta E_i}{k_B} \right\}$$

$$= Q \exp \left\{ \frac{-k_B + \lambda}{k_B} \right\}$$

---

[5]This is *not* the same as the total internal energy because U is representative of the system and surroundings, not just the system.

where Q is the *canonical partition function*[6]. For now, though, we'll use it to isolate λ:

$$\frac{1}{Q} = \exp\left\{\frac{-k_B + \lambda}{k_B}\right\}$$

$$\ln\left(\frac{1}{Q}\right) = \frac{-k_B + \lambda}{k_B}$$

$$-\ln Q = \frac{-k_B + \lambda}{k_B}$$

$$\lambda = -k_B \ln Q + k_B$$

We can plug this result for λ back into Equation (8.3.2) to afford an expression for the ith probability, p_i, in terms of the unknown β:

$$p_i = \exp\left\{\frac{-k_B - k_B \ln Q + k_B + \beta E_i}{k_B}\right\}$$

$$= \exp\left\{\frac{-k_B \ln Q + \beta E_i}{k_B}\right\}$$

$$= \frac{\exp\left\{\frac{\beta E_i}{k_B}\right\}}{Q} \tag{8.3.3}$$

Equation (8.3.3) looks promising, as it expresses a *Boltzmann factor*[7] normalized by some partition function Q.

All that's left is for us to find the parameter β. So, we'll return to entropy, in particular the Gibbs entropy:

$$S = -k_B \sum_{i=1}^{m} p_i \ln p_i$$

$$= -k_B \sum_{i=1}^{m} p_i \ln\left(\frac{\exp\left\{\frac{\beta E_i}{k_B}\right\}}{Q}\right)$$

$$= -k_B \sum_{i=1}^{m} p_i \left(\frac{\beta E_i}{k_B} - \ln Q\right)$$

$$= -\beta \sum_{i=1}^{m} E_i p_i + k_B \ln Q \sum_{i=1}^{m} p_i$$

$$= -\beta U + k_B \ln Q \tag{8.3.4}$$

Taking a brief detour back into the world of classical thermodynamics, recall that our definition for a differential amount of internal energy in a system is $dU = T dS - P dV$ so that at a constant volume (because each replica in the ensemble has a constant volume by the definition of our system), $(\partial U / \partial S)_V = T$. Rearranging Equation (8.3.4) and utilizing this derivative allows us to solve for β:

$$S = -\beta U + k_B \ln Q$$

$$U = -\frac{S}{\beta} + k_B \ln Q$$

$$\left(\frac{\partial U}{\partial T}\right)_V = T = -\frac{1}{\beta}$$

$$\beta = -\frac{1}{T}$$

A-ha! Now, we can write down our results for the canonical ensemble:

---

[6] We're sort of jumping the gun here since we haven't yet found β. Not to fear, though, we'll determine it later.

[7] A *Boltzmann factor* is an expression given as $e^{-\beta E_i}$. This is the most general expression. Particular examples include those expressions in the numerous ensembles we'll consider.

1. $Q = \sum_{i=1}^{m} e^{-E_i/k_B T}$ is the *canonical partition function*.

2. $p_i = \dfrac{1}{Q} e^{-E_i/k_B T}$ is the *Boltzmann factor* for that canonical ensemble.

3. $S = \dfrac{U}{T} + k_B \ln Q$ is the entropy of the canonical ensemble

Let's try and manipulate our expression for entropy to... make it nicer, I suppose. Recall the Helmholtz free energy, defined as $A = U - TS$[8]. With a little bit of algebraic gymnastics we find that

$$A = -k_B T \ln Q$$

Hopefully, this is a satisfying result because it is directly analogous to our result for entropy of the microcanonical ensemble where $S = k_B \ln \Omega$. Also, hopefully this makes some sense because for the microcanonical ensemble, a.k.a. the *NVE* ensemble, the entropy is an indicator of spontaneity since the system is isolated. Similarly, for the canonical ensemble, or the *NVT* ensemble, the Helmholtz free energy is an indicator of spontaneity since it is a closed system.

So we've got the Helmholtz free energy, but what about an expression for the internal energy of a system? First, recall Equation (8.3.1) which gives us an expression for the internal energy in terms of some energies and probabilities. However, now we have those probabilities:

$$U = \sum_{i=1}^{m} p_i E_i$$
$$= \sum_{i=1}^{m} \left(\frac{\exp\{\frac{\beta E_i}{k_B}\}}{Q} \right) E_i$$
$$= \frac{1}{Q} \sum_{i=1}^{m} E_i e^{-E_i/k_B T}$$

Here we're gonna make the following (absolutely horrendous) substitution,

$$e^{-E_i/k_B T} = \frac{d}{d(1/T)} \left[e^{-E_i/k_B T} \right] \left(\frac{-k_B}{E_i} \right)$$

which must be true by the chain rule. Thus,

$$U = \frac{1}{Q} \sum_{i=1}^{m} E_i e^{-E_i/k_B T}$$
$$= \frac{1}{Q} \sum_{i=1}^{m} -k_B \left(\frac{d}{d(1/T)} \left[e^{-E_i/k_B T} \right] \right)$$
$$= -\frac{k_B}{Q} \frac{d}{d(1/T)} \left(\sum_{i=1}^{m} -E_i/k_B T \right)$$
$$= -\frac{k_B}{Q} \frac{d}{d(1/T)} (Q)$$

This next substitution isn't as bad. Note that

$$\frac{d \ln Q(x)}{dx} = \frac{1}{Q} \frac{dQ(x)}{dx}$$

and since the partition function Q is a function of temperature we can rewrite our expression for the internal

---

[8]We consider the Helmholtz free energy here because it is an indicator of spontaneity for constant volume and constant temperature systems. Wait... these are the conditions of the canonical ensemble!

energy to afford

$$U = -\frac{k_B}{Q} \frac{d}{d(1/T)}(Q)$$
$$= -k_B \frac{d \ln Q}{d(1/T)}$$

I don't know what's going on with all these weird chain rule shenanigans but this is the last one we'll use to simplify the derivative. Note that

$$\frac{dy(x)}{d(1/x)} = -\frac{1}{1/x^2} \frac{dy(x)}{dx} = -x^2 \frac{dy(x)}{dx}$$

so that we can finally establish the following relationship for the internal energy of the canonical ensemble:

$$U = k_B T^2 \frac{d \ln Q}{dT} \tag{8.3.5}$$

Magnets: A Case Study

Here we'll consider a simple, one-dimensional model of a magnet. Suppose we have a one-dimensional lattice made up of N magnetic dipoles, each of which are caused by the spin of an electron, either up $(+1)$ or down $(+1)$. The magnetization M of the magnet is $M = \mu_B(N_\uparrow - N_\downarrow)$, where $N_\uparrow$ is the number of spins pointing up, $N_\downarrow$ is the number of spins pointing down, and μ_B is the Bohr magneton, the unit a magnetic dipole has.

Let's consider a small magnet such that $N = 6$. How many microstates does the lattice have? How many associated macrostates are there corresponding to a particular magnetization? First we'll address the number of microstates. At each point in the lattice an electron could be spinning one of two ways, either up or down. So, for 6 lattice points, there are $2^6 = 64$ associated microstates. To connect this to the number of macrostates, notice that the arrangement of up-spins and down-spins is binomially distributed so that for a a number k of up-spins in the lattice, there are $\binom{6}{k}$ corresponding microstates with the same overall magnetization. Below is a table illustrating all of our choices for k and the corresponding macrostate (magnetization):

Number of up-spins, k	# Microstates $\binom{6}{k}$	Magnetization, M
0	1	$-6\mu_B$
1	6	$-4\mu_B$
2	15	$-2\mu_B$
3	20	$0\mu_B$
4	15	$2\mu_B$
5	6	$4\mu_B$
6	1	$6\mu_B$

Amazing! Let's complicate the situation. Suppose that we apply a magnetic field B to the lattice of charges. The interaction between the field and spins pointing in the same direction is favorable, whereas those pointing in opposite directions are unfavorable. We can model the energy, E, schematically as

$$E = -BM$$

Given an applied magnetic field of $+B$ in the up-direction, write down an expression for the canonical partition function, Q, of the system. Okay! Luckily, most of the work has already been done. We know how many macrostates are present, the number of microstate associated to each macrostate, and even the magnetization of each macrostate. Building the partition function becomes child's play. In fact, I'll do it with

my eyes closed:

$$Q = \sum_{i=1}^{6} g_i e^{-E_i/k_B T}$$

$$= e^{6\mu_B B/k_B T} + 6e^{4\mu_B B/k_B T} + 15e^{2\mu_B B/k_B T} + 20 + 15e^{-2\mu_B B/k_B T} + 6e^{-4\mu_B B/k_B T} + e^{-6\mu_B B/k_B T}$$

The general form for each term in this series is given above in the summation, but I'll reiterate it here. For a particular macrostate, its contribution to the partition function takes the form

$$\binom{6}{k} e^{-(-BM_k)/k_B T}$$

where k is the number of up-spins in the lattice, and M_k is the associated magnetism with k up-spins. Like I said before, we computing all of these values previously. Although our expansion for Q is technically correct, oftentimes we define the ground state energy of the lattice to be zero such that Q can be rewritten as

$$Q = 1 + 6e^{2\mu_B B/k_B T} + 15e^{4\mu_B B/k_B T} + 20e^{6\mu_B B/k_B T} + 15e^{8\mu_B B/k_B T} + 6e^{10\mu_B B/k_B T} + e^{12\mu_B B/k_B T}$$

where $k = 6$ up-spins is chosen to be the ground state energy since there are only favorable interactions.

With the partition function, write down an expression for the probability that the magnet will be in its ground state with an applied magnetic field, $+B$. Above we just defined the ground state to be when $k = 6$ is the number of up-spins. Then, the probability of being in the ground state becomes

$$P(\text{ground state}) = \frac{1}{Q}$$

with Q acting as the partition function.

Now, sketch a plot of magnetization of the system as a function of temperature. COME BACK TO PLOT THIS IN PYTHON

Suppose we wish to generalize our one-dimensional model to including N magnetic dipoles, where N is some large number. If the magnet has a total magnetization M, how many microstates are there for the magnet to exist in? Express this number in terms of the known quantities, N, M, and μ_B. Initially, one might think that the number of microstates is given by $W = 2^N$, at least that's what I thought initially. However, note that we're being asked about some *fixed magnetization* so that we only care about a subset of the 2^N microstates with a particular magnetization M. This magnetization will depend on the arrangement of up-spins and down-spins in the lattice, given by the multinomial coefficient,

$$W = \binom{N}{N_\uparrow N_\downarrow} = \frac{N!}{N_\uparrow! N_\downarrow!}$$

The challenge then becomes expressing the number of up-spins and down-spins in terms of the observables. To do this, first notice that it's required that $N = N_\uparrow + N_\downarrow$. Moreover, keep in mind that we're given

$$M = \mu_B(N_\uparrow - N_\downarrow)$$

which allows us to substitute for either of $N_\uparrow$ or $N_\downarrow$ into the expression for the total number of dipoles. Doing

this for $N_\uparrow$,

$$N = N_\uparrow + N_\downarrow$$
$$= \left(\frac{M}{\mu_B} + N_\downarrow\right) + N_\downarrow$$
$$N - \frac{M}{\mu_B} = 2N_\downarrow$$
$$N_\downarrow = \frac{N}{2} - \frac{M}{2\mu_B}$$

Similarly, we can show that

$$N_\uparrow = \frac{N}{2} + \frac{M}{2\mu_B}$$

so that our final expression for the number of microstates in this lattice becomes

$$W = \frac{N!}{N_\uparrow!N_\downarrow!} = \frac{N!}{\left(\frac{N}{2} + \frac{M}{2\mu_B}\right)!\left(\frac{N}{2} - \frac{M}{2\mu_B}\right)!}$$

An important feature of magnets we've ignored until this point is that spins interact with their nearest neighbor as well as any applied magnetic field. When two adjacent spins point in the same direction, a favorable interaction is formed and contributes $-J$ to the overall energy of the microstate. Similarly, when adjacent spins point in opposite directions, an unfavorable interaction occurs which contributes $+J$ to the energy of the microstate. Consider a system of $N = 3$ dipoles and write down an expression for the canonical partition function in the absence of a magnetic field. To do this, notice that *the only energy being contributed to the microstate is coming from nearest neighbor interactions.* So, all we need to determine is the energy coupling of each microstate. Since 3 is a pretty small number, we can just draw each microstate out and determine the coupling energy associated with each:

Microstate	$\uparrow\uparrow\uparrow$	$\downarrow\uparrow\uparrow$	$\uparrow\downarrow\uparrow$	$\uparrow\uparrow\downarrow$	$\downarrow\downarrow\uparrow$	$\downarrow\uparrow\downarrow$	$\uparrow\downarrow\downarrow$	$\downarrow\downarrow\downarrow$
Energy	$-2J$	0	$+2J$	0	0	$+2J$	0	$-2J$

Thus, our partition function can be expressed as

$$Q = 2e^{-2J/k_BT} + 4 + 2e^{2J/k_BT}$$

which can be rewritten by taking the ground state to be when all three dipoles are facing in the same direction to be

$$Q = 2 + 4e^{2J/k_BT} + 2e^{4J/k_BT}$$

Lastly, a quick note on the ground state configuration of the lattice we described above with $N = 3$. Regardless of the presence of an external magnetic field, we would expect the ground state configuration of the material to be where all of the dipoles are pointing in the same direction due to favorable nearest-neighbor interactions. In the absence of a magnetic field, this direction is effectively chosen at random. In contrast, when an external magnetic field is present we'd expect the lattice to point in the same direction as the magnetic field because this would minimize the energy of the system. Either way, energy is minimized (and the ground state is achieved) when all dipoles are pointing in the same direction.

Two-State Systems: A Case Study

Two-state systems can be described by the equilibrium

$$D \rightleftharpoons N$$
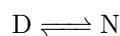
where N is the native state and D is the denatured state. Suppose that we have a two-state system in which the energy difference between the states is $h\nu$. Write down a partition function for a single molecule of this type and calculate its internal energy. Using the general form for the canonical partition function and also allowing $\Delta E = h\nu$ in this case, we have

$$Q = g_1 e^{-E_1/k_B T} + g_2 e^{-E_2/k_B T}$$
$$= 1 + e^{-h\nu/k_B T}$$

as the canonical partition function for this system. Above I allowed g_1 and g_2 to represent the multiplicities of each state, the native and denatured forms of the molecule. However, there is no preference associated with either state (or just none that we are given) so that $g_1 = g_2 = 1$. Moreover, I allowed $E_1 = 0$ to represent the ground state of the system and $E_2 = \Delta E = h\nu$ to be the energy difference between the denatured and native states. To calculate the internal energy of the system, recall Equation (8.3.5) which gives us the internal energy in terms of the partition function. Then,

$$U = k_B T^2 \frac{d \ln Q}{dT} = k_B T^2 \frac{d}{dt} \left[\ln \left(1 + e^{-h\nu/k_B T} \right) \right]$$
$$= k_B T^2 \left(\frac{\frac{h\nu}{k_B T^2} e^{-h\nu/k_B T}}{1 + e^{-h\nu/k_B T}} \right)$$
$$= \frac{h\nu e^{-h\nu/k_B T}}{1 + e^{-h\nu/k_B T}}$$

This is the internal energy of the system. With this expression, compute the heat capacity at a constant volume for this molecule. Recall Equation (4.2.2) which relates the internal energy to the heat capacity at a constant volume. Then, the calculation is trivial:

$$C_V = \left(\frac{\partial U}{\partial T} \right)_V = \left(\frac{\partial}{\partial T} \left[\frac{h\nu e^{-h\nu/k_B T}}{1 + e^{-h\nu/k_B T}} \right] \right)_V$$
$$= \frac{\left(1 + e^{-h\nu/k_B T} \right) \left(\frac{h^2 \nu^2}{k_B T^2} e^{-h\nu/k_B T} \right) - \left(h\nu e^{-h\nu/k_B T} \right) \left(\frac{h\nu}{k_B T^2} e^{-h\nu/k_B T} \right)}{\left(1 + e^{-h\nu/k_B T} \right)^2}$$
$$= \frac{\frac{h^2 \nu^2}{k_B T^2} e^{-h\nu/k_B T} + \frac{h^2 \nu^2}{k_B T^2} e^{-2h\nu/k_B T} - \left(\frac{h^2 \nu^2}{k_B T^2} e^{-2h\nu/k_B T} \right)}{\left(1 + e^{-h\nu/k_B T} \right)^2}$$
$$= \frac{h^2 \nu^2 e^{-h\nu/k_B T}}{k_B T^2 \left(1 + e^{-h\nu/k_B T} \right)^2}$$

This is the constant-volume heat capacity of the molecule.

Let's now consider two *different* types of two-state systems that operate on very different energy levels. Suppose that the first system is the electronic absorption between a singlet ground state to a singlet excited state in which the states differ by the energy of a green photon with $\lambda = 500$ nm. Additionally, suppose that we consider another system which represents the spin of an ^{1}H nucleus in the presence of a 7 T magnetic field[9] with a resonant frequency of 300 MHz. In either case, the probability of occupying the ground state, where $E_{gs} = 0$, is given by

$$P(\text{ground state}) = \frac{1}{1 + e^{E_{gs}/k_B T}}$$

where E_{gs} is to be determined with the given information. Firstly, for the ground state and excited state separated by a green photon, we have that the energy difference is given by

$$E = h\nu = \frac{hc}{\lambda} = \frac{(6.626 \times 10^{-34} \text{ J/s})(2.998 \times 10^8 \text{ m/s})}{500 \times 10^{-9} \text{ m}} = 3.97 \times 10^{-19} \text{ J}$$

---

[9]The SI units of a magnetic field are "teslas," denoted by T.

and therefore the probability of being in the ground state is given by

$$P(\text{ground state}) = \frac{1}{1 + e^{-h\nu/k_B T}} = \frac{1}{1 + 1.15 \times 10^{-42}} = 1$$

Now, for the system representing the spin of a hydrogen nucleus we have the energy difference between the ground state and excited state is given by

$$E = h\nu = (6.626 \times 10^{-34} \text{ J/s})(300 \times 10^6 \text{ s}^{-1}) = 1.99 \times 10^{-25} \text{ J}$$

so that the probability of being in the ground state becomes

$$P(\text{ground state}) = \frac{1}{1 + e^{-h\nu/k_B T}} = \frac{1}{1 + 1} = \frac{1}{2}$$

Now we consider an ensemble of N such two-state molecules. The rate constant for molecules to get excited is $k_{gs \to es} = I(\nu)B_{12}$ where $I(\nu)$ is the intensity of incident light at the resonant frequency and B_{12} is the "Einstein absorption coefficient." Moreover, the rate constant for molecules to relax is $k_{eq \to gs} = A_{21}$ where A_{21} is the "Einstein coefficient for spontaneous emission." In a *photostationary state*, the system reaches an equilibrium where the number of molecules in the ground state becomes constant. At the photostationary state, derive an expression for the equilibrium constant $K = A_{21}/B_{12}$. We'll start by expressing this two-state system with a reaction scheme:

$$N_{gs} \rightleftharpoons N_{es}$$
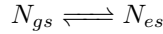
where gs and es represent the ground state and excited state. Then, the rates of formation are given by,

$$\frac{dN_{gs}}{dt} = -I(\nu)B_{12}N_{gs} + A_{21}N_{es}$$

$$\frac{dN_{es}}{dt} = -\frac{dN_{gs}}{dt} = I(\nu)B_{12}N_{gs} - A_{21}N_{es}$$

At the photostationary state, the rates of formation are zero so that we're left with the relatonship

$$\frac{dN_{es}}{dt} = 0 = -I(\nu)B_{12}N_{gs} + A_{21}N_{es}$$

$$I(\nu)B_{12}N_{gs} = A_{21}N_{es}$$

$$\frac{A_{21}}{B_{12}} = I(\nu)\left(\frac{N_{gs}}{N_{es}}\right)$$

Notice that N_{gs} and N_{es} are the proportion of the total number of molecules, N, which are in the ground states and excited states, respectively. So, we can rewrite the expression above as

$$\frac{A_{21}}{B_{12}} = I(\nu)\left(\frac{N\frac{1}{1+e^{-h\nu/k_B T}}}{N\frac{e^{-h\nu/k_B T}}{1+e^{-h\nu/k_B T}}}\right)$$

$$= I(\nu)e^{h\nu/k_B T}$$

which is the "equilibrium constant" for the photostationary state.

8.4 The Isothermal-Isobaric (NPT) Ensemble

8.5 The Grand Canonical Ensemble

8.6 Molecular Ensembles

Our discussion on energy levels makes the canonical ensemble relatively simple to write down for *discrete* systems, that is, systems in which particles can occupy a countable number of states[10]. How might we model continuous systems, such as those for an ideal gas? In Section **??** we derived some key facts about the microcanonical ensemble for the continuous case of an ideal gas; here we'll try to do the same for the canonical ensemble.

Recall that our partition function for the canonical ensemble as its discretized was derived as

$$Q(N, V, T) = \sum_{i=1}^{N} e^{-E_i/k_B T}$$

for a system of N particles. The corresponding expression in the continuous case will be expressed as an integral:

$$Q(N, V, T) = \int e^{-\mathcal{H}/k_B T} d_{\vec{x}_1} \ldots d_{\vec{x}_N} d_{\vec{p}_1} \ldots d_{\vec{p}_N} \tag{8.6.1}$$

where $d\vec{x}_i = dx_i dy_i dz_i$ and $d\vec{p}_i = dp_{x_i} dp_{y_i} dp_{z_i}$ are the differential coordinates and momenta of the particle respectively, and $\mathcal{H}$ is the *Hamiltonian*[11] Already we can see how deriving an expression for the partition function in the continuous case will be more difficult: Notice that Equation (8.6.1) *has units*, in particular, it has units of $action^{3N}$, given by (position×momentum)^{3N}. In other words, each of the differential terms dx_i and dp_i contributes a unit of action to the expression and we have $3N$ of those terms in total, hence the power of $3N$. Although we've already noticed an issue, using the canonical ensemble to derive results about an ideal gas will be exceedingly easier than using the microcanonical ensemble.

We'll start by rewriting Equation (8.6.1):

$$Q(N, V, T) = \int e^{-\mathcal{H}/k_B T} d_{\vec{x}_1} \ldots d_{\vec{x}_N} \ldots d_{\vec{p}_1} \ldots d_{\vec{p}_N}$$

$$= \int e^{-(KE+PE)/k_B T} d_{\vec{x}_1} \ldots d_{\vec{x}_N} \ldots d_{\vec{p}_1} \ldots d_{\vec{p}_N}$$

$$= \int e^{-PE/k_B T} d_{\vec{x}_1} \ldots d_{\vec{x}_N} \int e^{-\left(\sum_{i=1}^{N} \frac{m\vec{v}_i^2}{2k_B T}\right)} d_{\vec{p}_1} \ldots d_{\vec{p}_N}$$

$$= \int (1) d_{V_1} \ldots d_{V_N} \int e^{-\left(\sum_{i=1}^{N} \frac{\vec{p}_i^2}{2mk_B T}\right)} d_{\vec{p}_1} \ldots d_{\vec{p}_N}$$

$$= V^N \int e^{-\left(\sum_{i=1}^{N} \frac{\vec{p}_i^2}{2mk_B T}\right)} d_{\vec{p}_1} \ldots d_{\vec{p}_N} \tag{8.6.2}$$

In line 4 we substituted $dxdydz = dV$ for all N triples in the integral for the potential energy, affording V^N. Additionally, we expressed the kinetic energy in terms of momenta instead of velocity. To see why, we'll manipulate the kinetic energy integral below:

$$\int e^{-\left(\sum_{i=1}^{N} \frac{\vec{p}_i^2}{2mk_B T}\right)} d_{\vec{p}_1} \ldots d_{\vec{p}_N} = \int e^{-\left(\frac{\vec{p}_1^2 + \vec{p}_1^2 + \cdots + \vec{p}_N^2}{2mk_B T}\right)} d_{\vec{p}_1} \ldots d_{\vec{p}_N}$$

$$= \int e^{-\left(\frac{\vec{p}_1^2}{2mk_B T}\right)} d_{\vec{p}_1} \int e^{-\left(\frac{\vec{p}_2^2}{2mk_B T}\right)} d_{\vec{p}_2} \cdots \int e^{-\left(\frac{\vec{p}_N^2}{2mk_B T}\right)} d_{\vec{p}_N}$$

---

[10]The number of states may be countably *infinite*, yet countable nonetheless.

