$$dU = TdS - pdV + \mu dN \quad (1.68)$$

This equation is consistent with:

$$U = TS - pV + \mu N \quad (1.69)$$

DB, pp. 108-109 considers the possibility of having a mixture of protein molecules in the solution. In this case, there will be a chemical potential μ_j and term $\mu_j dN_j$ or $\mu_j N_j$ associated with each type of protein molecule. A more rigorous derivation of Eq. 1.69 is found in DB, p. 111.

In addition, if the protein molecules have charge q and are in an environment of electrical potential Ψ, there is an additional $(q\Psi)N$ term in eq. 1.69. This potential could be created by the electrodes in a gel apparatus or could be the potential across a cell membrane.

Because chemical changes are often driven by an increase in multiplicity and entropy, it is useful to write equations for dS and for S derived from Eqs. 1.66-1.69:

$$dS = (\partial S/\partial U)_{V,N}\, dU + (\partial S/\partial V)_{U,N}\, dV + (\partial S/\partial N)_{U,V}\, dN$$

$$= (1/T)dU + (p/T)dV + (\mu/T)dN \quad (1.70a)$$

$$S = U/T + pV/T + \mu N/T \quad (1.70b)$$

Eqs. 1.57-1.60 show that when two solutions are put in thermal contact, energy (dU) will be transferred from the solution with smaller $\partial S/\partial U$ (larger T) to the solution with larger $\partial S/\partial U$ (smaller T) to achieve maximum total multiplicity or entropy. The equilibrium state is when $\partial S/\partial U$ in the two solutions are equal; i.e. equal temperatures.

Similarly, if a permeable membrane is placed between two solutions with different protein concentrations and different μ, molecules will diffuse from the solution with higher concentration and higher μ to the solution with lower concentration and lower μ. Maximum total entropy will be achieved when the protein concentrations and protein μ's are equal in the two solutions.

If we have two gaseous samples separated by a moveable piston, then the piston will move to put greater volume on the side with higher pressure and smaller volume on the side with lower pressure. Maximum total entropy will be achieved when the pressures on the two sides are equal.

DB, Chapter 7 discusses the equalization of chemical potential and pressure at equilibrium.

One other aspect of practical thermodynamics is that changes in total energy (dU) can be divided into "work" (δw) and "heat" (δq) which are respectively defined as directed motion and random motion, respectively.

Some examples of work are slowly pushing against a piston, moving charge against a voltage difference (e.g. moving sodium ions to the more positive side of a membrane), creating concentration differences of solutes across a membrane, and forming chemical bonds. Work creates useful energy. For example, membrane proteins form a proton concentration difference across the mitochondrial membrane. The resulting flow of protons across the membrane is used to form a P-O chemical bond between phosphate and adenosine diphosphate (ADP) and this bond in the resulting adenosine triphosphate (ATP) serves as the energy currency in most living organisms. The bond can be broken to provide energy for other biochemical reactions.

The most important example of heat is the energy associated with increased temperature. The increased thermal energy causes greater molecular motion in all directions (e.g. molecular translation, vibration, rotation). In addition, heat is the energy associated with melting of solids. The resulting liquid has increased random molecular motion relative to the solid.

The equations for changes in U:

$$dU = \delta q + \delta w$$
$$\Delta U = q + w \qquad (1.71)$$

These equations are also known as the *first law of thermodynamics*.

U is a "state function" in that its value only depends on parameters such as V, T, and N. ΔU is therefore a fixed value if a process starts with particular parameters and ends with other particular parameters. For example, there would be a single ΔU value for starting with $[H^+] = 1.0 \times 10^{-7}$ M on both sides of a membrane and ending with $[H^+] = 1.5 \times 10^{-7}$ M on one side of the membrane and $[H^+] = 0.5 \times 10^{-7}$ M on the other side of the membrane.

By contrast, q and w can depend on the process of going between the two states. For example, one could dissipate the H^+ gradient by adding a peptide molecule which randomly forms ion channels in the membrane. Alternatively, the flow of H^+ could be limited to the ATP synthase integral membrane proteins and the chemical potential energy used to form the P-O bond in the reaction ADP + $PO_4^{3-} \rightarrow$ ATP. In the first case, no work is done and all of the chemical potential energy is dissipated as heat ($w = 0$ and $q = \Delta U$). In the second case, some of the chemical potential energy goes to formation of the P-O bond and $w \neq 0$.

