ELSEVIER

Biophysical Chemistry 57 (1996) 219-224

Biophysical Chemistry

Size effects in nonpolar solvation: lessons from two simple models

A.B. Schmidt *, R.M. Fine

Biosym Technologies, Inc., 4 Century Dr., Parsippany, NJ 07054, USA

Received 20 December 1994; revised 22 March 1995; accepted 22 March 1995

Abstract

Size dependence of the solute chemical potential μ_u is examined using the Ornstein–Zernike equation for two models of the nonpolar solute–solvent interactions. Simple Lennard–Jones interactions are assumed in the first model while the Lennard–Jones potential is distributed over the solute volume in the second model similar to the Hamaker theory for the colloid dispersion forces. In both models, while μ_u rises asymptotically as the third power of the solute size in agreement with asymptotic solution of the scaled particle theory, it increases faster at smaller sizes. Deviations from the cubic law are more pronounced at higher solvent densities and stronger molecular interactions. Within a relatively narrow size range typical for small organic molecules, μ_u can be approximated with a polynomial of the third or even the second power. However, the latter approximation is less accurate and cannot be employed for extrapolation to the larger size region.

Keywords: Solvation; Lennard–Jones fluids; Ornstein–Zernike equation

1. Introduction

Computer simulations of molecular systems provide important insights into hydration of nonpolar solutes [1] but are time expensive. Therefore, continuum solvation models remain an important tool for applications [2]. Usually the nonpolar contributions to the solvation energy in these models are assumed to have a linear dependence on the solvent-accessible surface area (SAS). Such an approach proceeds rather from observations (see [3] for a review) than from rigorous theoretical notions. Recently, the solute volume has been suggested as a leading parameter in nonpolar solvation [4]. Two arguments are usually provided to support SAS-based models. First, the volume work, which is proportional to the solute volume within the scaled particle theory (SPT) [5,6], is small at atmospheric pressure and therefore perhaps may be neglected [7]. Another argument points to strong correlations between the solute volumes and SAS that may indicate practical equivalence of both SAS and volume-based solvation models [8]. Indeed, the nonpolar solvation energies in the continuum models are usually fitted to the data for the linear alkanes whose either volume or SAS are proportional to the carbon number. Therefore these data cannot be employed for discerning the volume and

---

* Corresponding author.

SSDI 0301-4622(95)00060-7

surface effects. Moreover, both SAS and volume fits based on alkane data provide practically the same nonpolar components of the hydration energies for a wide class of 140 small organic molecules that differ significantly in sizes and shapes [9]. Therefore, the continuum models may be insensitive to a form of the size dependence of the nonpolar solvation energy while being applied to small molecules. The problem remains how accurate these models are for larger solutes (e.g. peptides and proteins). In the absence of data on hydration energies of large solutes, the latter problem must be explored using theoretical methods.

Recently, solvation of large Lennard–Jones (LJ) solutes was studied using the integral equations of the liquid theory [10,11]. Interaction-site hypernetted chain equation (HNC) and SPCE model of water were used in [10] while the Martynov–Sarkisov equation (MS) [12] and the LJ solvent were employed in [11]. It should be noted that HNC is accurate for fluids with the long-range pair potentials but MS is preferable for the short-range pair potentials [13]. While entropic contributions are very important for nonpolar hydration [14], the solute chemical potential in the LJ solvent has basically an enthalpic nature [11]. Despite drastic differences in solvent models, both studies [10,11] show a cubic-size asymptotic behavior of the solute chemical potential in agreement with the SPT asymptotic solution. Therefore the specifics of water as a solvent may be unimportant for establishing the asymptotic size dependence of the solvation energy. Possible similarity of the solvation free energies in LJ fluids and water has also been noticed elsewhere [15].

This communication continues to probe size effects in solvation using two LJ models. In the first model, the conventional LJ potential is employed to describe the solute–solvent interactions. In the second model, the solute–solvent pair potential is calculated as an integral over the solute volume assuming that each element of this volume interacts with the solvent molecules via the LJ potential. The latter model is similar to the Hamaker theory of the colloid dispersion forces [16] and can be a better simple pattern to represent multi-atomic solutes such as globular proteins. Solvent–solvent interactions in both models are assumed to have the LJ form.

We find that the solute chemical potential in both models increases even faster with the solute size than a cubic polynomial, approaching the cubic law only asymptotically. Within a finite size range, the solute chemical potential can be approximated by a polynomial of the third and even the second power that may explain an efficiency of the SAS-based solvation models applied to small molecules. However, the latter models are less accurate and cannot be employed for extrapolation to the larger solute size region.

