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Chapter 4

Solvation Thermodynamics and the Treatment of Equilibrium and Nonequilibrium Solvation Effects by Models Based on Collective Solvent Coordinates

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1. INTRODUCTION

Computing the free energy of solvation is important in rational drug design for both pharmacokinetics (drug transport to the site of action) and pharmacodynamics (drug interactions at the site of activity). In the former case, it is well recognized that bioavailability depends on the availability of a particular drug to have a favorable interaction with both water (for transport in the blood) and lipophilic media (for transport through cell membranes). The solubility and partitioning of a molecule in and between various media are thus critical physicochemical parameters that correlate strongly with biological activity.[1] Even though such effects are nonspecific with regard to receptor structure, they must be taken into account in rational drug design. Then, at the receptor, desolvation is a major contributor to ligand-protein binding, and the estimation of this effect plays an important role in structure-based drug design.[2] A third area where solvation effects must be considered is drug metabolism, since the kinetics and thermodynamics of the enzymatic biotransformations of drugs may be very dependent on solvation effects. Both the ability of a drug to survive deactivation and elimination and the nature of the potentially toxic metabolites of a drug may depend on solvation effects on kinetics.

For both nonspecific and structure-based approaches, physicochemical solvation parameters may be used directly, or they may be embedded in quantitative structure-activity relationships.[3] This chapter starts with a review of the thermodynamic equations that may be used for a quantitative description of the free energy of solutes in fluid media. Then it provides an overview of statistical mechanical models for solvation effects that are based on collective coordinates, both macroscopic coordinates such as the electric polarization of the solvent and microscopic collective coordinates such as the surface area of the solute-solvent interface. Such models are sometimes called implicit models (because the individual atomic coordinates of the solvent molecules are not treated explicitly) or continuum models (because the fine grained detail of the solvent is replaced by an averaged description in which the solvent is treated mathematically as a continuous medium).

2. MOLAR FREE ENERGY

An ideal gas obeys the equation of state

$$PV = nRT \tag{1}$$

where P is the pressure, V is the volume, n is the number of moles, R is the universal gas constant, and T is the absolute temperature. In convenient units, R takes a value of 0.08206 L atm mol^{-1} K^{-1}.

The chemical potential μ of an ideal gas is its molar Gibbs free energy. In mechanics and thermodynamics, absolute values of energies depend on how the zero of energy is defined, but physical observables only depend on energy differences. In order to standardize the tabulation of quantities useful for the calculation of energy differences, a system of standard states has been defined. The most common standard state for gases is an ideal gas at one atmosphere of pressure and the temperature of interest. At 298° K this corresponds to an ideal gas at a concentration of 0.04089 mol L^{-1}. This is not always the most convenient standard state for discussing gases in equilibrium with liquid solutions. Another useful choice of standard state is the ideal gas at a concentration of 1 mol L^{-1}; at 298° K this corresponds to a pressure of 24.45 atm = 18583 torr. It is always important to understand what standard state is being used when one uses tabulated thermodynamic data.

The chemical potential of an ideal gas at temperature T depends on pressure according to the following relation:

$$\mu = \mu^{\text{O}} + RT \ln\left(\frac{P}{P^{\text{O}}}\right) \tag{2}$$

where μ^{O} and P^{O} are the chemical potential and pressure in the standard state. The significance of this equation is that if μ^{O} is tabulated for a given temperature for a known value of P^{o}, we can calculate the molar free energy of an ideal gas at any other pressure at this temperature by using the tabulated values. If we change the standard state, i.e., if we change P^{o}, then a different μ^{o} must be tabulated, but the resulting μ calculated from Equation 2 must be independent of the choice of standard state. Consider two possible standard states 1 and 2. We must have

$$\mu^{\text{o}}(1) + RT \ln \frac{P}{P^{\text{o}}(1)} = \mu^{\text{o}}(2) + RT \ln \frac{P}{P^{\text{o}}(2)} \tag{3}$$

from which it follows that

$$\mu^{\text{o}}(1) = \mu^{\text{o}}(2) + RT \ln \frac{P^{\text{o}}(1)}{P^{\text{o}}(2)} \tag{4}$$

Let standard state 1 be the 1 atm ideal gas, and standard state 2 be the 1 mol L^{-1} ideal gas. Then, using the values of P^{o} given above we have, at 298° K,

$$\mu^{\text{o}}(1\text{ atm}) = \mu^{\text{o}}(1\,M) - RT \ln 24.45 = \mu^{\text{o}}(1\,M) - 1.89\text{ kcal/mol} \tag{5}$$

That is, the magnitude of the chemical potential changes by 1.89 kcal/mol on going from one standard state to the other.

Equations 1 and 5 apply only to ideal gases. For nonideal gases one writes[4a]

$$\mu = \mu^{\text{o}} + RT \ln\left(\frac{f}{f^{\text{o}}}\right) \tag{6}$$

where f is the fugacity of the gas. The fugacity is defined by Equation 6. In other words, we keep the simple form of Equation 2 by hiding the complicated behavior of the real gas (as opposed to an ideal gas) in the fugacity function.

It is conventional to define fugacity so that in the limit of a dilute gas, it becomes the pressure. Thus fugacity has units of pressure. When one deals with condensed phases and with gases in equilibrium with condensed phases, it becomes convenient to introduce a unitless generalization of fugacity, which is called activity. The activity is defined by[4b]

$$a = f/f^{\text{o}} \tag{7}$$

and therefore

$$\mu = \mu^{\circ} + RT \ln a \tag{8}$$

At equilibrium, all components of a mixture have the same molar free energy, i.e., the same chemical potential, in any phase in which they are present, and they have the same chemical potential as all other components. However it is not always convenient to use the same standard state for all components or even for the same component in all phases. Just as Equation 6 defines fugacity, Equation 7 or 8 defines activity. Furthermore, Equations 6–8 define f and a for all substances, not just gases. However we should keep in mind that we do not use the same standard state for a substance in all the phases, mixtures, or pure states in which it may occur or for all components of a mixture.

To proceed we will first summarize the treatment of ideal mixtures. Then we will consider nonideal mixtures.

3. IDEAL MIXTURES

An ideal mixture is one for which[4c]

$$f_{\mathrm{A}} = f_{\mathrm{A}}^{\bullet} X_{\mathrm{A}} \tag{9}$$

for every component A, where f_{A} is the fugacity of A in the mixture, X_{A} is the mole fraction of A in the mixture, i.e.,

$$X_{\mathrm{A}} = \frac{n_{\mathrm{A}}}{n_{\mathrm{A}} + n_{\mathrm{B}}} \tag{10}$$

and $f_{A}^{\bullet}$ is the fugacity of pure A at the same temperature and pressure of the mixture. Note that one can postulate ideal mixtures of ideal gases, but one can also postulate ideal mixtures of nonideal components, such as real gases and liquids.

