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Biophysical Chemistry 51 (1994) 203–216

Biophysical Chemistry

Solvation of large molecules: Some exact results on the dependence on volume and surface area of the solute

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Received 8 September 1993; accepted 20 October 1993

Abstract

The solvation Gibbs and Helmholtz energies are evaluated exactly in two model systems. One is a modification of an interstitial model for water, the second is a non ideal gas mixture within the second virial approximation. In both systems the general form of the solvation Gibbs energy of a large solute s is $\Delta G_s^* = aV_s + bA_s$, where V_s and A_s are the volume and surface area of the solute s. We also show that this general form is likely to hold true in any real solution.

Key words: Solvation; Large molecules; Gibbs and Helmholtz energies

1. Introduction

About twenty years ago a new approach to solvation thermodynamics based on statistical thermodynamics has been suggested [1,2]. The older approach, based on thermodynamics of dilute solutions, required one to choose a standard state, for which to define a standard quantity of solvation such as the Gibbs energy, entropy, enthalpy, etc. of solvation. An examination of these standard quantities, on a molecular level, revealed that, besides being limited to very dilute solutions, in some cases these quantities diverge to plus or minus infinity where one should expect them to tend the zero [1,2].

The new approach removed all of these difficulties and generalized the concept of solvation. Starting with a new definition of the *solvation process*, one can define all the relevant thermodynamic quantities of this process. This new approach has eliminated the need to choose a standard state, the thermodynamic quantities of solvation could now be applied to any 'solute' molecule s, in any solvent (see section 2), including high concentrations of the solute, even a 'solvent' which consists of pure s molecules.

Very recently a 'correction' to this new approach has been suggested to account for the difference in size between the solute and solvent molecules [3,4]. The 'corrected' solvation quantities shows some satisfactory correlation with experimental quantities such as surface tension of water and Gibbs energies of folding of proteins.

Unfortunately, both the motivation for introducing the 'correction' as well as their apparent success in applications are based on erroneous concepts and argumentation. In a recent article [5] we have shown why the new approach referred to in the beginning of this section, does not need any correction, and furthermore the apparent

SSDI 0301-4622(94)00041-H

good correlation with some measured quantities has only mislead the authors to believe that their 'corrected' values were superior. This approach was also criticized in a recent review article [6].

In the present article we address ourselves to the question of the dependence of the solvation Gibbs and Helmholtz energies on the volume and on the surface area of the solute particles. We use in section 3 and 4 two exactly solvable models to show the explicit dependence of ΔG_s^* and of ΔA_s^* on volume and surface area of the solute s. We shall also show that the same type of dependence is expected in any liquid at any density. It will follow from these results that no correction to size differences between solute and solvent is needed.

2. Definitions

We define the solvation process of a molecules s in a solvent w as the process of transferring of a single molecule s from a fixed position in an ideal gas phase, g, into a fixed position in the liquid phase ℓ. The process is carried out at constant temperature T, pressure P, and composition of the liquid phase.

Using classical statistical mechanics, and the assumption of separability of the internal degrees of freedom of the molecules, one can write the chemical potential of s in the liquid phase as [7]

$$\mu_s^\ell = \mu_s^{*\ell} + kT \ln \rho_s^\ell \Lambda_s^3, \tag{2.1}$$

where ρ_s is the solute number density (N_s/V) and Λ_s^3 the momentum partition function (PF). $\mu_s^{*\ell}$ is the pseudo chemical potential of s. It can be shown that $\mu_s^{*\ell}$ is the Gibbs energy change for inserting s at a fixed position in the liquid phase. Writing the similar equation for the ideal gas phase as

$$\mu_s^g = \mu_s^{*g} + kT \ln \rho_s^g \Lambda_s^3. \tag{2.2}$$

We can define the solvation Gibbs energy, at constant P, T and composition as

$$\Delta G_s^* = \mu_s^{*\ell} - \mu_s^{*g}. \tag{2.3}$$

Statistical thermodynamics provides us with an expression for ΔG_s^* as follows

$$\Delta G_s^* = -kT \ln\langle \exp[-\beta B_s] \rangle, \tag{2.4}$$

where $\beta = (kT)^{-1}$, with T the absolute temperature and k the Boltzmann constant. B_s is the total interaction energy of s with all solvent molecules, being at some fixed configuration $\underset{\sim}{X} \ldots \underset{\sim}{X}_N$. The average, denoted by $\langle\ \rangle$ is over all configurations of the solvent molecules in the appropriate ensemble (here, the T, P, N ensemble).

Although ΔG_s^* is defined for a molecular process that cannot be carried out in a laboratory, it can be related to experimental quantities. For if the two phases are at equilibrium (eq.) then

$$\mu_s^\ell = \mu_s^g \tag{2.5}$$

and if it follows from (2.1) and (2.2) that

$$\Delta G_s^* = kT \ln\left(\rho_s^g/\rho_s^\ell\right)_{\text{eq}}, \tag{2.6}$$

which provides us with an experimental method of determining the solvation Gibbs energy, from which all other thermodynamic quantities can be derived by differentiation with respect to temperature and pressure.

Theoretically the calculation of ΔG_s^* from molecular quantities through Eq. (2.4) is very difficult. In the next two sections we shall calculate ΔG_s^* for two relatively simple systems. These are simple enough so that ΔG_s^* can be calculated explicitly, for large solutes s. On the other hand they are not trivial, in the sense that interactions among the molecules do exist and these determine the dependence of ΔG_s^* on both the volume and the surface area of the solute s.

3. A simple lattice model for the solvent

The model we use here is a simple extension of the interstitial model suggested for liquid water by Samoilove and Pauling [#1]. Some theoretical work was done on this model by Frank and Quist and by Mikhailov, and a more complete solution of the model, both for pure water and simple aqueous solutions, by Ben-Naim.

The system consists of the total of N_w solvent molecules (say water), N_L molecules of which

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[#1] For references on the lattice model for water, see ref. [8].