2. Theory

The excess Gibbs chemical potential of a molecule is given by the general expression [17–19]

$$\mu_\alpha/kT = -\sum_\beta n_\beta \int \big[h_{\alpha\beta}(r) - w_{\alpha\beta}(r) - 0.5 h_{\alpha\beta}(r)\big(w_{\alpha\beta}(r) + B'_{\alpha\beta}(r)\big)\big] \mathrm{d}\vec{r}, \tag{1}$$

where summation is performed over all molecular species that constitute a mixture, n_β is the concentration of species β,

$$g_{\alpha\beta} = 1 + h_{\alpha\beta} = \exp(-\phi_{\alpha\beta}/kT + w_{\alpha\beta}) \tag{2}$$

is the pair correlation function, $\phi_{\alpha\beta}$ is the pair potential. For the functional $B'_{\alpha\beta}$, an estimate [18]

$$B'_{\alpha\beta} = B_{\alpha\beta}/3, \tag{3}$$

can be employed. $B_{\alpha\beta}$ is the bridge functional determined by the direct correlation function, $c_{\alpha\beta}$,

$$c_{\alpha\beta} = h_{\alpha\beta} - w_{\alpha\beta} + B_{\alpha\beta}. \tag{4}$$

The relation between the pair and direct correlation functions is imposed by the Ornstein–Zernike equation [19,20]

$$h_{\alpha\beta}(1,2) = c_{\alpha\beta}(1,2) + \sum_\gamma n_\gamma \int c_{\alpha\gamma}(1,3) h_{\beta\gamma}(2,3) \mathrm{d}3. \tag{5}$$

Within HNC, $B'_{\alpha\beta} = B_{\alpha\beta} = 0$, and Eq. (1) coincides with the expression derived by Singer and Chandler [21] and employed in [10,22]. We use MS [12]

$$B_{\alpha\beta} = -0.5 w_{\alpha\beta}^2 \tag{6}$$

which is more accurate for fluids with the short-range pair potentials [13]. Further the indici u and v stand for a solute and solvent respectively. For highly diluted solutions ($n_u \ll n_v$),

$$\mu_u/kT = -n_v \int \left[h_{uv} - w_{uv} - 0.5 h_{uv}\left(w_{uv} + w_{uv}^2/6 \right) \right] d\vec{r} \tag{7}$$

and MS for mixtures [23] has the form

$$w_{uv} = n_v \int c_{uv}(1,3) h_{uv}(2,3) d3 - 0.5 w_{uv}^2$$
$$w_{vv} = n_v \int c_{vv}(1,3) h_{vv}(2,3) d3 - 0.5 w_{vv}^2. \tag{8}$$

First, the conventional LJ model is considered. In this model, the pair potential equals

$$\phi_{\alpha\beta} = 4\epsilon_{\alpha\beta}\left[(\sigma_{\alpha\beta}/r)^{12} - (\sigma_{\alpha\beta}/r)^{6} \right] \tag{9}$$

with the mixing rules: $\sigma_{\alpha\beta} = 0.5(\sigma_\alpha + \sigma_\beta)$, $\epsilon_{\alpha\beta} = (\epsilon_\alpha \epsilon_\beta)^{1/2}$. The potential (9) treats a solute as a single atom. For a simple model of a large multi-atomic solute, the Hamaker theory of the colloid dispersion forces [16] can be employed. In this model, a solute is treated as an impenetrable sphere of the radius σ_u. Each solute volume element interacts with a solvent molecule via the LJ potential, i.e., with the same coordinate function as in Eq. (9). Then an effective solute–solvent pair potential results from integration over the solute volume

$$\phi_{uv} = A\left[r^6 + O(r^5) \right] / (r^2 - \sigma_u^2)^9 - B/(r^2 - \sigma_u^2)^6, \; r > \sigma_u \tag{10}$$

where the constants A and B determine the strength of the 'soft' repulsive and attractive solute–solvent interactions respectively, and $O(r^5)$ is a polynomial of the fifth power. Within the solute, 'hard' repulsion is assumed

$$\phi_{uv} = \infty, \; r \leqslant \sigma_{uv}. \tag{11}$$

It should be noted that the Hamaker theory describes interactions between two macroscopic particles, and the 'soft' repulsion is neglected in this theory. In the statistical approach, inclusion of the 'soft' repulsion is necessary to balance an extremely high (and non-physical) attraction at small distances between the solute and solvent molecules. Since the qualitative behaviour of the 'soft' repulsion is determined by the coordinate term of the highest order, the polynomial $O(r^5)$ is neglected further. Yet for simplicity, the constants A and B are scaled so that thee potential (10) is similar to the LJ potential (9) at large distances $r \gg \sigma_u$. Then