[11]The *Hamiltonian* is an operator which corresponds to the total energy of a system, including both the kinetic and potential energy. This operator comes up much more often in quantum mechanics where I'll provide a larger discussion on it. For now, however, we'll use to to represent the total energy of a system.

In the last line we have a succession of Gaussian integrals, each of which has a mean of zero and variance mk_BT. Furthermore, they're unnormalized so that they'll evaluate to the normalization factor. Continuing with integration,

$$\int e^{-\left(\frac{\vec{p}_1^2}{2mk_BT}\right)}d\vec{p}_1 \int e^{-\left(\frac{\vec{p}_2^2}{2mk_BT}\right)}d\vec{p}_2 \cdots \int e^{-\left(\frac{\vec{p}_N^2}{2mk_BT}\right)}d\vec{p}_N = \sqrt{2\pi mk_BT}\sqrt{2\pi mk_BT}\cdots\sqrt{2\pi mk_BT}$$

$$= (2\pi mk_BT)^{3N/2}$$

Thus, our partition function for the canonical ensemble of an ideal gas is given by

$$Q = V^N(2\pi mk_BT)^{3N/2}$$

But Sam! You forgot about the issue that this partition function has units! That is an excellent point. So, how might we remedy this?

Well, we need a quantity with units of action, preferably one that can be expressed as position times momentum. This quantity is given exactly by the *Heisenberg uncertainty principle,* which asserts that $\Delta x \Delta p \propto h$, that is, the product of the uncertainty in the position and momentum of a particle is directly proportional to Planck's constant. So, dividing our expression by h^{3N} will afford a dimensionless number. Hence, our partition function for the molecular ensemble is

$$Q = \frac{V^N(2\pi mk_BT)^{3N/2}}{h^{3N}} \tag{8.6.3}$$

Interestingly, if you consider the quantity $\sqrt{2\pi mk_BT}/h$, you'll notice that it has units of $(\text{length})^{-1}$, encouraging us to rewrite the partition function in a new way, using a *wavelength* λ,

$$Q = \left(\frac{V}{\lambda^3}\right)^N \tag{8.6.4}$$

where $\lambda = h/\sqrt{2\pi mk_BT}$ is the *De Broglie* or *thermal wavelength*, and it expresses how much "space" a particle of an ideal gas occupies.

The other problem associated with our partition function is more subtle than the last, however, it will become more clear when we consider the entropy of the ensemble. Recall from Section **??** our expression for the entropy of a particle within the canonical ensemble:

$$S = \frac{U}{T} + k_B \ln Q$$

$$=$$

8.6.1   Molecular Ensembles in Two Dimensions

ff

8.7   The Maxwell-Boltzmann Distribution

The *Maxwell-Boltzmann distribution* is a probability distribution that gives the provides the probability of finding a particle at some speed as a function of temperature. The density function for this distribution is,

$$f(v) = 4\pi\left(\frac{m}{2\pi k_BT}\right)^{3/2}v^2 e^{-\frac{1}{2}\left(\frac{mv^2}{k_BT}\right)}, \quad -\infty < v < \infty \tag{8.7.1}$$

8.8 Information Theory Applied to Statistical Mechanics

Information theory is the study of data quantification, storage, and communication, and is at the intersection of myriad scientific fields, one of which is statistical mechanics. The key measure of information theory is *Shannon entropy*[12] which quantifies the amount of uncertainty involved in the outcome of some process. For example, there is more entropy associated with rolling a fair, 6-sided die than there is tossing a fair coin since there are more possible outcomes for rolling the die. Additionally, we might also say that the outcome of rolling the die offers more *information* about the system since there is more entropy associated with each outcome.

The idea of "information content" in an outcome is one of the core ideas of Shannon entropy. To restate in more general terms what I said above, if we are observing a process and a highly likely event occurs, the outcome carries very little information. Inversely, if a very unlikely event occurs, the outcome is much more informative. Claude Shannon (the same guy who "Shannon entropy" is named after) posited that the information of an event must meet a specific set of axioms, all of which are satisfied by defining the information content as

$$I(x) = -\log_2(p_x) \tag{8.8.1}$$

where p_x is the probability of event x occurring.[13]

Insofar as we've discussed entropy it's been constrained to the context of thermodynamics which, while that's good considering this is a thermodynamics class, after all, doesn't offer other, possibly more helpful, ways of building an intuition behind what the entropy of a system characterizes. To provide a complete connection from information theory and some computer science to thermodynamics, we'll motive our discussion by asking the simple question: what exactly causes our computers to heat up?

8.8.1 Entropy as Uncertainty

Within the study of information theory, the *Shannon entropy* of an outcome is defined as the expectation of the information, written

$$H(x) = \langle I(x) \rangle = -\sum_{i=1}^{N} p_i \log_2(p_i) \tag{8.8.2}$$

where the outcome x consists of N particles. To quickly provide some intuition behind how we could use this formula, consider the entropy of the alphabet. Suppose that we choose letters at random. Assuming that each letter of the alphabet has an equal probability of being chosen, the entropy is given by

$$H_{\text{alphabet}} = -\sum_{i=1}^{26} \frac{1}{26} \log_2\left(\frac{1}{26}\right) = \log_2 26 \approx 4.7 \tag{8.8.3}$$

Interestingly, and potentially obviously depending on how much one has payed attention during lecture, the Shannon entropy of a particular outcome *is exactly the same as the Gibbs entropy* (up to a constant), which is derived directly from the Boltzmann equation, $S = k_B \ln W$. Note that,

$$S = k_B \ln W = -k_B \sum_{i=1}^{N} p_i \ln p_i = -k_B \ln 2 \sum_{i=1}^{N} p_i \left(\frac{\ln p_i}{\ln 2}\right) = -k_B \ln 2 \sum_{i=1}^{N} p_i \log_2 p_i = (k_B \ln 2)H \tag{8.8.4}$$

Let us suppose we didn't recognize this equivalence and instead used the Shannon entropy to determine the

---

[12]I'll try my best to distinguish between Shannon entropy and thermodynamic entropy throughout this section but you'll probably just have to figure out which one I'm talking about based on context clues. I believe in you!

[13]The choice of base for the logarithm is arbitrary and will only effect the units in the end. The most common choice is base 2 which affords units of "bits". Another common choice is to use the natural base e, affording units of "nats".

values of the p_i which will maximize the entropy. As we saw with the definition of information content in Equation (8.8.1) , the information is monotonically decreasing as the probability of any one outcome decreases. In other words, the Shannon entropy for a probability distribution will increase as the probability of any outcome from the distribution decreases. Conveniently, the postulate of *a priori* equal probabilities with $p_i = \frac{1}{\Omega}$ where Ω is the sample space, satisfies this property. Then, the Shannon entropy is given by

$$H = -\sum_{i=1}^{\Omega} \frac{1}{\Omega} \log_2 \frac{1}{\Omega}$$

$$\left(\frac{1}{k_B \ln 2} \right) S = \log_2 \Omega$$

$$S = k_B \ln \Omega \tag{8.8.5}$$

which agrees exactly with the Boltzmann equation.

The equivalence illustrated in Equations (8.8.4) and (8.8.5) prompts us to rethink (if not already having thought) of *entropy as uncertainty.* For example, suppose we are interested in a gas contained within a box. All of the particles have some well-defined position and momentum and if we knew all of these position and momenta there would only be one microstate possible for the gas and therefore zero entropy. Clearly, though, the entropy of a gas is nonzero. It's nonzero exactly because we don't know the positions and momenta of the particles. Hence, entropy is not necessarily a property of the gas but instead a property of our knowledge of the gas.

8.8.2   The Irreversibility of Information Storage

In the preceding section we made an informal connection between thermodynamic entropy and Shannon entropy, relying on an observation as opposed to a rigorous derivation. This connection, however, can not only be shown rigorously but also proven to be an equivalence. That is, showing that thermodynamic entropy and Shannon entropy are exactly the same. This result will require slightly more work...

Recall the question that sparked our discussion regarding computers and their tendency to heat up as we use them. Clearly, some energy is being dissipated by our machines during this process. In 1961, the physicist Rolf Landauer was interested in minimizing this energy loss and considered the existence of a computer which could operate with no loss of energy. He considered a model of a bit[14] with a double-well, illustrated in Figure 8.1. The first question Landauer posited was whether or not we could switch the sign of the bit from 0 to 1 without expending any energy.
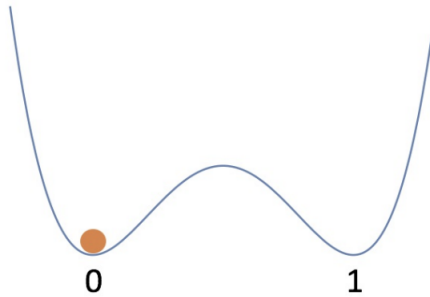

Figure 8.1: Double well model of bit storage.

Seemingly, the answer is yes. Following the scheme in Figure 8.2, attaching a counterweight to the ball representing our bit and giving an infinitesimal nudge to the counterweight will allow us to switch the sign of

---

[14]A "bit" is the unit of storage for a system using binary. That is, a binary integer represented by either 0 or 1 requires 1 bit of storage.

the bit. Another infinitesimal nudge to stop the counterweight stops the ball, affording a reversible reaction without the expenditure of energy.[15]
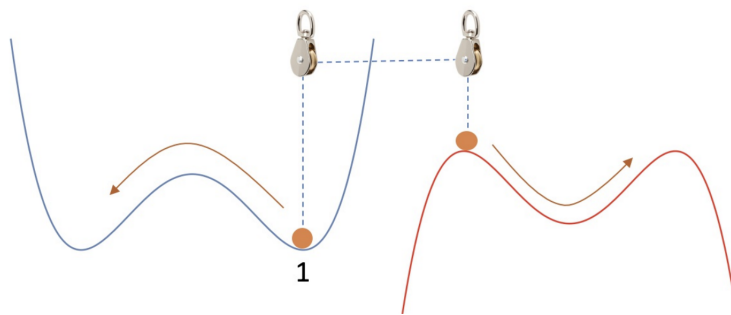

Figure 8.2: Double well model of bit storage using pulleys to avoid expending energy to switch the sign of a bit.

At this point we need to address the issue of knowing the initial state of the bit. Above, we naively assumed that every time we go to switch the sign of the bit we "guess" correctly, in that we don't try and switch the state of a 0 bit to 0. So, can our pulley system address the issue of not knowing the initial state of the bit? The answer is no.

In particular, the answer is no for any sort of over-engineered apparatus you can think of. The reason is that we are using Newton's Laws to switch the sign of the bit (the infinitesimal nudge). Recall that Newton's Laws are time-invariant so that anything we do in the forward direction of time must be equally possible and well-defined in the reverse direction of time. Swapping a 1 to a 0 corresponds to swapping a 0 to a 1 in the reverse direction. So, a function or process which can simultaneously swap a 1 and a 0 to a 0 is clearly not invertible. If the final state of the system is a 0 how can we be sure of the initial state (assuming that we've created the machine I've already said was impossible to create)?[16]

The calculation described above, swapping a bit regardless of whether it is a 1 or a 0 to a 0, is performed all the time by computers. How? Well, the process is fairly straightforward *if we're allowed to dissipate energy.* For example, if there is friction in our double-well model, the process could involve smacking a mallet on the "1" side with enough energy to knock the bit down the well and over the adjacent hill. If there is no bit present on the 1 side, the 0 remains a 0. If there is a bit present, the 1 rolls up the hill and is slowed by friction, ultimately resting in the well corresponding to 0. Note that this wouldn't work if friction we're not present since the ball would have enough energy to roll back up the hill and arrive in the "1" well again. To address the question of how realistic a system like this is, suppose that the ball representing our bit is stored in the spin of a magnet on some magnetic tape. The mallet, then, may be an external magnetic field. No matter how you imagine our information to be stored, we arrive at the conclusion that *erasing energy requires energy to be dissipated as heat,* also known as *Landauer's principle.*

Erasing information is an essential step in computation; every time information is stored the corresponding information which existed there previously is erased. Take, for example, what I'm writing now. " " contains some information, it's meaningless, but it's something. "1" now it contains new information, potentially more meaningful to you and I. In any case, the information stored in the empty space was erased upon the addition of the 1.

The key element to showing that the erasure of information is impossible without the loss of energy was the reversibility of the laws of physics. Thus, thermodynamic entropy increases when information is discarded. The connection between thermodynamic entropy and information entropy has been pushed further by

---

[15]If I may interject to comment on the setup of our apparatus. Clearly, using counterweights and pulleys to store information in a computer is unrealistic. This, however, is a thought experiment and so the plausibility of our setup is of no concern. That's an issue for the engineers.

[16]More technically you might say that we require an invertible function which is also *not* injective. Even writing this down makes me fear the NSA is listening and is going to have me off'd. A function is invertible *if and only if* it is injective. So, the required function to make our imaginary apparatus work is nonsense!

scientists asking question such as, "what is the minimum amount of energy required to perform a computation?" More generally, what are the limits of computing? This is getting more into the realm of computer science than I care for, so those answers will be relegated to another time.

8.8.3 Maxwell's Demon

With our newly established expertise in information theory we can tackle one of the most famous and vexing paradoxes regarding entropy, invented by James Maxwell in 1867. As originally postulated, the paradox is stated as follows:

> ... if we conceive of a being whose faculties are so sharpened that he can follow every molecule in its course, such a being, whose attributes are as essentially finite as our own, would be able to do what is impossible to us. For we have seen that molecules in a vessel full of air at uniform temperature are moving with velocities by no means uniform, though the mean velocity of any great number of them, arbitrarily selected, is almost exactly uniform. Now let us suppose that such a vessel is divided into two portions, A and B, by a division in which there is a small hole, and that a being, who can see the individual molecules, opens and closes this hole, so as to allow only the swifter molecules to pass from A to B, and only the slower molecules to pass from B to A. He will thus, without expenditure of work, raise the temperature of B and lower that of A, in contradiction to the second law of thermodynamics.

In layman's terms, we can imagine a container of gas with a partition in the middle separating sides A and B, each of which have an equal amount of energy contained within them on average. A "demon" observes the molecules on both sides and allows molecules with an above average-velocity to pass into side A while only allowing the below average-velocity particles to stay on side B, all while dissipating very little energy compared to that gained by the system upon establishing an energy gradient. Thus, we're left with a box that has an energy gradient between the two sides, with A having particles with an average energy greater than that of the average energy of the particles on side B. Since the box started with a uniform energy across the partition separating sides A and B we've seemingly violated the second law of thermodynamics.

To prove that this situation does not in fact violate the second law of thermodynamics we'll invoke Landauer's principle. In order for the demon to allow the molecule to pass through the partition it must first acquire some information about the particle, whether it be the speed, momentum, or energy. Then, to accurately judge which side the *next* particle should belong to the demon must erase the information previously stored about the speed, momentum, or energy to make space for the corresponding information of the new particle. Discarding the previously held information immediately causes an increase in entropy, as we've seen. Moreover, the demon cannot store any information indefinitely, implying that the storage of *any* information regarding the system of gas particles ultimately causes an increase in entropy.[17]

This thought experiment clarifies why information entropy is equivalent to thermodynamic entropy. Suppose that the demon described above also kept a finite tape of 0's in his back pocket. For every bit of information he gathers about a particle approaching the partition, he may record the info on the tape with either a 1 or a 0 (recall that we're assuming the information he gathered regarding the particles can be represented in binary). Then, we must include the tape in our definition of the system. In doing so, the entropy of the gas may very well decrease as he selects for which particles enter side A and which enter side B, however, the entropy of the *system* never decreases because the information stored in the particles isn't lost but instead transferred to the tape.

In this way, Maxwell's demon was resolved after over 100 years of turmoil. In his lectures on computation Feynman comments on Landauer's principle:

---

[17]This was illustrated by Charles Bennett in a paper titled "The Thermodynamics of Computation — a Review," published in 1982.

This realization that it is the erasure of information, and not measurement, that is the source of entropy generation in the computational process, was a major breakthrough in the study of reversible computation.

CHAPTER

9

HELIX-COIL THEORY

The *helix-coil transition model* is a formalized application of the partition functions developed in statistical mechanics to help analyze the multistate conformational transitions of linear polymers. In particular, we'll be considering the formation of an α-helix from a polypeptide chain.

You're probably already familiar with α-helices as they are among the most common types of protein secondary structure.[1] The reason these structures are so common is due to the natural stability and optimality of the intermolecular interactions and bond lengths. Some common examples are α keratin, a principle component of the epidermis and related appendages such as hair and nails, as well as collagen, which bears strong, insoluble fibers responsible for connective tissue.

As a motivating example, consider a polypeptide of length 5, that is, one composed of 5 amino acid residues. We can model the partitioning of energy states using the canonical ensemble. Although using the NPT ensemble would be better suited to this situation, we'll stick with the canonical ensemble for convenience. An important aspect of our model to keep in mind is that *entropy is inherently represented*. That is, microstates which are energetically favored are necessarily entropically favored. For our case of 5 residues... ya know I was about to try and make a table but then I thought better of it. There's a representation of all 32 microstates in the lecture slides or either of the two textbooks for this class just go look at those.

The favorable macrostates are so because they have a greater *degeneracy*, that is, they are represented more. Hence, we can rewrite our canonical partition function as

$$Q = \sum_{i=1}^{m=2^N} \lambda_i e^{-\frac{E_i}{RT}} \tag{9.0.1}$$

where λ_i represents the frequency of the microstate and $m = 2^N$ is the total number of microstates for N amino acid residues. For example, in the case of one helical residue among four other coils, there are $\binom{5}{1} = 5$ degenerate states and therefore $\lambda_1 = 5$. Experiments can't observe the populations of 32 unique microstates, hence, we define the *fractional helicity* as

$$\langle f_H \rangle = \sum_{i=1}^{m} p_i f_{H,i} = \frac{1}{Q} \sum_{i=1}^{m} f_{H,i} e^{-\frac{E_i}{RT}} \tag{9.0.2}$$

---

[1]Alongside β-sheets.

Since f_H is defined as the *average number of helical residues divided by the length of the peptide*, we can express the expression above alternatively,

$$\langle f_H \rangle = \frac{\langle j \rangle}{N} = \frac{1}{N} \sum_{j=1}^{N} j \times p_j \tag{9.0.3}$$

where j is the average helicity of the macrostate[2] Although a summation over the number of residues offers a significant simplification from a summation over the total number of microstates, our work is far from done[3]. In the succeeding sections we'll develop models which significantly reduce the complexity of our expressions for the partition function, affording considerable insight into key aspects of helix-coil energetics.

P.S. I used Q to express the partition function in the case of every model, so depending on the context Q will take on a different expression. I don't think this will cause any confusion, but just in case it does, try and use context clues I guess.

9.0.1 The Noncooperative Model

The simplest model for helix formation we'll consider is *noncooperative formation* in which each residue can be thought of as being "independent" of its neighbor. That is, the existence of a helical coil in the polymer does not influence the formation of helical coils in adjacent residues.

This assumption allows us to use a single expression for the free energy associated with the helical transition. That is, if the change in free energy associated with one helical residue is given by $\Delta \tilde{G}^\circ_{c \to h}$, then the change in free energy for the same transition across five residues is $5\Delta \tilde{G}^\circ_{c \to h}$. To simplify this expression we can define a new variable representing the free energy conversion for a single residue as

$$\kappa = e^{-\Delta \tilde{G}^\circ_{c \to h}/RT} \tag{9.0.4}$$

κ can be thought of as a pseudo-equilibrium constant for a single residue[4]. If we consider the simple example mentioned a moment ago for the difference between the transition of one residue versus five residues to the helical transition, we could express the transition energy of one residue as κ and the transition energy as κ^5 (convince yourself that this is true. It isn't very hard).

With the energy associated with the coil-to-helix transition found, we can now try and discern the partition function for all possible states of a peptide within the noncooperative model. The partition function is given exactly as we're used to,

$$Q = \sum_{j=1}^{N} g_j e^{-\Delta \tilde{G}^\circ_j/RT}$$

which is analogous to Equation (9.0.1). Here, however, we've used g_j to represent the degeneracy of each microstate. Since the likelihood of each microstate is independent of one another (this is our primary assumption under the noncooperative model), the degeneracy factor can be represented as a binomial coefficient and the partition function can be simplified:

$$Q = \sum_{j=1}^{N} \binom{N}{j} e^{-\Delta \tilde{G}^\circ_j/RT} = \sum_{j=1}^{N} \binom{N}{j} e^{-j\Delta \tilde{G}^\circ_{c \to h}/RT} = \sum_{j=1}^{N} \binom{N}{j} \kappa^j$$

$$Q = (1 + \kappa)^N \tag{9.0.5}$$

---

[2] The switch between using i and j as our iteration variables is intentional: i is used in a summation through all *macrostates* whereas j is used in a summation through all *residues*.

[3] Is our work ever done? The answer is no. Always strive to be better.

[4] It's not quite an equilibrium constant because there is more chemistry going on after folding. Intermolecular interactions between residues on the peptide also contribute to the free energy of transition but aren't captured by κ.

Equation (9.0.5) illustrates clearly the utility of the noncooperative model: The partition function for the peptide can be represented in a simple, concise expression. Intuitively, this result should make sense. For each residue we're effectively flipping a coin, as each one can either exist in the coiled or helical state. With N residues, then, there are 2^N microstates. The partition function, however, considers *energies*, not just microstates. So, the change in free energy associated with the transition can either be 0 (where the residue exists in the coiled conformer) or $\Delta \tilde{G}^{\circ}_{c \to h}$ (where the residue has transitioned to the helix). The Boltzmann factors come naturally from either of these two values and the partition function with those, using the same logic mentioned a moment ago.

With the partition function defined we can ascertain the fractional helicity of peptide using Equation (9.0.3):

$$\langle f \rangle = \frac{\langle j \rangle}{N} = \frac{1}{N} \sum_{j=1}^{N} j p_j$$

$$= \frac{1}{N} \sum_{j=1}^{N} j \frac{\binom{N}{j} \kappa^j}{(1+\kappa)^N} = \frac{1}{N(1+\kappa)^N} \sum_{j=1}^{N} \binom{N}{j} j \kappa^j$$

Here we can take advantage of the chain rule to reexpress

$$j \kappa^j = \kappa \frac{d(\kappa^j)}{d\kappa}$$

and substitute into our expression above:

$$\frac{1}{N(1+\kappa)^N} \sum_{j=1}^{N} \binom{N}{j} j \kappa^j = \frac{1}{N(1+\kappa)^N} \sum_{j=1}^{N} \binom{N}{j} \kappa \frac{d(\kappa^j)}{d\kappa}$$

$$= \frac{\kappa}{N(1+\kappa)^N} \frac{d}{d\kappa} \sum_{j=1}^{N} \binom{N}{j} \kappa^j$$

$$= \frac{\kappa}{N(1+\kappa)^N} \frac{d(1+\kappa)^N}{d\kappa}$$

$$= \frac{\kappa}{N(1+\kappa)^N} \left(N(1+\kappa)^{N-1} \right)$$

$$= \frac{\kappa}{1+\kappa} \tag{9.0.6}$$

Equation (9.0.6) constitutes the fractional helicity for the noncooperative model of an α-helix.

Here is a list of all the results we've derived for the noncooperative model:

$Q = (1+\kappa)^N$ is the partition function for a polymer with N residues. Here, $\kappa = e^{-\Delta \tilde{G}^{\circ}_{c \to h}/RT}$ is the "pseudo-equilibrium constant."

$p_i = \frac{\binom{N}{i} \kappa^i}{(1+\kappa)^N}$ is the probability of a polymer having i helical residues under the noncooperative model.

$\langle f_H \rangle = \frac{\kappa}{1+\kappa}$ is the fractional helicity of a polymer under the noncooperative model.