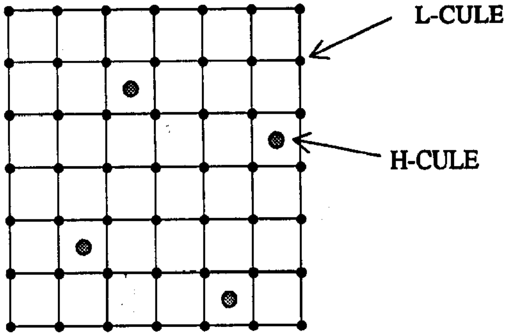

Fig. 1. Lattice model with interstitial molecules. There are N_L molecules that build the cubic lattice (L-cules) and N_H molecules that occupy the $N_0 = N_L$ holes in the lattice. The total number of molecules is $N_w = N_L + N_H$.

form a regular lattice, through hydrogen-bonding (these are referred to as L-cules). The structure of the lattice could be an ice-like, or a clathrate one. For our purpose we take the simplest cubic lattice, Fig. 1. The rest of the solvent molecules, $N_H = N_w - N_L$ (H-cules) occupy interstitial holes within the lattice.

For simplicity we assume that each hole can accommodate only one H-cule, and neither the L-cules nor the H-cules have any translational or internal degrees of freedom. Clearly the condition $N_H \leqslant N_L$ must be satisfied, since the total number of holes, in this model is equal to N_L (neglecting surface effects of the macroscopic system).

The total energy of the system consists of interaction energies between lattice molecules and between the H-cules and their surrounding holes. No interaction is presumed between two molecules occupying different holes. Thus we write

$$E = N_L E_L + N_H E_H = \frac{6 N_L E_{LL}}{2} + N_H E_H \qquad (3.1)$$

where E_L is the lattice energy per L-cule, and E_H is the interaction energy between an H-cule and its surroundings. In the cubic lattice each point has six neighbors and each L–L bond contributes an energy E_{LL}.

The volume of the system is determined only by the number of lattice molecules, i.e.

$$V = N_L V_L. \qquad (3.2)$$

The canonical partition function (PF) is thus

$$Q(T, V, N_w) = \binom{N_L}{N_H} \times \exp[-\beta(N_L E_L + N_H E_H)]. \qquad (3.3)$$

Since V and N_w are fixed, also N_L is fixed and therefore only one energy level exists in this system. The configurational degeneracy is simply the number of ways of distributing N_H particles in N_L interstitial holes (note that the number of holes N_0 is equal to N_L.) The Helmholtz energy is given by

$$\begin{aligned} A(T, V, N_w) &= -kT \ln Q(T, V, N_w) \\ &= -kT[N_L \ln N_L - N_H \ln N_H - (N_L - N_H) \\ &\quad \times \ln(N_L - N_H)] + N_L E_L + N_H E_H \\ &= (-kT/V_L)[V \ln V - (V_L N_w - V) \\ &\quad \times \ln(V_L N_w - V) - (2V - V_L N_w) \\ &\quad \times \ln(2V - V_L N_w)] + V E_L / V_L \\ &\quad + E_H (V_L N_w - V)/V_L, \end{aligned} \qquad (3.4)$$

where in the last form we have expressed the Helmholtz energy explicitly as a function of the independent variables T, V, N_w (as well as the molecular parameters, V_L, E_L and E_H).

From (3.4) one can obtain all the thermodynamic quantities of the system. In particular the pressure of this system is obtained from

$$\begin{aligned} \bar{P} &= -\frac{\partial A}{\partial V} \\ &= \frac{kT}{V_L}\left[\ln\left(\frac{V(V_L N_w - V)}{(2V - V_L N_w)^2}\right) + \frac{(E_H - E_L)}{kT}\right] \\ &= \frac{kT}{V_L}\left[\ln\left(\frac{N_L N_H}{(N_L - N_H)^2}\right) + \frac{E_H - E_L}{kT}\right]. \end{aligned} \qquad (3.5)$$

The pressure, in the cannonical ensemble, is denoted by $\bar{P}$ to distinguish it from the pressure in the isobaric–isothermal ensemble discussed below.

Next we write the T, P, N_w, PF, by summing over all possible volumes of the system

$$\begin{aligned}\Delta(T, P, N_w) &= \sum_V Q(T, V, N_w) \exp(-\beta PV) \\ &= \sum_{N_L} \binom{N_L}{N_H} \exp[-\beta(N_L E_L + N_H E_H + PV)],\end{aligned} \tag{3.6}$$

where the sum over V is essentially a sum over all possible N_L from N_L, (min) $= \frac{1}{2}N_w$ to N_L, (max) $= N_w$.

We now take the maximal term in (3.6), to obtain the equilibrium condition

$$\begin{aligned}&\frac{N_L^* N_H^*}{(N_L^* - N_H^*)^2} \\ &\quad = \exp[-\beta(E_H - E_L) - \beta P V_L] = K(P, T),\end{aligned} \tag{3.7}$$

where N_L^* and N_H^* are the most probable, or the average, values of N_L and N_H in the T, P, N_w ensemble. Note the similarity between (3.5) and (3.7). In (3.5) N_L and N_H are fixed but $\bar{P}$ is the 'average' pressure in the T, V, N_w ensemble, in (3.7) P is fixed and N_L^* and N_H^* are the average quantities in the T, P, N_w ensemble.

Eq. (3.7) can also be viewed as the equilibrium constant for the conversion

$$2(\text{empty holes}) \to (\text{occupied hole}), \tag{3.8}$$

define the corresponding 'mole fractions'

$$Y_0(\text{of empty holes}) = \frac{N_L^* - N_H^*}{N_L^*}, \tag{3.9}$$

$$Y_1(\text{of occupied holes}) = \frac{N_H^*}{N_L^*}. \tag{3.10}$$

(Note that in this model N_L^* is the total number of holes.) Then the equilibrium condition is

$$\frac{Y_1}{Y_0^2} = K(P, T). \tag{3.11}$$

To create an occupied hole, one must destroy two empty holes (one by eliminating an L-cule, and the second by filling an empty hole).