$$\phi_{uv} = 4\epsilon_{uv}\left[z^6/(z^2 - R^2)^9 - 1/(z^2 - R^2)^3 \right], \; z > R \tag{12}$$

where $z = r/\sigma_v$, $R = \sigma_u/\sigma_v$. We use the term 'distributed' LJ (DLJ) for both the potential (11)–(12) and the model that employs this potential to describe the solute–solvent interactions. The solvent–solvent interactions retain the LJ form (9) within the DLJ model. One may expect that the conventional LJ model underestimates while the DLJ model overestimates the solute–solvent interactions.

3. Results and discussion

Numerical solution to the Eqs. (8) was obtained using the method similar to that of [23] on the grid of 1024 points with the mesh size of $0.05\sigma_v$. First, we consider the qualitative behaviour of the chemical potential of the LJ solute. The ratio $x = \mu_u/[kT(1+R)^3]$ is listed in Table 1 for several combinations of the dimensionless solvent density $\rho = n\sigma_v^3$ and the LJ parameters. The values of R at which the function $x(R)$ becomes constant (i.e. obeys the cubic law imposed by SPT) rise with the solvent density. Increase of the solute–solvent interaction strength also complicates behaviour of $x(R)$. Within the parameter region where $x(R)$ is an increasing function, μ_u rises faster than the third power of the solute size.

Table 1
The ratio $x = \mu_u/[kT(1+R)^3]$ for the LJ solute

R					
2	4	8	16	20	25
$\rho = 0.2$, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.01$					
0.055	0.056	0.057	0.057	0.057	0.057
$\rho = 0.4$, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.01$					
0.125	0.131	0.134	0.136	0.136	0.136
$\rho = 0.4$, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.1$					
0.163	0.178	0.184	0.186	0.186	0.187
$\rho = 0.8$, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.01$					
0.329	0.361	0.377	0.384	0.385	0.386
$\rho = 0.8$, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.4$					
0.600	0.738	0.861	0.885	0.889	0.894

Therefore, it is interesting to check how accurate can be the lower order approximations employed in the current continuum solvation models.

To examine the size effects in nonpolar solvation, the solute chemical potentials for both LJ and DLJ models were calculated using Eq. (7) and then were fitted to the simple approximations

$$\mu_u/kT = \alpha_v + \beta_v(1+R)^3 \tag{13}$$

where $(1+R)^3$ accounts for the excluded volume, and

$$\mu_u/kT = \alpha_s + \beta_s(1+R)^2 \tag{14}$$

where $(1+R)^2$ accounts for SAS. In the continuum solvation models, SAS is determined by rolling the water molecule over the molecular surface of the solute. A water molecule is assumed to be a sphere of radius $a_w = 1.4$ Å that is consistent with its diameter of 2.77 Å within SPT [6]. Typical radius of the united model of the methyl group $a_m = 2$ Å. Then the water, methane, and decane molecular volumes equal $V_w = 11.5$ Å^3, $V_m = 33.5$ Å^3, and $V_d = 198$ Å^3, respectively. Therefore, the solute/solvent size ratio R for those alkanes usually employed for fitting the nonpolar solvation energies in the continuum models is in a relatively narrow range from $a_m/a_w = 1.4$ to $(V_d/V_w)^{1/3} = 2.6$. Solvation specifies of those solutes with the size less than 3 Å (i.e. about $2a_w$) differs from that of larger solutes [24]. Therefore preferable lower limit of the solute sizes chosen for fitting should be equal $R = 2$. Dimensionless solvent density was assigned 0.8 (cf. with that of water $\rho = 0.71$ [6]). The LJ parameters $\epsilon_{\alpha\beta}/kT$ equal 0.27 and 0.35 for water–water and methane–water interactions, respectively [5]. Two parameter combinations were chosen to account for weak and strong interactions: $\epsilon_v/kT = \epsilon_u/kT = 0.01$ and $\epsilon_v/kT = \epsilon_u/kT = 0.4$. It should be noted that the combination of the weak solute and strong solvent interactions does not have specific features [11].