Consider an ideal mixture of ideal gases, A and B. Equation 9 yields

$$P_{\mathrm{A}} = P_{\mathrm{A}}^{\bullet} X_{\mathrm{A}} \tag{11}$$

where $P_{\mathrm{A}}^{\bullet}$ is the pressure of pure A at the same pressure and temperature as the mixture. The pressure of the mixture is

$$P = (n_{\mathrm{A}} + n_{\mathrm{B}})RT/V \tag{12}$$

Substituting $P_A^\bullet = P$ along with Equations 10 and 12 into Equation 11 gives

$$P_A = n_A RT/V \tag{13}$$

which is the expected result.

Now apply Equation 9 to a liquid solution in equilibrium with its vapor. We assume that both the solute and the solvent are liquids in their pure state at the temperature and pressure of interest. Substituting Equation 9 into Equation 6 yields

$$\mu_A = \mu_A^o + RT \ln\left(\frac{f_A^\bullet X_A}{f_A^o}\right) \tag{14}$$

When X_A is unity, the left-hand side becomes the chemical potential of the pure substance:

$$\mu_A^\bullet = \mu_A^o + RT \ln\left(\frac{f_A^\bullet}{f_A^o}\right) \tag{15}$$

Note that the standard state fugacity now carries a subscript, because for A it is defined by the nonideal behavior of A. Substituting Equation 15 into Equation 14 yields[4d, 5]

$$\mu_A = \mu_A^\bullet + RT \ln X_A \tag{16}$$

This is independent of standard state, but we can also view it as a version of Equation 14 in which we conveniently choose the standard state as the pure liquid (we shall abbreviate this as liq.s.s. to denote the (pure) liquid standard state). Therefore

$$f_A^o(\text{liq.s.s}) = f_A^\bullet \tag{17}$$

This illustrates the statement made earlier that the most convenient choice of standard state may depend on the problem. For gas-phase problems involving A, it is convenient to choose the standard state for A as an ideal gas at 1 atm pressure. But, where the vapor of A is in equilibrium with a solution, it is sometimes convenient to choose the standard state as the pure liquid. Since f_A is the same for the pure liquid and the vapor in equilibrium with the pure liquid, we may equivalently equate $f_A^{\bullet}$(liq.s.s.) to either the fugacity of the pure liquid or the vapor in equilibrium with it. In general this vapor does not have a pressure of 1 atm nor does it have a concentration of 1 mol L^{-1}. Thus this standard state is not equivalent to either of the two gaseous standard states mentioned above.

Suppose that the vapor of A in equilibrium with the liquid is an ideal gas. Then Equation 2 yields

$$\mu_A = \mu_A^o + RT \ln \frac{P_A}{P^o} \tag{18}$$

where P_A is the vapor pressure of A in equilibrium with the liquid, and

$$\mu_A^{\bullet} = \mu_A^o + RT \ln \frac{P_A^{\bullet}}{P^o} \tag{19}$$

where $P_A^{\bullet}$ is the vapor pressure of pure A. Substituting Equations 18 and 19 into Equation 16 yields

$$RT \ln \frac{P_A}{P^o} = RT \ln \frac{P_A^{\bullet}}{P^o} + RT \ln X_A \tag{20}$$

which simplifies to

$$P_A = P_A^{\bullet} X_A \tag{21}$$

which is Raoult's law.[4e] Thus Equation 9 may be considered to be a generalization of Raoult's law.[7] Note that Equations 18–21 are equally applicable to a solution of one or more solutes B, C, D, etc. in liquid A. Raoult's law says that the partial pressure of each will be proportional to its concentration.

4. NONIDEAL SOLUTIONS

In actuality, Raoult's law is only an approximation for real systems. Although it is a good approximation for many solvents, for which $X_A \approx 1$ if the solution is dilute, it is often a very poor approximation for solutes, for which $X_A < 0.5$. In the limit as $X_A \rightarrow 0$, though, there is still a linear relationship

$$P_A \xrightarrow[X_A \to 0]{} k_A^X X_A \tag{22}$$

but k_A^X does not equal $P_A^\bullet$. Equation 22 is called Henry's law,[4f] and k_A^X is called the Henry's law constant. For small X_A, the molarity M_A and molality m_A are linear functions of X_A; thus there is also a linear relation between P_A and molarity or molality:

$$P_A \xrightarrow[M_A \to 0]{} k_A^M M_A \tag{23}$$

$$P_A \xrightarrow[m_A \to 0]{} k_A^m m_A \tag{24}$$

Equations 23 and 24 are alternative forms of Henry's law, and k_A^M and k_A^m are alternative forms of the Henry's law constant.

We can equate the chemical potential of the solute to the chemical potential of the vapor in equilibrium with it. Assume the vapor is an ideal gas:

$$\mu_A(\text{solute}) = \mu_A(\text{vapor}) = \mu_A^o(\text{g.s.s.}) + RT \ln P_A / P^o(\text{g.s.s.}) \tag{25}$$

$$= \mu_A^o(\text{g.s.s.}) + RT \ln \frac{k_A^X}{P^o(\text{g.s.s.})} + RT \ln X_A \tag{26}$$

where quantities referring to the gaseous standard state are labeled g.s.s. In this case, it may be convenient to use Equation 8 and let

$$a_A = X_A \tag{27}$$

Comparing Equations 26 and 27 to Equation 8 implies a new standard state (to be denoted as the Henry's Law standard state or HL s.s.) whose chemical potential is related to that for the gaseous standard state by

$$\mu_A^o(\text{HL s.s.}) = \mu_A^o(\text{g.s.s.}) + RT \ln \frac{k_A^X}{P^o(\text{g.s.s.})} \tag{28}$$

With the liquid standard state we have

$$\mu_A = \mu_A^o + RT \ln X_A \qquad (29)$$

or

$$\mu_A = \mu_A^o + RT \ln a_A \qquad (30)$$

Both Equations 29 and 30 are valid in the region where the limit of Equation 22 holds, but at higher concentrations of A, Equation 29 fails to hold. However, Equation 30 is a special case of Equation 8 and as such it defines the activity μ for any value of X_A. Thus,

$$a_A \neq X_A \qquad (31)$$

but

$$a_A \xrightarrow[X_A \to 0]{} X_A \qquad (32)$$

It is then convenient to define an activity coefficient γ_A such that[9]

$$a_A = X_A X_A \qquad (33)$$

at all X_A. Equation 31 then implies

$$\gamma_A \xrightarrow[X_A \to 0]{} 1 \qquad (34)$$

The activity coefficient measures the deviation from ideality. Substituting Equation 33 into Equation 30 yields

$$\mu_A = \mu_A^o + RT \ln \gamma_A X_A \qquad (35)$$

Equation 29 implies that μ_A^o is the chemical potential of a hypothetical solution in which $X_A = 1$, but the vapor pressure over the solution still obeys Henry's law as extrapolated from infinite dilution. Thus the standard state is a hypothetical Henry's law solution of unit mole fraction.

The numerical value of the activity clearly depends upon the standard state, and one often encounters other choices for the standard state for solutes. For example, just as we obtained Equations 29 and 30 from Equation 22, we could have obtained similar looking equations from Equations 23 or Equation 24. However, the derivation requires a mention of one more thermodynamic convention if we wish to avoid nonsensical logarithms of quantities with units. Notice that Equation 22 implies that k_A^X has units of pressure; thus the logarithms in Equations 26 and 28 are well defined. At first, it might appear that the constants in Equations 23 and 24 have different units. However, the convention that is followed in thermodynamics is that M_A and m_A are the unitless numerical values of the molarity and molality; thus one can take their logarithms.

