1.3: Physical-Chemical Foundations

The types and numbers of chemical reactions that occur in biological cells are staggering. Compared to both physical and chemical reactions that occur in a controlled and closed environment, biological reactions occur in open systems with input and output of both energy and chemical "feedstocks". Yet they are governed by the same physical principles that control all reactions. We can gain insight into biological reactions and how they are controlled by considering the same principles you have used in a myriad of preceding classes, energy changes, equilibria and thermodynamics. Let's review them!

Reactions and Energy Changes

Why do reactions vary in extent from completely irreversible in the forward reaction to reversible reactions favoring the reactants? It might help to understand a simple physical reaction before we try more complicated chemical reactions. Let's start with a simple ball on a hill. Does a ball at the top of a hill roll downhill spontaneously, or does the opposite happen? No one has ever seen a ball roll spontaneously uphill unless a lot of energy was added to the ball. This physical reaction appears to be irreversible and occurs because the ball has lower potential energy at the bottom of the hill than it does at the top. The gap in the potential energy is related to the "extent" and spontaneity of this reaction. As we have undoubtedly observed before, processes in nature tend to go to a lower energy state. By analogy, we will consider the driving force for a chemical reaction to be the free energy difference, ΔG, between reactants and products. ΔG determines the extent and spontaneity of the reaction.

Reversible/Irreversible Reactions, Extent of Reactions, Equilibria

Consider a hypothetical reversible reaction in which you start with some reactants, \( [\text{A}] \) and \( [\text{B}] \), each at a 1 M
concentration (1 mol of each/L solution), but no products, $\text{\langle P \rangle}$ and $\text{\langle Q \rangle}$. For ease assume that the total volume of solution is 1 L, so that we start with 1 mol each of $\text{\langle A \rangle}$ and $\text{\langle B \rangle}$. At time $t=0$, the concentration of products is 0. The reaction can be written as:

\[
\text{\langle A + B \rangle} \rightleftharpoons \text{\langle P + Q \rangle}
\]

As time progresses, the amounts or concentrations of $\text{\langle A \rangle}$ and $\text{\langle B \rangle}$ decrease as the amounts or concentrations of products $\text{\langle P \rangle}$ and $\text{\langle Q \rangle}$ increase. At some time, no further changes occur in the amount or concentrations of remaining reactants or products. At this point, the reaction is in equilibrium, a term used often in our common vocabulary to denote a system that is undergoing no net change.

Most of the reactions that we will study occur in solution, so we will deal with concentrations (in mol/L or mmol/mL = M). Let's consider how the concentration of reactants and products change as a function of time. Depending on the extent to which a reaction is reversible, 4 different scenarios can be imagined:

**Scenario 1: Irreversible reaction in which the reverse reaction occurs to a negligible extent.**

In this reaction, the reverse reaction occurs to such a small extent that we can neglect it. The only reaction that occurs is the conversion of reactants to products. Hence all the reactants are converted to product. At equilibrium $[A] = 0$. Since 1 mol of A reacted, it must form 1 mol of P and 1 mol Q - i.e. the concentration of products at equilibrium is 1 M. At an earlier time of the reaction, (let's pick a time when $[A] = 0.8$ M), only part of the reactants have reacted (in this case 0.2 M), producing an equal amount of products, P and Q. Graphs of $[A]$ and $[P]$ as a function of time are shown below. $[A]$ decreases in a nonlinear fashion to 0 M while $[P]$ increases in a reciprocal fashion to 1 M concentration. This is illustrated in the graph below.

Examples of irreversible reactions are reactions of strong acids (nitric, sulfuric, hydrochloric) with bases (OH- and water), or the much more complicated combustion reactions like the burning of sugars (like trees) and hydrocarbons (like octane) to form CO$_2$ and H$_2$O.