3.1. LJ model

First, the chemical potential was calculated using Eq. (7) for weak interactions within the range $2 \leqslant R \leqslant 4$ and then fitted to Eq. (13)

$$\mu_u/kT = (-1.15 \pm 0.12) + (0.370 \pm 0.002)(1+R)^3,$$
$$\epsilon_v/kT = \epsilon_u/kT = 0.01,\ 2 \leqslant R \leqslant 4. \tag{15}$$

The latter approximation is not only an accurate fit within the range of R considered but also allows for extrapolation into the region of high $R < 20$ with the error less than 5% (see Table 2). The fit to Eq. (14)

$$\mu_u/kT = (-12.7 \pm 1.8) + (2.27 \pm 0.11)(1+R)^2,$$
$$\epsilon_v/kT = \epsilon_u/kT = 0.01,\ 2 \leqslant R \leqslant 4 \tag{16}$$

Table 2
Chemical potential of a solute (μ_u/kT)

R	2	3	4	5	6	8	10	12	16	20
LJ model, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.01$										
Eq. (7)	8.96	22.4	45.2	79.5	128	275	507	840	1890	3570
Eq. (15)	8.83	22.5	45.1	78.9	126	269	491	812	1820	3430
Eq. (16)	7.72	23.6	44.0	69.0	98.5	171	262	371	643	988
LJ model, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.4$										
Eq. (7)	16.2	46.1	92.3	161	281	628	1160	1930	4350	8230
Eq. (17)	16.7	45.7	93.5	165	264	566	1040	1720	3840	7250
Eq. (18)	14.3	48.0	91.3	144	207	361	554	786	1370	2100
DLJ model, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.01$										
Eq. (7)	74.9	227	514	982	1670	3890	7530			
Eq. (19)	67.4	234	508	918	1490	3230	5940			
Eq. (20)	54.4	247	495	797	1160	2030	3230			
DLJ model, $\epsilon_v/kT = \epsilon_{uv}/kT = 0.4$										
Eq. (7)	156	453	1010	1870	3200	7420	14300			
Eq. (21)	142	466	998	1790	2900	6280	11600			
Eq. (22)	117	491	973	1560	2260	3970	6110			

can provide the errors up to 10% within the range of R employed for fit. However the extrapolation errors quickly increase from 12% at $R = 5$ to 30% at $R = 6$. At strong molecular interactions, both Eq. (13)

$$\mu_u/kT = (-4.43 \pm 1.26) + (0.783 \pm 0.016)(1+R)^3, \quad \epsilon_v/kT = \epsilon_u/kT = 0.4, 2 \leqslant R \leqslant 4 \qquad (17)$$

and Eq. (14)

$$\mu_u/kT = (-29.1 \pm 2.5) + (4.82 \pm 0.14)(1+R)^2, \quad \epsilon_v/kT = \epsilon_u/kT = 0.4, 2 \leqslant R \leqslant 4 \qquad (18)$$

remain quite accurate within the range of R used for fitting. However, the volume fit (17) can provide extrapolation errors of more than 10% at $R > 10$. The SAS-based for (18) produces an error of 40% at $R = 6$ and therefore is not useful for extrapolation.

3.2. DLJ model

Though the DLJ potential has a longer range than the LJ potential, the qualitative behaviour of $\mu_u(R)$ is similar for both models. For weak interactions, Eq. (13)

$$\mu_u/kT = (-74.3 \pm 11.9) + (4.83 \pm 0.11)(1+R)^3, \quad \epsilon_v/kT = \epsilon_u/kT = 0.01, 2 \leqslant R \leqslant 4 \qquad (19)$$

is quite accurate for interpolation though it can have extrapolation errors of more than 10%. Eq. (14)

$$\mu_u/kT = (-287 \pm 52) + (33.8 \pm 2.4)(1+R)^2, \quad \epsilon_v/kT = \epsilon_u/kT = 0.01, 2 \leqslant R \leqslant 4 \qquad (20)$$

can be employed only for interpolation, with errors up to 20%. Similar conclusions can be drawn for the strong interactions where the chemical potential can be approximated as

$$\mu_u/kT = (-118 \pm 16) + (9.13 \pm 0.14)(1+R)^3, \quad \epsilon_v/kT = \epsilon_u/kT = 0.4, 2 \leqslant R \leqslant 4 \qquad (21)$$

or

$$\mu_u/kT = (-521 \pm 89) + (64.0 \pm 4.1)(1+R)^2, \quad \epsilon_v/kT = \epsilon_u/kT = 0.4, 2 \leqslant R \leqslant 4. \qquad (22)$$

Though the quantitative conclusions for the LJ fluids cannot be automatically extended to hydration phenomena, they indicate advantages of the volume-based models over the SAS-based models. The excluded volume fit (13) is obviously more accurate and hopefully can be employed for extrapolation, at least when the molecular interactions are weak. The SAS fit (14) can be useful for interpolation only taking into account that the errors of 10–20% for the nonpolar solvation energy of the small organic molecules usually do not exceed 0.5 kcal/mol which is within the accuracy limits of the current continuum models [2,9]. This means in particular that if the SAS-based solvation model is fitted to the data for the first ten alkanes, it may be safely applicable only for those solutes not larger than decane.