S is also a state function as is reasonable because the multiplicity *W* should only depend on parameters such as V, T, and N.

A process which is done slowly is considered "reversible" while one which is done quickly is considered "irreversible". For example, dissipation of the gradient by ATP synthase would occur more slowly and would be more reversible than dissipation by peptide ion channels. Reversible processes are important because from Eqs. 1.68 and 1.71:

$$\delta w_{rev} = -p_{ext}dV + (\Delta\mu)dN + (q\Delta\Psi)dN$$
$$\delta q_{rev} = TdS \qquad (1.72)$$

The $p_{ext}dV$ term includes the external pressure on the system and the change in volume of the system and implies that the system pressure is only slightly different from the external pressure. The $(\Delta\mu)dN$ term refers to the work done to increase the chemical potential ($\Delta\mu$) of a small number of molecules (dN), for example by creating a concentration gradient across the membrane. The $(q\Delta\Psi)dN$ term refers to the electrical work of moving the dN molecules to a region with higher electrical potential.

The second eq. 1.72 can be rewritten:

$$dS = \delta q_{rev}/T \tag{1.73}$$

and is important because it shows that measurements of q_{rev} can yield ΔS for a biochemical process. As one example, the value of ΔS for unfolding of a protein molecule could provide information about the structure of the unfolded state relative to the folded state.

Our premise that our biochemical systems will tend towards distributions of molecules and energies with highest multiplicity or entropy is the *second law of thermodynamics* and is based on the simple argument that we will observe the most probable distribution.

In the examples so far, the biochemical system has been thermally and diffusionally isolated from its surroundings. In many cases, it is more realistic to consider that the biochemical system and its "surrounding bath" can interact in some way. In this instance, the second law of thermodynamics is more properly stated that the system and surrounding bath tend towards distributions with the largest total entropy. A common example is a biochemical solution (the "system") held at constant temperature through thermal contact with a water bath and open to the atmosphere at ~1 atm pressure. In this case, the water bath and surrounding atmosphere would be the "bath".

Calorimetric and other measurements are often made on the biochemical system but not on the surrounding bath and it is useful to have other thermodynamic state functions which are: (1) specific for the biochemical system; and (2) which will provide information about the biochemical system in contact with the surrounding bath.

These other state functions are listed along with their utility. I do not include the electrical potential part of the functions. The enthalpy H:

$$H = U + pV \tag{1.74}$$

$$dH = dU + pdV + Vdp = TdS - pdV + pdV + Vdp + \mu dN = TdS + Vdp + \mu dN \tag{1.75a}$$

$$(\partial H/\partial S)_{p,N} = T$$
$$(\partial H/\partial p)_{S,N} = V$$
$$(\partial H/\partial N)_{S,p} = \mu \tag{1.75b}$$

In containers open to the atmosphere, dp = 0 and diffusion to the surroundings is limited ($dN \approx 0$). Under these circumstances:

$$dH = TdS \approx \delta q \quad (1.76a)$$
$$\Delta H = T\Delta S \approx q \quad (1.76b)$$

where q is the heat associated with the biochemical process. This heat is a quantity measurable by calorimetry. Eq. 1.76b assumes that T is approximately constant during the process.

The Gibbs free energy G:

$$G = H - TS \quad (1.77)$$

$$dG = -SdT + VdP + \mu dN \quad (1.78)$$

$$(\partial G/\partial T)_{p,N} = -S$$
$$(\partial G/\partial p)_{T,N} = V$$
$$(\partial G/\partial N)_{T,p} = \mu \quad (1.79)$$