**Scenario 2: Reversible reaction in which the forward reaction is favored.**

Again $[A]$ decreases and $[P]$ increases, but in this case, some $A$ remains since the reaction is reversible. As $[A]$ and $[B]$ decrease, $[P]$ and $[Q]$ increase, which increases the chance that they will collide and form the product. Since P and Q can react to form reactants, the $[A]$ at equilibrium is not zero as is shown below.
Scenario 3: Reversible Reaction in which forward and reverse reactions are equally favored.

Again [A] decreases and [P] increases, but in this case, some A remains since the reaction is reversible. As [A] and [B] decrease, [P] and [Q] increase, which increases the chance that they will collide and form the product. Since P and Q can react to form reactants, the [A] at equilibrium is not zero as is shown below. Because the reactants and products are equally favored, their concentrations will be equal at equilibrium.

Scenario 4: Reversible Reaction in which the reverse reaction is favored.

Again [A] decreases and [P] increases, but in this case, some A remains since the reaction is reversible. As [A] and [B] decrease, [P] and [Q] increase, which increases the chance that they will collide and form the product. Since P and Q can react to form reactants, the [A] at equilibrium is not zero as is shown below. Because the reaction favors reactants, their concentration will be higher at equilibrium than the products.
An example of this kind of reaction, one that favors reactants, is the reaction of acetic acid (a weak acid) with water.

\[
\text{CH}_3\text{CO}_2\text{H}(\text{aq}) + \text{H}_2\text{O}(\text{l}) \rightleftharpoons \text{H}_3\text{O}^+ (\text{aq}) + \text{CH}_3\text{CO}_2^- (\text{aq})
\]

Equilibrium Constants

Without a lot of experience in chemistry, it is difficult to just look at the reactants and products and determine whether the reaction is irreversible, or reversible, favoring either reactants or products (with the exception of obvious irreversible reactions described above). However, this data can be found in tables of equilibrium constants. The equilibrium constant, as its name implies, is constant, independent of the concentration of the reactants and products. A \(K_{\text{eq}} > 1\) implies that the products are favored. A \(K_{\text{eq}} < 1\) implies that reactants are favored. When \(K_{\text{eq}} = 1\), both reactants and products are equally favored. For the more general reaction,

\[
\text{aA} + \text{bB} \rightleftharpoons \text{pP} + \text{qQ}
\]

where \(a\), \(b\), \(p\), and \(q\) are the stoichiometric coefficients,

\[
\begin{equation}
K_{\text{eq}} = \frac{[\text{P}]_\text{eq}^p [\text{Q}]_\text{eq}^q}{[\text{A}]_\text{eq}^a [\text{B}]_\text{eq}^b}
\end{equation}
\]

where all the concentrations are those at equilibrium. For a simple reaction where \(a\), \(b\), \(p\), and \(q\) are all 1, then \(K_{\text{eq}} = ([\text{P}]/[\text{A}])[\text{[Q]}]/[\text{B}]\).

(Note: Equilibrium constants are truly constant only at a given temperature, pressure, and solvent condition. Likewise, they depend on concentration to the extent that their activities change with concentration.)

For an irreversible reaction, such as the reaction of a 0.1 M HCl (aq) in water, \([\text{HCl}]_{\text{eq}} = 0\), you cannot easily measure a \(K_{\text{eq}}\). However, if we assume the reaction goes in reverse to an almost imperceptible degree, \([\text{HCl}]_{\text{eq}}\) might equal 10-10 M. Hence \(K_{\text{eq}} \gg 1\).

In summary, the extent of reactions can vary from completely irreversible (favoring only the products) to reactions that favor the reactants.
Our next goal is to understand what controls the extent of a reaction. That is, of course, the change in the Gibbs free energy. Two different pairs of factors influence the ΔG. One pair is concentration and inherent reactivity of reactants compared to products (as reflected in the Keq). The other pair is enthalpy/entropy changes. We will now consider the first pair.