The Gibbs energy of the system is obtained from the maximal term in (3.6),

$$\begin{aligned}G(T, P, N_w) &= -kT \ln \Delta(T, P, N_w) \\ &= -kT[N_L^* \ln N_L^* - N_H^* \ln N_H^* - (N_L^* - N_H^*) \\ &\qquad \times \ln(N_L^* - N_H^*)] + N_L^* E_L + N_H^* E_H + P N_L^* V_L \\ &= A(T, P, N_w) + PV(T, P, N_w).\end{aligned} \tag{3.12}$$

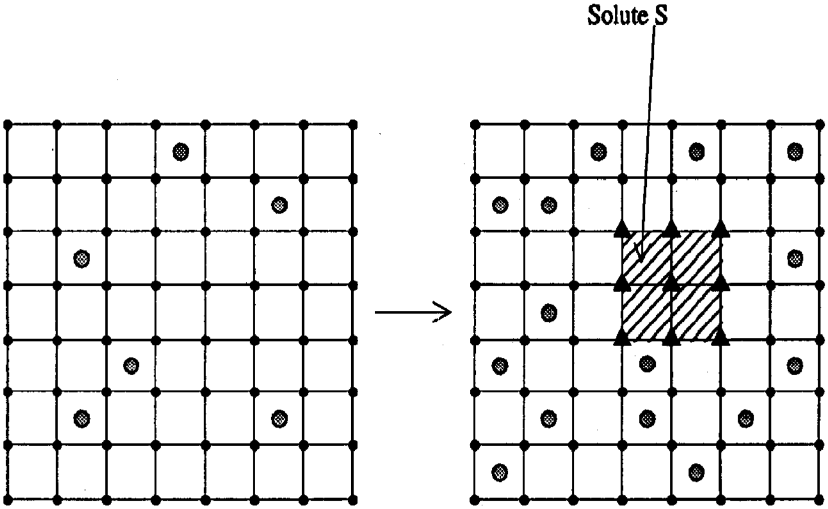

Fig. 2. Insertion of a solute s at a fixed position. In this 2D illustration, the process is carried out at constant volume (or area). If the solute s occupies $\ell^2 = 9$ lattice points, then $N_L' = N_L - 9$ and $N_H' = N_H + 9$. The number of holes changes to $N_0' = N_0 - (\ell - 1)^2 = N_0 - 4$.

It is easy to verify that the average volume in T, P, N_w ensemble is

$$\bar{V}(T, P, N_w) = \frac{\partial G}{\partial P} = N_L^* V_L. \tag{3.13}$$

We are now ready to compute the solvation Helmholtz and the Gibbs energies of a large solute in this system. Let μ_s be the chemical potential of the solute s in a very dilute solution in w. Since we shall be interested in the limit of very dilute solution of s in pure w, it is sufficient to consider the addition of one s to our solvent system. The solute is chosen as a cube occupying ℓ^3 lattice points. If we introduce s at T, V, N_w constants, then ℓ^3 L-cules must be replaced by s, and forced to occupy empty holes. A schematic insertion process of a solute in a two-dimensional lattice is depicted in Fig. 2.

The canonical PF of N_w solvent molecules and one solute molecule s of size ℓ^3 is written as

$$Q(T, V, N_w, N_s = 1) = N_L \binom{N_0'}{N_H'} \exp[-\beta E(N_w, N_s = 1)], \tag{3.14}$$

where N_L, as before is the number of L-cules that determined the fixed volume of the system, but now

$$V = N_L V_L = (N_L' + \ell^3) V_L. \tag{3.15}$$

The appearance of N_L (and not N_L') in (3.14) is a result of the configurational degeneracy – there are N_L places to put the solute s (neglecting surface effects of the macroscopic system). N_0' is the number of holes of the new system. In the pure w, $N_0 = N_L$ because of the choice of the cubic lattice. But placing a solute of size ℓ^3 has eliminated $(\ell - 1)^3$ holes, hence

$$N_0' = N_0 - (\ell - 1)^3 = N_L - (\ell - 1)^3,$$

$$N_L' = N_L - \ell^3, \quad N_H' = N_H + \ell^3,$$

$$N_w = N_L' + N_H' = N_L + N_H. \tag{3.16}$$

The combinational factor is (3.14) in the number of ways of arranging the new N_H' molecules in the N_0' holes. The energy of the system is written as

$$E(N_w, N_s = 1) = 3N_L E_{LL} - N_{SL}(E_{LL} - E_{SL}) - \tfrac{1}{2}(6\ell^3 - N_{SL}) E_{LL} + N_H' E_H. \tag{3.17}$$

The first term is the energy of the original pure w system (each L-cule forming six bonds of energy E_{LL}, and each bond belongs to two L-cules hence $3N_L E_{LL} = N_L E_L$).

The second term on the rhs of (3.17) is the change of all the LL (lattice–lattice) bonds on the surface of s into SL (solute–lattice) bonds. The total number of solute–solvent bonds is

$$N_{SL} = 8 \times 3 + 12 \times 2(\ell - 2) + 6(\ell - 2)^2. \tag{3.18}$$

There are eight vertices, contributing 3 SL bonds each, twelve edges contributing $2(\ell - 2)$ SL bonds each, and six faces contributing $(\ell - 2)^2$ SL bonds each. These N_{SL} bonds that originally contributed $N_{SL} E_{LL}$ are now contributing $N_{SL} E_{SL}$ to the total energy. The third term on the rhs of (3.17) is the total number of LL bonds that were replaced by internal bonds within s (and hence the latters do not contribute to the energy level of the system). Denoting by N_{SS} the number of internal bonds within s (i.e. those bonds that were replaced by the introduction of s) we have the relation

$$6\ell^3 = N_{SL} + 2N_{SS}, \tag{3.19}$$

hence, $N_{SS} = \frac{1}{2}(6\ell^3 - N_{SL})$ that appears in (3.17). The last term of the rhs of (3.17) is the total interaction energy of the new N_H' particles with their holes.

The chemical potential of s is

$$\mu_S = \left(\frac{\partial A}{\partial N_s} \right)_{T,V,N_w} = -kT \ln \frac{Q(T, V, N_w, N_s = 1)}{Q(T, V, N_w)} = \mu_s^* - kT \ln(N_L). \tag{3.20}$$

The pseudo-chemical potential μ_s^* is simply the change in the Helmholtz energy for placing s at some fixed point in the solvent at T, V, N_w constants. The only difference between μ_s and μ_s^*

arising from the degeneracy – i.e. there are N_L points to place s at a fixed position.