If we take the standard state as the hypothetical 1 molar Henry's law solution (sometimes shortened to "hypothetical ideal 1 molar solution," where the ideality referred to is Henry's law ideality in molarity units, that is, the proportionality of partial pressure and molarity, not Raoult's law ideality) we get

$$\mu_A^o(1\,M\ \text{sol.s.s.}) = \mu_A^o(\text{g.s.s.}) + RT \ln \frac{k_A^M}{P_A^o(\text{g.s.s.})} \tag{36}$$

$$\mu_A = \mu_A^o + RT \ln a_A \tag{37}$$

$$a_A = \gamma_A M_A \tag{38}$$

$$\gamma_A \xrightarrow[M_A \to 0]{} 1 \tag{39}$$

where 1 *M* sol.s.s. denotes the 1 molar hypothetical solute standard state. Furthermore if we take a hypothetical 1 molal Henry's law solute as the standard state (1 *m* sol.s.s.) we get

$$\mu_A^o(1\,m\ \text{sol.s.s.}) = \mu_A^o(\text{g.s.s.}) + RT \ln \frac{k_A^m}{P_A^o(\text{g.s.s.})} \tag{40}$$

$$\mu_A = \mu_A^o + RT \ln a_A \tag{41}$$

$$a_A = \gamma_A m_A \tag{42}$$

$$\gamma_A \xrightarrow[m_A \to 0]{} 1. \tag{43}$$

One cannot emphasize too often that the numerical values of μ_A^o, a_A, and γ_A depend on the choice of standard state. The usual thermodynamic convention is to say what standard state is used in words, not in the equation itself, but in many cases we have indicated it in the equation for clarity.

Before closing this section we note that even in nonideal solutions we can use the standard state of Equation 16 for the solute. Since Equation 16 only holds for ideal solutions, one generalizes to obtain[4g]

$$\mu_\mathrm{A} = \mu_\mathrm{A}^\bullet + RT \ln a_\mathrm{A} \tag{44}$$

with

$$a_\mathrm{A} = \gamma_\mathrm{A} m_\mathrm{A} \big/ m_\mathrm{A}^\bullet \tag{45}$$

where $m_\mathrm{A}^\bullet$ is the molality of the standard state. Now, however, γ_A does not tend to unity as X_A tends to 0. However, comparing Equations 44 and 45 to Equations 34 and 35 yields

$$\lim_{X_\mathrm{A} \to 0} \gamma_\mathrm{A}(\text{liq.s.s.}) = e^{[\mu_\mathrm{A}^\mathrm{o}(\text{HL s.s.}) - \mu_\mathrm{A}^\bullet]/RT} \tag{46}$$

Thus, γ_A of Equation 45 tends to a constant value in dilute solutions. This constant value is sometimes called the limiting activity coefficient γ_A^∞. Consideration of Equations 21 and 22 allows us to evaluate this limit:

$$\gamma_\mathrm{A}^\infty \equiv \lim_{X_\mathrm{A} \to 0} \gamma_\mathrm{A}(\text{liq.s.s.}) = k_\mathrm{A}^X \big/ P_\mathrm{A}^\bullet \tag{47}$$

Alternatively, we may write:

$$k_A^X = P_A^\bullet \gamma_A^\infty \tag{48}$$

This shows that knowledge of the vapor pressure of A and its limiting activity coefficient allows us to calculate the Henry's law constant.[7]

5. ELECTROLYTES

Electrolytes are solutes that carry an electrical charge. As charged species typically have negligible vapor pressures, it is convenient to introduce yet another standard state for their description.[8, 9] In general, the same conditions of concentration, temperature, and pressure are assumed as for a non-electrolyte (e.g., the HLss standard state), but the chemical potential of an anion is defined as

$$\mu_{A^-} = \mu_A + \Delta G^o_{(A/A^-)}(\text{e.s.s.}) \tag{49}$$

where $\Delta G^o_{(A/A^-)}$(e.s.s.) denotes the standard-state free energy change for the reaction

$$A_{(sol)} + 1/2\, H_{2(g)} \rightarrow A^-_{(sol)} + H^+_{(sol)} \tag{50}$$

In Equation 50 the chemical potential of non-electrolyte A depends on the usual choice of standard-state conventions described above, and the chemical potentials of both $H_{2(g)}$ and $H^+_{(sol)}$ are taken to be zero (this defines e.s.s., the electrolyte standard state). By setting the standard-state free energy of the solvated proton equal to zero, this standard-state convention incorporates the absolute potential, ΔG^o_{NHE}, of the hydrogen electrode process producing one proton in solution,

$$1/2\, H_{2(g)} \rightarrow e^-_{(g)} + H^+_{(sol)} \tag{51}$$

into the magnitude of the chemical potential of the electrolyte. In water as solvent, the absolute potential of this electrode is 4.44 eV.[10]

For a cation, the analogous equations defining the standard-state chemical potential for A^+ are

$$\mu_{A^+} = \mu_A + \Delta G^o_{(A^+/A)}(\text{e.s.s.}) \tag{52}$$

$$A^+_{(sol)} + 1/2\, H_{2(g)} \rightarrow A_{(sol)} + H^+_{(sol)} \tag{53}$$

where $\Delta G^o_{(A^+/A)}$(e.s.s.) in Equation 52 refers to the standard-state free energy change for Equation 53.

Note, in using Equations 50 and 53 above, that tabulations of thermodynamic data for electrolytes tend to employ a 1 molar ess concentration for all species in solution. For situations defined to have a standard-state pH value different from 0 (which corresponds to a 1 molar concentration of solvated protons), the standard-state chemical potentials for anions and cations are determined as

$$\mu_{A^-}(\text{e.s.s.}; \text{pH} = k) = \mu_{A^-}(\text{e.s.s.}) - kRT \tag{54}$$

$$\mu_{A^+}(\text{e.s.s.}; \text{pH} = k) = \mu_{A^+}(\text{e.s.s.}) + kRT \tag{55}$$

Note the analogy between Equations 54 and 55 and Equation 4.

An example of the use of these standard states for working with solvation effects on one-electron oxidation potentials is provided elsewhere.[11]

6. SOLVATION

We are now in a position to consider the difference in chemical potential between a solute in its (hypothetical) standard state in a liquid solution and that same chemical species in its gas-phase standard state. This difference is the standard-state molar free energy of solvation ΔG_S^o (also referred to as the standard state molar free energy of transfer from the vapor phase to a liquid solution). We define

$$\Delta G_S^o = \mu_A^o(\text{solute}) - \mu_A^o(\text{vapor}) \tag{56}$$

where we have used different standard states for each phase. Thus the superscript on ΔG_S^o unlike all previous standard-state superscript in these notes refers not to a particular standard state of one substance, but rather to the fact that the dissolution process being considered is a hypothetical one involving a transfer from one standard state to another. (This may be compared to the situation for heat of formation, which is the enthalpy of forming one mole of a substance in its standard state from the elements, each in their own standard state. In that case, there are different standard states for different substances in the initial and final states of the transfer process.)