**Contributions of Molecule Stability (K_{eq}) and concentration to ΔG**

Consider the reactions of hydrochloric acid and acetic acid with water.

\[
\begin{align*}
\ce{HCl (aq) + H2O (l)} & \ce{-> H3O^{+}(aq) + Cl^{-} (aq)} \\
\ce{CH3CO2H (aq) + H2O (l) } & \ce{-> H3O^{+} (aq) + CH3CO2^- (aq)}
\end{align*}
\]

Assume that at t = 0, each acid is placed into water at a concentration of 0.1 M. When equilibrium is reached, there is essentially no HCl left in solution, while 99% of the acetic acid remains. Why are they so different? We rationalized that HCl (aq) is a much stronger acid than H_{3}O^+(aq) which itself is a much stronger acid than CH_{3}CO_{2}H (aq). Why? All we can say is there is something about the structure of these acids (and the bases) that makes HCl much more intrinsically unstable, much higher in energy, and hence much more reactive than the acid it forms, H_{3}O^+(aq). Likewise, H_{3}O^+(aq) is much more intrinsically unstable, much higher in energy, and hence more reactive than CH_{3}CO_{2}H (aq). This has nothing to do with concentration since the initial concentration of both HCl (aq) and CH_{3}CO_{2}H (aq) were identical. This observation is reflected in the K_{eq} for these acids (>>1 for HCl and <<1 for acetic acid). This difference in intrinsic stability of reactants compared to products (which is independent of concentration) is one factor that contributes to ΔG.

The other factor is concentration. A 0.25 M (0.25 mol/L or 0.25 mmol/ml) solution of acetic acid does not conduct electricity, implying that very few ions of H_{3}O^+(aq) + CH_{3}CO_{2}^- (aq) exist in the solution. However, if more concentrated acetic acid is added, a dim light becomes evident. Adding more reactants seemed to drive the reaction to form more products, even though the reverse reaction is favored if one considers only the intrinsic stability of reactants and products. Before the concentrated acid was added, the system was at equilibrium. Adding concentrated acid perturbed the equilibrium, which drove the reaction to form additional products. This is an example of Le Chatelier's Principle, which states that if a reaction at equilibrium is perturbed, the reaction will be driven in the direction that will relieve the perturbation. Hence:

- if more reactant is added, the reaction shifts to form more products
- if more product is added, the reaction shifts to form more reactants
- if products are selectively removed (by distillation, crystallization, or further reaction to produce another species), the reaction shifts to form more product.
- if reactants are removed (as above), the reaction shifts to form more reactants.
- if heat is added to an exothermic reaction, the reaction shifts to get rid of the excess heat by shifting to form more reactants. (opposite for an endothermic reaction).

**Change in Free Energy G**

Without doing a complicated derivation, these simple examples suggest that the total \(\langle\Delta G\rangle\) can be expressed as the...
sum of the two contributions showing the effects of the intrinsic stability ($K_{eq}$) and concentration:

\begin{equation}
\Delta G_{\text{total}} = \Delta G_{\text{stability}} + \Delta G_{\text{concentration}}
\end{equation}

which becomes for the simple reaction $\ce{A + B <=> P + Q}$ (after a rigorous derivation):

\begin{equation}
\begin{aligned}
\Delta G &= \Delta G^0 + R T \ln \frac{[P][Q]}{[A][B]} \\
&= \Delta G^0 + R T \ln Q_{rx}
\end{aligned}
\end{equation}

where $\Delta G^0$ reflects the contribution from the relative intrinsic stability of reactants and products and the second term reflects the contribution from the relative concentrations of reactants and products (which has nothing to do with stability). $Q_{rx}$ is the reaction quotient which for the reaction $A + B \leftrightarrow P + Q$ is given by:

\begin{equation}
Q_{rx} = \frac{[P][Q]}{[A][B]}
\end{equation}

at any point in the reaction.