From (3.4) and (3.10) we can write the pseudo-chemical potential of s, retaining only terms proportional to ℓ^2 and ℓ^3, as

$$\begin{aligned}\mu_s^* &= -kT[\ln N_0' \ln N_0' - N_0 \ln N_0 - N_H' \ln N_H' \\ &\quad + N_H \ln N_H - (N_0' - N_H') \ln(N_0' - N_H') \\ &\quad + (N_0 - N_H) \ln(N_0 - N_H)] \\ &\quad + E(N_w, N_s = 1) - E(N_w) \\ &= kT\ell^3 \ln \frac{N_0 N_H}{(N_0 - N_H)^2} - 3kT\ell^2 \\ &\quad \times \ln \frac{N_0}{N_0 - N_H} - 6\ell^2(E_{LL} - E_{LS}) \\ &\quad - (3\ell^3 - 3\ell^2)E_{LL} + \ell^3 E_H = \bar{P} V_L \ell^3 \\ &\quad - 3\ell^2\left(kT \ln \frac{N_0}{N_0 - N_H} - 3E_{LL} + 6E_{LS}\right). \end{aligned} \tag{3.22}$$

In the last form on the rhs of (3.27) we have used the pressure equation from (3.5).

We note also that introducing the solute s will change the pressure of the system, the new pressure can be obtained from

$$\bar{P}' = \frac{-\partial A(T, V, N_w, N_s = 1)}{\partial V}$$

and the change in pressure is

$$\begin{aligned}(\bar{P}' - \bar{P})V_L &= kT\left[-\frac{(\ell - 1)^3}{N_0} + \frac{\ell^3}{N_H} + 2\frac{\ell^3 + (\ell - 1)^3}{N_0 - N_H}\right] \\ &\geqslant 0.\end{aligned}$$

This is always positive, but it is negligibly small for macroscopic system, i.e. $\ell^3 \ll N_w$.

Next we calculate the chemical potential in the T, P, N_w ensemble. This is defined, for very dilute solutions by

$$\begin{aligned}\mu_s &= \left(\frac{\partial G}{\partial N_s}\right)_{T,P,N_w} \\ &= -kT \ln \frac{\Delta(T, P, N_w, N_s = 1)}{\Delta(T, P, N_w)} \\ &= \mu_s^*(T, P, N_w, N_s = 1) - kT \ln N_0^* \end{aligned} \tag{3.23}$$

Following the same steps as before, but now expanding about the equilibrium quantities N_L^* and N_H^* we obtain, for the pseudo chemical potential, in the T, P, N_w ensemble the expression

$$\begin{aligned}&\mu_s^*(T, P, N_w, N_s = 1) \\ &\quad = PV_L \ell^3 \\ &\qquad - 3\ell^2\left(kT \ln \frac{N_0^*}{N_0^* - N_H^*} - 3E_{LL} + 6E_{LS}\right). \end{aligned} \tag{3.24}$$

We now see that if we choose a T, V, N_w system in such a way the $\bar{P}$ is equal to P of the T, P, N_w the two pseudo-chemical potentials will have the same value. Similarly if we choose the average volume of the T, P, N_w system (see 3.13) to be the same as V in the T, V, N_w system the two pseudo-chemical potentials will also be the same. This conclusions follows from the equivalent definitions of the chemical potential

$$\mu_s = \left(\frac{\partial A}{\partial N_s}\right)_{T,V,N_w} = \left(\frac{\partial G}{\partial N_s}\right)_{T,P,N_w} \tag{3.25}$$

and therefore has a more general validity [1]. Since the Helmholtz or the Gibbs energies of solvation involves difference between μ_s^* and the corresponding pseudo-chemical potential in an ideal gas, we have the equality

$$\begin{aligned}\Delta\mu_s^* &= \Delta G_s^*(T, P, N_w, N_s = 1) \\ &= \Delta A_s^*(T, V, N_w, N_s = 1) \end{aligned} \tag{3.26}$$

provided that $\bar{P} = P$ or $\bar{V} = V$ as noted before. It should be noted that the equality (3.26) holds for *two different* processes, one at constant pressure the other at constant volume. If we compare ΔG_s^* and ΔA_s^* for the *same* process we have

$$\begin{aligned}&\Delta G_s^*(T, P, N_w, N_s = 1) \\ &\quad = \Delta A_s^*(T, P, N_w, N_s = 1) + P\,\Delta V_s^*, \end{aligned} \tag{3.27}$$

where ΔV_s^* is the change in volume for the same process, this can be calculated from

$$V_s^* = \left(\frac{\partial \mu_s^*}{\partial P}\right)_T = \ell^3 V_L - 3\ell^2 V_L N_H^* / N_w. \tag{3.28}$$

The above results are of course more general [1]. We have rederived them here, to show how they appear in the specific model of this section. One can always calculate the chemical potential either in the T, V, N or in the T, P, N ensemble (Eq. (3.25)). The fact that the volume is kept constant in the first equality on the rhs on (3.25) does not mean that Eq. (2.6), based on the second equality on the rhs on (3.25), does not take into account volume changes – as argued by Sharp et al. [3].

4. Solvation in a second-virial-approximation system

We consider here a fluid system of two components, a solvent w and a solute s which slightly deviates from ideal gas. This is a non-trivial system where interactions exist and therefore solvation effects can be studied in an explicit manner.

Within the second virial approximation the equation of state of the two component system is given by

$$P/kT = (\rho_s + \rho_w) + \left[x_s^2 B_{ss} + x_w^2 B_{ww} + 2x_s x_w B_{sw}\right](\rho_s + \rho_w)^2, \tag{4.1}$$

where $B_{\alpha\beta}$ is defined by

$$B_{\alpha\beta} = \frac{-1}{16\pi^2} \int \left\{\exp\left[-\beta U_{\alpha\beta}(X_1 X_2)\right] - 1\right\} \mathrm{d}X_2, \tag{4.2}$$

and $U_{\alpha\beta}(X_1 X_2)$ is the pair potential for the pair of species α and β at a configuration X_1, X_2. The inverse relation is

$$\begin{aligned}\rho_T &= (\rho_s + \rho_w)\\ &= P/kT - \left[x_s^2 B_{ss} + x_w^2 B_{ww} + 2x_s x_w B_{sw}\right]\\ &\quad \times (P/kT)^2 + \dots\end{aligned} \tag{4.3}$$

The chemical potential of say the s component is given by

$$\mu_s(T, P, x_s) = kT \ln\left(x_s \Lambda_A^3 P/kT\right) + PB_{ss} - Px_w^2(B_{ss} + B_{ww} - 2B_{sw}) \tag{4.4}$$

and a similar expression applies for the chemical potential of w. With the above equations one can derive all the thermodynamic quantities of the system. In particular one can show that the solvation Gibbs energy at constant T, P is equal to the solvation Helmholtz energy at constant T, V, provided that $\bar{V}$ in the former system is equal to V in the latter. This has been proved explicitly in section 3, and in generally in ref. [7]. Hence, there is no need to repeat it here. Instead we focus on some other aspects of the solvation thermodynamics here.