Now substitute Equations 2 and 35 into Equation 56:

$$\Delta G_S^o(\text{HL s.s.}) = \mu_A(\text{solute}) - \mu_A(\text{vapor}) - RT \ln \gamma_A X_A + RT \ln \frac{P_A}{P^o} \tag{57}$$

where the parenthetical notation on the left-hand side indicates that we are using a Henry's law standard state for the solute. If the vapor is in equilibrium with the solution, the first two terms on the right-hand side of Equation 57 cancel, and we have

$$\Delta G_S^o(\text{HL s.s.}) = RT \ln \frac{P_A}{P^o X_A \gamma_A} \tag{58}$$

Using Equation 34 allows us to write this as

$$\Delta G_S^o(\text{HL s.s.}) = RT \lim_{X_A \to 0} \ln \frac{P_A}{P^o X_A} \tag{59}$$

To evaluate the logarithm, we must measure the vapor pressure P_A of A in equilibrium with a solution where its mole fraction is X_A in the limit where the solution becomes infinitely dilute. That is, in the limit of infinite dilution where γ is 1, the free energy of solvation can be obtained from measurement of the solute vapor pressure (in the appropriate standard state units) over a solution of known concentration.

Substituting Equation 22 into Equation 59 yields

$$\Delta G_S^o(\text{HL s.s.}) = RT \ln k_A^X / P^o \tag{60}$$

Now substituting Equation 48 yields

$$\Delta G_S^o(\text{HL s.s.}) = RT\left(\ln \frac{P_A^\bullet}{P^o} + \ln \gamma_A^\infty \right) \tag{61}$$

Thus the free energy of solvation may be calculated from the Henry's law constant or from the vapor pressure of the pure substance and the limiting activity coefficient. Thus, if the deviation of the solution from Raoult's law behavior is known, calculation of the standard state free energy of solvation requires only the vapor pressure of the pure substance (in the standard state units). For an ideal solution that behaves according to Raoult's law, γ^∞ would be 1, leading to the observation that ΔG_S^o would depend simply on the vapor pressure of the pure solute.

In our quantum mechanical solvation modeling,[12-27] we take the standard state of the vapor to be a 1 molar ideal gas at 298° K and the standard state of the solute to be a hypothetical 1 molar Henry's law solute at the same temperature and pressure. Free energies of solvation, ΔG_S^o, for this choice of standard states, may be derived by employing the theory given above. First, we combine Equations 28 and 36 to get

$$\mu^{\circ}_{\mathrm{A}}(1\,M\ \mathrm{sol.s.s}) = \mu^{\circ}_{\mathrm{A}}(\mathrm{HL\ s.s}) + RT\ \ln \frac{k^{M}_{\mathrm{A}}}{k^{X}_{\mathrm{A}}} \tag{62}$$

$$= \mu^{\circ}_{\mathrm{A}}(\mathrm{HL\ s.s.}) - RT\ \ln M^{\bullet}_{\mathrm{A}} \tag{63}$$

Equation 63 follows from Equation 62 by combining Equations 22 and 23. Clearly, the ratio of Henry's law constants is the molarity of the solution in which the mole fraction of solute A is unity, i.e., the molarity of pure liquid A. We next note that Equation 56 implies

$$\Delta G^{\circ}_{\mathrm{S}}(1\,M\ \mathrm{sol.s.s.}) = \Delta G^{\circ}_{\mathrm{S}}(\mathrm{HL\ s.s.}) + \mu^{\circ}_{\mathrm{A}}(1\,M\ \mathrm{sol.s.s.}) - \mu^{\circ}_{\mathrm{A}}(\mathrm{HL\ s.s.}) \tag{64}$$

and using Equation 63 then yields

$$\Delta G^{\circ}_{\mathrm{S}}(1\,M\ \mathrm{sol.s.s.}) = \Delta G^{\circ}_{\mathrm{S}}(\mathrm{HL\ s.s.}) - RT\ \ln M^{\bullet}_{\mathrm{A}} \tag{65}$$

Combining this with Equations 60 and 61 yields

$$\Delta G^{\circ}_{\mathrm{S}}(1\,M\ \mathrm{sol.s.s.}) = RT\ \ln \frac{k^{X}_{\mathrm{A}}}{P^{\circ} M^{\bullet}_{\mathrm{A}}} \tag{66}$$

and

$$\Delta G^{\circ}_{\mathrm{S}}(1 M \mathrm{sol.s.s.}) = RT\ \ln \frac{P^{\bullet}_{\mathrm{A}} \gamma^{\infty}_{\mathrm{A}}}{P^{\circ} M^{\bullet}_{\mathrm{A}}} \tag{67}$$

where, for a 1 M gaseous standard state, P° should be set to 24.45 atm, as discussed between Equations 1 and 2. Other transformations of standard states may be accomplished equivalently.

Let's do a numerical example: 1,2-ethanediol. We will use Equation 67 since $\gamma^{\infty}_{\mathrm{A}}$ is known to be 0.8.[28] The density is[29] 1.113 g cm^{-1}; therefore

$$M^{\bullet} = \frac{1.113\mathrm{g}}{\mathrm{m}^3} \frac{10^3\,\mathrm{cm}^3}{\mathrm{L}} \frac{\mathrm{mol}}{62.07\mathrm{g}} = 17.93 \tag{68}$$

The vapor pressure is[30] 0.010 kPa; therefore

$$P^{\bullet} = 0.010 \text{ kPa} \frac{\text{atm}}{101.325 \text{ kPa}} = 9.87 \times 10^{-5} \tag{69}$$

Finally, Equation 67 yields ($T = 298°$ K):

$$\Delta G_S^o = 0.592 \text{ kcal mol}^{-1} \ln \frac{(9.87 \times 10^{-5})(0.8)}{(24.45)(17.93)} = -9.19 \text{ kcal mol}^{-1} \tag{70}$$

Notice that if we had used the Henry's law standard state for the solute, we would have obtained –7.48 kcal/mol (which can be derived by combining Equations 63, 68, and 70). Note that if $\gamma_A^\infty = 0.9$, the free energy of solvation would be less negative by only 0.07 kcal/mol. Thus, when the solution is nearly ideal ($\gamma_A^\infty \approx 1$), the free energy of solvation is primarily determined by the vapor pressure.

Note that we previously[16] quoted ΔG_S^o as –9.6 kcal/mol and as[17] –9.3 kcal/mol. These values differ from the present value by 0.4 kcal/mol (apparently a math error) and 0.1 kcal/mol (apparently a round-off error), respectively.