**Meaning of $\Delta G$**

Remember that $\Delta G$ is the "driving" force for a reaction, analogous to the difference in potential energy for a ball on a hill. Go back to that analogy. If the ball starts at the top of the hill, does it roll downhill? Of course. It goes from high potential energy to low potential energy. The reaction can be written as: Ball \text{top} $\rightarrow$ Ball \text{bottom} for which the change in potential energy, $\Delta PE = PE_{\text{bottom}} - PE_{\text{top}} < 0$. If the ball starts at the bottom, will it go to the top? Obviously not. For that reaction, Ball \text{bottom} $\rightarrow$ Ball \text{top}, $\Delta PE > 0$. If the top of the hill was at the same height at the bottom of the hill (obviously an absurd situation), the ball would not move. It would effectively be at equilibrium, a state of no change. For this reaction, Ball \text{top} $\rightarrow$ Ball \text{bottom}, the $\Delta PE = 0$. As the ball starts rolling down the hill, its potential energy gets closer to the potential it would have at the bottom. Hence the $\Delta PE$ changes from negative to more and more positive until it gets to the bottom at which case the $\Delta PE = 0$ and movement ceases. If the $\Delta PE$ is not 0, the ball will move until the $\Delta PE = 0$.

Likewise, for a chemical reaction that favors products, $\Delta G < 0$. The system is not at equilibrium and the reaction will go in the direction of products. As the reaction proceeds, products buildup, and there is less of a driving force for reactants to go to products (LeChatilier's Principle), so the $\Delta G$ becomes more positive until the $\Delta G = 0$ and the reaction is at equilibrium. A reaction that has a $\Delta G > 0$ is likewise not at equilibrium so it will go in the appropriate direction until equilibrium is reached. Hence for the reaction $A + B \leftrightarrow P + Q$,

- if $\Delta G < 0$, the reaction goes toward products $P$ and $Q$
- if $\Delta G = 0$, the reaction is at equilibrium and no further change occurs in the concentration of reactants and products.
If $\Delta G > 0$, the reaction goes toward reactants A and B.

We can not measure easily the actual free energy $G$ of reactants or products, but we can measure $\Delta G$ readily. These points are illustrated in the graph below of $\Delta G$ vs time for the hypothetical reaction $A + B \leftrightarrow P + Q$. (Also notice the two insert graphs - in blue and red - which show, in analogy to the ball on the hill graphs, the values of $\Delta G$ at the two points where the perturbation to the equilibrium were made.)

Notice the $\Delta G$ is constantly changing until the system reaches equilibrium. Initially, the equilibrium is perturbed so that the system is not in equilibrium (shown in blue). The perturbation was such that the products are favored. After equilibrium was reached, the system was perturbed again, this time in a fashion to favor the reverse reaction. Notice in this case the $\Delta G$ for the reaction as written: $A + B \leftrightarrow P + Q$ is positive - i.e. it is not in equilibrium. Therefore the reaction (as written) goes backwards to products. It is important to realize that the reported $\Delta G$ is for the reaction as written.

Now let’s apply $\Delta G = \Delta G^0 + RT \ln Q = \Delta G^0 + RT \ln ([P][Q]/([A][B])$ to two reactions we discussed above:

- $\text{HCl(aq)} + \text{H}_2\text{O(l)} \leftrightarrow \text{H}_3\text{O}^+(\text{aq}) + \text{Cl}^-(\text{aq})$
- $\text{CH}_3\text{CO}_2\text{H(aq)} + \text{H}_2\text{O(l)} \leftrightarrow \text{H}_3\text{O}^+(\text{aq}) + \text{CH}_3\text{CO}_2^-(\text{aq})$

Assume that at time $t=0$, 0.1 mole of HCl and CH$_3$CO$_2$H were added to two different beakers. At this point the forward reaction is favored, but obviously to different extents. The $RT \ln Q$ would be identical for both acids since each reactant is present at 0.1 M, but no products yet exist. However, the $\Delta G^0$ is negative for HCl and positive for acetic acid since HCl is a strong acid. Hence at $t=0$, $\Delta G$ for the HCl reaction is much more negative than for acetic acid. This is summarized in the table below. The direction of the arrow shows if products (\text{-->) or reactants (\text{<---}) are favored. The size of the arrow shows very approximately to what extent the $\Delta G$ term is favored.