9.1   Cooperativity

Cooperativity in protein folding is the phenomenon where one part of a peptide chain folding into a tertiary structure makes it more likely that adjacent parts of the peptide do the same. The converse to this is also true: The *unfolding* of one part of a protein influences adjacent residues to do the same, hence why denaturation can happen so quickly at sufficient temperatures.
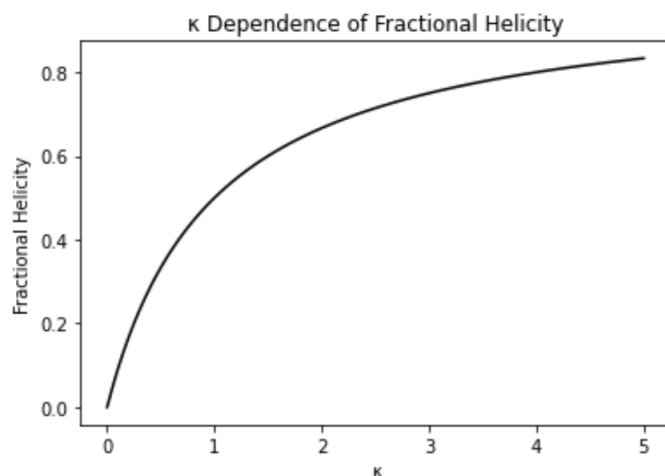
Figure 9.1: The fractional helicity of a polymer as a function of κ takes the shape of a *rectangular hyperbola*, indicative of a noncooperative relationship. This type of graph is in contrast to a *sigmoid* which (typically) indicates cooperativity.
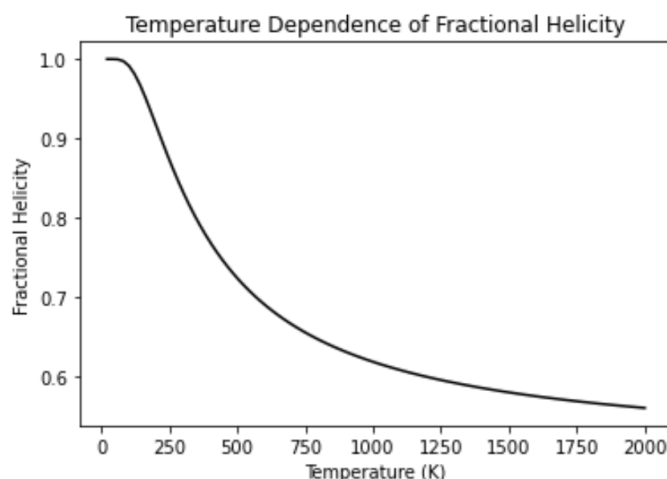

Figure 9.2: The fractional helicity of a polymer as a function of temperature follows an exponential decay. Notice, however, that this exponential decay is *very slow*. At 2000 K the peptide maintains a fractional helicity greater than 50%, even though there are barely any proteins which haven't denatured well before this temperature. This discrepancy between our intuition and our results incentives the definition of a cooperative model for α-helix formation. Note that above, a value of $\Delta \tilde{G}^{\circ}_{c \to h} = -4$ kJ/mol was chosen for no reason aside from that was what Dr. Fried used in the slides.

Depending on the context, cooperativity can take on slightly different meanings and is why I specified cooperativity among proteins instead of just in general. In enzymatic catalysis, for example, cooperativity can be thought of in terms of ligand binding.

The most simple model of cooperativity we could invoke for polymer folding is one where each residue may affect those that it's directly adjacent to but no others. This requires we define a *coupling strength*, oftentimes denoted J,[5] and is typically negative as to be energetically favorable. Just as there is an associated Boltzmann constant for the change in free energy of folding, κ, there is one for coupling, denoted τ:

$$\kappa = e^{-\Delta \tilde{G}^{\circ}_{c \to h}/RT}, \quad \tau = e^{-J/k_B T}$$

The Hamiltonian (recall that the Hamiltonian is an operator which represents the total energy of a system)

---

[5]You may recognize J from the splitting of peaks in NMR spectra. In the context of cooperativity, however, the term "coupling" takes on a slightly varied meaning.

for a polymer of N residues becomes

$$\mathcal{H} = J \sum_{i=1}^{N} \sigma_i \sigma_{i+1} + \Delta \tilde{G}_{c \to h}^\circ \sum_{i=1}^{N} \sigma_i, \quad \sigma_i \in \{0, 1\} \tag{9.1.1}$$

where $\sigma_i = 1$ corresponds to the existence of a helical residue on the peptide and $\sigma_i = 0$ a coiled residue.

9.1.1   The Zipper Model

The *zipper model* is a model for cooperative protein folding that assumes that once helices form, they "zip up" into a continuous block. With this simplification, the coupling constant τ is introduced into the partition function such that the Boltzmann factor for each microstate is of the form $\kappa^j \tau^{j-1}$. This simplification omits the microstates which have blocks of helices separated by one or more coiled segments. As an example, for a pentapeptide the zipper model does not accurately model microstates such as *hchch* or *hchhhh*. In practice, however, this loss is negligible as long as τ is large, normally at $\tau = 10^3$ or greater.

The simplification in the zipper model allows us to write the partition function as a sum over all helical levels j, where $j = 1, \ldots, N$ for a peptide with N residues, using the Boltzmann factor $\kappa^j \tau^{j-1}$ described above. With a little bit of mathematical intuition (and page 386 of Barrick) we can deduce that the number of microstates *involving helical residues* can be counted by

$$W = N - j + 1$$

Then, the partition function can be described by

$$Q = 1 + \sum_{j=1}^{N} W \kappa^j \tau^{j-1} = 1 + \sum_{j=1}^{N} (N - j + 1) \kappa^j \tau^{j-1} \tag{9.1.2}$$

where the $+1$ term accounts for the completely coiled peptide chain. Equation (9.1.2) is adequate for short peptide chains where the summation can be computed by hand easily. For longer chains, however, a closed form solution for the partition function would be far less computationally-intensive. With a little bit of algebraic gymnastics, beginning with bringing κ and τ to the same power, this can be achieved:

$$Q = 1 + \sum_{j=1}^{N} (N - j + 1) \kappa^j \tau^{j-1}$$

$$= 1 + \frac{1}{\tau} \sum_{j=1}^{N} (N - j + 1) \kappa^j \tau^j$$

$$= 1 + \frac{1}{\tau} \left[\sum_{j=1}^{N} (N + 1)(\kappa \tau)^j - \sum_{j=1}^{N} j(\kappa \tau)^j \right]$$

$$= 1 + \frac{1}{\tau} \left[\sum_{j=1}^{N} (N + 1)(\kappa \tau)^j - \kappa \sum_{j=1}^{N} \frac{\partial}{\partial \kappa} (\kappa \tau)^j \right]$$

The derivative in the last line is introduced the same way as it was in Equation (9.0.6), this time making sure to keep τ constant. Notice that we have two summations, each of which is a *power series*. I cover the derivation of a closed form solution to the power series in Section 1.1 so that we can rewrite the expression above as

$$Q = 1 + \frac{1}{\tau} \left[(N + 1) \frac{\kappa \tau [(\kappa \tau)^N - 1]}{\kappa \tau - 1} - \kappa \frac{\partial}{\partial \kappa} \left(\frac{\kappa \tau [(\kappa \tau)^N - 1]}{\kappa \tau - 1} \right) \right] \tag{9.1.3}$$

and evaluating the derivative affords the desired closed form solution for the partition function of the zipper

model:

$$Q = 1 + \kappa \left[\frac{(\kappa\tau)^{N+1} - (N+1)(\kappa\tau) + N}{(\kappa\tau - 1)^2} \right] \tag{9.1.4}$$

Using the partition function we can define the fractional helicity for a polymer under the zipper model. As before, when we did this for the noncooperative model, this can be done using the probabilities of a microstate containing j helices:

$$\langle f_H \rangle = \frac{1}{N} \sum_{j=1}^{N} j p_j = \frac{1}{NQ} \sum_{j=1}^{N} j(N - j + 1)\kappa^j \tau^{j-1} \tag{9.1.5}$$

The derivation is really long and uses a lot of techniques we've already covered in finding closed form solutions to the partition functions, so I'm not gonna do it here. Ultimately, we arrive at the following closed form solution for the fractional helicity:

$$\langle f_H \rangle = \frac{2\kappa^2\tau[1 - (\kappa\tau)^N] + N\kappa[1 - \kappa\tau][1 + (\kappa\tau)^{N+1}]}{N(\kappa\tau - 1)\{1 + \kappa(N - 2\tau) + \kappa^2\tau[\tau - 1 - N + (\kappa\tau)^N]\}} \tag{9.1.6}$$

Graphing fractional helicity versus κ affords a sigmoid, corroborating the assumption about this model being cooperative. Another trend that appears is that *longer peptides* show sharper helical transitions as a function of κ. This is because longer peptides have more initiation sites and once a helix has been initiated, longer stretches of the helix can propagate and the peptide becomes helical by cooperativity.

Additionally, if we graph fractional helicity versus τ, unsurprisingly, we find that helix formation likelihood increases as τ increases. A rather surprising aspect of this plot, however, is that even at $\tau = 1$ when there are no favorable or unfavorable interactions between helices, α-helix formation is still largely sigmoidal whereas we would expect a rectangular hyperbola, which is the case of noncooperativity. This discrepancy arises due to the fact that the partition function omits those microstates which are helical *with gaps*. This assumption is okay when τ is large (discussed earlier) so that "gapped" microstates have negligible populations. For small τ values, these microstates are significantly populated, thereby changing the shape of the plot.
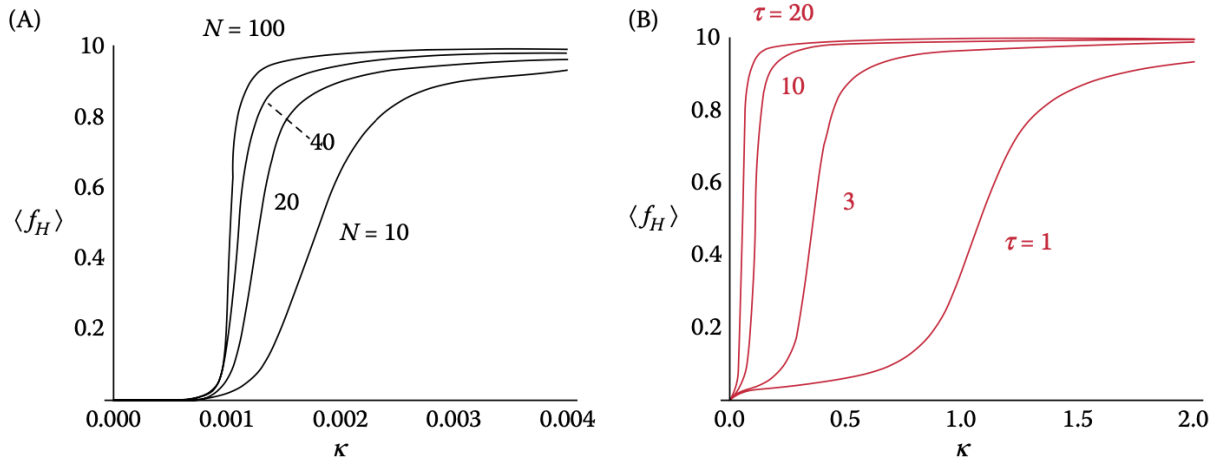

Figure 9.3: (A) The fractional helicity as a function of κ as the length of the polymer increases. Clearly, as N tends to infinity the affinity for a polymer to become an α-helix increases. (B) The fractional helicity as a function of κ as the coupling constant is (modestly) increased. For $\tau = 1$, the unexpected shape is a result of the assumptions made under the zipper model, as discussed above. As τ increases, the affinity for the polymer to become helical increases which agrees with our intuition.

Here is a list of all results we've derived for the zipper model for α-helix formation:

$$Q = 1 + \kappa \left[\frac{(\kappa\tau)^{N+1} - (N+1)(\kappa\tau) + N}{(\kappa\tau - 1)^2} \right] \text{ is the partition function for the zipper model.}$$

$$p_i = \frac{(N - i + 1)\kappa^i \tau^{i-1}}{Q} \text{ is the probability of there being } i \text{ helices in a peptide of } N \text{ residues.}$$

$$\langle f_H \rangle = \frac{2\kappa^2\tau[1 - (\kappa\tau)^N] + N\kappa[1 - \kappa\tau][1 + (\kappa\tau)^{N+1}]}{N(\kappa\tau - 1)\{1 + \kappa(N - 2\tau) + \kappa^2\tau[\tau - 1 - N + (\kappa\tau)^N]\}} \text{ is a closed-form solution to the fractional}$$
helicity of a polymer under the zipper model.

9.1.2   The Nearest-Neighbor Model

The *nearest-neighbor model* for α-helix formation remedies the assumptions and issues made by and raised in the zipper model by utilizing a *transfer matrix*, allowing us not only to model microstates with helical segments separated by coiled segments but also heteropolymers, that is, polymers which have peptide segments with different κ values. Moreover, the nearest-neighbor model can accurately represent α-helix formation when coupling is modest, i.e., when τ is small.

The transfer matrix we'll utilize is given as

$$T = \begin{bmatrix} \kappa\tau & 1 \\ \kappa & 1 \end{bmatrix} \tag{9.1.7}$$

where the columns of T represent the Boltzmann factor associated with the helical and coiled configurations, respectively, contingent on the conformation of the adjacent residues. To build the partition function we need to generate 2^N terms, each representing the possible microstate of a particular residue, either helical or coiled. This is done by multiplying T by itself N times. Ultimately, in order to attain the scalar partition function it can be shown that

$$Q = \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} \kappa\tau & 1 \\ \kappa & 1 \end{bmatrix}^N \begin{bmatrix} 1 \\ 1 \end{bmatrix} \tag{9.1.8}$$

where the row vector eliminates the top row of T^N, and the column vector combines remaining terms in the bottom row into a single sum. Barrick provides an example of utilizing Equation (9.1.8) for an $N = 10$ homopolymer and I think the equation is kinda pretty and also provides some intuition behind the various combinations that are formed in the nearest-neighbor model, so I'm gonna use that example here as well, factoring slightly different than is provided on page 391 of Barrick. For an $N = 10$ homopolymer,

$$\begin{aligned}
Q = {}& 1 \\
& + 10\kappa \\
& + 9\kappa^2(4 + \tau) \\
& + 8\kappa^3(7 + 7\tau + \tau^2) \\
& + 7\kappa^4(5 + 15\tau + 9\tau^2 + \tau^3) \\
& + 6\kappa^5(1 + 10\tau + 20\tau^2 + 10\tau^3 + \tau^4) \\
& + 5\kappa^6\tau(1 + 10\tau + 20\tau^2 + 10\tau^3 + \tau^4) \\
& + 4\kappa^7\tau^3(5 + 15\tau + 9\tau^2 + \tau^3) \\
& + 3\kappa^8\tau^5(7 + 7\tau + \tau^2) \\
& + 2\kappa^9\tau^7(4 + \tau) \\
& + \kappa^{10}\tau^9
\end{aligned}$$

A few things to notice: 1) The sum of the coefficients in each row of the equation above sum to the the corresponding value in the 10th row of Pascal's triangle. That is, for row 5 in the equation above (taking the first row to be row 0) with 5 helical residues, hence the factor of κ^5, the coefficients sum to

$$6(1 + 10 + 20 + 10 + 1) = \binom{10}{5} = 252$$

2) The partition function is symmetric with respect to the number of ways to arrange the helical coils in the polymer which connects directly to Pascal's triangle at what we just mentioned about the coefficients of the terms in each row. 3) Lastly, the ways of arranging the helical residues and the coefficients that come about for each term are a result of the order of the coupling constant, τ. Notice that as the number of helices increases in the expression above, the order of κ increases linearly and doesn't depend on the number of ways to arrange the residues. In contrast, the coefficients of τ (within the parentheses) vary drastically depending on how many helices are present, and in particular, they vary with the Nth row of Pascal's triangle. That is all to say, the expressions for the partition function could be determined analytically without needing to go through all the matrix multiplication, all that it would require is some cheeky combinatorics and more willpower than is typically necessary than for anything else in this class.

With some newfound intuition for the partition function of the nearest-neighbor model we can analyze the predicted fractional helicity of a polymer under this model. Just as in the case of the zipper model, the fractional helicity can be expressed as a summation over each possible microstate with j helical residues:

$$\langle f_H \rangle = \frac{1}{N} \sum_{j=1}^{N} j p_j$$

Now, recall Equation (9.1.5) which contains a similar expression for the fractional helicity of a polymer under the zipper model. The $(N - j + 1)$ term represents all of the combinations of helical residues that are permitted under this model. In contrast to this case, however, we've seen how this combinatorial coefficient for the nearest-neighbor model will be slightly more complex. So, we'll simplify our lives by expressing this coefficient as $f(\tau, j, N)$, indicating that it's a function of τ, j, and N. Hence, the fractional helicity becomes

$$\langle f_H \rangle = \frac{1}{N} \sum_{j=1}^{N} j f(\tau, j, N) p_j$$

$$= \frac{1}{NQ} \sum_{j=1}^{N} f(\tau, j, N) j \kappa^j$$

$$= \frac{\kappa}{NQ} \sum_{j=1}^{N} f(\tau, j, N) \frac{d(\kappa^j)}{d\kappa}$$

$$= \frac{\kappa}{NQ} \frac{d}{d\kappa} \sum_{j=1}^{N} f(\tau, j, N)(\kappa^j)$$

$$= \frac{\kappa}{NQ} \frac{dQ}{d\kappa} \tag{9.1.9}$$

Equation (9.1.9) is the fractional helicity of a polymer under the nearest-neighbor model. Similar to the derivations of some of the partition functions and fractional helicity expressions above, the derivative originally introduced in the derivation of Equation (9.0.6) was utilized in line 3.

Here is a list of the key results for the nearest-neighbor model:

$Q = \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} \kappa\tau & 1 \\ \kappa & 1 \end{bmatrix}^N \begin{bmatrix} 1 \\ 1 \end{bmatrix}$ is the partition function for the nearest-neighbor model.

$p_i = \dfrac{f(\tau, i, N)\kappa^i}{Q}$ where $f(\tau, i, N)$ is the really weird coefficient that isn't easy to express combinatorially, is the probability of there being i helices in a peptide of N residues.

$\langle f_H \rangle = \dfrac{\kappa}{NQ} \dfrac{dQ}{d\kappa}$ is a closed-form solution to the fractional helicity of a polymer under the zipper model.

Before ending our discussion on α-helix formation I'll extend the nearest-neighbor model approach to a heteropolymer which will accommodate variation in a peptide sequence. In principle, differences in the
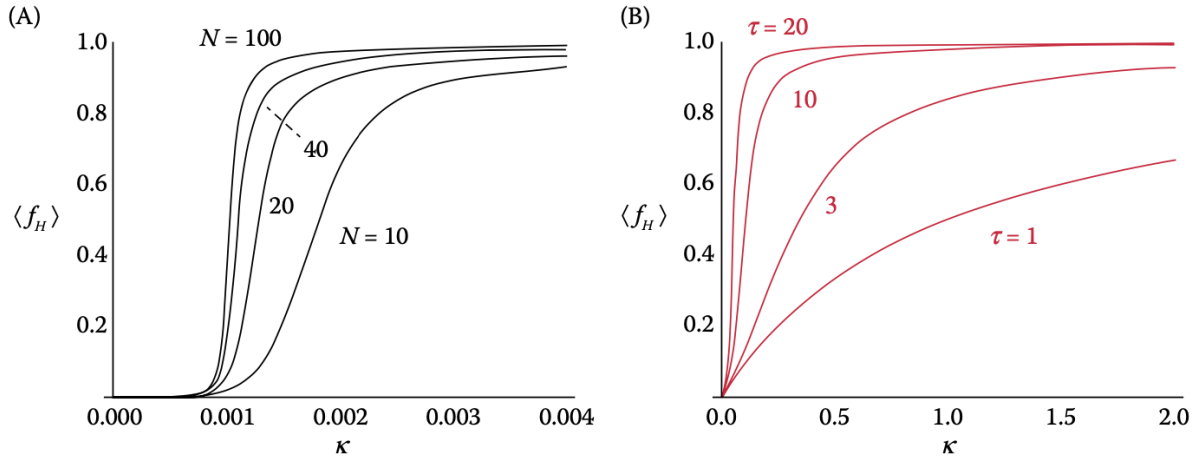
Figure 9.4: The shapes of the graphs of fractional helicity versus κ as the length of the peptide chain changes and as the coupling constant τ changes are similar for the zipper model and nearest-neighbor model. The contrast lies in the shapes of the plots which vary τ: For $\tau = 1$ in figure above, a rectangular hyperbola appears which agrees with our intuition about cooperativity. Recall that for the zipper model the case of $\tau = 1$ leads to inaccurate results, as expected. The nearest-neighbor model remedies those discrepancies.

transfer matrix for this model could arise due to variations in κ or in τ (or both) but in practice it is far simpler to restrict effects on the transfer matrix to only κ. Then, our matrix becomes

$$T = \begin{bmatrix} \kappa_i \tau & 1 \\ \kappa_i & 1 \end{bmatrix}$$

where κ_i represents the Boltzmann factor for some residue on a polymer. Barrick uses the example of an α-helix found in the myoglobin of sperm whales on page 393, a protein which houses $N = 24$ residues. Finding the partition function by hand is unwieldy, yet trivial to a computer which is why I'll leave that calculation to you, in case you're interested. Additionally, variation in T creates a scenario where the matrix product does not easily factor into something compact leading to messy expressions for the partition function and fractional helicities of the protein.

9.2   Flory Theory

Paul Flory was a smart man, smarter than many of us will ever be. He was among one of the first scientists to prove that polymers are covalently linked macromolecules and went on to show that these covalent bonds are responsible for the principle differences between polymers and their monomeric constituents. He introduced *Flory theory* which addressed the problem of modeling real conformations of polymer chains using estimates for both the energetic and entropic contributions. Surprisingly, this simple model is incredibly accurate for real polymers. Although, it may be shown that this accuracy is due the cancellation of errors across the energetic and entropic terms. As we'll see, Flory theory *overestimates* both the the energetic and entropic contributions to the free energy, and since these contributions increase and decrease the free energy, respectively, their influences effectively cancel one another out.

   To begin our discussion on Flory theory we'll first establish some basic definitions and parameters. In the most basic sense, we can consider a polymer as a long molecule consisting of repeating monomers linked together by bonds. Define the bond vector between any adjacent monomers as $\vec{\tau}$ with magnitude $||\vec{\tau}|| = b$. Additionally, we can define the end-to-end distance of the polymer as $\vec{R} = \sum_i \vec{\tau}_i$ with magnitude $||\vec{R}|| = R$. The distinction of making $\vec{\tau}$ and $\vec{R}$ vectors is important because the bond between any two monomers can be pointing in any direction. Although, since the length of the bond between any two monomers will be constant, normally we won't have to worry about direction.

We can use a 1-dimensional monomer as a motivating example for this section. Each monomer can move in one of two directions, either "forward" or backward." Since this choice is random, the situation is effectively that of flipping a coin. So, the distribution of directions for each vector (in other words, how many ways does the monomer move forwards or backwards over the entire polymer) follows a binomial distribution. For a polymer of length N with $N = n_1 + n_2$, where n_1 indicates the number of times a monomer is moving in direction 1 and n_2 is defined similarly for the other direction, the number of ways for this polymer to be arranged is

$$W = \frac{N!}{n_1! n_2!}$$

If we define $R/b = L$ as the displacement of the polymer (the distance from the beginning to the end of the polymer), then we have $L = n_1 - n_2$ which implies $(N + L)/2 = n_1$ and $(N - L)/2 = n_2$ and we can rewrite the number of microstates for this 1-dimensional polymer as

$$W = \frac{N!}{(\frac{N+L}{2})!(\frac{N-L}{2})!} \tag{9.2.1}$$

Now we can use Stirling's approximation to write this in a more computationally friendly manner. First,

$$\ln W = N \ln N + N \ln 2 - \frac{N+L}{2} \ln(N + L) - \frac{N-L}{2} \ln(N - L)$$

Here we'll assume that N is large so that $N \gg L/N$. Moreover, define $\varepsilon = L/N$ so that our expression may be simplified as,

$$\ln W = N \ln N + N \ln 2 - \frac{N(1+\varepsilon)}{2} \ln \left[N(1+\varepsilon) \right] - \frac{N(1-\varepsilon)}{2} \ln \left[N(1-\varepsilon) \right]$$

Here I took advantage of the fact that

$$\left(\frac{\frac{1}{N}}{\frac{1}{N}} \right) \frac{N+L}{2} = \frac{1 + \frac{L}{N}}{2/N} = \frac{N}{2}(1 + \varepsilon)$$

to make the first substitution above, and used a similar technique for the remaining expressions. The introduction of ε will prove useful because of the *quadratic approximation to* $\ln(1+x)^6$ (that's not a power of 6 it's a footnote). It's some pretty straightforward calculus to arrive at the approximation, so I'll just do it here quickly:

Recall that any second-order approximation can be modeled as

$$T_2(x) = f(x_0) + f'(x_0)(x - x_0) + \frac{f''(x_0)(x - x_0)^2}{2!}$$

where x_0 is the point at which we're centering the approximation ($x_0 = \varepsilon_0 = 0$ in this case) and $f(x)$ is the function of interest ($f(x) = \ln(1 + x)$ in this case). Finding these derivatives and plugging in $\varepsilon_0 = 0$ affords

$$T_2(x) = \ln(1 + \varepsilon_0) + \frac{1}{1 + \varepsilon_0}(\varepsilon - \varepsilon_0) + \left(-\frac{1}{(1 + \varepsilon_0)^2} \right) \frac{(\varepsilon - \varepsilon_0)^2}{2!}$$

$$= \ln(1 + 0) + \frac{1}{1}(\varepsilon) + \left(-\frac{1}{(1)^2} \right) \frac{\varepsilon^2}{2!}$$

$$= \varepsilon - \frac{\varepsilon^2}{2}$$

---

[6]We only care about the quadratic approximation and not any other higher order terms because the accuracy of the approximation increases negligibly once adding the third-, fourth-, fifth-order terms, etc.