The second law suggests that all processes tend towards greater total multiplicity and entropy and at constant temperature and pressure:

$$dS_{tot} = dS_{sys} + dS_{bath} \geq 0$$

$$TdS_{tot} = TdS_{sys} + TdS_{bath} \geq 0$$

$$-TdS_{bath} - TdS_{sys} \leq 0 \quad (1.80)$$

In a constant pressure process without diffusion, $TdS_{bath} = \delta q_{bath} = -\delta q_{sys} = -dH$. The first equality is based on assumption that the bath is large and therefore all of its processes occur slowly and reversibly. Dropping the sys subscript, we can write Eq. 1.80:

$$dH - TdS = dG \leq 0 \quad (1.81a)$$

$$\Delta H - T\Delta S = \Delta G \leq 0 \quad (1.81b)$$

The first equality comes from $dG = dH - TdS - SdT = dH - TdS$ at constant temperature. So under constant temperature and pressure, a process will occur in the direction that $dG < 0$ and equilibrium (no more change) will occur when $dG = 0$. This is an important result because dG for a biochemical process can be derived from calorimetric measurements on the system (i.e. reaction vessel). Eqs. 1.81 show that under conditions of temperature and pressure, maximum total entropy will be generally be achieved by processes which decrease system enthalpy and increase system entropy.

ΔG is also important in terms of defining the maximum possible non-pV work which can come from a process at constant pressure and temperature. The last line of Eq. 1.80 can be rewritten:

$$\delta q \leq TdS = \delta q_{rev} \quad (1.82)$$

where the last equality uses Eq. 1.73. Using Eqs. 1.82 and 1.71:

$$\delta w = dU - \delta q \geq dU - \delta q_{rev} = dU - TdS$$

$$\delta w \geq d(G + TS - pV) - TdS = dG + SdT - pdV - Vdp$$

$$\delta w - \delta w_{rev,pV} \geq dG$$

$$w - w_{rev,pV} \geq \Delta G \tag{1.83}$$

Because negative energy from the system is available for work, Eq. 1.83 shows that ΔG defines the maximum possible non-pV work which can be obtained from a biochemical process. For example, ΔG for H^+ traversing the membrane will set the maximum number of ATP which can be formed.

The Helmholtz free energy F:

$$F = U - TS \tag{1.84}$$

$$dF = -SdT - pdV + \mu dN \tag{1.85}$$

$$(\partial F/\partial T)_{V,N} = -S$$
$$(\partial F/\partial V)_{T,N} = -p$$
$$(\partial F/\partial N)_{T,V} = \mu \tag{1.86}$$

Under conditions of constant T and V, $dF \leq 0$ defines the direction of a biochemical process and ΔF defines the maximum possible non-pV work which can be obtained from the process.

"Maxwell relations" can be useful second-derivative equations for the state functions. For example:

$$[\partial(\partial G/\partial T)_{p,N}/\partial p]_{T,N} = [\partial(\partial G/\partial p)_{T,N}/\partial T]_{p,N}$$

$$-(\partial S/\partial p)_{T,N} = (\partial V/\partial T)_{p,N} \tag{1.87}$$

Eqs. 1.79 were used for the second equation. So, a measurement of the temperature dependence of the molar volume of a protein solution provides information about how its entropy changes upon compression. This could provide insight into the structural differences between a folded and an unfolded protein. More information is found in DB, Chapter 9.

1.D. Calorimetric experiments on protein unfolding

Calorimetric measurements provide values of some thermodynamic parameters of biochemical processes. As described in VJH, section 2.5.2, one common experimental calorimetry is differential scanning calorimetry. In this method, heat energy is added to two different solutions

to raise the temperature of each solution by the same amount. For example, one solution contains only buffer and the other solution contains protein and buffer. Under constant pressure, the difference between the added energy of the protein + buffer solution and the buffer-only solution provides information about the enthalpy of the protein.

More specifically, the calorimeter measures the heat capacity C_p as a function of temperature:

$$C_p = dH/dT = T \times dS/dT \quad (1.88)$$

Heat capacity has significance both because it is a commonly measured experimental property and because it is proportional to the mean-squared-deviation of the system energy from its most probable value U. For a derivation, see DB, Chapter 12, pp. 230-232. In general, this means that heat capacity is a measure of the density of energy levels near U.

As shown in VJH, Fig. 2.8, calorimetry of a typical protein solution over much of the 280 – 370 K temperature range yields positive C_p with a linear dependence on temperature. The increase in C_p with T is consistent with a higher density of energy levels at higher energy.

In addition, near a "melting temperature" (T_m), many proteins undergo a phase transition from a compact folded native states (n) to more extended denatured states (d). There is a large increase in C_p near T_m because the d states have significantly higher energy relative to the n states.

