

## Review of Chemical Thermodynamics 7.51 September 1999

If you haven't had thermodynamics before, you'll probably need to do some background reading. Possibilities include: Moore, W.J. (1972) *Physical Chemistry*, 4th edition, Prentice-Hall, Inc.; Eisenberg, DS & Crothers, DM (1979) *Physical Chemistry with Applications to the Life Sciences*, Addison-Wesley Publishing Co.; Tinoco, I, Sauer, K., & Wang, JC (1994) *Physical Chemistry: Principles and Applications in Biological Sciences*, 3rd Edition, Prentice-Hall, Inc., van Holde, KE (1985) *Physical Biochemistry*, Prentice-Hall, Inc.

Thermodynamics allows us to predict how chemical reactions will change as a function of temperature and how changes in the structure of molecules might affect the equilibrium properties of a population of these molecules.

There are four basic thermodynamic properties:

**$\Delta G$**  — Change in **free energy** between reactants and products; this measures the ability of the system to do work. Reactions with negative  $\Delta G$ 's proceed spontaneously and can be used to do work. Reactions with positive  $\Delta G$ 's require an input of energy for the reaction to proceed.

**$\Delta H$**  — Change in **enthalpy** between reactants and products; this is the heat given off or absorbed by a reaction at constant pressure. Reactions that absorb heat have positive  $\Delta H$ 's and those that produce heat have negative  $\Delta H$ 's.

**$\Delta S$**  — Change in **entropy** between reactants and products; entropy is a statistical measure of the number of states or accessible conformations. A positive  $\Delta S$  is an indication that the disorder or number of accessible of the system is increasing and vice versa.

**$\Delta C_p$**  — Change in **heat capacity** between reactants and products; when a solution of molecules is heated, some of the thermal energy increases the kinetic energy of molecules, increasing the temperature, whereas some of the energy results in faster vibrations or rotation of the molecule. Heat capacity measures how much energy can be stored by a molecule in these internal vibrations or rotations.

### **$\Delta G$ provides a basic accounting function for chemical reactions.**

The free energy change for a reaction can be calculated from the equilibrium constant for that reaction using the equation shown below.

$$\Delta G^\circ = -RT \ln K$$

gas constant                      equilibrium constant  
 ↓                                      ↓  
 ↑                                      ↑  
 standard Gibb's free energy      absolute temperature

$\Delta G^\circ$  is a function of the equilibrium constant for the reaction, the gas constant  $R$  ( $1.98 \cdot 10^{-3}$  kcal/mol-deg), and the absolute temperature (in  $^\circ\text{K}$ ). Remember that  $T(^{\circ}\text{K}) = T(^{\circ}\text{C}) + 273$ . Some politically correct biochemists use kJ/mol rather than kcal/mol. The conversion is relatively painless as  $1 \text{ kcal/mol} \approx 4.2 \text{ kJ/mol}$  and  $R = 8.3 \cdot 10^{-3} \text{ kJ/mol-deg}$  in these units.

$\Delta G^\circ$  is called the standard Gibb's free energy, where the naught specifies a standard set of reaction conditions that include **constant pressure** (almost always 1 atm for biochemical reactions), a given **temperature**, and a set of **standard-state concentrations**. The temperature used in calculating  $\Delta G^\circ$  is that for which  $K_{\text{eq}}$  for the reaction was measured. The standard-state concentrations of reactants and products are assumed to be  $1 \text{ M}$  unless different values are explicitly specified.

It's useful to be able to estimate  $\Delta G^\circ$  values without using a calculator. The easiest way to do this is to use  $\Delta G^\circ = -2.3RT \log(K) \approx -1.35 \log(K)$  at room temperature. So an equilibrium constant of  $10^{-10} \text{ M}$  corresponds to a  $\Delta G^\circ$  of 13.5 kcal/mol. Similarly, a 10-fold change in  $K$  will change  $\Delta G^\circ$  by 1.35 kcal/mol.