References

[1] V. Lounnas, B.M. Pettitt, L. Findsen and S. Subramaniam, J. Phys. Chem., 96 (1992) 7157; D.E. Smith and A.D.J. Haymet, J. Chem. Phys., 98 (1993) 6445; B. Gulliot and Y. Guissiani, J. Chem. Phys., 99 (1993) 8075; A.A. Rashin and B.M. Bukatin, J. Phys. Chem., 98 (1994) 386; T. Lazaridis and M.E. Paulaitis, J. Phys. Chem., 98 (1994) 635.

[2] W.C. Still, A. Tempczyk, R.C. Hawley and T. Hendrickson, J. Am. Chem. Soc., 112 (1990) 6127; C.J. Cramer and D.G. Truhlar, J. Comput.-Aided Mol. Des., 6 (1992) 629; D. Sitkoff, K.A. Sharp, and B. Honig, J. Phys. Chem., 98 (1994) 1978; A.A. Rashin, L. Young and I.A. Topol, Biophys. Chem., 51 (1994) 359.

[3] C. Chothia, Ann. Rev. Biochem., 53 (1984) 537.

[4] A. Ben-Naim and R.M. Mazo, J. Phys. Chem., 97 (1993) 10829; A. Ben-Naim, Biophys. Chem., 51 (1994) 203.

[5] H. Reiss, H.L. Frisch and J.L. Lebowitz, J. Chem. Phys., 31 (1959) 369; H. Reiss, H.L. Frish, E. Helfand and J.L. Lebowitz, J. Chem. Phys., 32 (1960) 119; D.M. Tully-Smith and H. Reiss, J. Chem. Phys., 53 (1970) 4015; H. Reiss and R.V. Casberg, J. Chem. Phys., 61 (1974) 1107; F.H. Stillinger, J. Solution Chem., 2 (1973) 141.

[6] R.A. Pierotti, Chem. Rev., 76 (1976) 717; N. Nandi and I.N. Basumallick, Z. Phys. Chem. (Munich), 173 (1991) 179.

[7] P.J. Rossky, K.A. Sharp, B. Honig and S.K. Kumar, Biophys. Chem., 51 (1994) 212.

[8] Y. Marcus, Biophys. Chem., 51 (1994) 214.

[9] A.B. Schmidt and R.M. Fine, Mol. Simulation, 13 (1994) 347.

[10] J. Perkyns and B.M. Pettitt, Biophys. Chem., 51 (1994) 214.

[11] A.B. Schmidt, Biophys. Chem., 51 (1994) 393.

[12] G.A. Martynov and G.N. Sarkisov, Mol. Phys., 49 (1983) 1495.

[13] P. Ballone, G. Pastore, G. Galli and D. Gazzillo, Mol. Phys.,

59 (1986) 275; D. Gazzillo, J. Chem. Phys., 95 (1991) 4565; L. Lue and D. Blankschtein, J. Phys. Chem., 96 (1992) 8582.
[14] A. Ben-Naim and Y. Marcus, J. Chem. Phys., 81 (1984) 2016.
[15] L.R. Pratt and A. Pohorille, Proc. Natl. Acad. Sci. USA, 89 (1992) 2995; B. Madan and B. Lee, Biophys. Chem., 51 (1994) 279.
[16] H.C. Hamaker, Physica, 4 (1937) 1058.
[17] T. Morita and K. Hiroike, Progr. Theor. Phys., 25 (1961) 537.
[18] O.E. Kiselev and G.A. Martynov, J. Chem. Phys., 93 (1990) 1942.
[19] G.A. Martynov, Fundamental Theory of Liquids, Adam Hilger, New York, 1992.
[20] J.P. Hansen and I.R. McDonald, Theory of Simple Liquids, Academic Press, New York, 2nd edn., 1986.
[21] S.J. Singer and D. Chandler, Mol. Phys., 55 (1985) 621.
[22] D.A. Zichi and P.J. Rossky, J. Phys. Chem., 84 (1985) 1712; H.-A. Yu and M. Karplus, J. Chem. Phys., 89 (1988) 2366; H.-A. Yu, B. Roux and M. Karplus, J. Chem. Phys., 92 (1989) 5020.
[23] A.B. Schmidt, Phys. Rev. A, 45 (1992) 7636.
[24] A.A. Rashin and M.A. Bukatin, J. Phys. Chem., 95 (1991) 2942; Ibid, 98 (1994) 386.