Integration of C_p near T_m yields the "enthalpy of melting" ΔH_m. In Fig. 2.8, the large melting peak can be approximated as a triangle with height ~40 kJ/mol-K and base ~20 K. The area ΔH_m is then ~400 kJ/mol.

The value of T_m can be deduced as the temperature at which the integral is half of its final value and in Fig. 2.8, T_m ~315 K.

Eq. 1.76b yields $\Delta S_m = \Delta H_m/T_m$ and in this example ΔS_m ~1250 J/mol-K. The large positive value of ΔS_m is consistent with the notion that the unfolded d states have a larger degree of disorder and multiplicity relative to the folded n states.

Eq. 1.81b yields $\Delta G_m = \Delta H_m - T_m\Delta S_m = 0$. The latter equality is consistent with equal populations of n and d protein at T_m.

After denaturation, C_p is significantly higher than before denaturation and suggests that there is a higher density of energy levels in the d state than in the n state. This is consistent with the larger number of structures in the d state than in the n state. In Fig. 2.8, the change in C_p at T_m appears to be ~8 kJ/mol-K.

It is useful to consider the values of ΔG at temperatures other than T_m. For each temperature, consider that there is an enthalpy (H_n) and entropy (S_n) associated with the native states and an enthalpy (H_d) and entropy (S_d) associated with the denatured states. These enthalpies and entropies are temperature-dependent. For this approach:

$$\Delta H = H_d - H_n$$

$$\Delta S = S_d - S_n$$

$$\Delta G = \Delta H - T\Delta S \tag{1.89}$$

We approximate that for all temperatures, the heat capacity of the native states, C_{pn}, is a linear extrapolation of the experimental heat capacity at temperatures much lower than T_m. Similarly, we approximate that the heat capacity of the denatured states, C_{pd}, is a linear extrapolation of the experimental heat capacity at temperatures much higher than T_m.

$$C_{pn} = C_n^{\circ} + [C' \times (T - T_m)] = C_n^{\circ} + C'\Delta T$$

$$C_{pd} = C_d^{\circ} + C'\Delta T \tag{1.90}$$

We have approximated that the temperature dependences of C_{pn} and C_{pd} are equal. Using Eq. 1.88:

$$H_n = \int_{Tm}^{T} (C_n^{\circ} + C'\Delta T)\, dT \; - \; \Delta H_m/2$$

$$H_d = \int_{Tm}^{T} (C_d^{\circ} + C'\Delta T)\, dT \; + \; \Delta H_m/2 \tag{1.91}$$

$$S_n = \int_{Tm}^{T} (C_n^{\circ} + C'\Delta T)/T\, dT \; - \; \Delta S_m/2$$

$$S_d = \int_{Tm}^{T} (C_d^{\circ} + C'\Delta T)/T\, dT \; + \; \Delta S_m/2 \tag{1.92}$$

ΔH_m and ΔS_m have been evenly split between the n and d states. For $T = T_m$, Eqs. 1.90-1.92 yield $\Delta H = \Delta H_m$ and $\Delta S = \Delta S_m$, in agreement with the model.

At arbitrary T:

$$\Delta H = [(C_d^{\circ} - C_n^{\circ}) \times \Delta T] + \Delta H_m = (\Delta C_p^{\circ} \times \Delta T) + \Delta H_m$$

$$\Delta S = \{\Delta C_p^{\circ} \times \ln[T/T_m]\} + \Delta S_m = \{\Delta C_p^{\circ} \times \ln[1 + (\Delta T/T_m)]\} + \Delta S_m \approx [(\Delta C_p^{\circ} \times \Delta T)/T_m] + \Delta H_m/T_m \tag{1.93}$$

$$\Delta G = \{(\Delta C_p^{\circ} \times \Delta T) \times [1 - (T/T_m)]\} + \{\Delta H_m \times [1 - (T/T_m)]\}$$

$$= \{[(\Delta C_p^{\circ} \times \Delta T) + \Delta H_m] \times (-\Delta T/T_m)\} \tag{1.94}$$

For T_m = 315 K, ΔT = –20 K, ΔC_p^o = 8 kJ/mol-K, and ΔH_m = 400 kJ/mol, $\Delta G \sim$ +35 kJ/mol. Similarly, for ΔT = +20 K, $\Delta G \sim$ –35 kJ/mol. Thus, analysis of the calorimetric data suggests that the n states are highly favored below T_m and the d states are highly favored above T_m. This view is generally consistent with the "phase transition" character of protein unfolding; i.e. that its calorimetric characteristics are similar to melting a solid.