Okay, back to the chemistry stuff. With this approximation we can rewrite our expression for $\ln W$ as

$$
\begin{aligned}
\ln W &= N \ln N + N \ln 2 - \frac{N(1+\varepsilon)}{2} \ln \left[N + \varepsilon - \varepsilon^2/2\right] - \frac{N(1-\varepsilon)}{2} \ln \left[N - \varepsilon - \varepsilon^2/2\right] \\
&= N(\ln N + \ln 2) - \frac{N}{2}\left[\ln N + \varepsilon - \varepsilon^2/2 + \varepsilon \ln N + \varepsilon^2 - \varepsilon^3/2 + \ln N - \varepsilon - \varepsilon^2/2 - \varepsilon \ln N + \varepsilon^2 + \varepsilon^3/2\right] \\
&= N(\ln N + \ln 2) - \frac{N}{2}\left[2\ln N + \varepsilon^2\right] \\
&= N \ln N + N \ln 2 - N \ln N - \frac{N\varepsilon^2}{2} \\
&= N \ln 2 - \frac{N\varepsilon^2}{2} \\
&= N \ln 2 - \frac{L^2}{2N} = N \ln 2 - \frac{R^2}{2Nb^2}
\end{aligned}
$$

Thus,

$$
\begin{aligned}
W &= \exp\left\{N \ln 2 - \frac{R^2}{2Nb^2}\right\} \\
&= 2^N e^{-R^2/2Nb^2}
\end{aligned}
\tag{9.2.2}
$$

is the number of microstates for this random walk 1-dimensional polymer. If we wanted to consider the probability of any microstate, we'd be interested in the quantity

$$
\frac{W}{2^N} = e^{-R^2/2Nb^2}
$$

Upon further inspection, however, notice that the right-hand side of this equation is *unnormalized*. We can normalize the distribution by integration over the support of the possible values for R. Since $\vec{R}$ can point in the positive or negative direction in the case of 1-dimension, R (the magnitude) can be either positive or negative and therefore the support of R is from $-\infty$ to ∞. So,

$$
\int_{-\infty}^{\infty} e^{-R^2/2Nb^2} dR = \sqrt{2\pi Nb^2}
$$

which is exactly a Gaussian integral. I cover this sort of evaluation in Section 1.2 if you're interested. Thus, the probability distribution for the length of this 1-dimensional random walk polymer is

$$
P(R) = \frac{e^{-R^2/2Nb^2}}{\sqrt{2\pi Nb^2}}
\tag{9.2.3}
$$

which is exactly a normal distribution.

9.2.1   The Troubling Case of a 3D Polymer

The logic followed for finding the probability distribution of the end-to-end distance for a random walk polymer in one-dimension, Equation (9.2.3), can be applied identically to the case of a three-dimensional polymer by considering the movement in each of the possible three directions to be independent of one another. More technically, we would say that the movement in any of the x-, y-, and z-direction is *isotropic*.

Then, the probability distribution for R in three dimensions is given by

$$P(R) = P(R_x)P(R_y)P(R_z) = \left(\frac{e^{-R_x^2/2Nb^2}}{\sqrt{2\pi Nb^2}}\right)\left(\frac{e^{-R_y^2/2Nb^2}}{\sqrt{2\pi Nb^2}}\right)\left(\frac{e^{-R_z^2/2Nb^2}}{\sqrt{2\pi Nb^2}}\right)$$

$$= \frac{e^{-3(R_x^2+R_y^2+R_z^2)/2Nb^2}}{(2\pi Nb^2/3)^{3/2}}$$

$$= \left(\frac{3}{2\pi Nb^2}\right)^{3/2} e^{-3R^2/2Nb^2}$$

Here, I've adopted the notation $R = (R_x, R_y, R_z)$ to simplify the expression. Also, note that since we assumed that each of the directions are spatially isotropic with one another, the overall variance of the random walk must remain the same as if it were one-dimensional yet be distributed across three directions. Hence, the variances are given as

$$\langle R_x^2 \rangle = \langle R_y^2 \rangle = \langle R_z^2 \rangle = \frac{Nb^2}{3}$$

which accounts for the factor of $1/3$ in each of the expressions.[7] However, this expression is not our final answer for the probability density. In the case of one dimension, the endpoint of the polymer chain did not have any degrees of freedom. That is, for a predetermined end-to-end vector $\vec{R}$ there is only point for the end of the polymer to exist. This is in contrast to the three-dimensional case for which $\vec{R}$ could exist *anywhere on the surface of a sphere*, centered at the tail of $\vec{R}$.[8] Thus, the probability density of the end-to-end distance for the three-dimensional random walk polymer must be scaled by the surface area of this sphere, given as

$$P(R) = 4\pi R^2 \left(\frac{3}{2\pi Nb^2}\right)^{3/2} e^{-3R^2/2Nb^2} \tag{9.2.4}$$

where R is the magnitude of the end-to-end vector.

We could have also arrived at Equation (9.2.4) beginning from entropy for the same type of polymer. Using Equation (9.2.2) as a template, the number of microstates for the three dimensional polymer may be expressed as

$$W = 4\pi R^2 e^{-3R^2/2Nb^2}$$

where the $4\pi R^2$ takes the place of the 2^N term as the scaling factor in three dimensions, and the exponential is raised to the power of 3 to account for the dimension as well. Then, the entropy of this polymer is found using Boltzmann's equation:

$$S = k_B \ln W$$

$$= k_B \ln(4\pi R^2 e^{-3R^2/2Nb^2})$$

$$= \frac{-3k_B R^2}{2Nb^2} + k_B \ln(4\pi R^2)$$

The Helmholtz free energy which will take the place of the energy in our Boltzmann factor becomes

$$A = -TS$$

$$= -T\left[\frac{-3k_B R^2}{2Nb^2} + k_B \ln(4\pi R^2)\right]$$

$$= \frac{3k_B T R^2}{2Nb^2} - k_B T \ln(4\pi R^2)$$

---

[7]The variance is equal to the second moment of the distribution in this case because the mean of the distribution is zero.
[8]The two dimensional analogue to this would be scaling the possible endpoints by the surface area of a circle.

which affords the Boltzmann factor for this polymer:

$$e^{-A/k_BT} = \exp\left\{-\left(\frac{\frac{3k_BTR^2}{2Nb^2} - k_BT\ln(4\pi R^2)}{k_BT}\right)\right\}$$

$$= \exp\left\{-\frac{3R^2}{2Nb^2} + \ln(4\pi R^2)\right\}$$

$$= 4\pi R^2 e^{-3R^2/2Nb^2}$$

Thus, after properly normalizing we arrive at the probability density for the end-to-end distance of the three dimensional random walk polymer as

$$P(R) = 4\pi R^2 \left(\frac{3}{2\pi Nb^2}\right)^{3/2} e^{-3R^2/2Nb^2} \tag{9.2.5}$$

which agrees Equation (9.2.4).

9.2.2   Self-Avoiding Polymers

Our discussion of random walk polymers up until this point has focused on those which are driven entirely by entropy. Now, we introduce the idea of a *self-avoiding polymer*, one with a nonzero free energy term that depends on repulsion between monomers. Returning to the simplest version of a three-dimensional polymer with an entropy given by,

$$S(R) = \frac{3k_bR^2}{2Nb^2} \tag{9.2.6}$$

Flory suggested introducing a term representing the internal energy of the polymer which takes the form

$$A = U - TS$$

$$= \frac{vN^2}{R^3} - T\left(C - \frac{3k_BR^2}{2Nb^2}\right) \tag{9.2.7}$$

where the N^2/R^3 term is representative of the density of monomer pairs within the volume created by the polymer, v is a proportionality constant, and C is some constant to represent the ground state energy of the polymer; N^2 is indicative of the pairwise interaction and R^3 is directly proportional to the volume of the 'sphere' surrounding the polymer. This is why the interaction 'per' volume can be thought as a density. Intuitively, the idea of this repulsive energy term is similar to steric hindrance. It's important to note that v is positive so that the term vN^2/R^3 is always positive as well; This guarantees that the energy term will indeed be repulsive.

With this new expression for the internal free energy we can compute the equilibrium length of the polymer. At equilibrium, the free energy will be *minimized* and so $\partial A/\partial R = 0$:

$$\frac{\partial A}{\partial R} = \frac{\partial}{\partial R}\left[\frac{vN^2}{R^3} - T\left(C - \frac{3k_BR^2}{2Nb^2}\right)\right]$$

$$0 = \frac{-3vN^2}{R^4} + \frac{6k_BTR}{2Nb^2}$$

$$\frac{vN^2}{R^4} = \frac{k_BTR}{Nb^2}$$

$$R = \left(\frac{vb^2}{k_BT}\right)^{1/5} N^{3/5} \tag{9.2.8}$$

This result for the end-to-end length of the polymer using a simple model asserts that the length is proportional to the number of monomers to the power of 0.6, that is, $N^{3/5}$. Experimentally, the accepted

result for the exponent is 0.588, incredibly close to that predicted by Flory. At this point it's important to recognize that we would not have achieved this result had we assumed the energy of interaction between monomers could be favorable, that is, allowing v to be negative. It's a subtle difference, and modeling inter-polymer interactions as favorable would be weird, but important to understand to reinforce our understanding nonetheless.

Notice the temperature dependence of the equilibrium length for the polymer. When we increase the temperature of the polymer, the entropic term of the free energy in Equation (9.2.7) has a greater impact. Additionally, from Equation (9.2.8) we see that the equilibrium length of the polymer decreases as temperature increases. Thus, using Equation (9.2.6) the entropy of the polymer must also decrease with an increase in temperature and therefore the overall free energy of the polymer increases, corresponding to a greater number of monomer-monomer interactions which goes hand-in-hand with a smaller polymer size. That is all to say, our intuition is correct!

This result prompted a more generalized version of the free energy for a self-avoiding polymer in d dimensions. Typically, as chemists, nobody really cares about dimensions greater than three because why would you. However, I guess Flory was a physicist so he was interested in this. The power law we desire is relatively intuitive, though, using a similar argument as we did above regarding the density of interactions. Note that the volume of an n-dimensional sphere is directly proportional to the radius of the sphere to the nth power. Thus, the term introduced to the free energy in Equation (9.2.7) can be rewritten as vN^2/R^d for any d dimensions. In addition, we require that the entropy term be scaled by a factor of d which can be derived from the Boltzmann equation (at least I'm pretty sure you could derive it from the Boltzmann equation). Thus, a generalized expression for the free energy of a self-avoiding random walk polymer in d dimensions is given as

$$A = \frac{vN^2}{R^d} - T\left(C - \frac{dk_B R^2}{2Nb^2}\right) \tag{9.2.9}$$

Then, we can model the equilibrium length of the polymer to the number of monomers in the chain relation as

$$R \propto N^\nu, \quad \nu = \frac{3}{d+2} \tag{9.2.10}$$

where $\nu = 3/5$ was our result for three dimensions in Equation (9.2.8) which agrees with our result from Equation (9.2.10) for $d = 3$.

Real quick before talking about binding equilibria, the theoretical result that the internal energy for a self-avoiding random walk polymer is proportional to $1/R^d$ can be rationalized if we think of a polymer as a snake from Snake (like the video game). The game Snake becomes *a lot* easier as we add more dimensions because there are more directions to move and therefore less ways of getting "trapped." Hence, there are less arrangements of the polymer in which unfavorable monomer-monomer interactions occur in higher dimensions and the internal energy term decreases.

9.3 Binding Equilibria

Binding reactions and their equilibria are central to nearly biochemical process. From the binding of THC to cannabinoid receptors in your brain to the HGH injected by bodybuilders, drug binding is a large part of biological and physical science.

We'll begin by analyzing a simple bimolecular reaction involving the binding of a single ligand, x, to the active site of a macromolecule, M. This reaction can be written as

$$\text{M} + \text{x} \rightleftharpoons \text{Mx} \tag{9.3.1}$$

where the equilibrium constant is given by

$$K_{eq} = \frac{[\text{Mx}]}{[\text{M}][\text{x}]} = e^{-\Delta \tilde{G}^{\circ}_{rxn}/RT} = K_d^{-1} \tag{9.3.2}$$

K_d is the *dissociation constant* and used primarily by biochemists because it has "units" of molarity.[9]
Moreover, K_d represents the free ligand concentration at which the molecule is *half-saturated*, when
$[\text{Mx}] = [\text{M}]$.

The relationships outlined in Equation (**??**) provide simple thermodynamic descriptions of a single-site
binding event. However, to be useful in an experiment they must be able to be connected to actual binding
data. The most common of these statistics are *fractional saturation*, $\langle f_b \rangle$, and *average ligation number*, $\langle x_b \rangle$.
The fractional saturation is defined as the fraction of macromolecular binding sites that have ligand bound
and can be expressed as

$$\langle f_b \rangle = \frac{[\text{Mx}]}{[\text{M}] + [\text{Mx}]} \tag{9.3.3}$$

Similarly, the average ligation number is the average number of ligands bound per macromolecule and is
related to the fractional saturation by

$$\langle f_b \rangle = \frac{\langle x_b \rangle}{s}$$

where s is the number of active sites on the macromolecule. The fractional saturation can be related to the
equilibrium constant with relative ease using Equation (9.3.2):

$$\begin{aligned}
\langle f_b \rangle &= \frac{[\text{Mx}]}{[\text{M}] + [\text{Mx}]} \\
&= \frac{K_{eq}[\text{M}][\text{x}]}{[\text{M}] + K_{eq}[\text{M}][\text{x}]} \\
&= \frac{K_{eq}[\text{x}]}{1 + K_{eq}[\text{x}]}
\end{aligned} \tag{9.3.4}$$

Equation (9.3.4) is important and incredibly useful because it relates experimentally observable quantities,
$\langle f_b \rangle$ and [x], to a thermodynamically relevant quantity, the equilibrium constant. Notice that this expression
for $\langle f_b \rangle$ more clearly illustrates how a plot of $\langle f_b \rangle$ vs. [x] is a *rectangular hyperbola.*

As with conformational transitions (covered in Chapter 6), the midpoint of the binding curve is an
important parameter with direct connections to thermodynamics. We can evaluate the midpoint of the
binding curve by allowing $\langle f_b \rangle = 0.5$. Using Equation (9.3.4), then,

$$\begin{aligned}
0.5 &= \frac{K_{eq}[\text{x}]_m}{1 + K_{eq}[\text{x}]_m} \\
[\text{x}]_m &= \frac{1}{K_{eq}} = K_d
\end{aligned} \tag{9.3.5}$$

Thus, we see that the numerical value of the equilibrium constant strongly influences the shape of the
resultant binding curve. This result is similar to a titration curve for acid-base chemistry, where an acid is
half-protonated when $pH = pK_a$. Plotting the fractional saturation curve affords some nice curves and allows
us to see how the binding constant, K_{eq}, affects the shape of the graph. These graphs can be found in Figure
9.5.

Within an experiment we won't ever actually measure the fractional saturation directly. Instead, some
signal Y_{obs} is observed and recorded. In particular, Y_{obs} is assumed to be a signal originating from a

---

[9]In reality, equilibrium constants are never given a unit. So, it stands to reason that K_d is used because of its apparent
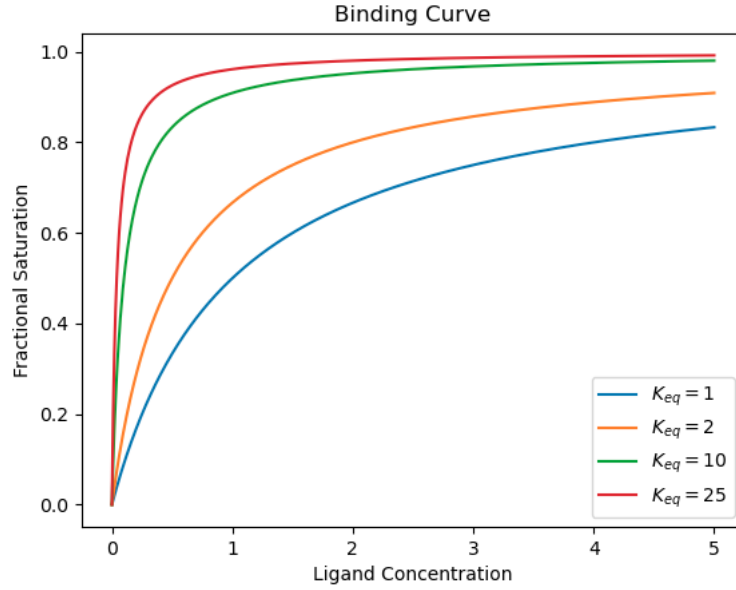dimensionality which makes it easier to talk about.

Figure 9.5: Binding curve of $\langle f_b \rangle$ vs. [x] for multiple equilibrium constants. The larger the equilibrium constant, the more affinity the ligand has for the active site on the molecule and the more steep the transition in the curves above. The curve which reaches $\langle f_b \rangle = 1$ the fastest (the red curve) would be the strongest binder and the one which reaches a fractional saturation of 1 the most slowly (the blue curve) is the weakest binder.

population-weighted average of unbound and bound macromolecule, expressed as

$$
\begin{aligned}
Y_{obs} &= Y_{free} f_{free} + Y_{bound} f_{bound} \\
&= Y_{free}(1 - f_{bound}) + Y_{bound} f_{bound} \\
&= Y_{free} + (Y_{bound} - Y_{free}) f_{bound} \\
&= Y_{free} + \Delta Y \left(\frac{K_{eq}[\text{x}]}{1 + K_{eq}[\text{x}]} \right)
\end{aligned}
\tag{9.3.6}
$$

Equation (9.3.6) offers a way of indirectly measuring the fractional saturation, $\langle f_b \rangle$. Also, above we defined $\Delta Y = Y_{bound} - Y_{free}$ which is the *amplitude*, or better yet *dynamic range*, of the data and is indicative of the total deflection swept out by the binding curve. Binding processes which give rise to a large amplitude provide greater confidence in our measurements for the fractional saturation and the equilibrium constant.

In most ligand binding experiments, a solution of macromolecule M is prepared at a known concentration and then a specific amount of ligand x is added at a known concentration. So, although we know the total amounts of ligand and macromolecule, once they're combined and the binding reaction begins its difficult to determine the concentrations of either. By invoking the conservation of mass to the reaction in Equation (9.3.1) we can say that

$$
[\text{x}]_{tot} = [\text{x}] + [\text{Mx}]
$$
$$
[\text{M}]_{tot} = [\text{M}] + [\text{Mx}]
$$

are the total concentrations of the ligand and macromolecule, respectively. Then, we can rewrite the equilibrium constant in Equation (9.3.2) using the known parameters as

$$
K_{eq} = \frac{[\text{Mx}]}{[\text{M}][\text{x}]} = \frac{[\text{Mx}]}{([\text{M}]_{tot} - [\text{Mx}])([\text{x}]_{tot} - [\text{Mx}])}
$$

which can be rewritten as a quadratic in [Mx] and solved accordingly:

$$[\text{Mx}] = K_{eq}([\text{M}]_{tot} - [\text{Mx}])([\text{x}]_{tot} - [\text{Mx}])$$

$$0 = K_{eq}([\text{M}]_{tot} - [\text{Mx}])([\text{x}]_{tot} - [\text{Mx}]) - [\text{Mx}]$$

$$= [\text{Mx}]^2 - \left([\text{M}]_{tot} + [\text{x}]_{tot} + \frac{1}{K_{eq}}\right)[\text{Mx}] + [\text{M}]_{tot}[\text{x}]_{tot}$$

$$[\text{Mx}] = \frac{[\text{M}]_{tot} + [\text{x}]_{tot} + (1/K_{eq}) \pm \sqrt{[[\text{M}]_{tot} + [\text{x}]_{tot} + (1/K_{eq})]^2 - 4[\text{M}]_{tot}[\text{x}]_{tot}}}{2} \tag{9.3.7}$$

Notice that we "created" this quadratic with the initial substitutions into the expression for the equilibrium constant and with that introduced some extraneous answers. To determine which of $(+)$ or $(-)$ we want after applying the quadratic formula we can evaluate our new expression for [Mx] in Equation (9.3.7) at $[\text{x}]_{tot} = 0$ M:

$$[\text{Mx}] = \frac{[\text{M}]_{tot} + (1/K_{eq}) \pm \sqrt{[[\text{M}]_{tot} + (1/K_{eq})]^2}}{2}$$

$$= \frac{[\text{M}]_{tot} + (1/K_{eq}) \pm \left([\text{M}]_{tot} + (1/K_{eq})\right)}{2}$$

Clearly, when $[\text{x}]_{tot} = 0$ M, $[\text{Mx}] = 0$ M must also be true because there is no ligand to bind. Hence, we'll be interested in the "minus" of $(\pm)$ in our quadratic. Then, plugging this result into Equation (9.3.6) for Y_{obs} affords

$$Y_{obs} = Y_{free} + \Delta Y \left(\frac{[\text{M}]_{tot} + [\text{x}]_{tot} + (1/K_{eq}) \pm \sqrt{[[\text{M}]_{tot} + [\text{x}]_{tot} + (1/K_{eq})]^2 - 4[\text{M}]_{tot}[\text{x}]_{tot}}}{2[\text{M}]_{tot}}\right) \tag{9.3.8}$$

9.3.1   Fluorescence Anisotropy

Fluorescence anisotropy is a phenomenon in which the light emitted by a fluorophore has unequal intensities along different axes of polarization.[10] When a fluorophore absorbs a photon an electron is excited to the excited state and, after a short waiting time, the electron emits that energy as either a photon (radiative emission) or as heat (non-radiative emission) and returns to the ground state. This excitation is associated with an *unequal* redistribution of electrons throughout the molecule such that only electrons which are oriented in the same way as the incoming light may be excited.[11]

If we limit our experiment to measuring only radiative emission (and disregarding the quantum yield, I suppose), the direction of the wave of light emitted by the excited fluorophore will change with respect to a few parameters, the most important of which (in our case) being the time that the electron stays in the excited state before being emitted. In the limit that the electron returns to the ground state immediately after being excited, that is, there is no waiting time, the direction of light will be *the exact same* as that absorbed. In the limit that the electron dawdles in the excited state, that is, the waiting time is long, there is a significant probability that the direction of the light which is emitted from the fluorophore is different from that absorbed. Typically, smaller fluorophores have shorter waiting times and larger fluorophores have longer waiting times. So, by measuring the type of light that the fluorophore emits and comparing it to the light which we initially shined at it, we can estimate how large or small the protein is!