Knowing  $\Delta G^\circ$  for a reaction allows one to calculate the equilibrium constant by using:

$$K_{\text{eq}} = e^{-\Delta G^\circ/RT}$$

What exactly does  $\Delta G^\circ$  measure? It's not the free energy required to completely convert  $1 \text{ M}$  reactants to  $1 \text{ M}$  products at some specified temperature and pressure. We do need to convert one mole of reactants to one mole of products but we're interested in the free energy of this process when the reaction proceeds without changing the concentrations of reactants and products. For the reaction,  $A+B \rightleftharpoons AB$ , imagine that we have a solution containing  $1 \text{ M}$  [A],  $1 \text{ M}$  [B], and  $1 \text{ M}$  [AB]. Now allow 1 molecule of A to bind 1 molecule of B to form a new AB complex. Clearly the bulk concentrations of A, B, and AB don't change in any way that would be measurable. If we could measure the amount of free energy that was produced or consumed by this single association event, then we would

multiply this value by  $6 \cdot 10^{23}$  molecules/mol to calculate  $\Delta G^\circ$  for the association reaction. We'll see below how  $\Delta G$  for a reaction changes when the concentrations of reactants and products are permitted to change

Recall that equilibrium constants are defined for the reaction proceeding from the molecular species of the reactants represented on the bottom of the equilibrium expression to those of the products represented on the top. When we use an equilibrium constant to calculate  $\Delta G^\circ$ , the resulting free energy change is also for the reaction proceeding from top to bottom.

$$\Delta G_{\text{diss}}^\circ = -RT \ln K_d = -RT \ln \frac{[A][B]}{[AB]} \leftarrow$$

Thus, for bimolecular reactions, if  $K_d$  is used to calculate  $\Delta G^\circ$ , then the free energy is that associated with dissociation of the complex and the free energy change will be positive if  $K_d < 1 \text{ M}$ . This makes sense. If  $K_d$  is  $10^{-6} \text{ M}$ , then it will require energy to dissociate the complex when all species are present at  $1 \text{ M}$  concentrations. If  $K_a$  is used to calculate  $\Delta G^\circ$ , then the free energy is that of association of the complex.

$$\Delta G_{\text{assn}}^\circ = -RT \ln K_a = -RT \ln \frac{[AB]}{[A][B]} \leftarrow$$

For a reaction with  $K_a > 1 \text{ M}^{-1}$  the free energy change of association will be negative when all species are present at  $1 \text{ M}$  concentrations. It will always be true that  $\Delta G_{\text{diss}}^\circ = -\Delta G_{\text{assn}}^\circ$ . When unimolecular equilibrium constants are used to calculate  $\Delta G^\circ$ , the resulting free energy change is again for the reaction proceeding from the species on the bottom to those on top.

$$\Delta G_{\text{unf}}^\circ = -RT \ln K_u = -RT \ln \frac{[U]}{[N]} \leftarrow$$

**$\Delta G^\circ$  is a function of  $\Delta H^\circ$ ,  $\Delta S^\circ$ , and temperature.**

$$\begin{array}{ccc}
 \text{free energy} & \text{enthalpy} & \text{entropy} \\
 \downarrow & \downarrow & \downarrow \\
 \Delta G^\circ & = & \Delta H^\circ - T\Delta S^\circ \\
 & & \uparrow \\
 & & \text{absolute temperature}
 \end{array}$$

$\Delta H^\circ$  for a reaction can be determined directly using a calorimeter and simply measuring the amount of heat that is produced or consumed by the reaction. As discussed below, we can also determine  $\Delta H^\circ$  by measuring the temperature dependence of the equilibrium constant.

$\Delta S^\circ$  for most chemical reactions is not measured directly but is calculated from  $\Delta G^\circ$ ,  $\Delta H^\circ$ , and the temperature. We can, however, calculate  $\Delta S^\circ$  for simple dilution processes. The entropy of a state is proportional to the number of energetically accessible states.

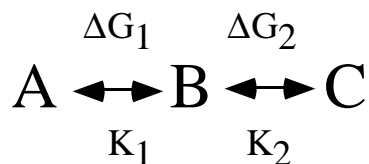
$$S = R \ln (\# \text{ states})$$

$$\Delta S = R \ln \frac{[\# \text{ final states}]}{[\# \text{ initial states}]}$$

In dilution reactions, the number of states is inversely proportional to concentration; there are more states accessible to a molecule at low concentrations than at high concentrations. Thus, the change in entropy upon dilution is positive (favorable) as long as the initial concentration is higher than the final concentration.