It is interesting to compare the calorimetric result with studies of thermal unfolding by optical methods which probe protein structure. Example methods include fluorescence and circular dichroism spectroscopy. For several proteins, these methods show that the structure changes rapidly near T_m and changes little at temperatures significantly above or significantly below T_m.

1.E. The connections between thermodynamics and statistical mechanics

We will now complete the mathematical connections between statistical mechanics and its probabilistic view in Eqs. 1.1-1.64 and classical thermodynamics and experimental observables in Eqs. 1.65-1.88.

Eq. 1.62 describes the partition function q for a single particle. In practice, experiments are typically done with N identical particles where N is a large number (e.g. 10^{17}). The partition function Q of the N particles will be the product of partition functions q from each particle. This is rigorously true for "distinguishable particles" such as atoms or molecules in a solid lattice:

$$Q = q^N \tag{1.95}$$

For "indistinguishable particles" such as gas phase molecules which move, or to a lesser extent, liquid-phase molecules:

$$Q = q^N/N! \tag{1.96}$$

The partition function is reduced because it is not possible to distinguish, for example, molecule 1 in state k, molecule 2 in state m from molecule 1 in state m, molecule 2 in state k. See DB, pp. 182-183 for a more rigorous explanation.

We now consider that Q has t total states, each with an energy E_j. A partition function expression analogous to Eq. 1.62 for Q:

$$Q = \sum_{j=1}^{t} \exp(-E_j/kT) \tag{1.97}$$

A probability expression analogous to Eq. 1.63:

$$p_j = \exp(-E_j/kT)/Q \tag{1.98}$$

An expression for the total energy U analogous to the Eq. 1.64 expression for the average energy $\langle\varepsilon\rangle$:

$$U = Q^{-1} \times \sum_{j=1}^{t} [E_j \times \exp(-E_j/kT)] = kT^2 \times (\partial \ln Q/\partial T) = NkT^2 \times (\partial \ln q/\partial T) \quad (1.99)$$

The last two equalities are straightforward mathematical derivations. Using Eqs. 1.23, 1.32, and 1.97:

$$S = k \times \ln W = k \times (-\sum_{j=1}^{t} p_j \ln p_j) = (k \times \ln Q) + [kT \times (\partial \ln Q/\partial T)] \quad (1.100)$$

Eqs. 1.84, 1.86, 1.99, and 1.100 can be used to derive:

$$F = -kT \times \ln Q \quad (1.101)$$

$$\mu = -kT \times (\partial \ln Q/\partial N)_{T,V} \quad (1.102)$$

$$p = kT \times (\partial \ln Q/\partial V)_{N,V} \quad (1.103)$$

The take-home message is that macroscopic observable quantities such as U, S, F, μ, and p can in principle be derived from the combination of statistical mechanics relationships based on the assumption of maximum probability, thermodynamic relationships which were developed from calorimetric and mechanical measurements on macroscopic quantities of matter, and the $S = k \times \ln W$ relationship which inter-relates statistical mechanics and thermodynamics.

1.F. The ideal gas model

In order for Eqs. 1.99-1.103 to be useful, Q must be calculated. Q can in principle be calculated using either Eq. 1.95 or 1.96 and q calculated for a single molecule based on its quantum mechanical states and energies. This is a reasonable approach for gas phase molecules and for pure crystals but is more difficult for biomacromolecules in aqueous solution or membranes.