Obviously, this model is very simplified. Fluorescence experiments can do a lot more than this, but this example utilizes how we might use it in the context of ligand binding. In fact, in the references there is a very

---

[10]*Anisotropy* is defined as "having a physical property that has a different value when measured in different directions." A very simple example is wood which is stronger along the grain than across it. When we talk about fluorescence anisotropy we're referring to asymmetric distribution of orientations for the waves of light emitted by the fluorophore upon excitation.
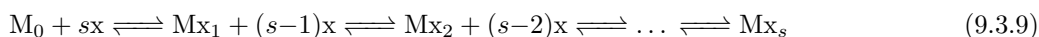
[11]The "orientation" with respect to an electron and a wave are seemingly unrelated at first. An electron has an associated spin whereas a wave has an associated... orientation. I like to think about it in terms of vectors: the vector associated with the electron has a direction determined by the *angular momentum* of the particle (in fact, this is one of the quantum numbers associated with each electron) and the vector associated with the wave is that normal to the "surface" formed by the wave. Then, light will be absorbed by the electron which has an angular momentum vector *in the same direction* as the normal vector to the wave.

informative book about all sorts of fluorescence experiments (and fluorescence anisotropy, of course) that I like enough to also draw your attention to here:
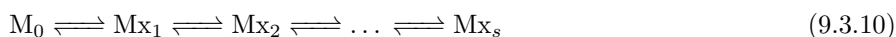
`https://link.springer.com/chapter/10.1007\%2F978-0-387-46312-4_10`

9.3.2   Numerous Binding Sites

Many macromolecules have multiple binding sites and the single-site scheme discussed up until this point proves insufficient in describing these systems, in addition to being mechanistically incorrect. Considering only a single type of ligand which can bind to some macromolecule,[12] we can represent the reaction with the following scheme,

$$M_0 + sx \rightleftharpoons Mx_1 + (s-1)x \rightleftharpoons Mx_2 + (s-2)x \rightleftharpoons \ldots \rightleftharpoons Mx_s \tag{9.3.9}$$

or more simply

$$M_0 \rightleftharpoons Mx_1 \rightleftharpoons Mx_2 \rightleftharpoons \ldots \rightleftharpoons Mx_s \tag{9.3.10}$$

A key feature of macromolecule binding events is that they can be energetically coupled such that binding can either encourage or discourage the affinity of the macromolecule for ligand. This phenomenon is referred to as *cooperativity* (I'm pretty sure I already talked about it somewhere).

   Assuming I have in fact talked about cooperativity somewhere else in this paper, we'll begin to draw some parallels between multisite binding phenomena and single-site binding. The fractional saturation for a molecule with multiple binding sites can be represented as a sum of the concentrations of all forms of macromolecule with ligand bound, times the fractional saturation of the macromolecule in each corresponding ligation state, divided by the total concentration of macromolecule. Symbolically,

$$\langle f_b \rangle = \frac{\frac{1}{s}[Mx_1] + \frac{2}{s}[Mx_2] + \cdots + \frac{s}{s}[Mx_s]}{[Mx_1] + [Mx_2] + \cdots + [Mx_s]}$$
$$= \frac{1}{s} \left(\frac{\sum_{k=1}^{s} k[Mx_k]}{\sum_{k=1}^{s} [Mx_k]} \right)$$

This expression for the fractional saturation can be cumbersome. We can try and simplify it by substituting $K_i[M][x]_i = [Mx]_i$ for each of the bound terms above, but even then we're left with many, difficult to measure quantities. So, instead, we can utilize the relationships given in Figure 9.6 to express each of the $[Mx]_i$'s with rearranged versions of the *overall binding constants* to yield

$$\langle f_b \rangle = \frac{1}{s} \left(\frac{\beta_1[M_0][x] + 2\beta_2[M_0][x]^2 + \cdots + s\beta_s[M_0][x]^s}{[M]_0 + \beta_1[M_0][x] + \beta_2[M_0][x]^2 + \cdots + \beta_s[M_0][x]^s} \right)$$
$$= \frac{1}{s} \left(\frac{\beta_1[x] + 2\beta_2[x]^2 + \cdots + s\beta_s[x]^s}{\beta_1[x] + \beta_2[x]^2 + \cdots + \beta_s[x]^s} \right)$$

Notice that the denominator of the fractional saturation as its been expressed most simply is a simple polynomial in the ligand concentration, [x]. We can refer to this expression as the *binding polynomial*, defining

$$P = 1 + \beta_1[x] + \beta_1[x]^2 + \cdots + \beta_s[x]^s = 1 + \sum_{i=1}^{s} \beta_i[x]^i \tag{9.3.11}$$

   P closely resembles expressions we've seen for partition functions in statistical mechanics, *except* for the fact that P is a polynomial and not a sum of exponentials. However, recall from Chapter 6, in Equation

---

[12]We'd refer to the macromolecule as being "homotropic" in this case. If the molecule was instead capable of binding all sorts of different ligands it would earn the title of "heterotropic."

(A)

Stepwise reaction	Stepwise binding constant	Units
$M_0 + x \rightleftharpoons Mx$	$K_1 = \dfrac{[Mx]}{[M_0][x]}$	M^{-1}
$Mx + x \rightleftharpoons Mx_2$	$K_2 = \dfrac{[Mx_2]}{[Mx][x]}$	M^{-1}
...	...	...
$Mx_{s-1} + x \rightleftharpoons Mx_s$	$K_s = \dfrac{[Mx_s]}{[Mx_{s-1}][x]}$	M^{-1}

(B)

Overall reaction	Overall binding constant	Units
$M_0 + x \rightleftharpoons Mx$	$\beta_1 = \dfrac{[Mx]}{[M_0][x]}$	M^{-1}
$M_0 + 2x \rightleftharpoons Mx_2$	$\beta_2 = \dfrac{[Mx_2]}{[M_0][x]^2} = K_1 K_2$	M^{-2}
...	...	...
$M_0 + sx \rightleftharpoons Mx_s$	$\beta_t = \dfrac{[Mx_s]}{[M_0][x]^s} = \prod_{i=1}^{s} K_i$	M^{-s}

Figure 9.6: For a macromolecule with s binding sites, ligand binding can be described as a series of steps, each of which is the binding event of a single ligand, represented by part (A) of the figure. Alternatively, multisite binding can be described as a collection of overall binding reactions in which the reactants are i ligands and the product contains i bound ligands, represented in (B).

(5.1.21) we defined the chemical potential of a species in a solution. Using this expression we can relate the concentration of a species in solution to an exponential as

$$[\mathrm{x}]^i = \left(e^{-(\mu_x^\circ - \mu_x)/RT} \right)^i \tag{9.3.12}$$

Substituting Equation (9.3.12) into the binding polynomial affords a partition function that allows the chemical potential of one of the reactants to vary, which is appropriate for a ligand binding experiment.[13] With P thoroughly defined, we can use it to concisely express the fractional saturation $\langle f_b \rangle$ (for the last time):

$$
\begin{aligned}
\langle f_b \rangle &= \frac{1}{s} \left(\frac{\sum_{i=1}^{s} i\beta_i [\mathrm{x}]^i}{P} \right) \\
&= \frac{[\mathrm{x}] \sum_{i=1}^{s} i\beta_i [\mathrm{x}]^{i-1}}{sP} \\
&= \frac{[\mathrm{x}] \sum_{i=1}^{s} \beta_i (d[\mathrm{x}]^i / d[\mathrm{x}])}{sP} \\
&= \frac{[\mathrm{x}]}{sP} \frac{d\left(\sum_{i=1}^{s} \beta_i [\mathrm{x}]^i \right)}{d[\mathrm{x}]} \\
&= \frac{[\mathrm{x}]}{sP} \frac{d\left(1 + \sum_{i=1}^{s} \beta_i [\mathrm{x}]^i \right)}{d[\mathrm{x}]} \\
&= \frac{[\mathrm{x}]}{sP} \frac{dP}{d[\mathrm{x}]} = \frac{1}{s} \frac{d\ln P}{d\ln [\mathrm{x}]}
\end{aligned}
\tag{9.3.13}
$$

Equation (9.3.13) offers the fractional saturation of a macromolecule with multiple binding sites. Figure 9.7 illustrates the differences in shapes between the fractional saturation curves of macromolecules with two active sites, one of which is positively cooperative and the other of which is negatively cooperative.

9.3.3 The Hill Model

The Hill Model is one of the simplest models for cooperativity in ligand binding and was first introduced in an attempt to analyze the binding of oxygen to hemoglobin. Essentially, the Hill model assumes *infinite cooperativity* such that once a single ligand is bound to a multi-site molecule, all other binding sites are

---

[13]This is analogous to the partition function of the "grand canonical ensemble," something that I hope I already had the chance to discuss in the chapter on Statistical Mechanics.
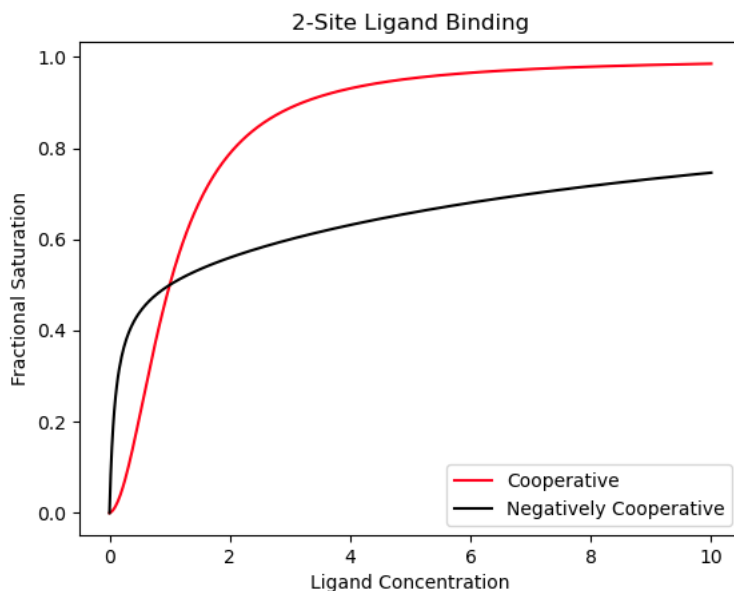
Figure 9.7: The curves shown above illustrate the shapes of the binding curves for a (positively) cooperative and negatively cooperative macromolecule with two binding sites (the shape holds for any number of n binding sites, though). The equilibrium constants for the cooperative binding are $K_1 = 0.1$ M^{-1} and $K_2 = 10$ M^{-1}. The equilibrium constants for the negatively cooperative binding are $K_1 = 10$ M^{-1} and $K_2 = 0.1$ M^{-1}.

immediately bound as well. Schematically, this can be written as

$$\mathrm{M_0} + n\mathrm{x} \rightleftharpoons \mathrm{Mx}_n, \quad K_d = \frac{[\mathrm{M_0}][\mathrm{x}]^n}{[\mathrm{Mx}_n]}$$
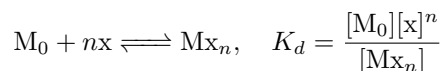
where n is the number of active sites on the molecule and therefore also the number of ligands necessary for the reaction to proceed. Following a similar procedure as we did to derive the fractional saturation of a single-site macromolecule in Equation (9.3.4) we can show that the fractional saturation for a macromolecule following the Hill model is given by

$$\langle f_b \rangle = \frac{[\mathrm{x}]^n}{K_d + [\mathrm{x}]^n} \tag{9.3.14}$$

Historically, n is known as the *Hill constant*, and it increases with increasing cooperativity of a reaction. Thus, it provides a convenient and simple characterization for a ligand binding reaction. For $n > 1$, binding reactions are *positively cooperative*, for $n < 1$, binding reactions are *negatively cooperative*, and for $n = 1$ binding reactions are *noncooperative*. It's important to note, however, that the Hill model is exactly that, *a model*. For example, the binding of diatomic oxygen to hemoglobin would have a Hill constant of $n = 4$. Experimentally, it's been determined that the binding curve fits $n \approx 3$ more appropriately. Additionally, diseases which affect the blood can decrease the Hill constant of hemoglobin further, such as the genetic defects associated with sickle-cell anemia.

Equation (9.3.14) can be used to derive the *Hill plot* which affords more information about the thermodynamics of the binding reaction. Don't worry though, only a small amount of algebraic gymnastics is

necessary to get us there

$$\langle f_b \rangle (K_d + [\text{x}]^n) = [\text{x}]^n$$

$$\langle f_b \rangle K_d = [\text{x}]^n (1 - \langle f_b \rangle)$$

$$\frac{\langle f_b \rangle}{1 - \langle f_b \rangle} = \frac{[\text{x}]^n}{K_d}$$

$$\ln \left(\frac{\langle f_b \rangle}{1 - \langle f_b \rangle} \right) = n \ln[\text{x}] - \ln K_d \qquad (9.3.15)$$
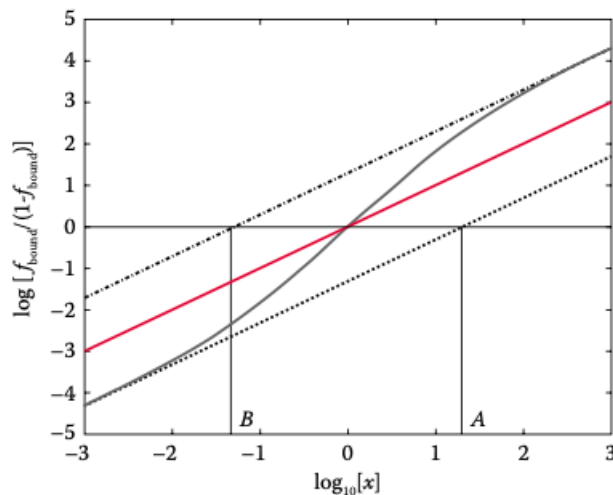
Equation (9.3.15)

Figure 9.8: This is the Hill plot for a two-site macromolecule. Here we've used $K_1 = 0.1$ M^{-1} and $K_2 = 10$ M^{-1}. The Hill plot (in grey) limits to a slope of 1 along the dotted lines which represent limiting ligand concentrations. At these concentrations, binding appears as if to singles-site macromolecules. At the midpoint, the slope of the binding curve is steeper than that of the reference line (in fact, the slope approaches 2), reflecting positive cooperativity. The case of negative cooperativity would have a grey curve which would look reflected over the red (reference) line.

<div align="center">

CHAPTER

10

CHEMICAL KINETICS

</div>

A key theme running through the advancement of chemical kinetics is complexity. It includes the investigation of how experimental conditions influence the speed of a reaction and inform us about a reaction's mechanism and transition state. In contrast to thermodynamics, kinetics affords a *rate of reaction*, not a direction.

Chemical kinetics is one of the oldest branches of chemistry and is responsible for assigning rate constants to reactions and understanding the mechanisms behind chemical transformations. It is the 'macroscopic' treatment of the *time-evolution* of a system *not in equilibrium*. Hence, it allows us to differentiate between things which are actually impossible versus things that are incredibly slow, e.g., the conversion of glucose to water, carbon dioxide, and energy without any external motivation.

As a motivating example, consider the transformation of diamond to graphite, $C_{(d)} \rightleftharpoons C_{(g)}$. This reaction is exergonic with $\Delta \tilde{G}^{\circ}_{rxn} \approx -2.9$ kJ/mol. So, we'd expect this reaction to occur spontaneously at room temperature... which it does. Then why is it we never see this decay into graphite during fancy dinner parties when everyone is wearing diamond jewelry? It's because the reaction takes a *very long time*.[1] Though, at exceptionally high temperatures we can observe this reaction with an appreciable rate. With this idea in mind we can add to our list of contrasts between thermodynamics and kinetics:

Stability refers to thermodynamics. Using our example of the decay from diamond to graphite, diamond is considered unstable whereas graphite is stable.

Persistence refers to kinetics. In this example, both diamond and graphite may be called persistent because the rate of decay from one phase to the other is immensely slow. The opposite of persistent is *transient*.

Kinetics is all about time-evolution and so we'll begin our kinetic description of a chemical reaction using differential equations. Consider the chemical transformation

$$A \longrightarrow B$$
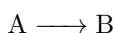
We can express the rate of this reaction as

$$\text{rate} = \frac{d[B]}{dt}$$

---

[1] So long, in fact, that the average domesticated turkey would have to survive 10^8 times longer than it would on average to ever witness the reaction take place.

By the law of conservation of energy, for every B that is formed there must be a corresponding A which disappears and we can therefore express the rate alternatively as

$$\text{rate} = -\frac{d[A]}{dt} \tag{10.0.1}$$

More generally, for any chemical reaction of the form $aA + bB \longrightarrow gG + hH$ we can express the rate as

$$\text{rate} = \frac{1}{\nu_A}\frac{d[A]}{dt} = \frac{1}{\nu_B}\frac{d[B]}{dt} = \frac{1}{\nu_G}\frac{d[G]}{dt} = \frac{1}{\nu_H}\frac{d[H]}{dt}$$
$$= -\frac{1}{a}\frac{d[A]}{dt} = -\frac{1}{b}\frac{d[B]}{dt} = \frac{1}{g}\frac{d[G]}{dt} = \frac{1}{h}\frac{d[H]}{dt}$$

where ν_i are the reaction coefficients as defined in Section 6.2. Empirical evidence shows that the rates of reactions for chemical transformations of this form can be expressed as

$$\text{rate} = k[A]^x[B]^y \tag{10.0.2}$$

where k is the *rate constant* and the reaction is said to be xth order in A and yth order in B. Since the rate of a reaction must also have units of molarity per second, the units for the rate constant must change depending on the order of reaction and can be expressed concisely as $M^{-(x+y-1)}\text{ s}^{-1}$.

Keep in mind that the *order* of a reaction is different from the *molecularity* of a reaction. The *molecularity* of a reaction is the number of molecules that come together to react in an *elementary* step of a reaction. It is equal to the sum of the stoichiometric coefficients of reactants. So, in the case of an elementary process, the molecularity and order of a reaction are the same. The subtle yet important difference between these two concepts may be expressed using a simple example. Consider the following two processes:

Bimolecular	*Unimolecular* "Activation"
$A + B \longrightarrow P$	$A \longrightarrow I$
	$I + B \longrightarrow P$
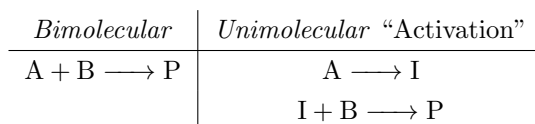
Here, A and B are reactants and I is some intermediate. The bimolecular reaction would be second-order overall and first-order with respect to both A and B, with a rate expression

$$\text{rate} = k[A][B]$$

Assuming that the activation step $A \longrightarrow I$ is rate-limiting and that the formation of product P is rapid, the unimolecular reaction would be first-order overall, first order with respect to A, and zero-order with respect to B, with an expression for the rate as

$$\text{rate} = k[A]$$

A great example of a bimolecular process would be an SN2 reaction, which proceeds through a concerted backside attack. Similarly, an example of unimolecular process might be an SN1 reaction where the high-energy intermediate forms (oftentimes we think of a carbocation) before another reactant comes in to attack the intermediate. Another common unimolecular reaction would be an intramolecular reaction, such as the Cope rearrangement. A more rare type of reaction is a *termolecular* process in which three molecules simultaneously come together to react.

Another example which may illustrate the important difference between order and molecularity is the formation of amyloid-β (Aβ) which is found in the brains of people with Alzheimer's disease. Aβ can form complex oligomers, following a reaction scheme such as

$$24\,(A\beta) \rightleftharpoons 12\,(A\beta)_2 \rightleftharpoons 6\,(A\beta)_4 \rightleftharpoons \ldots \rightleftharpoons (A\beta)_{24}$$
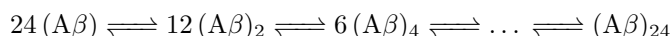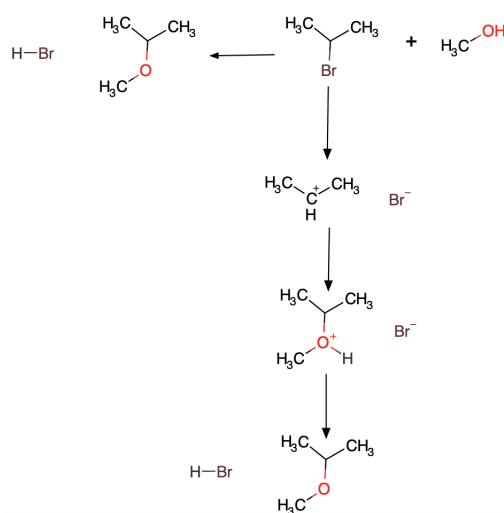
Figure 10.1: The difference between a bimolecular and unimolecular reaction. Above, the synthesis of 2-methoxypropane can happen through either an SN1 or SN2 reaction which have different rate laws.

Needless to say, it's certainly not the case that 24 copies of $A\beta$ come together at once to form the oligomer in a single step. Thus, it becomes more clear how the molecularity, the number of monomers coming together to form an intermediate complex in this scheme, can be much different from the empirically determined reaction order. A logical question, then, is which intermediates do form? Which steps of the process are rate-limiting?

The answer to these questions can *never* be proven, only supported or better yet disproven. Consider the following illustrative example: Suppose that for the simple reaction $A + B \longrightarrow P$ we collect some data and seek to determine the mechanism by which the reaction proceeds.

$[A]_0$ (mM)	Initial $d[A]_0/dt$ (mM/s)
10	-0.1
20	-0.4
30	-0.9

If we suppose that the reaction is modeled by rate $= k[A]^x[B]^y$, the data would suggest that $x = 2$, consistent with the mechanism

$$A + A \longrightarrow I$$
$$I + B \longrightarrow P$$
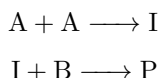
but not the mechanism $A + B \longrightarrow P$. Of note is that fact that integer exponents are most common for rate laws and will always be the case for elementary reactions (in which the molecularity of the reaction and reaction order are the same). For complex processes, however, it is possible to have fractional exponents in the rate law.[2]

In the table of data for this experiment notice that we always collected *initial* concentrations. This is because we always know and can control the initial concentration of the starting species. So, we can also always be sure that when we measure the initial rate of reaction we are using the correct initial concentrations. In theory, the rate law is a *law* and can be used to estimate the rate at any time during the reaction. However, measuring the concentrations of all species simultaneously at a single time is very difficult and therefore estimating the rate of reaction at any single time is very difficult.

---

[2]A complex reaction is one that involves more than one step. It is in direct contrast to an elementary reaction.

10.0.1   Mechanism vs. Molecularity vs. Reaction Order

A useful illustration of the distinctions between mechanism, molecularity, and reaction order comes from the analysis of *intramolecular* versions of typically *intermolecular* reactions. Consider the SN2 reaction between an alkyl iodide and an amine. The reaction is second-order overall, first-order in both the amine and alkyl iodide, and bimolecular (hence the "2" in SN2). The intermolecular reaction involves a backside attack of the nucleophilic amine on the halogenated carbon, displacing the iodide in a single step (Reaction I in Figure 10.2). This reaction will be second-order, with rate law

$$\text{rate} = k[\text{Amine}][\text{Alkyl Iodide}]$$

Now, consider the a long chain molecule that terminates on one end with an amine and on the other an iodide. Two types of SN2 reactions are possible: If two *different* molecules react (Reaction III), we still have the intermolecular reaction described above, and the product of the reaction would ultimately be a polymer (Reaction IV). Alternatively, an *intermolecular* reaction could occur in which the amine at one terminus of the molecule interacts with the iodide at the other terminus, producing a cyclic product (Reaction II).

The differing kinetic orders of these two reactions provides a simple means to select one product over the other. The polymerization reaction depends on the square of the concentration of the reactant from reaction III, whereas the cyclization is first-order with respect to the same reactant. Thus, we can mathematically show what we intuitively know to be true: High concentrations of disubstituted reactant will favor polymerization whereas low concentrations will favor cyclization. How can we determine at what concentration the favorability of either reaction changes?
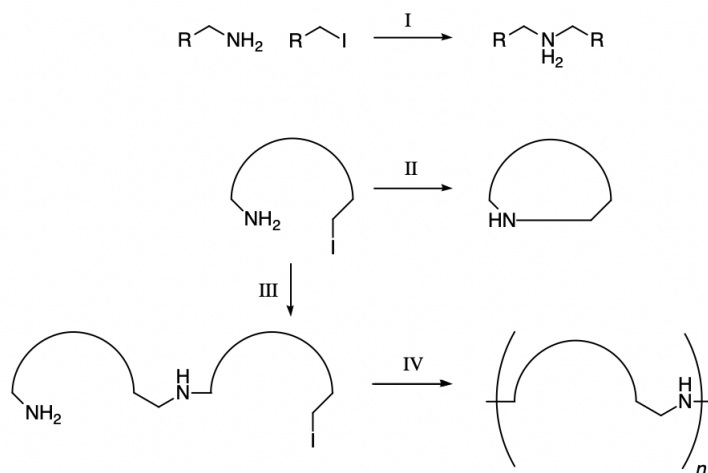

Figure 10.2: The difference between an intramolecular and intermolecular SN2 reaction.