$$\Delta S_{\text{dil}} = R \ln \frac{[\# \text{ final states}]}{[\# \text{ initial states}]} = R \ln \frac{[\text{initial conc}]}{[\text{final conc}]}$$

**In linked reactions,  $\Delta G$ 's are additive.**



For coupled equilibria, we know that the equilibrium constant for the overall reaction is the product of the equilibrium constants for each step.

$$K_{\text{eq}} = K_1 K_2 = \frac{[\text{B}][\text{C}]}{[\text{A}][\text{B}]} = \frac{[\text{C}]}{[\text{A}]}$$

The free energy change for the overall reaction from A to C is just the sum of the free energy changes for each step.

$$\Delta G_{\text{overall}} = \Delta G_1 + \Delta G_2$$

If we substitute  $-RT \ln K_1$  for  $\Delta G_1$  and  $-RT \ln K_2$  for  $\Delta G_2$  and then simplify, we get

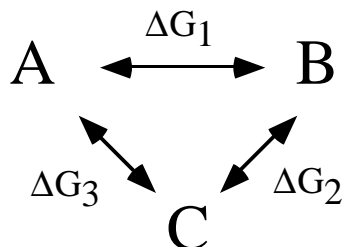
$$\Delta G_{\text{overall}} = -RT \ln K_1 K_2 = -RT \ln K_{\text{eq}}$$

In coupled reactions,  $\Delta H^\circ$  and  $\Delta S^\circ$  are also additive.

$$\Delta S_{\text{overall}} = \Delta S_1 + \Delta S_2$$

$$\Delta H_{\text{overall}} = \Delta H_1 + \Delta H_2$$

In any cyclic process, the overall changes in  $\Delta G$ ,  $\Delta H$ , and  $\Delta S$  must be zero and the overall product of the equilibrium constants must be 1.



$$\Delta G_1 + \Delta G_2 + \Delta G_3 = 0$$

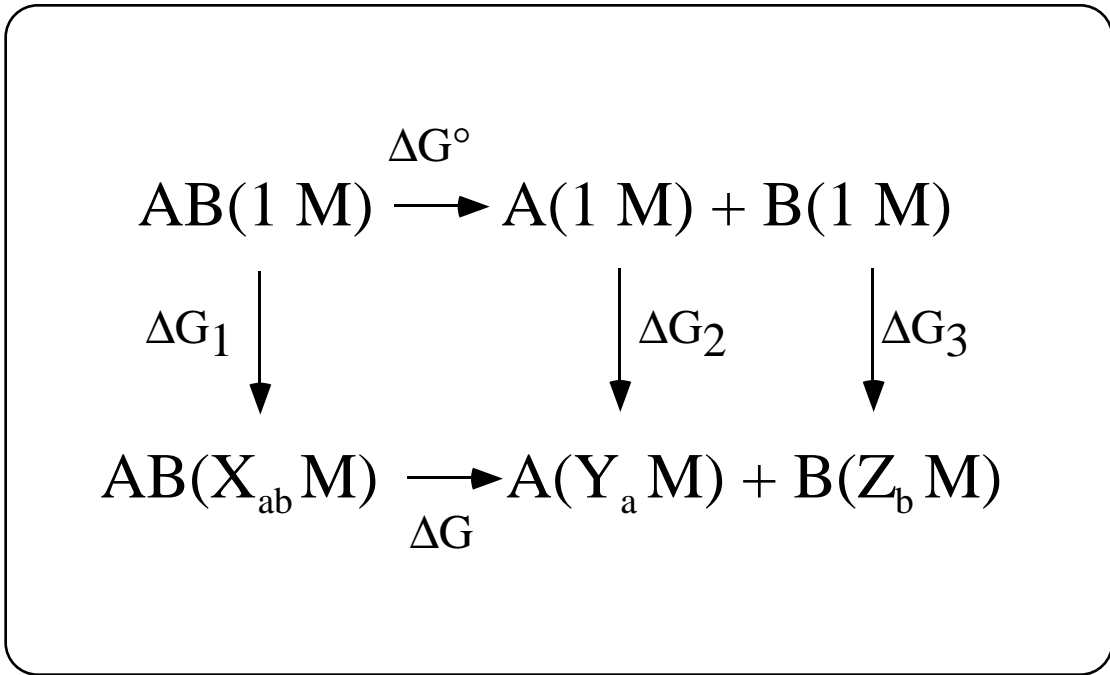
### Why do concentrations matter for $\Delta G$ ?