First we examine the solvation Gibbs energy of s in a dilute solution of pure w. Taking $\rho_s \ll \rho_w$ we obtain

$$\Delta G^*(T, P) = 2PB_{sw}. \tag{4.5}$$

Assume for simplicity that U_{sw} is a function of the distance R only we can write

$$\begin{aligned}B_{sw} &= -\tfrac{1}{2}\int_0^\infty \{\exp[-\beta U_{sw}(R)] - 1\} 4\pi R^2\, \mathrm{d}R\\ &= \frac{1}{2}\frac{4\pi\sigma^3}{3} + \tfrac{1}{2}\int_\sigma^{\sigma+\delta} \beta U_{sw}(R) 4\pi R^2\, \mathrm{d}R,\end{aligned} \tag{4.6}$$

where σ is the distance at which $U(R)$ becomes very large and positive, and we have assumed that $-\beta U(R)$ is small compared to unity in the entire range of the potential, between σ and $\sigma + \delta$. If we denote by $\overline{U}_{sw}$ an average value of $U_{sw}(R)$ within this range we obtain

$$B_{sw} = \frac{1}{2}\frac{4\pi\sigma^3}{3} + \tfrac{1}{2}\beta\overline{U_{sw}}\left[(\sigma + \delta)^3 - \sigma^3\right]\frac{4\pi}{3}. \tag{4.7}$$

For large solutes $\sigma = \frac{1}{2}(\sigma_{ss} + \sigma_{ww})$ is roughly the distance of closest approach between s and w, and since $\delta \ll \sigma$ the second term is proportional to the surface area of s.

Thus denoting by

$$V_{sw} = \frac{4\pi\sigma^3}{3} \tag{4.8}$$

the excluded volume of s with respect to w, and by

$$A_{sw} = \frac{4\pi}{3}\left[(\sigma + \delta)^3 - \sigma^3\right] \tag{4.9}$$

the surface area of s with respect to w, we have for the solvation Gibbs energy

$$\Delta G_s^*(T, P) = PV_{sw} + P\beta\overline{U_{sw}}A_{sw}. \qquad (4.10)$$

The first term is proportional to the excluded volume V_{sw}, whereas the second term is proportional to the surface area of the solute s. This is the same behavior we obtained in the lattice model discussed in section 3.

The same behavior is also expected to be true for a large solute in any solvent at any density. A qualitative argument is the following. The solvation Gibbs energy of s in a very dilute solution in w is given by [1]

$$\Delta G_s^* = -\int_0^P \mathrm{d}P \int_0^\infty [g_{sw} - 1] 4\pi R^2 \,\mathrm{d}R, \qquad (4.11)$$

where g_{sw} is the pair correlation function for s and w at infinite dilution ($\rho_s \ll \rho_w$). Denoting the average value of g_{sw} in the range of (0, P), by $\bar{g}$ we can write

$$\bar{g}_{sw}(R) = \begin{cases} 0, \quad for\, R \leqslant \sigma, \\ \exp\left[-\beta\overline{W}_{sw}(R)\right] \sim 1 - \beta\overline{W}_{sw}(R), \\ \quad \sigma \leqslant R \leqslant \sigma + \delta, \end{cases} \qquad (4.12)$$

where $\overline{W}_{sw}$ is the average potential of average force (in the range of pressures 0, P) between s and w. Thus using (4.12) in (4.11) we find

$$\Delta G_s^* = PV_{sw} + P\beta W_{sw} A_{sw}, \qquad (4.13)$$

which has the same form as (4.10) with $\overline{U}_{sw}$ being replaced by an average (with respect to pressures (0, P) and within the range $\sigma \leqslant R \leqslant \sigma + \delta$) of the potential of average force. This suggests that the leading terms of ΔG_s^*, for large solutes, are the same as in the particular cases discussed in this and in the previous section.

5. Discussion and conclusions

We have shown that the Gibbs and Helmholtz energies of solvation can be written as a sum of two terms, one proportional to the *volume* and the second to the *surface area* of a large solute s. For very large solutes, the volume term will dominate the solvation work. Since these are exact results, there is no need to 'correct' for solute to solvent volume ratio, as was suggested recently [3,4]. (The expression for a solute of any size is given in the Appendix.)

We shall now discuss what we believe were the erroneous motivations for introducing such 'corrections', and how the apparent success of the 'corrected' values has mislead people to accept them.

Within the simple lattice models theories of solution, there is indeed the assumption of equal or nearly equal size of two species say A and B. If also the strength of the interaction fulfills a condition of the form [9]

$$W = W_{AA} + W_{BB} - 2W_{AB} \approx 0, \qquad (5.1)$$

then one gets a symmetrical ideal (SI) solution.

Once the two species A and B are considerably different in size, say monomers and *m*-mers, one must introduce a correction to the SI solution behavior to account for the difference in size of the molecule. This has lead to the Flory–Huggins theory of solutions [10,11]. However these corrections are valid within the context of *symmetric ideal solution*, where the assumption of equal size is introduced explicitly.

Solvation thermodynamics are usually studies in a *dilute ideal* (DI) solution (though one can generalize the concept to any concentration). In these systems the *ideality* arises not from *similarity* between A and B, but from the condition on the relative densities, say $\rho_A \ll \rho_B$. If A is very dilute in B then it becomes DI, no matter how different are the sizes or strengths of interactions between AA, AB and BB. Corrections to DI solutions are introduced to account for the occurrence of solute-solute interactions, not for dissimilarities between A and B.