Interpretation of some biochemical phenomena is based on the "ideal gas" model system which is N non-interacting particles in a fixed volume V at fixed temperature T. Calculation of q for a single particle begins with the quantum mechanical states for a particle of mass m in a box whose x, y, and z dimensions are a, b, and c. Each state is characterized by a set of quantum numbers n_x, n_y, and n_z, which each can have positive integral values. The energy of each state:

$$\varepsilon_{nx,ny,nz} = (h^2/8m) \times [(n_x^2/a^2) + (n_y^2/b^2) + (n_z^2/c^2)] \quad (1.104)$$

The partition function q:

$$q = \sum_{nx=1}^{\infty} \sum_{ny=1}^{\infty} \sum_{nz=1}^{\infty} \exp(-n_x^2h^2/8ma^2kT) \times \exp(-n_y^2h^2/8mb^2kT) \times \exp(-n_z^2h^2/8mc^2kT)$$

$$\approx \int_0^\infty \exp(-n_x^2h^2/8ma^2kT)\, dn_x \times \int_0^\infty \exp(-n_y^2h^2/8mb^2kT)\, dn_y \times \int_0^\infty \exp(-n_z^2h^2/8mc^2kT)\, dn_z$$

$= \Lambda^{-3} V$ where:

V (box volume) = a × b × c

$$\Lambda = (h^2/2\pi mkT)^{1/2} \qquad (1.105)$$

Using Eqs. 1.64 and 1.99:

$$\langle\varepsilon\rangle = 3kT/2 \quad \text{and} \quad U = 3NkT/2 \qquad (1.106)$$

Using Eq. 1.106, it is reasonable that $\langle\varepsilon_x\rangle = \langle\varepsilon_y\rangle = \langle\varepsilon_z\rangle = kT/2$. Newtonian physics tells us the average magnitudes of linear momenta $\langle\rho_x\rangle = \langle\rho_y\rangle = \langle\rho_z\rangle = (\langle 2m\varepsilon_x\rangle)^{1/2} = (mkT)^{1/2}$. So $\Lambda \sim h/\rho_x$ with the choice of x being arbitrary. This is the deBroglie wavelength from quantum mechanics for a particle with momentum ρ_x. It is very interesting that the partition function can be viewed from a quantum mechanical perspective. The quantum mechanical parameter (deBroglie wavelength) incorporates temperature which is a property only associated with a large number of molecules.

Λ^{-3} has units of inverse volume and is sometimes referred to as the *quantum concentration*, and is a measure of the concentration of thermally accessible particle translational states. For a protein of mass 10 kD at 310 K, $\Lambda^{-3} \sim 2 \times 10^9$ M which is at least 10^{12} times greater than the typical protein concentration in solution. This suggests that there are many more thermally accessible translational states than protein molecules. This calculation is of course predicated on the supposition that the translational motion of protein molecules in solution is well modeled by an ideal gas.

Using Eqs. 1.96, 1.100, and 1.105, Stirling's approximation for N! = N × (lnN – 1), and some algebra, the ideal gas:

$$S = Nk \times [\ln(\Lambda^{-3}V/N) + 5/2] = Nk \times [\ln(\Lambda^{-3}/c) + 5/2]$$

where c = N/V (molecular concentration) (1.107)

Using Eq. 1.101:

$$F = NkT \times \ln(N/e\Lambda^{-3}V) \qquad (1.108)$$

Using Eq. 1.103:

$$p = NkT/V = ckT \qquad (1.109)$$

This is the ideal gas law and experiments on real gases are consistent with this law. These 18th-19th experiments provided the initial impetus for developing statistical mechanics and also provided the numerical value of k.

Using Eq. 1.102:

$$\mu = kT \times \ln(c/\Lambda^{-3}) \tag{1.110}$$

This equation is rigorously true for the ideal gas model. A useful modification for biophysical chemistry is incorporation of a reference concentration c^o:

$$\mu = [kT \times \ln(c^o/\Lambda^{-3})] + [kT \times \ln(c/c^o)] \tag{1.111}$$

A typical c^o is 1 M. This equation is still rigorously true for the ideal gas. For biomolecules in aqueous solution, it is typically modified:

$$\mu = \mu^o + [kT \times \ln(c/c^o)] \tag{1.112a}$$

$$\mu = \mu^o + [RT \times \ln(c/c^o)] \tag{1.112b}$$

For Eq. 1.112a, the chemical potential is in units of J/molecule while for Eq. 1.112b, the chemical potential is in units of J/mol. The μ^o term represents the chemical potential when $c = c^o$ and it is usually not be the ideal gas value of Eq. 1.111. Biochemical experiments often detect changes in chemical potential rather than absolute chemical potential and so the μ^o term may not be important.