For bimolecular reactions,  $\Delta G^\circ$  is the free energy change for converting reactants to products at the standard-state concentrations of 1 M. These aren't the concentrations of reactants and products that are likely to be of interest though.  $\Delta G$  for the reaction  $AB \leftrightarrow A+B$  can be calculated at non-standard state conditions by using the equation

$$\Delta G = \Delta G^\circ + RT \ln \frac{[Y_a][Z_b]}{[X_{ab}]}$$

where  $[Y_a]$ ,  $[Z_b]$ , and  $[X_{ab}]$  are the concentrations of  $[A]$ ,  $[B]$ , and  $[AB]$  for the reaction of interest.

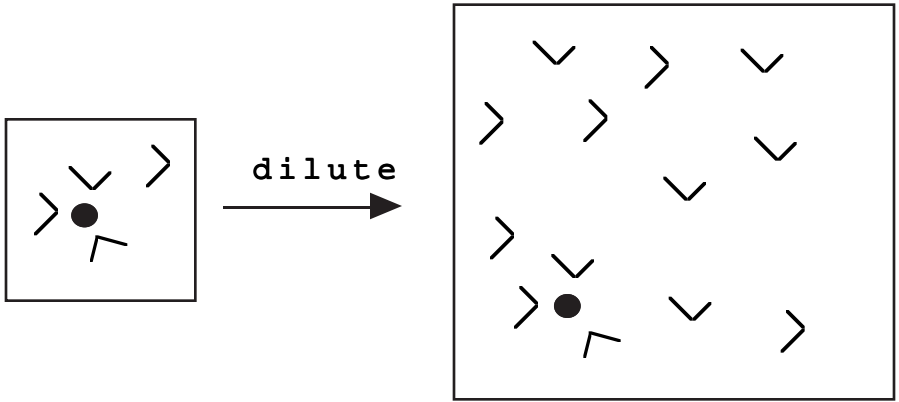
To derive this equation, construct a thermodynamic cycle for a dissociation reaction. The top reaction is for dissociation under standard-state concentrations of 1 M for all reactants and products. The bottom reaction is for dissociation at any other set of concentrations of reactants and products. The vertical reactions are dilutions.



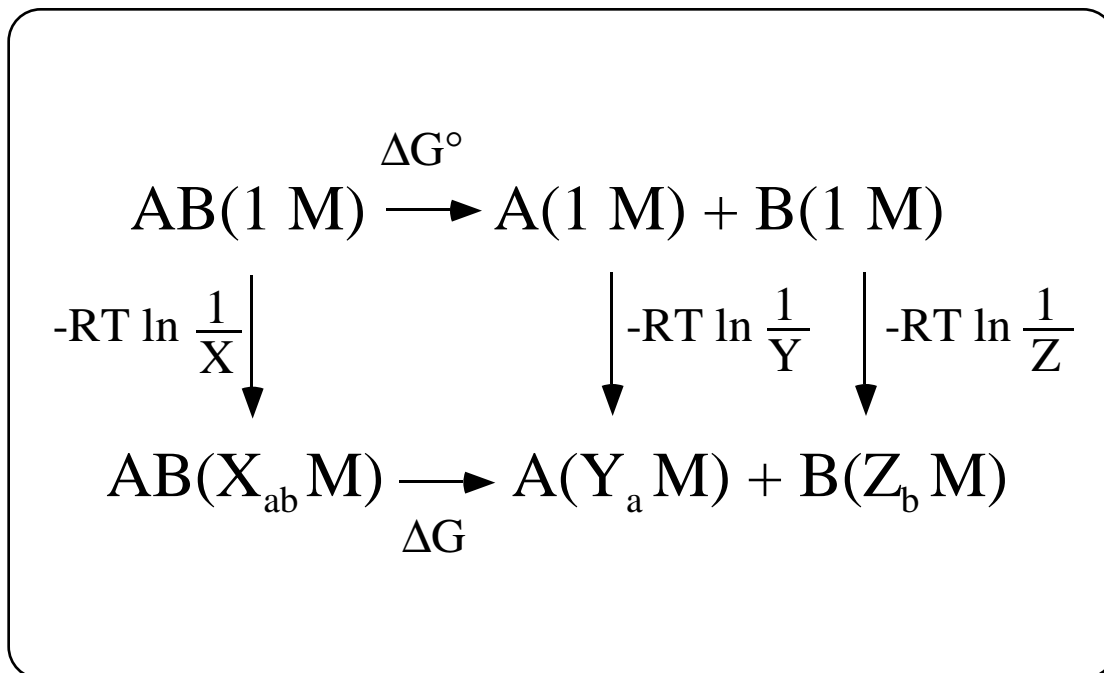
$$\Delta G^\circ + \Delta G_2 + \Delta G_3 = \Delta G + \Delta G_1$$