A special case of Equation 67 concerns the "free energy of solvation of A in A." Since a solution of A in A obviously satisfies Raoult's Law, we have $\gamma_A^\infty = 1$. Then Equation 67 can be used to find the solvation energy of A in A from the vapor pressure of A and its density.[31]

7. SOLUBILITY

Next consider the relationship between the free energy of solvation and the solubility of a solute. First, in keeping with all the developments above, we consider a solute that is a liquid in its pure state. By combining of Equations 55 and 61, we may write

$$\Delta G_S^o = RT \ln\left(\frac{P_A^{\bullet}}{P^o}\right) + RT\left(\frac{k_A^X}{P_A^{\bullet}}\right) \tag{71}$$

Then Equation 22 yields

$$\Delta G_S^o = RT \ln\left(\frac{P_A^{\bullet}}{P^o}\right) + \lim_{X_A \to 0} RT \ln\left(\frac{P_A}{P_A^{\bullet} X_A}\right) \tag{72}$$

$$= RT \ln\left(\frac{P_A^\bullet}{P^o}\right) + RT \ln\left(\frac{P_A}{P_A^\bullet X_A^\infty}\right) \tag{73}$$

where X_A^∞ refers to the mole fraction of solute in the infinitely dilute regime in which Henry's law is obeyed. In the special case of a liquid solute which is saturated in the solvent at such very dilute concentrations, we must have a case where the equilibrium chemical potentials of the pure liquid solute, the solute in solution, and the solute vapor over both of the phases are all equal. For the vapor over the pure liquid solute, we have

$$\mu_A^\bullet(\text{gas}) = \mu_A^o(\text{g.s.s.}) + RT \ln\left(\frac{P_A^\bullet}{P^o}\right) \tag{74}$$

while for the vapor over the solution we have

$$\mu_A^\bullet(\text{gas}) = \mu_A^o(\text{g.s.s.}) + RT \ln\frac{P_A}{P^o} \tag{75}$$

Since these two chemical potentials must be equal (given the equilibrium between the pure liquid and the saturated solution), it must be the case that $P_A^\bullet = P_A$, in which case Equation 72 becomes

$$\Delta G_S^o = RT \ln\left(\frac{P_A^\bullet}{P^o}\right) - RT \ln X_A^\infty \tag{76}$$

This equation has the expected behavior that ΔG_S^o becomes more positive with decreasing solubility of the solute. However, free energies of solvation for different solutes cannot be related to their relative solubilities unless the vapor pressures of the different solutes are similar or one takes account of this via Equation 76. Furthermore, if the solubility is high enough that Henry's law does not hold, then one must consider finite-concentration activity coefficients, not just the infinite-dilution limit.

The situation is more complicated for saturated solutions of solid solutes, since there is a free energy of fusion term associated with leaving the pure solid in order to dissolve into solution (or, in the other direction, we must take account of the free energy of crystallization). Since this term, like vapor pressure, will be different for different solutes, it is in general not appropriate to assign relative solubilities based on relative free energies of solvation. Furthermore, molecular modeling techniques for estimating crystallization energies are not as well developed as those for estimating solvation energies. For a discussion of solubility of solids in terms of infinite dilution activity coefficients, see Grant and Higuchi.[32]

A similar multiphase complication that should be kept in mind when discussing solutions at finite concentrations is possible micelle formation. It is well known that for many organic solutes in water, when the concentration exceeds a certain solute-dependent value, called the critical micelle concentration (cmc), the solute molecules are not distributed in a random uncorrelated way but rather aggregate into units (micelles) in which their distances of separation and orientations with respect to each other and to solvent molecules have strong correlations. Micelle formation, if it occurs, will clearly have a major effect on the apparent activity coefficient but the observation of the phenomenon requires more sophisticated analytical techniques than observation of, say, liquid-liquid phase separation.

8. MODELING: EQUILIBRIUM PROPERTIES

The reason we prefer to use 1 *M* for the standard state in both the gas phase and in liquid solution is that using the same concentration in the gas phase and solution eliminates an entropic term in the statistical mechanical free energy and allows us to focus on the interaction terms coupling the solute to the solvent.[33-35] In particular, using the standard state of Equation 67, we can write[33-35] the free energy of solvation of a rigid, non-rotating solute as

$$\Delta G^{\circ}_{S}(\mathbf{x}) = -RT\ln\left\langle \exp\left(-B/\tilde{k}T\right)\right\rangle_{\text{solvent}} \tag{77}$$

where **x** denotes the set of vibrational coordinates of the solute, $\tilde{k}$ is Boltzmann's constant, *B* is the potential energy of interaction between the solute and the solvent, and $\langle\cdots\rangle_{\text{solvent}}$ denotes an average over all possible solvent configurations. In practice we are interested in the free energy of solvation of a nonrigid, rotating solute, and this is given by

$$\Delta G^{\mathrm{O}}_{\mathrm{S}} = \left\langle \Delta G^{\mathrm{O}}_{\mathrm{S}}(\mathbf{x})\right\rangle_{\mathbf{x}} + \Delta G_{\mathrm{int}} \tag{78}$$

where $\langle\cdots\rangle_{\mathbf{x}}$ denotes an average over vibrational coordinates, G_{int} is the internal (i.e., conrovibronic, i.e., conformational-rotational-vibrational-electronic) free energy of the solute, and

$$\Delta G_{\text{int}} = G_{\text{int}}(\text{sol.}) - G_{\text{int}}(\text{g}). \tag{79}$$

In practice we often neglect the distinction between $\Delta G_{\text{S}}^{\text{o}}$ and $\Delta G_{\text{S}}^{\text{o}}(\text{x})$, although sometimes it is important to optimize the geometry in solution[21] or to at least include the conformational part.[14] (If one did try to include the rotational part, one would run into the problem that the 3 gas-phase rotations are converted in liquid solution into low-frequency librations that are strongly coupled to low-energy solvent motions). In the rest of this section we focus on $\Delta G^{\text{o}}(\mathbf{x})$.

There are two main approaches to calculating Equation 77. In the brute-force or atomistic approach the solvent molecules are treated explicitly, and the average is calculated by using Monte Carlo[36] or molecular dynamics[38, 39] methods to sample the solvent configurations. In the so-called continuum approach, the solvent is modeled by a field, i.e., a collective solvent coordinate, that does not depend on the instantaneous positions of the nuclei.[12, 15, 21, 22] The advantages of the atomistic approach are that it provides a detailed picture of the solvent and it can readily be applied to arbitrary systems provided a potential energy function is available. The advantages of the collective-solvent-coordinate model are lower cost, and earlier route to including quantum mechanical effects, and elimination of the need for potential energy functions for individual solute-solvent interactions. Since the atomistic approach is treated in a separate chapter of this text, the present chapter will only consider collective-solvent-coordinate approaches.

In general, collective-coordinate approaches separate $\Delta G_{\text{S}}^{\text{o}}(\mathbf{x})$ into two parts: bulk electrostatics (henceforth called just electrostatic or ΔG_{elec}) and the rest. This is an extrathermodynamic distinction, and there is no unique way to separate the two kinds of effects in either thermodynamics or statistical mechanics. In the most accurate collective-coordinate approaches, is modeled by self-consistent reaction field (SCRF) ΔG_{elec} theory.[12, 15, 21, 22, 39-49] The reaction field is the field acting on the solute due to the electric polarization of the solvent induced by the solute. The electric polarization of the solvent partially cancels the electric field lines emanating from the charges and partial charges of the solute, thereby reducing the self-energy and charge-charge interactions within the solute. This favors higher partial atomic charges in molecular solutes as compared to their gas-phase charge distributions.