In the scheme above, polymerization will be favored when reaction III occurs *faster* than reaction II, that is, when the ratio of their rate constants is greater than one. The ratio of these rate constants has units of molarity and is a characteristic of the particular system, known as the *effective molarity* (EM), defined as[3]

$$\text{EM} = \frac{k_{intra}}{k_{inter}} \tag{10.0.3}$$

Intuitively, the ratio of k_{intra}/k_{inter} should make sense (as opposed to k_{inter}/k_{intra}) because the first-order rate constant, k_{intra}, has units s^{-1} whereas the second-order rate constant, k_{inter}, has units $\text{M}^{-1}\,\text{s}^{-1}$ so that k_{inter} should always be in the denominator to achieve the proper units for EM.

---

[3]Note that this definition is more precisely known as the *kinetic effective molarity*. A *thermodynamic effective molarity* may also be defined as a ratio of equilibrium constants, however, we'll come to see that these ratios are equivalent by definition.

Now, we consider their ratios. For brevity, allow i to represent the disubstituted reactant in consideration:

$$\text{Rate of Reaction II:} \quad \frac{d[i]}{dt} = k_{intra}[i]$$

$$\text{Rate of Reaction III:} \quad \frac{d[i]}{dt} = k_{inter}[i]^2$$

$$\text{Reaction III/Reaction II:} \quad \frac{k_{inter}[i]^2}{k_{intra}[i]} = \frac{k_{inter}}{k_{intra}}[i] = \frac{[i]}{\text{EM}}$$

Thus, we see that when $[i] > \text{EM}$, the polymerized product will be favored over the cyclized product. Conversely, when $[i] < \text{EM}$, cyclization will occur more readily.

The Spatial Temporal Postulate

The *spatial temporal postulate* posits that "the rate of reaction between moieties A and B is proportional to the time that A and B reside within a critical distance of one another." Stated in words that actually make sense, the likelihood of a reaction occurring depends on how close and how long two functional groups come together. As a consequence, many *intramolecular reactions* are often faster than their *intermolecular* counterparts.

Within this postulate, the intuitive notion that time and space are critical factors for a reaction to occur are on display. Consider reaction I in Figure 10.2, in which an SN2 reaction is undergone between an amine and a halogenated alkane. The longer the amine and halogenated carbon spend close to one another with the correct geometry, the more likely the nucleophilic attack is to happen.

This postulate is oftentimes used to explain catalytic mechanisms where the distance between a catalyst and substrate determines binding, and the rate at which the catalyst can transform a substrate to product determines its catalytic efficiency.

10.1   First-Order Processes

A first-order process is one which has a rate law rate $= k[\text{A}]$ for some reactant A. As we've seen in Equation (10.0.1), the rate law can be equivalently expressed as a differential equation of the form

$$\text{rate} = -\frac{d[\text{A}]}{dt} = k[\text{A}]$$

which can be solved using separation of variables:

$$-\frac{d[\text{A}]}{dt} = k[\text{A}]$$

$$\int_{[\text{A}]_0}^{[\text{A}]_f} \frac{d[\text{A}]}{[\text{A}]} = -\int_0^t k\,dt$$

$$\ln[\text{A}]_f = -kt + \ln[\text{A}]_0$$

$$[\text{A}]_f = [\text{A}]_0 e^{-kt}$$

Oftentimes this equation is rewritten using a *time constant*, defined as $\tau = 1/k$, affording

$$[\text{A}] = [\text{A}]_0 e^{-t/\tau} \tag{10.1.1}$$

which is the *integrated rate law for a first-order process*. The time constant has plenty of utility, the first of which is immediately recognizable because it has units of seconds, as opposed to the rate constant which has units of s^{-1} for a first-order reaction. With the integrated rate law we can determine the *half-life* of a substance, defined as the time it takes for exactly 50% of a substance to decay/transform/disappear etc. At

this time, $[A] = \frac{1}{2}[A]_0$ so that

$$\frac{1}{2}[A]_0 = [A]_0 e^{-kt_{1/2}}$$

$$\frac{1}{2} = e^{-kt_{1/2}}$$

$$\ln\left(\frac{1}{2}\right) = -kt_{1/2}$$

$$t_{1/2} = \frac{\ln 2}{k} = \tau \ln 2 \tag{10.1.2}$$

It is important to keep in mind that the half-life of a substance is always shorter than the time constant (consider the expression for $t_{1/2}$ in terms of τ in Equation (10.1.2) to convince yourself this is true). The half-life is the time it takes for a substance to decay to half of the concentration it was initially and the time constant is the time it takes for the substance to decay to $1/e \approx 36.8\%$ of what it was initially.

A common misconception about the half-life of a chemical is that at $t_{1/2}$, half of the molecules in a substance suddenly react and disappear. Instead, it's actually the case that *the most amount of a substance's decay happens within the first few moments of a transformation.* Consider a graph of the integrated rate law for a first order reaction:
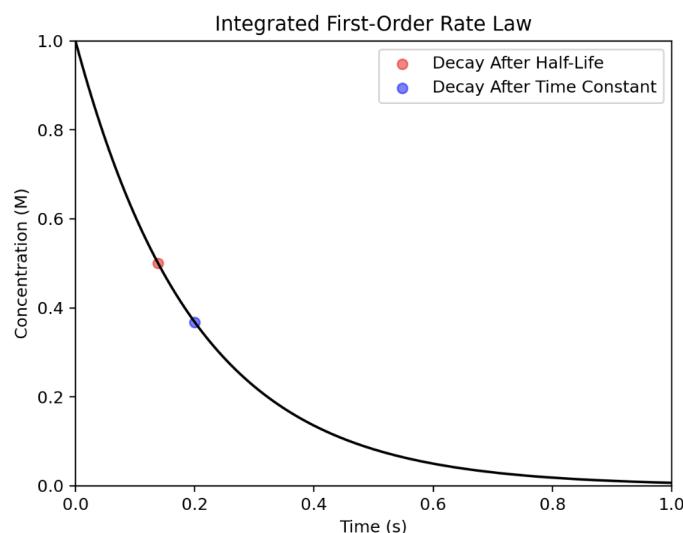

Figure 10.3: Exponential decay for a first-order reaction with $k = 5 \text{ s}^{-1}$ and initial concentration $[A]_0 = 1$ M.

It might be that the "continuous" nature of concentration that we illustrate in Figure 10.3 is obscuring our intuition. After all, molecules of A are transformed *discreetly* into product, not continuously, as if $1/3$ of A can be transformed while leaving alone the remaining $2/3$. Our motivation to "discretize" the rate of decay of a chemical may be made easier with a *Poisson point process,* or just *Poisson process.*

I'll preface the succeeding paragraph by saying I talk more than I probably should about probability. So, if you're not uber familiar with some of the notation it might be confusing. Not to fear, however, because everything regarding the Poisson process is to bolster our understanding of first-order reactions.

Recall the *Poisson distribution*, a discrete probability distribution with rate parameter λ, defined on the nonnegative integers:

$$P(x) = \frac{e^{-\lambda}\lambda^x}{x!}, \quad x \in \{0, 1, 2, \dots\}$$

The random variable X counts the number of events that occurs in a given amount of exposure time, according to the rate λ. Using our definitions regarding rate laws above, if we allow n to be the number of times a chemical decays over the course of a fixed interval of time θ, the rate of decay becomes $\lambda = k\theta$ and we

can model the decay using a Poisson distribution:

$$P(n) = \frac{e^{-k\theta}(k\theta)^n}{n!}$$

The Poisson process models this sort of chemical transformation *very well* for numerous reasons. Firstly, the *sum of two Poisson distributions is another Poisson distribution.*[4] Using this fact, consider two random variables which model the amount of decay for the same substance A. Let X count the decay at a time t and let Y count the decay at a time $t + T$. Then, if we let $S = Y - X$ be the difference in decay between the two states X and Y, we have that

$$P(S = n) = \frac{e^{-kT}(kT)^n}{n!}$$

which implies *the decay on the interval $t + T$ is independent of the decay that happens on the interval of time immediately before.* This result is connected to the *memoryless property* of the Poisson distribution which says that the distribution of points over a finite interval does not affect the distribution of points on any other finite interval for a Poisson process. Intuitively, this result should make sense for the transformation of a chemical: For a first-order reaction in which the rate law is dependent on a single species A, why would the rate *law* change as the concentration of A changes? Obviously it wouldn't, and the Poisson process agrees with this intuition.

Okay last thing I'll mention about the Poisson process: A Poisson distribution can be thought of as a *limit of binomial distributions.*[5] If we consider each point on the curve of Figure 10.3 separately, we can imagine that at each infinitesimally small interval of time dt that a molecule of A has two options, either to decay or not to decay. This is exactly a binomial! Think of flipping a coin except one side is life and the other is death. In theory, we could model chemical decay using a binomial, I suppose, but the Poisson distribution is a better choice because it does this intrinsically while also incorporating a rate parameter, something that we've seen (and could have already intuited) is immensely important to the study of chemical kinetics.

10.2 Second-Order Processes

A second-order reaction is just like a first-order reaction, except second-order. The principle difference in the case of a second-order reaction is that we have two types, one consisting of a reaction between a single species and itself and the other consisting of a reaction between two unique species.

As we'll come to see, the integrated rate laws for second-order processes (and nth-order processes for that matter) *depend on the initial concentrations of the reacting species.* Intuitively, this should make sense: In contrast to the first-order, unimolecular case, where we can think of a reactant just sort of "waiting" to react and is independent of the concentrations of any other species in solution, in the second-order, bimolecular case, the rate is dependent on how much of each reactant is present because two molecules are required for the reaction to proceed.

10.2.1 Type I Second-Order Processes

A *type I second-order process*, as it will be referred to, is a reaction of the form

$$2\,A \longrightarrow P$$

---
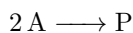
[4]The proof of this isn't difficult but it involves some concepts in probability that I am not willing to write here and explain. So, if you want to know more you can either ask me or just look it up yourself.

[5]Another thing that has a relatively simple proof, but not one that is important enough for me to elaborate on here.

with a corresponding rate law

$$\text{rate} = \frac{d[\text{P}]}{dt} = -\frac{1}{2}\frac{d[\text{A}]}{dt} = k[\text{A}]^2 \tag{10.2.1}$$

This reaction will be "type I" because it is defined by only a single species. Notably, second-order reactions have what can be thought of as a "critical concentration," in which the rate of reaction slows down or speeds up appreciably. In the scheme above, this is achieved at $[\text{A}] = 1$ M. The rationale behind this comes from the power of 2 in the expression for the rate law and is also somewhat mentioned in the discussion on effective molarity in Section 10.0.1.

By Equation (10.2.1) we have the relationship

$$-\frac{d[\text{A}]}{dt} = 2k[\text{A}]^2$$

and so oftentimes we'll refer to the *effective rate constant, $k_f = 2k$.* Determining the integrated rate law from this expression isn't too hard:

$$-\frac{d[\text{A}]}{dt} = k_f[\text{A}]^2$$

$$-\int_{[\text{A}]_0}^{[\text{A}]} \frac{d[\text{A}]}{[\text{A}]^2} = \int_0^t k_f dt$$

$$\frac{1}{[\text{A}]} - \frac{1}{[\text{A}]_0} = k_f t$$

$$\frac{1}{[\text{A}]} = \frac{1}{[\text{A}]_0} + k_f t \tag{10.2.2}$$

We can use Equation (10.2.2) to determine the half-life for a type I second-order process:

$$\frac{1}{\frac{1}{2}[\text{A}]_0} = \frac{1}{[\text{A}]_0} + k_f t_{1/2}$$

$$t_{1/2} = \frac{1}{k_f[\text{A}]_0} \tag{10.2.3}$$

The inverse proportionality between $t_{1/2}$ and the initial concentration of the single reacting species is indicative of the concentration dependence for processes of order > 1. Unlike the first-order unimolecular processes which we can think of as happening at a fixed rate regardless of the concentration, in order for a second-order, bimolecular reaction *to occur,* the reacting species must collide. Hence, a larger concentration of reacting species affords collisions which happen more often and therefore a faster rate.

10.2.2   Type II Second-Order Processes

A *type II second-order process*, as it will be referred to, is a reaction of the form

$$\text{A} + \text{B} \longrightarrow \text{P}$$
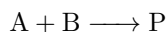
with a corresponding rate law

$$\text{rate} = \frac{d[\text{P}]}{dt} = -\frac{d[\text{A}]}{dt} = -\frac{d[\text{B}]}{dt} = k[\text{A}][\text{B}] \tag{10.2.4}$$

As we can see above, the rates of consumption for A and B are equal so that we can derive the relationship

$$\Delta[A] = \Delta[B]$$
$$[A]_0 - [A] = [B]_0 - [B]$$
$$[B]_0 - [A]_0 + [A] = [B]$$
$$\Delta + [A] = [B] \tag{10.2.5}$$

where $\Delta = [B]_0 - [A]_0$ is defined to simplify some expressions to come. With this definition, however, we're left to discover the integrated rate law for two cases, where $\Delta = 0$ or $\Delta \neq 0$. Also, note that the Δ used in the first line is to denote a change in concentration and has a different meaning than Δ in the expression $\Delta = [B]_0 - [A]_0$. Substituting Equation (10.2.5) into (10.2.4) affords an expression which can be integrated to derive an expression for the concentration of reactants as a function of time:

$$-\frac{d[A]}{dt} = k[A][B]$$
$$= k[A]\big(\Delta + [A]\big)$$
$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]\big(\Delta + [A]\big)} = -\int_0^t k\,dt \tag{10.2.6}$$

The above integral is not exactly trivial, and you could just look it up in the textbook or on google, but where's the fun in that? Instead, we'll evaluate it using fractional decomposition. First, suppose that we can rewrite

$$\frac{1}{[A]\big(\Delta + [A]\big)} = \frac{\alpha}{[A]} + \frac{\beta}{\Delta + [A]} \tag{10.2.7}$$

where α and β are some constants to be determined. Cross-multiplying affords the relation

$$1 = \alpha\big(\Delta + [A]\big) + \beta\big([A]\big)$$
$$= \alpha\Delta + [A]\big(\alpha + \beta\big) \tag{10.2.8}$$

Here, notice that Δ *is a constant.* It depends on the initial concentrations of each species A and B, however, these concentrations are fixed. In contrast, [A] is dependent on time and *is a variable.* The left-hand side of Equation (10.2.8) is purely constant so that we can rewrite

$$1 = \alpha\Delta \;\Rightarrow\; \alpha = \frac{1}{\Delta}$$
$$0 = [A]\big(\alpha + \beta\big) \;\Rightarrow\; \alpha = -\beta$$

Thus, Equation (10.2.7) can be rewritten as

$$\frac{1}{[A]\big(\Delta + [A]\big)} = \frac{1}{\Delta[A]} - \frac{1}{\Delta\big(\Delta + [A]\big)}$$

and substituted into (10.2.6) to assist integration:

$$\int_{[A]_0}^{[A]} \left(\frac{1}{\Delta[A]} - \frac{1}{\Delta(\Delta + [A])} \right) d[A] = -\int_0^t k\, dt$$

$$\int_{[A]_0}^{[A]} \frac{d[A]}{\Delta[A]} - \int_{[A]_0}^{[A]} \frac{d[A]}{\Delta(\Delta + [A])} = -kt$$

$$\frac{1}{\Delta} \left[\ln\left([A]\right) - \ln\left(\Delta + [A]\right) \right]_{[A]_0}^{[A]} = -kt$$

$$-\frac{1}{\Delta} \left[\ln\left(\frac{[A]}{\Delta + [A]}\right) - \ln\left(\frac{[A]_0}{\Delta + [A]_0}\right) \right] = kt$$

$$-\frac{1}{\Delta} \left[\ln\left(\frac{[A]}{[B]}\right) - \ln\left(\frac{[A]_0}{[B]_0}\right) \right] = kt$$

$$\frac{1}{\Delta} \left[\ln\left(\frac{[B]}{[A]}\right) - \ln\left(\frac{[B]_0}{[A]_0}\right) \right] = kt$$

$$\frac{1}{[B]_0 - [A]_0} \ln\left(\frac{[B]/[B]_0}{[A]/[A]_0}\right) = kt \tag{10.2.9}$$

Equation (10.2.9) is the *integrated rate law for a type II second-order reaction.* Recall, however, that our expression for Δ held only when $[B]_0 \neq [A]_0$ and therefore this expression is valid only when $\Delta \neq 0$. In the case where $[B]_0 = [A]_0$, the concentrations of [A] and [B] reduce to the expression for a type I second-order reaction with $k = k_f$ in Equation (10.2.2).

Finally, the idea of a half-life does not apply to reactions of this type. Unless the reactants are mixed in stoichiometric proportion (for the reaction discussed in this section that would be 1:1), the concentrations of the reacting species will not be half of their initial concentrations at identical times.

10.3   Nth-Order Processes of a Single Component

The principles governing the rate of an nth-order reaction of a single species are very similar to those of a first-order reaction, aside from the order of reaction. In general, we could model the rate of reaction for this sort of process as

$$\text{rate} = -\frac{d[A]}{dt} = k[A]^n \tag{10.3.1}$$

for any integer $n > 1$. This can be solved in a similar manner to the corresponding equation for a first-order process, using separation of variables:

$$-\frac{d[A]}{dt} = k[A]^n$$

$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]^n} = -\int_0^t k\, dt$$

$$-\frac{1}{n-1} \left(\frac{1}{[A]^{n-1}} - \frac{1}{[A]_0^{n-1}} \right) = -kt$$

$$\frac{1}{[A]^{n-1}} = (n-1)kt + \frac{1}{[A]_0^{n-1}} \tag{10.3.2}$$

Equation (10.3.2) is the integrated rate law for an nth-order process. The half-life for an nth-order reaction can be found just as we did in the first-order case by allowing $[A] = \frac{1}{2}[A]_0$:
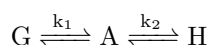
$$\frac{1}{\left(\frac{1}{2}[A]_0\right)^{n-1}} = (n-1)kt_{1/2} + \frac{1}{[A]_0^{n-1}}$$

$$\frac{2^{n-1} - 1}{[A]_0^{n-1}} = (n-1)kt_{1/2}$$

$$t_{1/2} = \frac{2^{n-1} - 1}{k(n-1)[A]_0^{n-1}} \tag{10.3.3}$$

Notably, the half-life for an nth-order process *depends on the initial concentration.* Because of this, the concept of a half-life becomes far less useful for reactions which aren't first-order.

10.4 Parallel Pathways

Iodine Clock

We know turn our attention to reactions of the form,

$$G \overset{k_1}{\rightleftharpoons} A \overset{k_2}{\rightleftharpoons} H$$

where a single reactant A may react to form either of two products, G or H. The set of rate equations for this sort of transformation may be modeled as

$$\frac{d[A]}{dt} = -k_1[A] - k_2[A] = -(k_1 + k_2)[A]$$

$$\frac{d[G]}{dt} = k_1[A]$$

$$\frac{d[H]}{dt} = k_2[A]$$

We can solve for the concentration of A as a function of time first, and then substitute this expression into the differential equations for G and H to solve for their time-dependent concentration as well. Solving for [A] as a function of time,

$$\frac{d[A]}{dt} = -(k_1 + k_2)[A]$$

$$\int_{[A]_0}^{[A]} \frac{d[A]}{d[A]} = \int_0^t -(k_1 + k_2)dt$$

$$\ln[A] - \ln[A]_0 = -(k_1 + k_2)t$$

$$[A] = [A]_0 e^{-(k_1 + k_2)t} \tag{10.4.1}$$

Equation (10.4.1) is the integrated rate law of a parallel pathway reaction. Since the rate constants k_1 and k_2 are restricted positive, the rate of decay of A will *always* be greater in a parallel pathway reaction than in the first-order reaction of A to either of the two products. Intuitively, this makes sense because in this reaction scheme there are more ways for A to be transformed than there are in just a normal first-order reaction.

Now we can find expressions for [G] and [H] as a function of time. First, [G]:

$$\frac{d[\text{G}]}{dt} = k_1[\text{A}]$$

$$\frac{d[\text{G}]}{dt} = k_1[\text{A}]_0 e^{-(k_1+k_2)t}$$

$$\int_{[\text{G}]_0}^{[\text{G}]} d[\text{G}] = \int_0^t k_1[\text{A}]_0 e^{-(k_1+k_2)t} dt$$

$$[\text{G}] - [\text{G}]_0 = k_1[\text{A}]_0 \left[\frac{-1}{k_1+k_2} e^{-(k_1+k_2)t} \right]_0^t$$

$$[\text{G}] = \frac{k_1[\text{A}]_0}{k_1+k_2} \left(1 - e^{-(k_1+k_2)t} \right) + [\text{G}]_0$$

Notice that in the limit that $k_2 \to 0$, that is, when the reaction A $\longrightarrow$ H stops happening, all of $[\text{A}]_0$ eventually becomes G. This is sort of like a check to make sure our expression is correct. Hopefully unsurprisingly, we can derive a similar expression for [H],

$$[\text{H}] = \frac{k_2[\text{A}]_0}{k_1+k_2} \left(1 - e^{-(k_1+k_2)t} \right) + [\text{H}]_0$$

and in the limit as $k_1 \to 0$ we see a similar result.

The key result that can be seen between these two expressions is that the fraction of A that is transformed into either G or H *depends on how quickly G and H are made relative to one another*. This was indirectly implied when referring to the final concentrations of product in the limit as one of the rate constants went to zero. If we instead consider concentration of product in the limit that time is allowed to tend to infinity, we find that

$$\frac{[\text{G}]_\infty}{[\text{H}]_\infty} = \lim_{t\to\infty} \left(\frac{\frac{k_1[\text{A}]_0}{k_1+k_2}\left(1 - e^{-(k_1+k_2)t}\right)}{\frac{k_2[\text{A}]_0}{k_1+k_2}\left(1 - e^{-(k_1+k_2)t}\right)} \right) = \frac{k_1}{k_2} \tag{10.4.2}$$

Thus, we find that the ratio of products when the parallel pathway reaction is allowed to go to completion is dependent on how quickly the products are created relative to one another. Equation (10.4.2) affords a results very different from what we would expect from thermodynamics which would insist that the product which prevails at equilibrium is the one with the lowest free energy, not necessarily the one which is formed more rapidly. However, this result makes more sense when we consider the fact that no sort of reversibility among the reactants and products was allowed, implying that even though G may have a lower free energy than H, for example, G cannot react to form H in any way.

10.4.1   The Curtin-Hammett Principle

The Curtin-Hammett principle is concerned with product ratios for a parallel pathway reaction scheme of the form

$$\text{P}_1 \xrightleftharpoons{\text{slow}} \text{I}_1 \xrightleftharpoons{\text{fast}} \text{I}_2 \xrightleftharpoons{\text{slow}} \text{P}_2$$
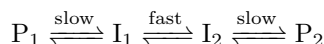
where the activation energy for the interconversion of I_1 and I_2 is far less than either of the activation energies for the formation of product. Then, the principle states that the ratio of the products is determined by the relative heights of the highest energy barriers leading to the different products and is not significantly influenced by the relative energies of the isomers, conformers, or intermediates formed prior to the highest energy transition states.

In Figure 10.4 we have a reaction in which a pair of intermediates, I_1 and I_2, can readily equilibrate because their activation energies to form either of P_1 or P_2 is much higher. By the Curtin-Hammett principle, since the activation energy to go from I_1 to P_1 is less than that of the competing reaction, the major product in
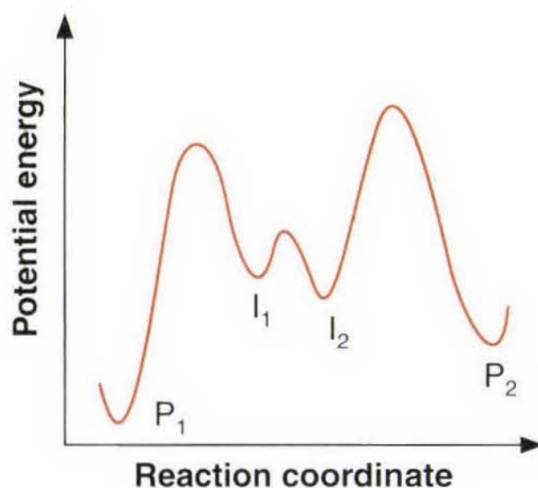
Figure 10.4: Reaction coordinate diagram demonstrating the Curtin-Hammett principle.

Figure 10.4 will be P_1.