Because  $\Delta G_1$ ,  $\Delta G_2$ , and  $\Delta G_3$  are free energies of dilution, only the entropy change will matter because bonds aren't being made or broken. Thus  $\Delta H_{\text{dil}} = 0$  and

$$\Delta G_{\text{dil}} = \Delta H_{\text{dil}} - T\Delta S_{\text{dil}} = -T\Delta S_{\text{dil}}$$



Hence, the thermodynamic cycle becomes:



$$\Delta G + RT \ln (X_{ab}) = \Delta G^\circ + RT \ln (Y_a) + RT \ln (Z_b)$$

rearranging terms gives,

$$\Delta G = \Delta G^\circ + RT \ln \frac{[Y_a][Z_b]}{[X_{ab}]}$$

There are two special conditions: When  $[Y_A] = [Z_B] = [X_{AB}] = 1 \text{ M}$ , then  $\Delta G = \Delta G^\circ$ , as would be expected because there would be no dilution. When  $[Y_A]$ ,  $[Z_B]$ , and  $[X_{AB}]$  are equilibrium concentrations, then

$$\Delta G = -RT \ln \frac{[A][B]}{[AB]} + RT \ln \frac{[A][B]}{[AB]} = 0$$

There are a number of ways to express the fact that  $\Delta G = 0$  for a system that has come to equilibrium. Systems at equilibrium can't do work. No free energy is gained or lost by



converting reactants to products under equilibrium conditions. At equilibrium, there is no net driving force for the reaction.

For a unimolecular reaction,  $A \rightleftharpoons B$ , the free energy change at concentrations other than standard state can be calculated from:

$$\Delta G = \Delta G^\circ + RT \ln \frac{[\text{products}]}{[\text{reactants}]}$$

It's important to understand why the free energy change is a function of reactant and product concentrations for all reactions.  $\Delta G$  can be viewed as an indicator of whether the local free energy landscape for the reaction is uphill or downhill; negative  $\Delta G$ 's represent downhill reactions and positive  $\Delta G$ 's represent uphill reactions. Consider a dissociation reaction,  $AB \rightleftharpoons A+B$ , with  $K_d = 1 \mu\text{M}$ . Now initiate different dissociation reactions with different initial concentrations of  $[AB_0] = [A_0] = [B_0]$ . To what extent will each dissociation reaction proceed.

$[AB_0] = [A_0] = [B_0] = 1 \text{ M}$	dissociation uphill	$\Delta G = 8.2 \text{ kcal/mol}$
$[AB_0] = [A_0] = [B_0] = 1 \mu\text{M}$	system at equilibrium	$\Delta G = 0.0 \text{ kcal/mol}$
$[AB_0] = [A_0] = [B_0] = 1 \text{ pM}$	dissociation downhill	$\Delta G = -8.2 \text{ kcal/mol}$

For the unimolecular reaction,  $A \rightleftharpoons B$ ,  $\Delta G$  will be equal to  $\Delta G^\circ$  as long as  $[A_0] = [B_0]$  because the entropy of dilution of the reactants will be equal to the entropy of dilution of the products in the thermodynamic cycle. If  $[A_0] \neq [B_0]$ , then  $\Delta G \neq \Delta G^\circ$ . Consider, a reaction with an equilibrium constant of  $K$ .

$[A_0] = 10 \cdot [B_0]/K$	$A \rightarrow B$ downhill	$\Delta G = -1.35 \text{ kcal/mol}$
$[A_0] = [B_0]/K$	system at equilibrium	$\Delta G = 0.0 \text{ kcal/mol}$
$10 \cdot [A_0] = [B_0]/K$	$A \rightarrow B$ uphill	$\Delta G = 1.35 \text{ kcal/mol}$

Again, the free energy landscape can be uphill or downhill depending on the concentrations of reactants and products.