Formally we write the chemical potential of A in a mixture of A and B in the following two forms [7]:

$$\mu_A^{(SI)} = \mu_A^P + kT \ln x_A + (\text{corrections due to dissimilarity of A and B}), \qquad (5.2)$$

$$\mu_A^{(DI)} = \mu_A^0 + kT \ln x_A + (\text{corrections due to solute–solute interactions}). \qquad (5.3)$$

Here μ_A^P is the chemical potential of pure A, whereas μ_A^0 is not a chemical potential of A in any real system, it includes the solvation Gibbs energy of A in the mixture. Thus in dealing with corrections due to SI solutions one must account for difference in sizes of A and B. Such a correction is not needed for DI solutions where μ_A^0 includes the entire solvation Gibbs energy for *any* solute in *any* solvent. We believe that confusing the SI with the DI has lead to 'correcting' of the latter with a correction which is appropriate for the former solution (for a more complete discussion the reader is referred to ref. [8] ch. 4 and ref. [7], ch. 6).

The second point we address ourselves to is the apparent better agreement of the 'corrected' solvation Gibbs energies with experimental quantities. More specifically Sharp et al. noted a discrepancy between the macroscopic and microscopic surface tension for the water–hydrocarbon interface a discrepancy pointed out earlier by Tanford [4]. By 'correcting' the value of the Gibbs energy of solvation they achieved a 'reconciliation' between the macroscopic and microscopic surface tension. Unfortunately, the basic relation between ΔG_s^* and the surface area of the solute s, from which one can obtain the surface tension, does not exist. As we have seen in the previous sections

$$\Delta G_s^* = aV_s + bA_s, \tag{5.4}$$

clearly a term including the microscopic surface tension of water is included within ΔG_s^*. It is difficult to separate this term explicitly. But even if we could isolate it, the microscopic, surface tension does not have to be the same as the macroscopic surface tension; there is no need to reconcile between these two quantities. Moreover, if one *assumes* that ΔG_s^* is entirely due to surface effects, then the 'surface tension' thus obtained is not even a microscopic surface tension, the latter certainly should not be related to the macroscopic surface tension.

A similar improved correlation between the 'correct' solvation Gibbs energies and standard Gibbs energies of folding of proteins was noted by Sharp et al. [3]. The flaws of this type of correlation have been discussed in details elsewhere [5].

In conclusion, the solvation Gibbs energy of any solute s, as defined in section 2 is, in general, dependent both on the volume and on the surface area of the solute.

The relation between ΔG_s^* and experimentally measurable quantities is an exact relation (within classical statistical mechanics). As such it needs no 'correction' due to differences in size (perhaps a correction due to quantum effects for very small solutes at very low temperatures will be found appropriate). Therefore any appended correction leads to a spurious measure of the solvation Gibbs energies or the so-called hydrophobic effect.

Acknowledgement

This work was partially supported by the basic research foundation, administered by the Israel Academy of Sciences and Humanities.

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Appendix

The solvation Gibbs (or Helmholtz) energy of a solute s of any size. In section 3 we derived the expression for the pseudo-chemical potential for large solutes in a lattice model. For any solute of size ℓ^3 (the number of sites occupied by the solute) the chemical potential of s is given by

$$\mu_s = -kT \ln \frac{Q(T, V, N_w, N_s = 1)}{Q(T, V, N_w)}, \qquad (A.1)$$

where the two PFs in (A.1) are given in (3.3) and in (3.14) respectively. The pseudo-chemical potential is related to the chemical potential through

$$\mu_s = \mu_s^* - kT \ln N_L, \qquad (A.2)$$

where N_L is the number of sites in the pure solvent.

For a cubic solutes occupying ℓ^3 sites, we can expand $Q(T, V, N_w, N_s = 1)$ about $Q(T, V, N_w)$ to obtain

$$\mu_s^* = kT\ell^3 \ln\left(\frac{N_L N_H}{(N_s - N_H)^2} \right) + \ell^3(E_H - 3E_{LL}) + kT(-3\ell^2 + 3\ell - 1) \ln\left(\frac{N_L}{N_L - N_H} \right) - \frac{N_{SL}E_{LL}}{2} + N_{SL}E_{SL}, \qquad (A.3)$$

where N_{SL} is given by (see (3.18))

$$N_{SL} = 8 \times 3 + 12 \times 2(\ell - 2) + 6(\ell - 2)^2. \qquad (A.4)$$

For $\ell = 1$ expression (A.3) reduces to

$$\mu_s^*(\ell = 1) = kT \ln \frac{N_H}{N_L - N_H} + E_H + 6(E_{SL} - E_{LL}). \qquad (A.5)$$

When $N_H = 0$ there is infinite 'attraction' to convert an L-cule to an H-cule. On the other hand when $N_H = N_L$ all the holes are occupied and there is infinite 'repulsion' to add another H-cule to the system. E_H is the new interaction energy of the H-cule released into the holes, and the last term on the rhs of (A.5) is the change of six LL bonds into six SL bonds.

Discussion to the paper by A. Ben-Naim

Comments

By P.J. Rossky, K.A. Sharp, B. Honig and S.K. Kumar

In the paper cited, the author has solved two model problems for solvation and demonstrated that, for these two models, the excess chemical potential of transfer from the gas phase to dilute solution can be expressed in terms of the solute volume and surface area in the form $\mu^{ex} = aV_s + bA_s$. In this comment, we do not challenge these technical results. Rather, first, we point out that the author omits an important perspective on this relation which follows when the present results are considered in the context of other earlier work showing the identical behavior. Second, we point out that the author's criticisms of the earlier exploration of volume dependence by Sharp et al. [1] have no basis in the results presented and only serve to mislead readers as to the true unresolved issues in the current understanding of solvation. In fact, we show that the content of the earlier work of Sharp et al. is exactly the same as those of the present author.