<table>
<thead>
<tr>
<th>Reaction at $t=0$</th>
<th>$\Delta G^0$</th>
<th>$RT \ln Q$</th>
<th>$\Delta G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{HCl(aq)} + \text{H}_2\text{O(l)}$</td>
<td>$\text{----------&gt;}$</td>
<td>$\text{----------&gt;}$</td>
<td>$\text{-----------&gt;}$</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CO}_2\text{H(aq)} + \text{H}_2\text{O(l)}$</td>
<td>$\text{&lt;----------}$</td>
<td>$\text{----------&gt;}$</td>
<td>$\text{-&gt;}$</td>
</tr>
</tbody>
</table>
Now when equilibrium is reached, no net change occurs in the concentration of reactants and products, and ΔG = 0. In the case of HCl, there is just an infinitesimal amount of HCl left, and 0.1 M of each product, so concentration favors HCl formation. However, the intrinsic relative stability of reactants and products still favors products. In the case of acetic acid, most of the acetic acid remains (0.099 M) with little product (0.001 M) so concentration favors products. However, the intrinsic relative stability of reactants and products still favors reactants. This is summarized in the table below.

<table>
<thead>
<tr>
<th>Reaction at equilib.</th>
<th>ΔG°stab</th>
<th>RTln Q</th>
<th>ΔG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl(aq) + H₂O(l)</td>
<td>--------&gt;</td>
<td>&lt;--------&gt;</td>
<td>favors neither, = 0</td>
</tr>
<tr>
<td>CH₃CO₂H(aq) + H₂O(l)</td>
<td>&lt;--------</td>
<td>--------&gt;</td>
<td>favors neither, = 0</td>
</tr>
</tbody>
</table>

Compare the two tables above (one at time t= 0 and the other at equilibrium). Notice:

- ΔG° does not change in a given set of conditions, since it has nothing to do with concentration.
- Only RTln Q changes during the course of a reaction until equilibrium is achieved.

**Meaning of ΔG°**

To get a better meaning of the significance of ΔG°, let's consider the following equations under two different conditions:

\[
\Delta G = \Delta G^0 + RT \ln \frac{[P][Q]}{[A][B]} = \Delta G^0 + RT \ln Q_{rx}
\]

**Condition I: Reaction at equilibrium, ΔG = 0**

The equation reduces to:

\[
\Delta G^0 = -RT \ln \frac{[P]_{eq}[Q]_{eq}}{[A]_{eq}[B]_{eq}} = -2.303 RT \log K_{eq}
\]

This supports our idea that ΔG° is independent of concentration since K_{eq} should also be independent of concentration.

**Condition II: Concentration of all reactants and products is 1 M (standard state, assuming solution reaction)**

The equation reduces to:

\[
\Delta G = \Delta G^0 + RT \ln \frac{[1][1]}{[1][1]} = \Delta G^0 + 2.303 RT \log 1 = \Delta G^0
\]
\[
\Delta G = \Delta G^o + RT \ln \left( \frac{[1]}{[1]} \right) \\
= \Delta G^o + 2.303 RT \log 1 \\
= \Delta G^o
\]

This implies that when all reactants are at this concentration, defined as the standard state (1 M for solutes), the ΔG at that particular moment just happens to be the ΔG° for the reaction. If one of the reactants or products is H₃O⁺, it would make little biological sense to calculate ΔG° for the reaction using the standard state of [H₃O⁺] = 1 M, or a pH of -1. Instead, it is assumed that the pH = 7, [H₃O⁺] = 10⁻⁷ M. A new symbol is used for ΔG° under these conditions, ΔG°'.