## Temperature dependence of $\Delta G$ , $\Delta H$ , $\Delta S$ , and $K_{eq}$ .

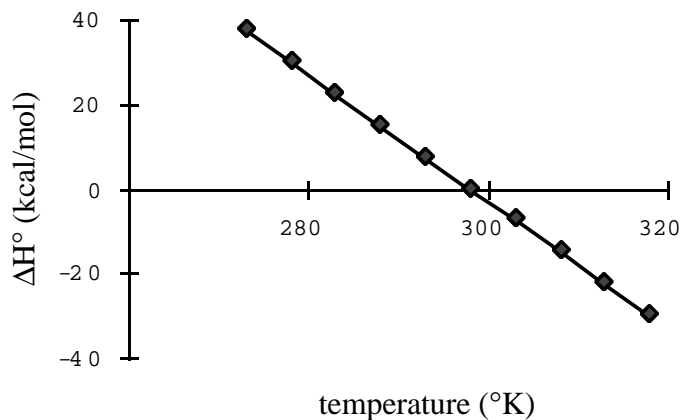
The equation  $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$  can be deceptive because it looks like a simple linear equation with temperature ( $T$ ) as the only variable. In fact, however, both  $\Delta H^\circ$  and  $\Delta S^\circ$  change as a function of temperature if there is a difference in the heat capacities of the reactants and products.

$$\frac{\partial \Delta H}{\partial T} = \Delta C_p$$

The integrated solution is

$$\Delta H = \Delta C_p \cdot T + \Delta H_{0^\circ K}$$

Thus,  $\Delta H^\circ$  is a simple linear function of temperature and one can measure  $\Delta C_p$  as the slope of a plot of  $\Delta H^\circ$  values determined at different temperatures. In the plot shown below,  $\Delta C_p = -1.5$  kcal/mol-degree and  $\Delta H^\circ = 0$  kcal/mol at 298 °K. Notice that  $\Delta H^\circ$  for the reaction changes sign, and the reaction changes from being endothermic to exothermic at this temperature.



Knowing  $\Delta C_p$  and  $\Delta H^\circ$  at one temperature allows  $\Delta H^\circ$  to be calculated at any other temperature.

$$\Delta H_1 = \Delta H_2 + \Delta C_p \cdot (T_1 - T_2)$$

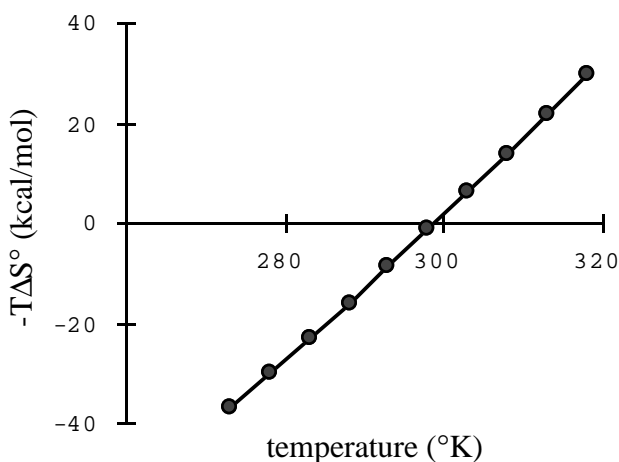
Entropy is also a function of temperature.

$$\frac{\partial \Delta S}{\partial T} = \frac{\Delta C_p}{T}$$

The integrated solution in this case is:

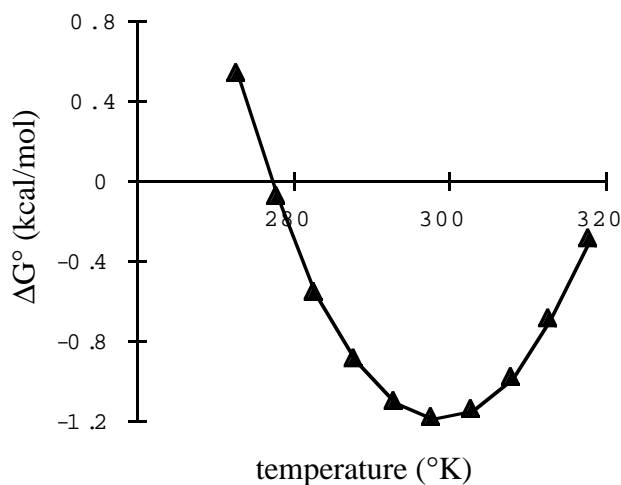
$$\Delta S_1 = \Delta S_2 + \Delta C_p \cdot \ln (T_1/T_2)$$

The graph below, for a reaction with  $\Delta C_p = -1.5$  kcal/mol and  $\Delta S_2 = 0.004$  kcal/mol-deg at 298 °K, shows how  $-T\Delta S$  changes with temperature. The plot has a very slight curvature that reflects the logarithmic dependence on temperature. For the reaction shown,  $\Delta S^\circ$  for the reaction changes sign near room temperature.



Because the heat capacity change determines how the enthalpy and entropy of the reaction change with temperature,  $\Delta H^\circ$  and  $\Delta S^\circ$  will be independent of temperature if and only if  $\Delta C_p$  is equal to 0, which is rare in biological systems.

Because  $\Delta H^\circ$ ,  $\Delta S^\circ$ , and  $T$  are all functions of temperature,  $\Delta G^\circ$  will also change with temperature as shown in the plot below where at 298 °K,  $\Delta H^\circ = 0$  kcal/mol,  $\Delta S^\circ = 0.004$  kcal/mol-deg, and  $\Delta C_p = -1.5$  kcal/mol.



In comparing the plots of  $\Delta H^\circ$ ,  $T\Delta S^\circ$  and  $\Delta G^\circ$  as a function of temperature, notice that there are large changes in  $\Delta H^\circ$  and  $T\Delta S^\circ$  as one goes from 270 to 315 °K but relatively small changes in  $\Delta G^\circ$ . This occurs because the change in  $\Delta H^\circ$  compensates for much of the change in  $T\Delta S^\circ$ , a process called enthalpy-entropy compensation. To see how  $\Delta G^\circ$  changes with temperature, start with:

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

taking the derivatives of all terms with respect to T

$$\frac{\partial \Delta G^\circ}{\partial T} = \frac{\partial \Delta H^\circ}{\partial T} - T\frac{\partial \Delta S^\circ}{\partial T} - \Delta S^\circ \frac{\partial T}{\partial T}$$

substitute  $\Delta C_p$  for  $\frac{\partial \Delta H^\circ}{\partial T}$  and substitute  $(\Delta C_p/T$  for  $\frac{\partial \Delta S^\circ}{\partial T}$ ) and notice that the first two terms cancel each other. This cancellation is the origin of enthalpy-entropy compensation; the major part of the change in  $T\Delta S^\circ$  with temperature directly cancels the change in  $\Delta H^\circ$  with temperature.

$$\frac{\partial \Delta G}{\partial T} = -\Delta S$$

Thus, the slope of the plot of  $\Delta G^\circ$  vs temperature is  $-\Delta S^\circ$  and  $\Delta G^\circ$  will reach a minimum or maximum value when  $\Delta S^\circ = 0$ .

Equilibrium constants also change as a function of temperature in a manner shown by the van't Hoff equation. The derivation of this relationship is shown below.

$$-RT \ln (K) = \Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

$$-R \ln (K) = \frac{\Delta H^\circ}{T} - \Delta S^\circ$$

$$-R \frac{\partial \ln (K)}{\partial T} = \Delta H^\circ \frac{\partial(1/T)}{\partial T} + \left( \frac{1}{T} \frac{\partial \Delta H^\circ}{\partial T} \right) - \left( \frac{\partial \Delta S^\circ}{\partial T} \right)$$

$\downarrow$   
 $\frac{\Delta C_p}{T}$

$\downarrow$   
 $-\frac{\Delta C_p}{T}$

$$-R \frac{\partial \ln (K)}{\partial(1/T)} = \Delta H^\circ \frac{\partial T}{\partial T}$$