If the solute were simply a collection of point charges surrounded by a continuous dielectric medium with the bulk dielectric constant ε of the solvent, the self-energy and the strength of charge-charge interactions in the solute would be reduced by a factor of ε. This is called dielectric screening. However, the solute itself occupies a finite volume, and solvent is excluded from this volume. This reduces the dielectric screening and is called dielectric descreening. In the early days of solvation modeling, the solute was represented as a sphere or ellipsoid;[39-45] such a model provides only a crude accounting for dielectric descreening. Modern theories represent the solute as a superposition of atomic spheres centered at the nuclei; this is much more realistic.

The electric polarization of the solvent has three components: electronic, "atomic" (i.e., translational and vibrational), and orientational. The polarization of a nonpolar solvent is almost entirely electronic; this leads to $\varepsilon \approx 2$. Polar solvents can have much larger dielectric constants, e.g. ε is 13.9 for 1-pentanol, 37.7 for methanol, and 78.3 for water.[50]

The electrostatic contribution to the free energy of solvation is one half the interaction energy of the solute with the reaction field. The factor of one half comes from the fact that the free energy cost of polarizing the solvent is one half of the favorable interaction energy that one gains; the simplicity of this result is a consequence of assuming linear response of the solvent to the solute.[21, 43, 45]

The chief uncertainties in calculating G_{elec} are (i) the charge distribution of the solute and (ii) the location of the boundary at which one switches between solute screening and descreening. We will consider these in order. In molecular mechanics modeling, one associates standard partial charges to the various atoms of common functional groups. This is only satisfactory for zero-order estimates. Better charges may be obtained from quantum mechanical electronic structure calculations employing a self-consistent field (SCF), i.e., in which each orbital is optimized self-consistently in the field of the others. If the orbitals are optimized not only in the field of the other occupied orbitals but also self-consistently with the reaction field, one obtains the SCRF method. In our own most recent work, the charges used in the SCRF calculations are obtained from the orbitals by what is called a class IV mapping.[51] This mapping contains semiempirical parameters that makes up for the lack of complete electron correlation and other deficiencies of the electronic structure method. Our most recent set of mapping parameters is called Charge Model[52, 53] (CM2).

In most of our own solvation models,[12-17, 19-26] the interaction of the solute partial atomic charges with electric polarization of the solvent dielectric medium outside the overlapping spheres representing the solute is calculated by the generalized Born[42, 54-57] (GB) approximation. We have also developed a semiempirical model[27] based on the conductor-like screening model[58] (COSMO), which uses the $\varepsilon = \infty$ limit of the Poisson equation and then scales the results to finite ε. (We have also used a pairwise descreening model[18] discussed below.) The COSMO model uses the continuous solute electron density function $\rho(\mathbf{r})$ rather than replacing it by a set of partial atomic charges.[18, 58, 59] In principle this allows a more accurate treatment of lone pairs and atomic dipoles, but it cannot take advantage of the improvement in accuracy afforded by the class IV mapping.

A third class of solvation models is based directly on the Poisson equation for finite ε, based either on $\rho(\mathbf{r})$[48, 60] or its multipole expansion.[47, 61] The approach based on $\rho(\mathbf{r})$ is usually called polarized continuum model (PCM). It is unclear if the extra accuracy of using the Poisson equation is sufficient to offset its chief disadvantage, which is sensitivity to the portion of the solute charge that lies outside the set of overlapping solute spheres. This results in a spurious contribution to the solvation energy is variously called outlying charge error or escaped charge error.[60] The outlying charge error is usually compensated by a renormalization procedure,[61] but it can still be severe, especially for anions. The use of a truncated multipole expansion eliminates the outlying charge error in principle, but suffers from the fact that the multipole expansion is slowly convergent for large molecules.

An alternative to the GB, COSMO, and Poisson electrostatic calculations is to model the solution to the Poisson equation in terms of pair potentials between solute atoms; this procedure is based on the physical picture that the solvent screens the intra-solute Coulombic interactions of the solute, except for the critical descreening of one part of the solute from the solvent by another part of this solute. This descreening can be modeled in an average way to a certain level of accuracy by pairwise functions of atomic positions.[18, 64, 65] One can obtain quite accurate solvation energies in this way, and it has recently been shown that this algorithm provides a satisfactory alternative to more expensive explicit-solvent simulations even for the demanding cases of 10-base-pair duplexes of DNA and RNA in water.[66]

The electrostatic methods just discussed suitable for nonelectrolytic solvent. However, both the GB and Poisson approaches may be extended to salt solutions, the former by introducing a Debye-Hückel parameter[67] and the latter by generalizing the Poisson equation to the Poisson-Boltzmann equation.[68] The Debye-Hückel modification of the GB model is valid to much higher salt concentrations than the original Debye-Hückel theory because the model includes the finite size of the solute molecules.

Perhaps the most widely discussed source of uncertainty in electrostatic calculations is the location of the solute/solvent boundary. The most common treatment is to place the boundary at the surface of a set of overlapping spheres centered at the nuclei. But what radius should one use for those spheres? One common answer is van der Waals radii times 1.2.[46] In our own quantum mechanical solvation models,[12-27] and those of several others[59, 69], these radii are empirical parameters. Recently Barone et al.[70] have modified the PCM to use charge-dependent united-atom spheres instead of all-atom spheres, and they optimized the electrostatic radii for a particular normalization scheme, known as the ICOMP = 4 scheme. The resulting model is called the united-atom Hartree-Fock (UAHF) model.

The "correct" radii for electrostatic solvation calculations have been debated for over 50 years. But there can be no correct answer. The model that the dielectric constant changes from unity to ε at a definite point is wrong. The solute boundary region fluctuates as a consequence of solute vibrations and solvent motions, and the dielectric constant, to the extent that it is even defined in a microscopic space, also fluctuates and changes gradually over this region. The latter aspect of solvent polarization is sometimes treated as a form of dielectric saturation, i.e., one notes that at high enough fields (e.g., close to a polar or changed solute), the permittivity (dielectric constant) of the solvent is not constant, it is reduced and depends on the field.[71, 72] Thus we believe that it is futile to hope to find the "best" radii by considering only electrostatics. Instead we recommend finding reasonable radii that clearly define a bulk electrostatic contribution, however arbitrary, and then concentrating on making the non-electrostatic term (mentioned above) be *consistent* with this choice. In our work, we do this by parameterizing the non-electrostatic term against experimental data.

Some of the physical effects that must be included in the non-electrostatic term are:

1) cavitation, i.e., the free energy cost of making a cavity in the solvent to allow room for the solute;

2) dispersion, i.e., the change in solvent-solvent dispersion forces and the introduction of solute-solvent dispersion forces when the solute is placed in the cavity (the change in solvent-solvent dispersion forces due to having made the cavity are in principle in the cavitation term, but one can see that the effects are not neatly separable);

3) exchange repulsion of solute and solvent and the change in intrasolvent exchange repulsion (Exchange repulsion is ultimately due to the Pauli exclusion principle which prevents the charge clouds of atoms from overlapping significantly without a large energy penalty. Those who appreciate advanced quantum mechanics realize that, due to the Hellmann-Feynman theorem,[73-75] all such quantum effects can still be calculated by electrostatics, i.e., once you know the wave function, everything is electrostatics. That is one reason why, when we speak carefully, we say that the so called non-electrostatic term is actually a measure of the deviation of the solvation energy from a bulk electrostatic model):

4) the deviation of other solute-solvent interactions from bulk electrostatics, e.g., the fact that a hydrogen bond is not explainable in terms of bulk electrostatics;

5) other changes in solvent structure due to the introduction of the solute, e.g., those changes that are responsible for the hydrophobic[76-82] effect.