As an example, we can calculate the chemical potential difference at 310 K for $[H^+]$ across a membrane with $[H^+] = 10^{-5}$ M on one side of the membrane and $[H^+] = 10^{-7}$ M on the other side of the membrane. $\Delta\mu = RT \times \ln(10^{-7}\ M/10^{-5}\ M) \approx -12$ kJ/mol. So, ~12 kJ of free energy or work is available if 1 mol of H^+ flows across the membrane.

The second term in Eqs. 1.112 is also based on an ideal gas model. For biomolecules in aqueous solution, there may be a further modification:

$$\mu = \mu^o + [RT \times \ln(\gamma c/c^o)] \tag{1.113}$$

where γ is called the activity coefficient and may depend on the biomolecule, the biomolecule concentration, pH, and salt concentration. The activity coefficient is the fudge factor put into the expression for the chemical potential so that the concentration dependence of the chemical potential retains ideal gas behavior. A magnitude of γ much different than 1 means that the biomolecule is behaving "non-ideally".

DB, Chapters 10 and 11 have more discussion about models to calculate partition functions as well as the ideal gas model.

1.G. Chemical equilibrium

The chemical potential plays an important role in describing the equilibrium condition for a chemical reaction (or for simple binding). Consider a generic chemical reaction:

$$aA + bB \rightarrow xX + yY \tag{1.114}$$

with a, b, x, and y as the stoichiometric coefficients. At constant temperature and pressure, the free energy of reaction is a minimum:

$$dG = 0 = \mu_X dN_X + \mu_Y dN_Y - \mu_A dN_A - \mu_B dN_B \tag{1.115}$$

Stoichiometry relates dN_A, dN_B, dN_X, and dN_Y relative to a normalized number of reacting molecules dN:

$$dN \times [(x \times \mu_X) + (y \times \mu_Y) - (a \times \mu_A) - (b \times \mu_B)] = 0 \tag{1.116}$$

In order for the entire left-hand expression to equal 0 for arbitrary dN, the expression in brackets must equal 0. Using Eq. 1.112b:

$$[(x \times \mu_X^o) + (y \times \mu_Y^o) - (a \times \mu_A^o) - (b \times \mu_B^o)]$$

$$= -RT \times [(x \times \ln c_X/c^o) + (y \times \ln c_Y/c^o) - (a \times \ln c_A/c^o) - (b \times \ln c_B/c^o)] \tag{1.117}$$

The left-hand expression in brackets is ΔG^o, the standard free energy of the reaction; i.e. the free energy of a moles of A reacting with b moles of B to yield x moles of X and y moles of Y. Using some algebra, Eq. 1.117 can be rewritten:

$$\Delta G^o = -RT \times \ln[(c_X/c^o)^x (c_Y/c^o)^y / (c_A/c^o)^a (c_B/c^o)^b] = -RT \times \ln K_{eq} \tag{1.118}$$

It is interesting to understand that the important equilibrium constant expression is based on the chemical potential for the ideal gas. For biomolecular equilibria, the "fudge factor" activity coefficients of Eq. 1.113 are sometimes necessary:

$$\Delta G^o = -RT \times \ln K_{eq} \times \ln(\gamma_X^x \gamma_Y^y / \gamma_A^a \gamma_B^b) \tag{1.119}$$

It is often possible to measure the temperature dependence of the equilibrium constant in a biochemical reaction and this measurement can provide values of calorimetric quantities. Using Eq. 1.118 and $\Delta G^o = \Delta H^o - T\Delta S^o$:

$$\ln K_{eq} = 1/R \times (\Delta S^o - \Delta H^o/T)$$

$$d(\ln K_{eq})/dT = \Delta H^o/RT^2$$

$$d(\ln K_{eq})/d(1/T) = -\Delta H^o/R \tag{1.120}$$

The middle and bottom equations assume that ΔS^o is temperature-independent. Over small temperature ranges, ΔH^o may be temperature-independent and the "van't Hoff enthalpy" and "van't Hoff entropy" may be derived from Eqs. 1.120.