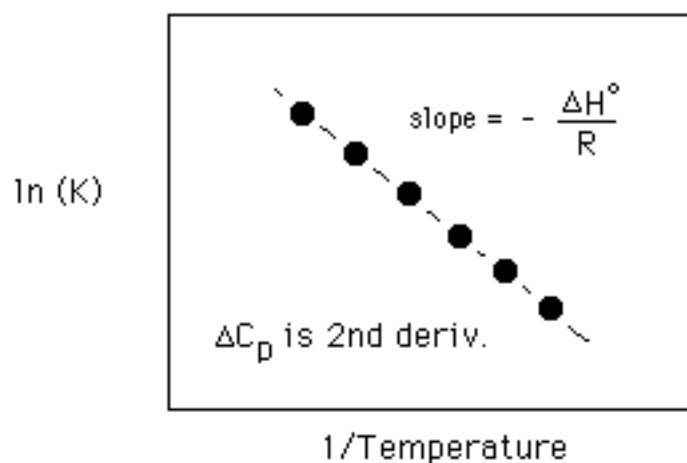
$$\frac{\partial \ln (K)}{\partial(1/T)} = -\frac{\Delta H^\circ}{R}$$

$\ln(K)$  and therefore  $K$  change with temperature unless  $\Delta H^\circ = 0$ .

An alternative form of the van't Hoff equation is:

$$\frac{\partial \ln (K)}{\partial T} = \frac{\Delta H^\circ}{RT^2}$$

By measuring equilibrium constants at different temperatures, we can calculate  $\Delta H^\circ$  from a slope of the plot of  $\ln(K)$  vs.  $1/T$ . If  $\Delta C_p \neq 0$ , then the van't Hoff plot will be curved and  $\Delta C_p$  can be calculated as the second derivative. If  $\Delta C_p = 0$ , then the van't Hoff plot will be linear and  $\Delta H^\circ$  will be independent of temperature.



### **Review of how thermodynamic parameters are determined.**

The equilibrium constant ( $K$ ) is calculated from the equilibrium concentrations of reactants and products.

The free energy change for a reaction under standard-state conditions ( $\Delta G^\circ$ ) is calculated from  $-RT \ln(K)$ .

The free energy change for a reaction under non standard-state concentrations ( $\Delta G$ ) is calculated from  $\Delta G^\circ + RT \ln([\text{products}]/[\text{reactants}])$ .

The enthalpy change for a reaction under standard-state conditions ( $\Delta H^\circ$ ) is determined by calorimetry or by measuring equilibrium constants at different temperatures and using the van't Hoff equation.

The heat-capacity change for a reaction under standard-state conditions ( $\Delta C_p$ ) is determined by measuring the temperature dependence of  $\Delta H^\circ$ .

The entropy change for a reaction under standard-state conditions ( $\Delta S^\circ$ ) is calculated as  $(\Delta H^\circ - \Delta G^\circ)/T$ .

### Summary of useful equations.

$$\Delta G^\circ = -RT \ln (K) = \Delta H^\circ - T\Delta S^\circ$$

$$K_{eq} = e^{-\Delta G^\circ/RT}$$

*for  $AB \rightleftharpoons A+B$*

$$\Delta G = \Delta G^\circ + RT \ln \frac{[Y_a][Z_b]}{[X_{ab}]}$$

*for reactants  $\rightleftharpoons$  products*

$$\Delta G = \Delta G^\circ + RT \ln \frac{[\text{products}]}{[\text{reactants}]}$$

*temperature dependence of thermodynamic parameters*

$$\Delta H = \Delta H_{ref} + \Delta C_p \cdot (T - T_{ref})$$

$$\Delta S = \Delta S_{ref} + \Delta C_p \cdot \ln (T/T_{ref})$$

$$\Delta G = \Delta H_{ref} - T\Delta S_{ref} + \Delta C_p \cdot (T - T_{ref} - T \cdot \ln (T/T_{ref}))$$

$$\frac{\partial \Delta H}{\partial T} = \Delta C_p$$

$$\frac{\partial \Delta S}{\partial T} = \frac{\Delta C_p}{T}$$

$$\frac{\partial \Delta G}{\partial T} = -\Delta S$$

$$\frac{\partial \ln (K)}{\partial (1/T)} = -\frac{\Delta H^\circ}{R}$$

$$\frac{\partial \ln (K)}{\partial T} = \frac{\Delta H^\circ}{RT^2}$$