It is important to recognize that the fundamental equation for the transfer value of the 'pseudo' chemical potential is not different from that most widely used. It is simply the expression for what is now more conventionally termed the excess chemical potential (see, for example, the review [2]). The main point made in Ben-Naim's paper is that both volume- and area-dependent terms are expected in a correct evaluation of the transfer free energy. This fact has appeared in numerous earlier contexts. The original scaled particle theory [3] has the same form, Stillinger's modification [4] does as well, and analytical solutions for solvable approximations for hard sphere liquids [5] also share this form. In all these other cases, the solution has, in addition, explicit terms which vary as smaller powers of the solute diameter, although these terms are of decreasing importance as the diameter increases. Further, in each of these earlier cases, the coefficient a in the expression $\mu^{ex} = aV_s + bA_s$ is shown to be equal to the relevant fluid pressure. An examination of the results in Ben-Naim's paper demonstrates the important fact that the same is true in the present models, although it is never pointed out by the author. Thus, the present work provides an additional route leading to a well established result, which is of some interest. However, the statement by Ben-Naim that the volume-dependent terms will dominate for large solutes may well be physically irrelevant; for any reasonable size solute, the importance of this work term will depend critically on the pressure. This fact is evident in old applications of scaled particle theory [4], as well as noted in older work on protein solvation published by Ben-Naim himself [6]. Using atmospheric pressure, as in applications of scaled particle theory to aqueous solutions [3,4], even for a volume the size of a protein (say 5000 cm^3/mol), the magnitude of this term would only be about 0.1 kcal/mol. While there may be significant volume-dependent contributions, for example for chain molecules, Ben-Naim's discussion is not germane to this separate issue.

What is new in this paper is Ben-Naim's view that these observations provide some basis for criticism of the earlier work by Sharp et al. [1]. However Ben-Naim's arguments here, together with previous criticisms of this paper with Mazo [7], both of which contain elements of a diatribe, are simply incorrect, despite their repeated allegations that the derivation of Sharp et al. is based on faulty logic. These criticisms are based on a misunderstanding of the origin and intended use of the 'correction' put forth by Sharp et al. [1]. This is immediately apparent when one notes the incorrect identification by Ben-Naim [10] of the modified ΔG of Sharp et al. [1] with the value of ΔG^* of the present article (Eq. (2.6)). In Sharp et al. [1], the volume-dependent contribution to transfer free energies was identified with an ideal gas term which takes the form $1-r$, where r is a ratio of partial molar volumes of solute to solvent. In fact it can be shown from a lattice treatment that this is nothing but the lattice analog, in the Flory approximation, of the PV term that has been derived from scaled particle theory, and also the Ben-Naim approach. The appearance of this term in the recent statistical mechanical treatment of solvation entropies by Laziridis and Paulaitis [8] and in the derivation by Lee in this volume [9], confirm its generality. The arguments [7] used to dismiss the Sharp et al. approach [1] were further based, first, on confusion regarding the use by Sharp et al. of a constant volume *step* in a constant pressure *cycle*, and on spurious counter examples to the $1-r$ term. The error in the analysis of counter examples include the incorrect assumption that a point solute has a vanishing partial molar volume, and, conversely, the use of an ideal gas solute which does cause an increase in partial molar volume.

The key issue in solvation thermodynamics of relevance here is not *whether* there is a volume dependence of the chemical potential but rather whether this should be accounted for explicitly in the *use* of experimentally determined partition coefficients. As we expect all workers in the field are well-aware, practical applications of transfer free energies in the biophysical community have assumed only a surface area dependence and no volume dependence. Hence, if *only* an area dependence of the free energy contribution is desired (for example in analyzing protein substrate interactions where volume changes are minimal), one must 'correct' μ_{ex} by subtracting the term aV_S. The work of Sharp et al. [1] emphasized this point and made one estimate of this term via a Flory–Huggins-like expression. As Ben-Naim has provided two more model systems where volume-dependent contributions to the transfer free energy can be independently analytically derived, the technically sound points of the paper only reinforce the original concerns of Sharp et al. regarding the recognition of the existence of volume dependent terms and the importance of determining their quantitative significance.

The issue can perhaps best be summarized with reference to Lee's paper [9] where it is pointed out that whether one dissects out only $\ln(\rho_s)$ or the combination $\ln(\rho_s)+r-1$ as the standard part of the free energy, the total entropy and free energy remain unchanged and the criterion must be based on usefulness. This question of usefulness has by no means been resolved. Thus, it would probably be productive if future debates would focus on the physical basis and magnitude of volume-dependent contributions to solubility, not on their presence.

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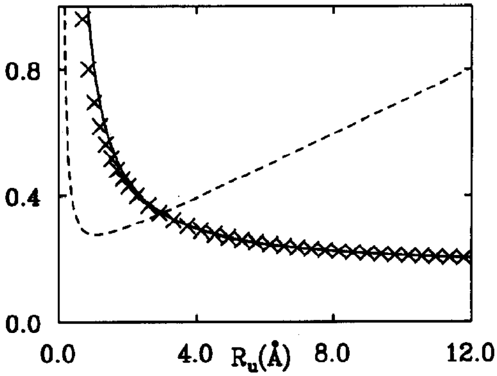

Fig. C1. $\beta\Delta\mu^{(0)}_{\mu,\text{sol}}/V_u$ (kcal/(mol Å^3)) versus R_u (solid line), $\beta\Delta\mu^{(0)}_{u,\text{sol}}/A_u$ (kcal/(mol Å^2)) versus R_u (dashed line) and $\beta\Delta\mu^{(0)}_{u,\text{sol}}/V_u = a + bA_u/V_u$ (kcal/(mol Å^3)) versus R_u (crosses), for a Lennard-Jones sphere in SPCE water.

By J. Perkyns and B.M. Pettitt

It is important to be reminded that significant results can be achieved from simple models. Ben-Naim argues convincingly that his models contain all the features necessary to obtain the correct large size limiting behavior of solvation free energies. It would be interesting to know the relative sizes of the coefficients *a* and *b* in Eq. (5.4), i.e. how large a solute must be before the volume term dominates.