**Heat, Enthalpy and Entropy**

Consider the association reaction of hydrogen atoms into molecular hydrogen

\[
\text{H + H} \rightarrow \text{H₂}. \nonumber
\]

Does this reaction occur spontaneously? It does. You should remember that individual \(\text{H}\) atoms are unstable since they don't have a completed outer shell of electrons - in this case, a duet. As they approach, they can interact to form a covalent bond and in the process release energy. The bonded state is a lower energy state than two separated H atoms. This should be clear since energy has to be added to a molecule of \(\text{H₂}\) to break the bond. We call this the **bond dissociation energy**.

![Energy diagram](https://bio.libretexts.org/Bookshelves/Biochemistry/Fundamentals_of_Biochemistry_(LibreTexts)/01%3A_Unit_I-_Structure_a…)

Now consider a more complicated reaction, the burning of octane.

\[
\text{2C₈H₁₈(l) + 25O₂(g) \rightarrow 16CO₂(g) + 18H₂O(g)} \nonumber
\]
To carry out this reaction, every C-C, C-H and O-O bond in the reactants must be broken (which requires an input of energy) but lots of energy is released on the formation of C-O and H-O covalent bonds in the products. Is more energy needed to break the bonds in the reactants or is more energy released on the formation of bonds in the product? The answer should be clear. The products must be at a lower energy than the reactants since huge amounts of heat and light energy are released on the combustion of gasoline and other hydrocarbons.

These reactions suggest that energy must be released for a reaction to proceed to any extent in a given direction.

Now consider, however, the following reaction:

\[
\ce{Ba(OH)2(s) + 2NH4SCN(s) -> 10H2O(l) + 2NH3(g) + Ba(SCN)2(aq)}
\]

When these two solids are added to a beaker and stirred, a reaction clearly takes place, as evidenced by the formation of a liquid (water) and the smell of ammonia. What is surprising is that heat is not released into the surroundings in this reaction. Rather heat was absorbed from the surroundings turning the beaker so cold that it freezes to a piece of wood (with a layer of water added to the wood) on which it was placed. This reaction seems to violate our idea that a reaction proceeds in a direction in which heat is liberated. Reactions, which liberate heat and raise the temperature of the surroundings, are called **exothermic** reactions. Reactions, which absorb heat from the surroundings and hence lower the temperature of the surroundings, are **endothermic** reactions. To answer the question we need to consider entropy.

### A review of thermodynamics

You may remember from General Chemistry that the change in the internal energy of a system, \(\Delta E\), is given by:

\[
\begin{aligned}
\Delta E_{\text{sys}} &= q + w \\
&= q - P_{\text{ext}} \Delta V \\
\end{aligned}
\]

where \(q\) is the heat (thermal energy) transferred to (+) or from the system (-), \(w\) is the work done on (+) or by (-) the system. This is one expression for the 1st Law of Thermodynamics.

If only pressure/volume (PV) work is done (and not electrical works for example), \((w = - P_{\text{ext}} \Delta V)\), where \(P_{\text{ext}}\) is the external pressure resisting a volume change in the system, \(\Delta V\). Under these conditions, the heat transfer at constant \(P\), \(q_P\) is given by:

\[
\begin{aligned}
\Delta E_{\text{sys}} - w &= \Delta E_{\text{sys}} + P_{\text{ext}} \Delta V \\
&= q_P \\
&= \Delta H_{\text{sys}}
\end{aligned}
\]
\(q_p\), which can easily be measured in a coffee cup calorimeter, is equal to the **change in enthalpy**, \(\Delta H\), of the system.

For exothermic reactions, the reactants have more thermal energy than the products, and the heat energy (measured in kilocalories) released is the difference between the energy of the products and reactants. When heat energy is used to measure the difference in energy, we call the energy enthalpy (\(\Delta H\)) and the heat released as the change in enthalpy (\(\Delta H\)), as illustrated below.
For exothermic reactions, $\Delta H < 0$. For endothermic reactions, $\Delta H > 0$.