This principle has highly beneficial implications in all sorts of areas. The reason I know about this principle is because of the following question: We all know and love the Wittig reaction from Orgo 2, but the "brother" reaction, the *Horner-Wadsworth-Emmons (HWE) reaction*, hosts as much if not more utility. The major contrast between the two couplings is the stereochemistry of the products. While the Wittig reaction utilizes a phosphonium ylide to convert carbonyls to Z-alkenes, the HWE reaction uses a phosphonate carbanion to produce the E-alkene.
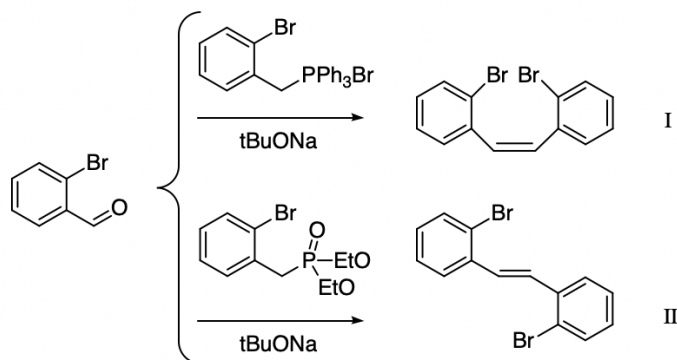

Figure 10.5: The Wittig product, I, in contrast with the HWE product, II. The only difference comes from the type of reagent being used which has an effect on the energy of the transition state for each reaction.

The difference between which is the major isomer for these reactions can be explained using the mechanisms for either of these reactions and the Curtin-Hammett principle. Obviously I *could* explain it if I wanted to, but it's beyond the scope of this course so I'll spare you the details.

10.5   Reversible Reactions

Near the end of Section 10.4, the contrasting results between kinetics and thermodynamics we arrive at for a reaction which is allowed to reach equilibrium is semi-explained on the basis of irreversibility between reactants and products. Now, we'll consider a reversible reaction and come to see that the kinetic result agrees with our thermodynamic intuition.

Consider a reversible reaction

$$A \underset{k_{-1}}{\overset{k_1,\,k_{-1}}{\rightleftharpoons}} B$$
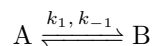
with forward rate constant k_1 and reverse rate constant k_{-1}. The rate of formation for A and B can be modeled as usual by

$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B]$$

$$\frac{d[B]}{dt} = k_1[A] - k_{-1}[B]$$

At equilibrium, we'd expect that the concentrations of each species will stop changing, that is, $d[A]/dt = d[B]/dt = 0$. Then, using either of the two rate equations we have that $k_1[A]_{\text{eq}} = k_{-1}[B]_{\text{eq}}$ and therefore

$$\frac{[B]_{\text{eq}}}{[A]_{\text{eq}}} = \frac{k_1}{k_{-1}} = K_{eq} \tag{10.5.1}$$

This equation is known as *detailed balance,* and it connects the mathematical results from kinetics to our thermodynamic intuition. More formally, it tells us that at equilibrium, each elementary process within a set of reactions is in equilibrium with its reverse process and that the equilibrium constant may be expressed in terms of rate constants.

Most formally, the principle of detailed balance states that at equilibrium, the forward rate of each step is equal to the reverse rate of that step. It's been recognized and proven in both classical mechanics and quantum mechanics the principle of microscopic reversibility, that is, the equations of mechanics are *time-reversal invariant.* This implies that for every possible type of interaction between particles the exact reverse is also possible.

Detailed balance also allows us to make explicit appeals to thermodynamics. If B is more stable than A and therefore $K_{eq} > 1$, the formation B will occur faster than the formation of A.

As far as the behavior of a reaction away from equilibrium goes, we turn back to the language of differential equations. By the conservation of mass, we have that $[B] = [A]_0 - [A]$ (or, equivalently, $[A] = [B]_0 - [B]$. Here we'll assume that $[B]_0 = 0$ so the former equation for $[B]$ will be used) which allows us to solve the expression for $d[A]/dt$ and express $[A]$ as a function of time:

$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}([A]_0 - [A])$$

$$= -k_1[A] + k_{-1}([A]_0 - [A])$$

$$[\dot{A}] + (k_1 + k_{-1})[A] = k_{-1}[A]_0 \tag{10.5.2}$$

[6]The solution to this differential equation isn't quite trivial, so I'm gonna provide the solution: This equation is classified as a *first-order, linear ordinary differential equation* and can be solved using an *integrating factor.* For the expression above, the integrating factor is defined as

$$e^{\int (k_1 + k_{-1})dt} = e^{(k_1 + k_{-1})t}$$

and when Equation (10.5.2) is multiplied through by this factor, a nice simplification is afforded by the

---

[6]Note that in Equation (10.5.2) I used the notation $[\dot{A}]$ to express the derivative of $[A]$ with respect to time. In general, this notation *always* refers to a derivative with respect to time.

product rule:

$$e^{(k_1+k_{-1})t}[\dot{A}] + e^{(k_1+k_{-1})t}(k_1 + k_{-1})[A] = e^{(k_1+k_{-1})t}k_{-1}[A]_0$$

$$\frac{d}{dt}\left[e^{(k_1+k_{-1})t}[A]\right] = e^{(k_1+k_{-1})t}k_{-1}[A]_0$$

$$e^{(k_1+k_{-1})t}[A] = \int k_{-1}[A]_0 e^{(k_1+k_{-1})t}dt$$

$$e^{(k_1+k_{-1})t}[A] = \frac{k_{-1}[A]_0}{k_1 + k_{-1}}e^{(k_1+k_{-1})t} + C$$

$$[A] = \frac{k_{-1}[A]_0}{k_1 + k_{-1}} + Ce^{-(k_1+k_{-1})t} \qquad (10.5.3)$$

In the second line of the sequence above, the product rule was invoked "backward" to allow simple integration by the fundamental theorem of calculus. Equation (10.5.3) is nearly our final answer, except for the constant C. To evaluate the constant in terms of physical characteristics of the system we can use the condition that at time $t = 0$, the concentration of A must be $[A] = [A]_0$. Then,

$$[A]_0 = \frac{k_{-1}[A]_0}{k_1 + k_{-1}} + Ce^{-(k_1+k_{-1})(0)}$$

$$C = [A]_0 - \frac{k_{-1}[A]_0}{k_1 + k_{-1}}$$

$$C = [A]_0\left(\frac{k_1}{k_1 + k_{-1}}\right)$$

Plugging this result back into Equation (10.5.3) affords our final result for the concentration of $[A]$ as a function of time:

$$[A] = [A]_0\left(\frac{k_1 e^{-(k_1+k_{-1})t} + k_{-1}}{k_1 + k_{-1}}\right) \qquad (10.5.4)$$

While at first glance it may look complicated, Equation (10.5.3) is still a simple exponential decay with time constant $\tau = 1/(k_1 + k_{-1})$. In contrast to previous examples, however, in the limit as $t \to \infty$ the concentration of $[A]$ remains nonzero since the reaction is reversible.
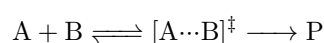
10.6 Transition State Theory

Transition state theory (TST) is directed toward the calculation of rate constants at equilibrium. Inspired by thermodynamics, TST explains the rates of elementary reactions under the assumption that the activated complexes of a transition state are in quasi-equilibrium with the reactants. Then, the rate of reaction is directly proportional to the concentration of these complexes multiplied by some frequency with which they are converted to products.

The basic ideas of TST can be summarized as follows:

1. Rates of reaction can be studied by examining activated complexes near the transition state.

2. The activated complexes are in *quasi-equilibrium* with the reactant molecules.

3. The activated complexes can convert into products, and kinetic theory can be used to calculate the rate of this conversion.

Arguably the most important feature of this theory is the notion that reactants can be thought of as in equilibrium with the transition state complex as opposed to being in equilibrium with the product. This idea affords a reaction scheme of the type

$$A + B \rightleftharpoons [A{\cdots}B]^{\ddagger} \longrightarrow P$$

where AB‡ represents the transition state the reaction passes through. This model begs the question, what is the probability of being in the transition state? Or, how can we estimate the "equilibrium" concentrations of reactants and the transition state complex? We'll start by defining a new quantity, the equilibrium constant for the reaction between the reactants and transition state:

$$\frac{[\text{A}\cdots\text{B}]^{\ddagger}}{[\text{A}][\text{B}]} = K_{\ddagger} = e^{-\Delta G^{\ddagger}/RT} \tag{10.6.1}$$

$\Delta G^{\ddagger}$ is the free energy change going from the reactants to the transition state and will be positive by the nature of the instability of the transition state complex. This is a good start to characterizing the energy associated with the transition state complex, however, it's not a rate!

To go about solving for the quantity we care about, the rate constant, we turn to Eyring, Evans, and Polanyi (all really smart scientists) who illustrated that the rate of a reaction is directly proportional to some frequency factor with which the transition state complexes are converted to products. I mentioned it only a few moments ago but I'll do it again just because it's the basis on which TST is founded, the notion that the rate constant can be determined this way relies on the fact that there is a quasi-equilibrium between reactants and the transition state complex.

The most basic assumption is that bonds of a reactant act like a harmonic oscillator, such that there energies can be modeled as $U = \frac{1}{2}kx^2$ where U is the potential energy stored in the bond, k is some proportionality constant, and x is the bond length. From classical mechanics we have the result that the angular momentum of the oscillator ω is given by $\omega = \sqrt{k/\mu}$ where μ acts as the "reduced mass" of the bond. While this information is all helpful, it won't be of great use in trying to find the rate constant for the reaction between the reactants and the transition state complex.

To make our lives harder/more fun, quantum mechanics tells us that the ground state energy of a harmonic oscillator must be *at least*

$$E = \frac{(\Delta p)^2}{2m} + \frac{1}{2}m(\omega \Delta x)^2$$

which is a sum of the kinetic and potential energies, and the uncertainty principle is invoked for the position and momentum of the particle. Recall that the Heisenberg uncertainty principle formally states that $\Delta x \Delta p \geq \hbar/2$. Taking the lower limit of this inequality (that is, making it an equality), we're left with

$$E = \frac{\hbar^2}{8m(\Delta x)^2} + \frac{1}{2}m(\omega \Delta x)^2 \tag{10.6.2}$$

and by differentiating the energy with respect to the uncertainty in position we can find the value of Δx such that the energy will be minimized, i.e., the energy of the ground state:

$$\frac{\partial E}{\partial \Delta x} = \frac{\partial}{\partial \Delta x}\left[\frac{\hbar^2}{8m(\Delta x)^2} + \frac{1}{2}m(\omega \Delta x)^2\right]$$

$$0 = -\frac{\hbar^2}{4m(\Delta x)^3} + m\omega^2 \Delta x$$

$$\frac{\hbar^2}{4m(\Delta x)^3} = m\omega^2 \Delta x$$

$$\Delta x = \sqrt{\frac{\hbar}{2m\omega}}$$

Substituting this result back into Equation (10.6.2) affords the ground state energy of a harmonic oscillator:

$$E_{gs} = \frac{\hbar^2}{8m \left(\sqrt{\frac{\hbar}{2m\omega}}\right)^2} + \frac{1}{2}m\omega^2 \left(\sqrt{\frac{\hbar}{2m\omega}}\right)^2$$
$$= \frac{\hbar\omega}{4} + \frac{\hbar\omega}{4}$$
$$= \frac{\hbar\omega}{2} \tag{10.6.3}$$

Why is that at all useful? I'm told it will be next semester. For now, though, it tells us that the ground state energy is simply $E_{gs} = \frac{1}{2}\hbar\omega$. In addition to this fact, recall from all the way back in Section 8.2.1 in our discussion of the microcanonical ensemble, Equation (8.2.13) tells us that the *average amount of kinetic energy carried per harmonic mode of an oscillator is* $k_B T/2$. To think that Dr. Fried didn't even cover this derivation in class and yet it's come up time and time again in later lectures and even on some exams blows my mind, but that's besides the point. What is not besides the point, however, is the relationship we're left with:

$$\frac{\hbar\omega}{2} = \frac{k_B T}{2}$$

for the ground state energy of a single harmonic mode associated with this harmonic oscillator.[7] Before arriving at our desired result, recall that the linear frequency, ν, of an oscillator is related to the angular frequency by the relationship $\nu = 2\pi\omega$ (also illustrated in Figure 10.6) so that we're left with

$$\frac{\hbar\omega}{2} = \frac{\hbar\nu}{4\pi} = \frac{k_B T}{2}$$
$$\frac{h\nu}{2} = \frac{k_B T}{2}$$
$$\nu = \frac{k_B T}{h} \tag{10.6.4}$$

Equation (10.6.4) (notice the units... it's in s^{-1}) is the frequency factor associated with the transformation of the transition state complex into product, also known as Eyring's frequency factor.

Finally, we can write an expression for the rate constant associated with crossing of the activated energy barrier as

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \tag{10.6.5}$$

where $k_B T/h$ is the frequency factor which describes the frequency with which molecules are vibrating about, weighted down by a Boltzmann factor which characterizes the probability that a particle will have sufficient energy to actually cross the activation energy barrier. This equation is also known as the *Eyring equation*. The benefit of the Eyring equation is that is allows us to calculate reaction rates based on thermodynamic properties of a system. In particular, by rearranging Equation (10.6.5) we can show that

$$\frac{kh}{k_B T} = e^{-\Delta G^{\ddagger}/RT}$$
$$\ln\left(\frac{kh}{k_B T}\right) = \frac{-\Delta G^{\ddagger}}{RT}$$
$$\ln\left(\frac{kh}{k_B T}\right) = \left(\frac{-\Delta H^{\ddagger}}{R}\right)\frac{1}{T} + \frac{\Delta S^{\ddagger}}{R} \tag{10.6.6}$$

---

[7]The "harmonic mode" refers to the frequency of the associated wave. Waves can have all sorts of frequencies! Some we can hear, and others we can't. What's important here is to recognized that waves associated with electrons and other particles are allowed to have only *certain* harmonic modes because their energies are quantized. Thus, when we refer to a "harmonic mode" we're referring to a particular quantum of energy associated with a wave. The ground state of a particle is one of these modes.
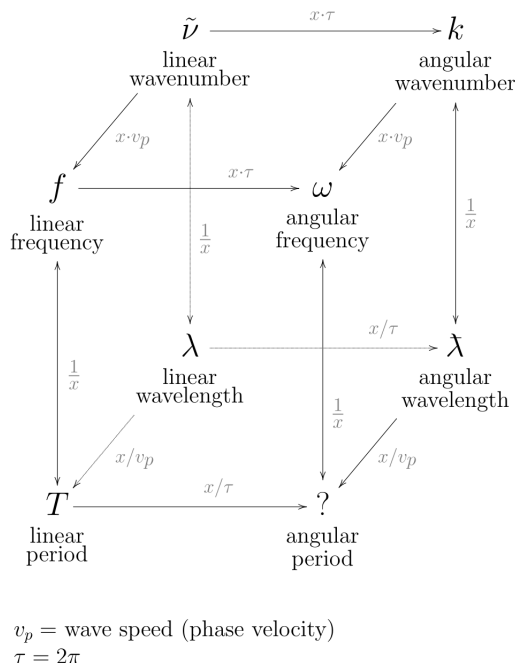
$$v_p = \text{wave speed (phase velocity)}$$
$$\tau = 2\pi$$

Figure 10.6: I've had this picture saved on my desktop for a while cause I think it's pretty helpful. The one relationship that we did need between the linear and angular frequencies is on there, as well as many more that are not nearly as useful for us.

which is the *Eyring plot*, affording a graph of $\ln(kh/k_B T)$ vs. $1/T$ with a slope proportional to the *enthalpy of activation* and an intercept proportional to the *entropy of activation*. Notice the *immense* similarity of the Eyring plot to the van't Hoff plot.

This equation is helpful because it tells us that the temperature dependence of a chemical reaction is a reflection of whether or not the transition state is enthalpically or entropically expensive to create. The entropic expense is related to how conformationally restricted the transition state is and the enthalpic expense comes from how much weaker/stronger the bonds of the transition state are or how much steric repulsion/hindrance is present.

During lecture Dr. Fried briefly discusses Arrhenius theory and how lame it is which is why I've opted to ignore it here as well. Notice that, in essence, we're performing the same exact experiment as we would have using the Arrhenius model, however, using TST we're gaining much more insight into the thermodynamics of the reaction.

Here's a question regarding kinetics and transition state theory: Consider the following reaction scheme.

$$P_1 \xleftarrow{\text{k}_1} R \xrightarrow{\text{k}_2} P_2$$
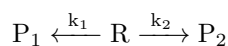
Suppose that at room temperature, $k_1 = 1 \text{ s}^{-1}$ and $k_2 = 4 \text{ s}^{-1}$. Moreover, suppose that $[R_0] = 1.0$ M. What are the concentrations of R, P_1, and P_2 as $t \to \infty$? Well, we could answer this question by writing out the rate laws and doing some calculus, similar to the derivation of Equation (10.4.1). However, I've already done this derivation (in Equation (10.4.1), obviously)! So instead we can argue that since these reactions *are not reversible* the ratio of products must followed detailed balance, such that

$$\frac{[P_1]}{[P_2]} = \frac{k_1}{k_2} = \frac{1}{4} = 0.25$$

Moreover, since neither reaction is reversible we know that all of the reactant will be converted to product as $t \to \infty$ which allows us to work out that at equilibrium, $[P]_1 = 0.2$ M and $[P]_2 = 0.8$ M.

Now, suppose that we have a single molecule of the reactant R, and at $t = 0$ it becomes "activated" so that

it is allowed to react. Sketch curves corresponding to the probability the R molecule still exists, and that P_1, after a given time, now exists. I did this here using Python to make it look sorta nice, using the parameters as they're described in the question.
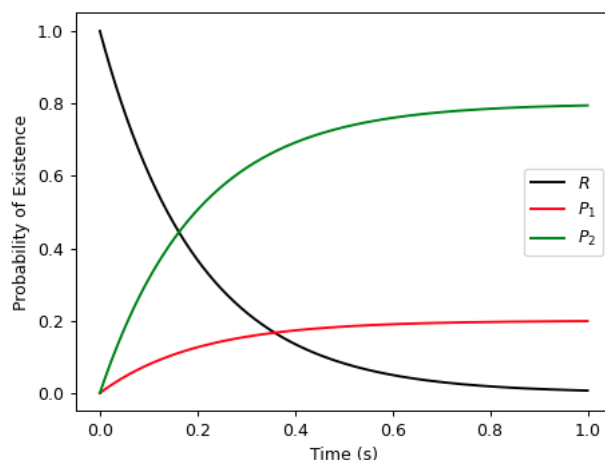

Figure 10.7: Probabilities of existence for each species in the reaction scheme.

The important aspects of Figure 10.7 are that the total waiting time $\tau = 1/(k_1 + k_2)$ for R is 0.2 s so that after that amount of time, R has decayed to $\frac{1}{e} \approx 36\%$ of its initial concentration. Similarly, make sure to note that in the graph for the probability of P_1 existing, the plot begins at 0 and increases exponentially to 0.2, the maximal concentration at equilibrium.

These probabilities are nice and all, but we can paint a slightly more detailed picture of the thermodynamics of these reactions using transition state theory. So, using TST, derive an equation for the product ratio $[P]_1/[P_2]$ as function of temperature and activation barriers, $\Delta G^{\ddagger}$. Again, we'll invoke detailed balance to do this. Moreover, we'll make use of Equation (10.6.5), the Eyring equation, to express the rate constants in terms of activation barriers:

$$\frac{[P_1]}{[P_2]} = \frac{k_1}{k_2} = \frac{\frac{k_B T}{h} e^{-\Delta G_1^{\ddagger}/RT}}{\frac{k_B T}{h} e^{-\Delta G_2^{\ddagger}/RT}}$$

$$= \exp\left\{\frac{-(\Delta G_1^{\ddagger} - \Delta G_2^{\ddagger})}{RT}\right\}$$

$$= \exp\left\{\frac{-\Delta\Delta G^{\ddagger}}{RT}\right\}$$

Great! Now, suppose that P_2 is a coveted molecule and so we're trying to design our synthesis in order to maximize the production of it. Further suppose we discover that increasing the temperature causes the selectivity of P_2 to increase. Use TST to infer what this implies about the relative values of the transition state activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, between the two reactions. To discover more about the parameters we'll turn to the Eyring equation again, in conjunction with detailed balance, this time substituting $\Delta G^{\ddagger}$ for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

$$\frac{[P_1]}{[P_2]} = \frac{\exp\left\{\frac{-(\Delta H_1^{\ddagger} - T\Delta S_1^{\ddagger})}{RT}\right\}}{\exp\left\{\frac{(-\Delta H_2^{\ddagger} - T\Delta S_2^{\ddagger})}{RT}\right\}}$$

$$= \exp\left\{\frac{-(\Delta H_1^{\ddagger} - \Delta H_2^{\ddagger})}{RT}\right\} \exp\left\{\frac{\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger}}{R}\right\}$$

Notice that in order for the selectivity of P_2 to increase with temperature, we require that $\Delta H_2^{\ddagger} > \Delta H_1^{\ddagger}$. This

way, the exponential term containing the enthalpies gets smaller (in absolute value) with temperature and the product ratio $[P]_1/[P_2]$ decreases. We've talked about this before, but whenever we consider the temperature effects on a reaction the enthalpy should come to mind. A greater enthalpy of activation would imply that the reaction is "more sensitive to temperature." This can also be rationalized using Le Chatelier's principle: if a reaction is highly exothermic, for example, then even a small increase in temperature will greatly shift the equilibrium distribution towards the reactants.

Now that's all fine and dandy, however, if we purport that $\Delta H_2^{\ddagger} > \Delta H_1^{\ddagger}$ then that would imply reaction 2 were *slower* than reaction 1 under the initial conditions (using the Eyring equation to help guide our logic once again). Clearly, this contradicts the given information because we know that $k_2 > k_1$. Hence, the only way for reaction 2 to be faster than reaction 1 under these given conditions granted $\Delta H_2^{\ddagger} > \Delta H_1^{\ddagger}$ is that $\Delta S_2^{\ddagger} > \Delta S_1^{\ddagger}$ to begin with.

Finally, suppose that we run some experiments to acquire some data and find that $\Delta S_2^{\ddagger} = -14$ cal/mol/K. Suppose that we also know that the standard entropy of the reactant R is $S^{\circ} = 350$ J/mol/K. At room temperature, how many microstates are associated with TS_2, the transition state between R and P_2? We can determine the number of microstates using Boltzmann's equation, however, we first need to find the entropy associated with the transition state. The entropy is given by

$$S^{\ddagger} = S^{\circ} + \Delta S^{\ddagger}$$

If you're having trouble visualizing this, trying drawing a reaction coordinate diagram. Making sure to convert units, we're left with

$$S^{\ddagger} = 350 \text{ J/mol/K} - 14\text{cal/mol/K}(4.184 \text{ J/cal}) = 291.42 \text{ J/mol/K}$$

Then, we can find the number of microstates associated with the transition state of P_2 as

$$S_2^{\ddagger} = Nk_B \ln W_2$$
$$W_2 = \exp\left\{\frac{291.42}{Nk_B}\right\} \approx 1.68 \times 10^{15}$$

Although we can calculate the transition state entropy at standard state conditions, what quantity would we need to know in order to see how $S_2^{\ddagger}$ changes with temperature? To see this, recall the second law of thermodynamics which states

$$dS = \frac{dq}{T}$$

for a reversible reaction. With a little bit of calculus we can show that

$$S = \int_{T_0}^{T} \frac{dq}{T} = \int_{T_0}^{T} \frac{C_P dT}{T} = C_P \ln\left(\frac{T}{T_0}\right) + C$$
$$S(T) = S(T_0) + C_P \ln\left(\frac{T}{T_0}\right)$$

where C_P is the heat capacity of the material. Since everything involved in this equation is a state function, we have

$$\Delta S(T) = \Delta S(T_0) + \Delta C_P \ln\left(\frac{T}{T_0}\right)$$

which also holds for the transition state

$$\Delta S^{\ddagger}(T) = \Delta S^{\ddagger}(T_0) + \Delta C_P^{\ddagger} \ln\left(\frac{T}{T_0}\right)$$

Thus, in order to determine how $S_2^{\ddagger}$ changes with temperature we require the heat capacity of the transition state.