When the non-electrostatic terms are semiempirical, they also make up in an average way for systematic deficiencies in the treatment of electrostatics, e.g., for the truncation of the distributed multipole representation of the solute charge density at the monopole term on each center.

There are three popular ways to treat the nonelectrostatic effects: (i) ignore them, (ii) combine specialized models for cavitation, dispersion, exchange repulsion, and so forth,[46-48, 70] (iii) employ atomic surface tensions.[12-27, 83-86] In the third approach, which is the most accurate in an empirical sense, one writes[22-27]

$$\Delta G_S^O(\mathbf{x}) = G_{\mathrm{elec}}(\mathbf{x}) + \sum_k \sum_i \sum_j \sum_\delta \sigma_{kij\delta} A_{ki}(\mathbf{x}) f_{kij}(\mathbf{x}) S_\delta \tag{80}$$

where $\sigma_{kij\delta}$ is an empirical atomic surface tension, $A_{ki}(\mathbf{x})$ is the solvent-accessible surface area of atom k corresponding to effective solvent radius r_{kij}, $f_j(\mathbf{x})$ is geometrical factor, and S_δ is a solvent descriptor. The use of more than one effective solvent radius allows a more physical treatment of the various separate effects (e.g., dispersion forces extend only a short distance into the solvent whereas solvent structural perturbations may penetrate into the solvent over a longer length scale), the geometrical factor takes account of chemical functionality (e.g., an H bonded to C is hydrophobic whereas an H bonded to O is not), and the use of several solvent descriptors is key to obtaining a universal model that works in any organic solvent. We believe that the solvent descriptors should include measures of the solvent's acidity, basicity, macroscopic surface tension, electronic polarizability (as indicated, e.g., by its index of refraction n), halogenic character, and aromaticity.[22-27] Descriptors representing these solvent characteristics may be thought of as collective solvent coordinates that interact with the solute through Equation 73.

Because surface curvature depends on radius and different atoms have different sizes, and because the atomic surface tension depends on atomic number, the atomic surface tensions also include surface curvature effects, which has recently been studied as a separate effect.[7] Local surface curvature may also correlate with nearest-neighbor proximity and thus may be implicitly included to some extent when semiempirical atomic surface tensions depend on interatomic distances in the solute.

It is actually possible to create a model based entirely on atomic surface tensions, and, at least for species with no net charge, it does quite well.[23-25, 87, 88] Such a model can be quite useful for drug design because of its speed and simplicity, but it is somewhat unsatisfactory theoretically because the correct physics is not *manifest*.

In drug design one often uses an organic solvent as a surrogate for a cell membrane or for the blood-brain barrier in designing the partitioning properties that are essential to bioavailability. For example, partitioning into 1-octanol, *n*-hexadecane, and chloroform have all been used to correlate or predict bioavailability. Table 1 indicates that these three solvents span a range of hydrogen bonding acidity, basicity, and polarity (as measured by Abraham's hydrogen bonding descriptors[89] α and β and the dielectric constant ε, respectively), but have very similar indices of refraction n and macroscopic surface tensions γ. Also included in Table 1 are estimated values for solvent descriptors to characterize phosphatidyl choline (PC) if it were to be a pure liquid (these previously unpublished estimates derive from analysis of various related molecules, long chain esters, phosphates, etc.) Note that, if we assume that partitioning into a PC bilayer (which would represent a reasonable model for a biomembrane) can be well modeled by the solvent descriptors in Table 1 in the same way that solvent/solvent partitioning can be, PC does not really look much like octanol, chloroform, or hexadecane. That is, it is not clear that any one of these solvent/solvent partitioning models should be expected to be terribly predictive of bioavailability when that property is tied to membrane crossing of drug molecules.

A better idea may be to develop specific effective solvent descriptors by using data on actual membranes.[23] Experimental partitioning data are available for the case of water/phosphatidyl choline bilayer for a variety of organic solutes.[23, 90] If we assume that the dielectric constant of the phosphatidyl choline bilayer is 5.0 (an estimate based on the dielectric constant of 1-octanol) and that the α value is zero (there are no hydrogen bond donors for this molecule), and regress the experimental partition coefficients on the remaining three solvent parameters n, γ, and β, the regression provides values of 1.40, 25, and 1.15 for these parameters when using the AM1/SM5.4 model[19, 20] for computing solvation free energies. The similarity between the estimates given above for these descriptors and the values obtained from regression speaks to the physicality of the model . The regression itself has an R value of 0.9 over 19 reasonably diverse solutes, which is high enough that one might anticipate useful performance for screening. The virtue of this approach is that it is quite general. Given any particular membrane model and some initial data for partitioning, one can

Table 1. Solvent descriptors.[a]

	n	α	β	γ	ε[b]
1-octanol	1.43	0.37	0.48	39	10
chloroform	1.45	0.15	0.02	38	5
n-hexadecane	1.43	0	0	39	2
phosphatidyl choline[c]	1.37	0	0.9	27	5

[a] α and β are Abraham's $\sum\alpha_2^{H}$ and $\sum\beta_2^{H}$, respectively. [b] In Tables 1–3, dielectric constants are rounded to nearest integer to highlight major trends, but unrounded values were used for all calculations. [c] Estimated.

Table 2. Free energies of solvation (kcal/mol) of three solutes in eight solvents.

Solute	Solvent (dielectric constant)							
	$C_{16}H_{34}$ (2)	CCl_4 (2)	ethyl ether (4)	$HCCl_3$ (5)	butyl acetate (5)	tributyl phosphate (8)	1-octanol (10)	water (78)
1-butanol	−3.5[a]	−4.2	−5.7	−5.3	−5.2	−6.3	−5.7	−4.7
	−3.6[b]	−4.6	−5.4	−5.1	−5.3	−6.4	−6.3	−4.8
butylamine	−3.6	−4.3	−4.4	−5.3	NA[c]	−4.3	−5.4	−4.3
	−3.7	−4.6	−4.6	−4.9	−4.3	−4.3	−5.3	−4.1
aniline	−5.4	−6.1	−6.5	−6.9	−7.3	−7.6	−6.7	−5.5
	−5.4	−6.4	−6.7	−6.5	−7.6	−7.3	−6.9	−5.1

[a]upper value: experiment; [b]lower value: SM5.2R/MNDO; [c]not available

design model-specific descriptors to help evaluate the bioavailability aspect of further drug design efforts.

How well can continuum solvation models distinguish changes in one or another of these solvent properties? This is illustrated in Table 2, which compares solvation energies for three representative solutes in eight test solvents. Three of the test solvents are those shown in Table 1, one is water, and the other four were selected to provide useful comparisons on the basis of their solvent descriptors, which are shown in Table 3. Notice that all four solvents in Table 3 have no acidity, which makes them more suitable, in this respect, than 1-octanol or chloroform for modeling biomembranes. Table 2 shows that the SM5.2R model, with gas-phase geometries and semiempirical molecular orbital theory for the wave function, does very well indeed in reproducing all the trends in the data.