Using the theory and molecular water solvent model from our contribution to this issue, we decided to investigate Ben-Naim's free energy expression quantitatively. We have used as a solute model a Lennard-Jones sphere ($\epsilon_{LJ} = 0.1$ kcal/mol) with varying sizes from smaller than the solvent up to approximately the size of myoglobin, covering solute sizes of interest to most biological solute models in present use. In Fig. C1 we present both the chemical potential at infinite dilution (Eq. (12) in our paper) divided by the solute volume $\beta\Delta\mu^{(0)}_{u,\text{sol}}/V_u$, and by the solute surface area $\beta\Delta\mu^{(0)}_{u,\text{sol}}/A_u$. Both results are plotted versus solute radius, R_u where we have taken the sum of solvent and solute radius $R_u + R_v = D$ to be the separation where the potential of mean force between the solute center and a water oxygen site is 1 kT. We then assume the radii to be proportional to Lennard-Jones sigma's giving $R_u = D\sigma_u/(\sigma_u + \sigma_v)$. Solute volume and surface area are also calculated using R_u.

The asymptotic approach of $\beta\Delta\mu^{(0)}_{u,\text{sol}}/V_u$ to a constant value clearly verifies the large solute size volume dependence for this model. Using data points at $R_u = 12.5$ and 6.0 Å, values of the coefficients were evaluated to be $a = 0.15$ kcal/(mol Å^3) and $b = 0.19$ kcal/(mol Å^2). The sum of the two terms using these evaluated coefficients is also plotted versus R_u, demonstrating that other terms are insignificant down to radii smaller than the solvent molecules (about 1.4 Å).

We conclude that Ben-Naim's principal result is strongly affirmed by this model in our theory. We note that the volume asymptote is also predicted by Schmidt (this issue) for a Lennard-Jones sphere solvent and a different theory. It would be interesting to see if it holds for model solutes of other symmetries and complexities, particularly when long-range forces are involved.

By Y. Marcus

(1) The surface areas and the volumes of fairly large solutes are well linearly correlated (whether or not the exclusion area and volume around the solute are taken into account (cf. R.S. Pearlman, in: Partition coefficient determination and f estimation, eds. W.J. Dunn, J.H. Block and R.S. Pearlman, Pergamon Press, 1985). So, if $V_s = p + qA_s$ or $A_s = V_s/q - p/q$, then:

$\Delta G^* = aV_s + bA_s = ap + (aq + b)A_s = (a + b/q)V_s - bp/q$. Hence in practice ΔG^* can be said to depend *either* on V_s *or* on A_s *or* on both and it is impossible to decide which of these quantities contributes to the observed thermodynamic function.

Responses by A. Ben-Naim to Comments

To Rossky, Sharp, Honig and Kumar

(1) …"the author omits an important perspective…". I do not know of any other *exact* results that were published. These results are admittedly derived for very simple models, but they also indicate that the same behavior is expected in general. "Other important perspectives" were noted earlier in ref. [1], but these are approximate theories only.

(2) "the content of the earlier work of Sharp et al. is exactly the same as those of the present author". Sharp et al. [2] claimed that Ben-Naim's solvation Gibbs energies are correct only "under special circumstances", namely when solvent and solute molecules have equal size. Therefore they suggested a correction term. In ref. [1] it was shown that such a correction is not needed, and ΔG^* as used earlier by Ben-Naim [3] includes any size dependence. In the present paper I have shown further the exact dependence in size for two simple systems. In my view, these finding prove *exactly the opposite* not "exactly the same" claims of Sharp et al.

(3) "the excess chemical potential". I have been using the term pseudo-chemical potential since 1974 [4]. I believe this term is useful in the context of solvation thermodynamics. The term "excess chemical potential" was used mostly in the context of "symmetrical ideal solutions" which is different from the "dilute ideal solutions" [4]. The latter is usually (though not always) the reference for solvation phenomena. I therefore still believe that the term "pseudo-chemical potential" is a useful concept and suggests to reserve the term "excess chemical potential" for symmetrical ideal solutions [5].

(4) The fact that the pressure is the coefficient of the volume dependence, is written explicitly in Eq. (3.22) and (4.10) of my paper. I do not understand why Rossky et al. say that "it is never pointed out by the author".

(5) The relative magnitude of the volume and surface terms is irrelevant to the present issue. The important point is that "the derivation of Sharp et al. is based on faulty logic". The arguments have been presented in ref. [1]. The present article only shows that Sharp et al. results cannot be correct. If any size dependence is already included in ΔG^*, one does not need to "correct" ΔG^* for size dependence.

In principle the Gibbs energies of solvation as used in ref. [3] should not be "corrected" by adding any volume terms. What I have demonstrated in the present paper is that any volume dependence is already contained in ΔG^* and this has the form of $P\Delta V$. Of course, numerically the term $P\Delta V$ might be small, some examples are shown in section 3.21 of ref. [3] for solvation of small molecules at normal temperature and pressure. However, the numerical experimental values of $P\Delta V$ have nothing to do with the main issue of my paper. Rossky et al., claim that "While these may be significant volume-dependent contributions for example for chain molecules, Ben-Naim's discussion is not germane to this separate issue". I certainly do not agree with this statement. Again, my claim is that any volume contributions are contained in ΔG^*, whether they are small or significant one need not add "correction" terms, such as derived from Flory–Huggins, or any other theories.

(7) The question of the relative "usefulness" of various standard states is not relevant to the issue discussed in this volume. I have advocated the use of ΔG^* as a measure of solvation of Gibbs energies. The arguments for preference of this quantity have been discussed in details in ref. [3]. If someone prefers other standard quantities, he or she must provide the relative supportive arguments. This has nothing to do with Sharp et al. work which specifically "corrected" the quantities ΔG^* as defined in ref. [3]. As such their "corrected" values where proved to be incorrect.

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To Perkyns and Pettitt

I found the results in their figure very satisfying. From my contribution it follows only that for large solutes the volume term must dominate. I was surprised to see that the volume term is significant down to solute-sizes of diameter similar to solvent molecules.

Note from the Editor of the Special Issue to the readers: Note that this comment and the response to it give a new spin to the controversy on the role of volume terms in the thermodynamics of transfer.

To Y. Marcus

ΔG^* is linear in n for *linear* hydrocarbons, and of course the surface area and molecular volume of the solutes are also linear in n. My paper is concerned with a solute of a general shape, for which the volume dependence must dominate at large volume. This aspect is discussed in a recent review written for *Current Opinion in Structural Biology* – to appear early in 1994.