10.6.1 Hammond's Postulate

10.7 Consecutive Reactions

Consecutive reactions, or *sequential reactions,* occur through a series of steps of which reactants are transformed into intermediates, which in turn are transformed into product. The scheme for a consecutive reaction may look like

$$A \xrightarrow{k_1} I \xrightarrow{k_2} P$$
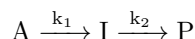
where A is a reactant, I is an intermediate, and P is the product. We can write rate laws for each step in the process as,

$$\frac{d[\text{A}]}{dt} = -k_1[\text{A}] \tag{10.7.1}$$

$$\frac{d[\text{I}]}{dt} = k_1[\text{A}] - k_2[\text{I}] \tag{10.7.2}$$

$$\frac{d[\text{P}]}{dt} = k_2[\text{I}] \tag{10.7.3}$$

which follow naturally from the elementary reaction steps in which a given species participates. To make solving a system of differential equations such as this possible, we'll begin by making two assumptions: Firstly, suppose that only A is present initially so that $[\text{I}]_0 = [\text{P}]_0 = 0$ M. With this, the first reaction in the series simplifies to the case of a first-order reaction and the concentration of A as a function of time simplifies as Equation (10.1.1) to

$$[\text{A}] = [\text{A}]_0 e^{-k_1 t} \tag{10.7.4}$$

With this expression we can solve Equation (10.7.2) for the concentration of I as a function of time. Plugging in our new expression for [A],

$$\frac{d[\text{I}]}{dt} = k_1[\text{A}]_0 e^{-k_1 t} - k_2[\text{I}]$$

$$[\dot{\text{I}}] + k_2[\text{I}] = k_1[\text{A}]_0 e^{-k_1 t} \tag{10.7.5}$$

In Section 10.5 we solved a similar sort of differential equation by the method of integrating factors. We'll take the same approach here. First notice that the integrating factor for this expression is given by

$$e^{\int k_2 dt} = e^{k_2 t}$$

and multiplying Equation (10.7.5) through by this factor affords

$$e^{k_2 t}[\dot{\text{I}}] + k_2 e^{k_2 t}[\text{I}] = k_1 e^{k_2 t}[\text{A}]_0 e^{-k_1 t}$$

$$\frac{d}{dt}\left[e^{k_2 t}[\text{I}]\right] = k_1[\text{A}]_0 e^{(k_2 - k_1)t}$$

$$e^{k_2 t}[\text{I}] = \int_0^t k_1[\text{A}]_0 e^{(k_2 - k_1)t} dt$$

$$e^{k_2 t}[\text{I}] = \frac{k_1}{k_2 - k_1}[\text{A}]_0 e^{(k_2 - k_1)t} + C$$

$$[\text{I}] = \frac{k_1}{k_2 - k_1}[\text{A}]_0 e^{-k_1 t} + Ce^{-k_2 t}$$

At $t = 0$, $[I]_0 = 0$ M and therefore

$$0 = \frac{k_1}{k_2 - k_1}[A]_0 + C$$

$$C = -\frac{k_1}{k_2 - k_1}[A]_0$$

so that we have an expression for the concentration of [I] as a function of time given by

$$[I] = \frac{k_1[A]_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \tag{10.7.6}$$

Lastly, we can use Equations (10.7.4) and (10.7.6) to solve for the concentration of P as a function of time. First, notice that the concentration of all species at any time t must be no greater than the initial concentration of A[8] so that we're left with the relation
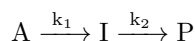
$$[A]_0 = [A] + [I] + [P]$$

$$[P] = [A]_0 - [A] - [I]$$

Thankfully this isn't a differential equation so we won't need to do any cheeky integration. Instead, we can substitute our expressions for [A] and [I] directly:

$$[P] = [A]_0\left(1 + \frac{k_1 e^{-k_2 t} - k_2 e^{-k_1 t}}{k_2 - k_1}\right) \tag{10.7.7}$$

Maximum Intermediate Species Concentration

For a reaction of the form,

$$A \xrightarrow{k_1} I \xrightarrow{k_2} P$$

we can use Equation (10.7.6) and the fact that for a maximum concentration it must be the case that $d[I]/dt = 0$ to determine the time at which the maximum possible intermediate species concentration occurs:

$$\frac{d[I]}{dt} = \frac{d}{dt}\left[\frac{k_1[A]_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)\right]$$

$$0 = \frac{k_1[A]_0}{k_2 - k_1}\frac{d}{dt}\left[\left(e^{-k_1 t_{max}} - e^{-k_2 t_{max}}\right)\right]$$

$$= \frac{k_1[A]_0}{k_2 - k_1}\left(-k_1 e^{-k_1 t_{max}} + k_2 e^{-k_2 t_{max}}\right)$$

$$k_1 e^{-k_1 t_{max}} = k_2 e^{-k_2 t_{max}}$$

$$e^{-(k_1 - k_2)t_{max}} = \frac{k_2}{k_1}$$

$$-(k_1 - k_2)t_{max} = \ln\left(\frac{k_2}{k_1}\right)$$

$$t_{max} = \frac{1}{k_1 - k_2}\ln\left(\frac{k_1}{k_2}\right) \tag{10.7.8}$$

---

[8]This reaction is a special case since all stoichiometric coefficients are 1. If this were not the case, we would need to divide the species concentrations by their reaction coefficients to ensure an equality of this type holds.

Earlier in this section we noted that we could simplify the system of differential equations

$$\frac{d[\text{A}]}{dt} = -k_1[\text{A}]$$
$$\frac{d[\text{I}]}{dt} = k_1[\text{A}] - k_2[\text{I}]$$
$$\frac{d[\text{P}]}{dt} = k_2[\text{I}]$$

by making two assumptions yet only ever mentioned one. The second assumption is that the concentration of I is *transient*, that is, it is slowly created and rapidly depleted so that [I] never "builds up" and we can approximate $d[\text{I}]/dt \approx 0$. This is also known as the *steady state approximation.* Then, by Equation (10.7.2).

$$0 = k_1[\text{A}] - k_2[\text{I}]$$
$$[\text{I}] = \frac{k_1[\text{A}]}{k_2} = \frac{k_1[\text{A}]_0}{k_2}e^{-k_1t}$$

which affords an expression for the concentration of P as a function of time by Equation (10.7.3):

$$[\text{P}] = k_2[\text{I}] = k_1[\text{A}]_0 e^{-k_1t} \tag{10.7.9}$$

Thus, we see that using the steady state approximation affords an expression for the concentration of P as a function of time *consistent with the first-order decay of the reactant* A. An important aspect of the steady state approximation to keep in mind is that *it has nothing to do with equilibrium.* Although the concentration of intermediate is effectively constant, the concentrations of reactant and product are rapidly changing throughout the same interval of time.

10.8 Enzyme Kinetics

Enzyme kinetics is simply the study of enzymatic rates. In many cases, the rate of a reaction and how the rate changes in different conditions reveal the path followed by the reactants and are therefore indicative of the reaction mechanism. In all of our discussion on enzyme kinetics we'll analyze reactions of the form

$$\text{E} + \text{S} \xrightleftharpoons[k_{-1}]{k_1} \text{ES} \xrightarrow{k_2} \text{P} + \text{E} \tag{10.8.1}$$

where E, S, ES, and P are the enzyme, substrate, enzyme-substrate complex, and product, respectively. The enzyme-substrate complex is sometimes also referred to as the Michaelis complex. Additionally, the rate constant k_2 is sometimes also referred to as the *catalytic constant*, denoted k_{cat}.

10.8.1 The Michaelis-Menten Model

The kinetics of reaction (10.8.1) may be modeled simply and elegantly, using the *Michaelis-Menten model,* which estimates the formation of product from ES as a first-order process so that we have the rate,

$$\frac{d[\text{P}]}{dt} = k_2[\text{ES}] \tag{10.8.2}$$

also referred to as the *velocity* of reaction.[9] The *initial velocity* v_0, is then the rate of product formation at some initial time $t = t_0$ where $[\text{ES}] = [\text{ES}]_0$. The overall rate of production of ES is the difference between

---

[9]The "velocity" of a reaction, more generally, refers to the rate of product formation for any chemical reaction, not just enzyme catalysis.

rates of the elementary reactions leading to its appearance and those resulting in its disappearance:

$$\frac{d[\text{ES}]}{dt} = k_1[\text{E}][\text{S}] - (k_{-1} + k_2)[\text{ES}]$$

If we assume steady state for the concentration of ES just as we did in Section 10.7, this expression simplifies as,

$$k_1[\text{E}][\text{S}] = (k_{-1} + k_2)[\text{ES}]$$

$$\frac{[\text{E}][\text{S}]}{[\text{ES}]} = \frac{k_{-1} + k_2}{k_1} = K_m \qquad (10.8.3)$$

where K_m is referred to as the *Michaelis constant*. Note that although K_m looks a lot like a *dissociation constant*, it isn't quite the same because of the transformation of ES $\xrightarrow{k_2}$ E + P. If the only reaction taking place was the reversible transformation E + S $\rightleftharpoons$ ES then K_m would in fact be a dissociation constant, but this is not the case.

In general, the quantities [ES] and [E] are not easily measurable, however, the total enzyme concentration

$$[\text{E}]_{\text{T}} = [\text{ES}] + [\text{E}]$$

is usually known. The total enzyme concentration is equal to the initial enzyme concentration, also, unless more enzyme is added throughout the duration of a reaction. Though, I can't think of any reason why not all of the enzyme would be added at once. Thus, Equation (10.8.3) can be rewritten as

$$K_m[\text{ES}] = [\text{E}][\text{S}]$$

$$K_m[\text{ES}] = ([\text{E}]_{\text{T}} - [\text{ES}])[\text{S}]$$

$$[\text{ES}](K_m + [\text{S}]) = [\text{E}]_{\text{T}}[\text{S}]$$

$$[\text{ES}] = \frac{[\text{E}]_{\text{T}}[\text{S}]}{K_m + [\text{S}]}$$

and substituting this result into Equation (10.8.2) affords the velocity of the reaction as a function of some directly measurable quantities:

$$v = \frac{d[\text{P}]}{dt} = \frac{k_2[\text{E}]_{\text{T}}[\text{S}]}{K_m + [\text{S}]} \qquad (10.8.4)$$

The initial velocity of the reaction is a direct consequence of this expression, also:

$$v_0 = \frac{k_2[\text{E}]_0[\text{S}]_0}{K_m + [\text{S}]_0} \qquad (10.8.5)$$

Equation (10.8.4) motivates us to define the point at which the *maximal velocity of reaction occurs*, v_{max}. The maximal velocity happens at high substrate concentrations when the enzyme is saturated, that is, when the enzyme is entirely in the ES form. Then, $v_{max} = k_2[\text{E}]_0$ and we obtain,

$$v_0 = \frac{v_{max}[\text{S}]_0}{K_m + [\text{S}]_0} \qquad (10.8.6)$$

known as the *Michaelis-Menten equation*. Equation (10.8.6) clearly illustrates the fact that the initial velocity of reaction is half-maximal when $[\text{S}]_0 = K_m$

It's important to keep in mind that the Michaelis constant is unique for every substrate-enzyme pair. The magnitude of K_m varies widely with the identity of the enzyme and the nature of the substrate, as well as the

temperature and pH of the solution. We can express K_m in Equation (10.8.3) alternatively as

$$K_m = \frac{k_{-1}}{k_1} + \frac{k_2}{k_1} = K_s + \frac{k_2}{k_1} \tag{10.8.7}$$

where K_s is the dissociation constant of the enzyme-substrate complex. As K_s (and therefore also K_m) *decreases*, the enzyme's affinity for a substrate *increases* so that we can think of K_m being a measure of the affinity of the enzyme for its substrate, provided that k_2/k_1 is small compared to K_s.

In the beginning of this section I mentioned that k_2 is sometimes also referred to as the catalytic constant, k_{cat}. More formally, k_{cat} is defined as,

$$k_{cat} = \frac{v_{max}}{[\text{E}]_0} \tag{10.8.8}$$

also known as the *turnover number*, because it is the number of reactions that each active site of the enzyme catalyzes per unit time. For enzymes with more complicated mechanisms than the one considered in the Michaelis-Menten model, k_{cat} is not always the same as k_2, and instead may be a function of several rate constants.

Keeping in mind that K_m is the concentration of substrate at which the velocity of the reaction is half-maximal, recognize that when $[\text{S}] \ll K_m$, very little ES is formed. Consequently, $[\text{E}] \approx [\text{E}]_0$ so that Equation (10.8.5) reduces to

$$v_0 = \frac{k_2[\text{E}]_0[\text{S}]_0}{K_m} \approx \left(\frac{k_{cat}}{K_m}\right)[\text{E}][\text{S}]_0 \tag{10.8.9}$$

Here, the ratio k_{cat}/K_m acts as a second-order rate constant for the enzymatic reaction. In particular this ratio is a measure of the *catalytic efficiency* of the particular enzyme-substrate pair being studied. There is an upper limit on the catalytic efficiency known as the *diffusion-controlled limit*, near 10^8 to 10^9 M^{-1}s^{-1}. Enzyme-substrate pairs with k_{cat}/K_m ratios near this limit catalyze a reaction almost every time they encounter one another and hence have achieved a state of virtual catalytic perfection.

Here is an example problem regarding enzyme kinetics and some transition state theory. Imagine a hypothetical reaction, S $\longrightarrow$ P, which has a rate constant $k_1 = 10^{-6}$ s^{-1} at $T = 298.15$ K. Suppose the rate of reaction doubles when the reaction is performed at 50°C as opposed to 25°C. What is the enthalpy of activation? Using transition state theory we can compare these two reaction rates. Recall Equation (10.6.5) which allows us to write a ratio of the rate constants as

$$\begin{aligned} \frac{k_2}{k_1} &= \frac{\frac{k_B T_2}{h}\exp\left\{-\Delta G^{\ddagger}/RT_2\right\}}{\frac{k_B T_1}{h}\exp\left\{-\Delta G^{\ddagger}/RT_1\right\}} \\ &= \frac{T_2\exp\left\{-\Delta G^{\ddagger}/RT_2\right\}}{T_1\exp\left\{-\Delta G^{\ddagger}/RT_1\right\}} \end{aligned}$$

where k_2 is the reaction rate when the temperature is raised, and T_1 and T_2 represent 25°C and 50°C, respectively. Importantly, notice that although the temperature is changing the change in Gibbs free energy to enter the transition state (which we can also think of as the activation energy) is *not* changing. Then,

substituting $k_2 = 2k_1$, we can evaluate the enthalpy of activation:

$$\frac{2k_1}{k_1} = \frac{T_2 \exp\left\{-\Delta G^{\ddagger}/RT_2\right\}}{T_1 \exp\left\{-\Delta G^{\ddagger}/RT_1\right\}}$$

$$\frac{2T_1}{T_2} = \exp\left\{\frac{-(\Delta H^{\ddagger} - T_2\Delta S^{\ddagger})}{RT_2} - \frac{-(\Delta H^{\ddagger} - T_1\Delta S^{\ddagger})}{RT_1}\right\}$$

$$\frac{2T_1}{T_2} = \exp\left\{\frac{-\Delta H^{\ddagger}}{RT_2} + \frac{\Delta H^{\ddagger}}{RT_1}\right\}$$

$$-R\ln\left(\frac{2T_1}{T_2}\right) = \Delta H^{\ddagger}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Evaluating this expression at $T_1 = 298.15$ K and $T_2 = 323.15$ K as given in the problem affords $\Delta H^{\ddagger} = 19.63$ kJ/mol as the enthalpy of activation for this reaction.

The one-way reaction illustrated above is nice, however, reality is rarely that simple. Suppose the substrate S can undergo an undesired reaction to a byproduct B, which occurs naturally at the rate $k_b = 10^{-5}$ s^{-1}. Fortunately, an enzyme E can accelerate the desired reaction $E + S \longrightarrow ES \longrightarrow E + P$ with rate constant $k_{cat} = 10^3$ s^{-1} and Michaelis constant $K_M = 10$ μM. How much of this enzyme is needed to ensure that 99% of S is converted to P if $[S]_0 = 1$ mM and $T = 25°C$? Here we'll need to consider the rates of reaction in either direction:

$$\frac{d[B]}{dt} = k_b[S]$$

$$\frac{d[P]}{dt} = k_{cat}[ES] = \frac{k_{cat}[E]_0[S]_0}{K_m + [S]_0}$$

where Equation (10.8.6) was used to rewrite the rate of formation of the product P. Before continuing, notice that $[S]_0 \gg K_M$ so that the denominator in the rate of formation of P is effectively just $[S_0]$. Then, finding the product ratio of the two products B and P is as simple as taking the ratio of their rates of formation:

$$\frac{d[B]/dt}{d[P]/dt} = \frac{k_b[S]}{\frac{k_{cat}[E]_0[S]_0}{K_m + [S]_0}}$$

$$\approx \frac{k_b[S]}{\frac{k_{cat}[E]_0[S]_0}{[S]_0}}$$

$$\frac{1}{99} = \frac{k_b[S]}{k_{cat}[E]_0}$$

$$\frac{1}{99} = \frac{(10^{-5}\text{ s}^{-1})(0.001\text{ M})}{(10^3\text{ s}^{-1})[E]_0}$$

$$[E]_0 = 9.9 \times 10^{-10}\text{ M}$$

Thus, we require that $[E_0] \approx 1$ nM in order to achieve 99% conversion to the desired product.

With the complication of a competing side reaction introduced, let's now ignore it. Instead, consider the free energy activation barrier of the reaction with and without an enzyme present. By how much does the enzyme lower the activation energy barrier for the $S \longrightarrow P$ reaction at standard conditions? In other words, we're looking for the quantity $\Delta\Delta G^{\ddagger}$. Hopefully by now it's obvious, but to determine this quantity we'll turn

to transition state theory. In particular, the Eyring equation:

$$\frac{k_{cat}}{k_1} = \exp\left\{\frac{-\Delta\Delta G^{\ddagger}}{RT}\right\}$$

$$\Delta\Delta G^{\ddagger} = -RT\ln\left(\frac{k_{cat}}{k_1}\right)$$

$$= -(8.3145)(298.15)\ln\left(\frac{10^3}{10^{-6}}\right)$$

$$= -51.37 \text{ kJ/mol}$$

Thus, the enzyme lowers the free energy activation barrier by 51.37 kJ/mol. I'll also point out that the expression for the change in activation energy is nothing we haven't seen before due to detailed balance, with the relationship $k_{cat}/k_1 = K_{eq}$.

The tangent regarding detailed balance aside, suppose that we perform some more experiments and determine that the reaction rate with the enzyme present doubles from 25°C to 50°C. Given this information, calculate $\Delta S_{cat}^{\ddagger}$. The subtle yet important aspect to this question is recognizing that *the temperature dependence of the catalyzed reaction is the same as the uncatalyzed reaction*. That is to say, the enthalpy of activation is the same whether or not the enzyme is present. In the very first question we considered where we wanted to find the enthalpy of activation, we could ignore the entropy because its contribution does not change with temperature (again, refer to the Eyring equation). In this case, however, the change in entropy is (almost definitely) changing with the introduction of an enzyme because the substrate S must bind to it, therefore limiting it's number of possible configurations. That is all to say, with the enzyme present we have $\Delta H^{\ddagger} = 19.63$ kJ/mol and the change in entropy can be found by applying transition state theory to the catalyzed rate constant only at room temperature:

$$k_{cat} = \frac{k_B T}{h}e^{-\Delta G_{cat}^{\ddagger}/RT}$$

$$\Delta G_{cat}^{\ddagger} = -RT\ln\left(\frac{k_{cat}h}{k_B T}\right)$$

$$= 55.9 \text{ kJ/mol}$$

Now we can use the classical definition of the change in Gibbs free energy (along with the enthalpy of activation derived earlier) to find the change in entropy of the catalyzed transition state:

$$\Delta G_{cat}^{\ddagger} = \Delta H_{cat}^{\ddagger} - T\Delta S_{cat}^{\ddagger}$$

$$55.9 \text{ kJ/mol} = 19.63 \text{ kJ/mol} - 298.15\Delta S_{cat}^{\ddagger}$$

$$\Delta S_{cat}^{\ddagger} = -121.65 \text{ J/mol}$$

This is change in entropy for the catalyzed reaction to the transition state. I think it's amazing how all of these ideas and calculations we've done here rely on the theory that the reactants are in "equilibrium" with the transition state, even though in some aspects of organic chemistry we're taught to think that the transition state is necessarily a real state of the system, only an abstraction to help explain mechanisms.

Before finishing let's connect everything we've learned about this enzyme. In particular, describe in thermodynamic terms how this enzyme works to accelerate the reaction and propose a molecular mechanism as to how it might achieve this effect. Notice that we've already discussed two aspects of the system. Firstly, the enthalpy of activation is not changed upon introduction of the enzyme and secondly (which is almost a consequence of the first thing), the enzyme catalyzes the reaction by lowering the entropic barrier of the activated complex. So, we wouldn't be crazy to propose a mechanism that focuses on lowering the entropic barrier of the reaction. How could an enzyme do this? Intuitively, an enzyme limiting the number of configurations of a substrate makes sense (think "lock and key" model). In order to have a limited number of

configurations actually *help* the reaction proceed would require that the enzyme limits the substrate to configurations which closely resemble the activated state and final product (Hammond's postulate). So, we might propose that the mechanism used by the enzyme brings together functional groups of the substrate which are required to react in, thereby limiting the total possible number of microstates of the substrate while not losing any which encourage a reaction.

This is actually a commonly used strategy by enzymes, though it is seldom the case that lowering the entropic barrier is the *only* contribution to catalysis. An interesting case of an enzyme that does in fact ignore trying to change the enthalpic barrier, though, are ribosomes, which functions nearly exclusively by entropic catalysis.

10.8.2   Enzyme Inhibition

10.9   Single Molecule Kinetics

10.9.1   Förester Resonance Energy Transfer (FRET)

10.10   The Chapman Cycle

`http://www.columbia.edu/itc/chemistry/chem-c2407/hw/ozone_kinetics.pdf`

`http://irina.eas.gatech.edu/ATOC3500_Fall1998/Lecture35.pdf`

Part II

Quantum Mechanics

BIBLIOGRAPHY

[1] Anslyn, Eric V. and Dennis A. Dougherty. *Modern Physical Organic Chemistry.* University Science Books, 2006.

[2] Barrick, Douglas. *Biomolecular Thermodynamics: From Theory to Application.* CRC Press, 2017.

[3] Engel, Thomas, and Philip Reid. *Thermodynamics, Statistical Thermodynamics, and Kinetics.* Pearson Education, 2019.

[4] Flory, Paul J. *Principles of Polymer Chemistry.* Cornell University Press, 1953.

[5] Fried, Stephen. AS.030.310 Physical Chemistry I, Johns Hopkins University, Baltimore, MD, 2021.

[6] Goodstein, David L. *States of Matter.* Prentice-Hall, 1975.

[7] Gremer, Lothar, et al. "Fibril structure of amyloid-β(1-42) by cryo-electron microscopy." *Science,* vol. 358, no. 6359, 2017, pp. 116-119. https://doi.org/10.1126/science.aao2825.

[8] Klippenstein, Stephen J. and Pande, Vijay S. and Truhlar, Donald G. "Chemical Kinetics and Mechanisms of Complex Systems: A Perspective on Recent Theoretical Advances." *Journal of the American Chemical Society,* vol. 136, no. 2, 2014, pp. 528-546. https://doi.org/10.1021/ja408723a.

[9] Lakowicz, Joseph R. *Principles of Fluorescence Spectroscopy.* Springer, Boston, MA, 2006.

[10] Pauling, Linus. *General Chemistry.* Dover Publications, 1970.

[11] Rubinstein, Michael, and Ralph H. Colby. *Polymer Physics.* 1st ed., Oxford University Press, 2003.

[12] Reid, Charles E. *Chemical Thermodynamics.* McGraw-Hill, Inc., 1990.

[13] Schwartz, Matthew. Physics 181 Statistical Mechanics and Thermodynamics, Harvard University, Cambridge, MA, 2021.

[14] Truhlar, Donald G. and Garrett C. Bruce. "Current Status of Transition-State Theory." *Journal of Physical Chemistry,* vol. 100, no. 31, 1996, pp. 12771-12800. https://doi.org/10.1021/jp953748q.

[15] Tolman, Richard C. *The Principles of Statistical Mechanics.* Dover Publications, 1979.

[16] Voet, Donald, Voet, Judith G., and Charlotte W. Pratt. *Fundamentals of Biochemistry: Life at The Molecular Level.* Wiley, 2016.