Table 3. Descriptors for more solvents.

	n	α	β	γ	ε
ethyl ether	1.35	0	0.41	24	4
butyl acetate	1.39	0	0.45	36	5
tributyl phosphate	1.42	0	1.21	28	8
carbon tetrachloride	1.45	0	0	38	2

9. NONEQUILIBRIUM PROPERTIES

Self-consistent reaction fields (SCRF) methods[17, 91] and other methods that predict the thermodynamic free energy of solvation are based on the assumption of thermodynamic equilibrium. This is certainly the correct model for calculating free energies of reaction, molecular partition coefficients of stable molecules, molecular solubilities, and ionic solubility products. There are, however, two types of problems where nonequilibrium effects may manifest themselves, namely spectroscopy and chemical dynamics. Nonequilibrium effects in these areas are discussed in two recent reviews.[21, 49] and the status of current understanding is summarized in the rest of this section. Understanding the differences between equilibrium solvation and solvation effects in spectroscopy is important for designing structure-property relationships, and understanding solvation effects on dynamics is important for modeling reactivity in general. For example, the fate of a drug lead in an aqueous biophase or the factors controlling transition state stabilization in a catalyzed reaction may depend significantly on nonequilibrium solvation effects.

In spectroscopy we may distinguish two types of process, adiabatic and vertical. Adiabatic excitation energies are by definition thermodynamic ones, and they are usually further defined to refer to at 0° K. In practice, at least for electronic spectroscopy, one is more likely to observe vertical processes, because of the Franck-Condon principle. The simplest principle for understandings solvation effects on vertical electronic transitions is the two-response-time model in which the solvent is assumed to have a fast response time associated with electronic polarization and a slow response time associated with translational, librational, and vibrational motions of the nuclei.[92] One assumes that electronic excitation is slow compared with electronic response but fast compared with nuclear response. The latter assumption is quite reasonable, but the former is questionable since the time scale of electronic excitation is quite comparable to solvent electronic polarization (consider, e.g., the excitation of a 4.5 eV $n \rightarrow \pi^*$ carbonyl transition in a solvent whose frequency response is centered at 10 eV; the corresponding time scales are 10^{-15} s and 2×10^{-15} s respectively). A theory that takes account of the similarity of these time scales would be very difficult, involving explicit electron correlation between the solute and the macroscopic solvent. One can, however, treat the limit where the solvent electronic response is fast compared to solute electronic transitions; this is called the direct reaction field (DRF). [49,93] The accurate answer must lie somewhere between the SCRF and DRF limits;[94] nevertheless one can obtain very useful results with a two-time-scale version of the more manageable SCRF limit, as illustrated by a very successful recent treatment of the vertical excitation of acetone in nine solvents.[95] In this treatment, solvent electronic polarization is treated by SCRF theory, but solvent nuclear polarization is frozen on the time scale of the electronic transition.

In chemical dynamics, one can distinguish two qualitatively different types of processes: electron transfer and reactions involving bond rearrangement; the latter involve heavy-particle (proton or heavier) motion in the formal reaction coordinate. The zero-order model for the electron transfer case is pre-organization of the nuclear coordinates (often predominantly the solvent nuclear coordinates) followed by pure electronic motion corresponding to a transition between diabatic electronic states.[96] The zero-order model for the second type of process is transition state theory[97] (or, preferably, variational transition state theory[80]) in the lowest adiabatic electronic state (i.e., on the lowest-energy Born-Oppenheimer potential energy surface).

Nonequilibrium considerations for electron transfer are similar to those for vertical photoexcitation discussed above, except that the pre-organization of the solvent prior to the electron transition makes the effective gap at the time of the electron transfer smaller, and thus the assumption of rapid electronic response of the solvent is even better.

It is generally believed that equilibrium solvation is a reasonable assumption or zero-order point for most reactions involving rearrangement of bonds. The most difficult case is probably the case of adiabatic reactions involving rearrangement or transfer of charged species; this includes proton transfer, S_N2 and S_N1 reactions, electrocyclic reactions, etc. In this case the equilibrium SCRF treatment is very reasonable for electronic response, and it should often be approximately valid for the nuclear solvent response as well. The reason for the latter statement is that the solute reaction coordinate motion is slowed down at the critical dynamical bottleneck region (a particle crossing a barrier is moving most slowly when it is at the top of the barrier), whereas the critical solvent motions appear to be very fast, with a time scale on the order of 10–400 fs.[98] In recent years there has been considerable effort devoted to trying to understand these nonequilibrium effects.[49] A general consensus is that they seldom (if ever) exceed a factor of 10, and more typically they contribute a factor of at most 2 or 3, and sometimes considerably less. We should keep in mind that factors of 10, 3, and 2 in the rate correspond to changes of 1.4, 0.6, and 0.4 kcal/mol, respectively, in the phenomenological free energy of activation at room temperature so these effects may become significant when this level of accuracy is required.

There are two major approaches to including nonequilibrium effects in reaction rate calculations. The first approach treats the inability of the solvent to maintain its equilibrium solvation as the system moves along the reaction coordinate as a frictional drag on the reacting solute system.[97, 99, 100] The second approach adds one or more collective solvent coordinate to the nuclear coordinates of the solute.[101-107] When these solvent coordinates are at their classical equilibrium position, the solvent is at equilibrium. But these collective coordinates can couple into the reaction coordinate and take on nonequilibrium values. It can be shown that the two approaches are equivalent.[108-111] The generalized-solvent-coordinate approach has been used successfully to explain kinetic isotope effects for H and Mu addition to benzene in water,[104] to predict the aqueous acceleration effect on the reaction of H with CH_3OH in water,[106] and to explain the frictional effect on the rate of contact ion pair dissociation in water.[107] The chief uncertainty in estimating such nonequilibrium effects is predicting the effective solvent time constant and the relevant "force constants" coupling the solute coordinates to the collective solvent coordinates. Two general approaches may be distinguished. One approach centers on the electrostatics of solvent polarization and therefore makes a strong connection between this process and the frozen-nuclear-polarization approximation in the theory of vertical photoexcitation.[101-103, 105] The other approach attempts to obtain the relevant parameters from macroscopic solvent descriptors such as macroscopic viscosity or macroscopic diffusion coefficients.[104-106] This latter approach may be useful for rough and ready estimates of the approximate size of the nonequilibrium effect but ultimately suffers from uncertainty as to whether the macroscopic frictional forces involved in diffusion or viscosity are the same as those that operate on atomic motions over very short time and distance scales.

Nonequilibrium solvent effects can indeed by significant at the kcal level–maybe even at a greater level, but so far there is no evidence for that when the reaction coordinate involves protonic or heavier motions. Our goal in this section has been to emphasize just how powerful and general the equilibrium model is. In addition, in both the previous section and the present section, we have emphasized the use of models based on collective solvent coordinates for calculating both equilibrium and nonequilibrium solvation properties.

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