The equation $\Delta E_{\text{sys}} = q + w = q - P_{\text{ext}}$ is one expression of the First Law of Thermodynamics. Another statement of energy conservation, is:

\[
\begin{align*}
\text{\Delta E}_{\text{tot}} &= \text{\Delta E}_{\text{universe}} = \text{\Delta E}_{\text{sys}} + \text{\Delta E}_{\text{surrounding}} = 0
\end{align*}
\]

Clearly, there must be something more that decides whether a reaction goes to a significant extent other than, if heat is released from the system. That is, the spontaneity of a reaction must depend on more than just $\Delta H_{\text{sys}}$. Another example of a spontaneous natural reaction is the evaporation of water (a physical, not chemical process). $\ce{H2O (l) → H2O (g)}$

Heat is absorbed from the surroundings to break the intermolecular forces (H bonds) among the water molecules (the system), allowing the liquid to be turned into a gas. If the surroundings are the skin, evaporation of water in the form of sweat cools the body. What are these reactions spontaneous and essentially irreversible even though they are endothermic? Notice that in both of these endothermic reactions (the reactions of Ba(OH)$_2$.8H$_2$O(s) and 2NH$_4$SCN(s) and the evaporation of water), the products are more disorganized (more disordered) than the products. A solid is more ordered than a liquid or gas, and a liquid is more ordered than a gas. In nature, ordered things become more disordered with time. Entropy (S), the other factor (in addition to enthalpy changes) is often considered to be a measure of the disorder of a system. The greater the entropy, the greater the disorder. For reactions that go from order (low S) to disorder (high S), the change in S, $\Delta S > 0$. For the reaction that goes from low order to high order, $\Delta S < 0$.

**Caution**

However, this common description of entropy is quite misleading. Macroscopic examples describing order/disordered states (such as the cleanliness of your room or the shuffling of a deck of cards) are inappropriate since entropy deals with microscopic states.

The driving force for spontaneous reactions is the dispersion of energy and matter. Increases in entropy for reactions that involve matter occurs when gases or solutes in solution are dispersed, leading to increases in positional entropy. For reactions involving energy changes, entropy increases when energy is dispersed as random, undirected thermal motion, leading to increases in thermal entropy. In this sense, entropy, $\Delta(S) \text{ (a measure of "spreadedness")}$ is a measure of the number of different ways (microstates) that particles or energy can be arranged ($W$), not a measure of disorder! $W$ is an abbreviation for the German word, **Wahrscheinlichkeit**, which means probability. It can be shown that for a solute dissolving in a solvent, $W_{\text{sys}} = W_{\text{solute}} \times W_{\text{solvent}}$. Note that this is a multiplicative function. Entropy is a logarithmic function of $W$ which allows additivity of solute and solvent $W$ values, a feature found in other thermodynamic state functions like $\Delta E$, $\Delta H$, and $\Delta S$. Hence

\[
\ln W_{\text{sys}} = \ln W_{\text{solute}} + \ln W_{\text{solvent}}
\]
Boltzmann showed that for molecules,

\begin{equation}
S = k \ln W
\end{equation}

where \(k\) is the Boltzmann constant \((1.68 \times 10^{-23} \text{ J/K})\), S units: J/K

or

\begin{equation}
S = k N_A \ln W = R \ln W
\end{equation}

Boltzmann realized the connection between the macroscopic entropy of a system and the microscopic order/disorder of a system through the equation \(S = k \ln W\). Increasing S (macroscopic property) occurs with increasing numbers of possible microscopic states for the atoms and molecules of a system.

The dissolution of a solute in water and the expansion of a gas into a vacuum, which both proceed spontaneously toward an increase in matter dispersal, are examples of familiar processes characterized by a \(\Delta S_{\text{sys}} > 0\). We will see in future chapters that entropy changes in the solvent, solutes, and in a protein are critical determinants of protein folding.

The spontaneity of exothermic and endothermic processes will depend on the

\begin{equation}
\Delta S_{\text{sys}} = \Delta S_{\text{surr}} + \Delta S_{\text{sys}}
\end{equation}

\(\Delta S_{\text{sys}}\) often depends on matter dispersal (positional entropy). \(\Delta S_{\text{surr}}\) depends on energy changes in the surroundings, \(\Delta H_{\text{surr}} = -\Delta H_{\text{sys}}\) (thermal entropy).

It is more convenient to express thermodynamic properties based on the system which is being studied, not on the surrounding. This can be readily done for the \(\Delta S_{\text{surr}}\) which depends both on \(\Delta H_{\text{sys}}\) and the temperature. First consider the dependency on \(\Delta H_{\text{sys}}\). Thermal energy flows into or out of the system, and since \(\Delta H_{\text{sys}} = -\Delta H_{\text{surr}}\),

\(\langle \Delta S_{\text{surr}} \rangle\) is proportional to \(-\Delta H_{\text{sys}}\)

- For an exothermic reaction, \(\Delta S_{\text{surr}} > 0\) (since \(\Delta H_{\text{sys}} < 0\)) and the reaction is favored;
- For an endothermic reaction, \(\Delta S_{\text{surr}} < 0\), (since \(\Delta H_{\text{sys}} > 0\)), and the reaction is disfavored;

\(\langle \Delta S_{\text{surr}} \rangle\) also depends on the temperature \(T\) of the surroundings:

\(\langle \Delta S_{\text{surr}} \rangle\) is proportional to \(1/T\)
If the $T_{\text{surr}}$ is high, a given heat transfer to or from the surroundings will have a smaller effect on the $\Delta S_{\text{surr}}$. Conversely, if the $T_{\text{surr}}$ is low, the effect on $\Delta S_{\text{surr}}$ will be greater. (Atkins uses the analogy of the effect of a sneeze in library compared to in a crowded street; An American Chemistry General Chemistry text uses the analogy of giving $5$ to a friend with $1000$ compared to one who has just $10$.) Hence,

$$\Delta S_{\text{surr}} = \frac{-\Delta H_{\text{sys}}}{T}$$

(Note: from a more rigorous thermodynamic approach, entropy can be determined from $dS = dq_{\text{rev}}/T$.)

Once again,

$$\Delta S_{\text{tot}} = \Delta S_{\text{surr}} + \Delta S_{\text{sys}}$$

$$\Delta S_{\text{tot}}$$ depends on both enthalpy changes in the system and entropy changes in the surroundings. Hence,

$$\Delta S_{\text{tot}} = \frac{-\Delta H_{\text{sys}}}{T} + \Delta S_{\text{sys}}$$

Multiplying both sides by $(-T)$ gives

$$-T \Delta S_{\text{tot}} = \Delta H_{\text{sys}} + T \Delta S_{\text{sys}}$$

The thermodynamic function Gibb’s Free Energy, $G$, can be defined as:

$$G = H - T S$$

At constant $(T)$ and $(P)$,

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

Hence

$$\Delta G_{\text{sys}} = \Delta H_{\text{sys}} - T \Delta S_{\text{sys}} = -T \Delta S_{\text{tot}}$$
Spontaneity is determined by \(\Delta S_{\text{tot}}\) OR \(\Delta G_{\text{sys}}\) since \(\Delta S_{\text{tot}} = -\Delta G_{\text{sys}}/T\). \(\Delta G_{\text{sys}}\) is widely used in discussing spontaneity since it is a state function, depends only on the enthalpy and entropy changes in the system, and is negative (as is the potential energy change for a falling object) for all spontaneous processes.

The second law of thermodynamics can be succinctly stated: For any spontaneous process, the \(\Delta S_{\text{tot}} > 0\). Unlike energy (from the First Law), entropy is not conserved.