Poisson–Boltzmann Continuum Solvation Models for Nonaqueous Solvents I. 1-Octanol

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A Poisson–Boltzmann continuum solvation model coupled with ab initio quantum calculation was developed for 1-octanol. It was applied to the calculation of the solvation free energies of various solutes consisting of C, H, and O in 1-octanol and their 1-octanol/water partition coefficients.

Numerous methods have been developed to model the solvent effect. Although explicit inclusion of solvent molecules is desirable, the daunting computational expense associated with the "explicit" solvent model led to the development of "implicit" continuum solvation models. Among a number of variants,[1,2] the Poisson–Boltzmann (PB) model[3,4] is the most rigorous and has been used to calculate various solvent effects of water.[5–7] Solvents other than water, however, have received much less attention. Cyclohexane is the only nonaqueous solvent for which a PB model has been developed.[8] Here, we report a PB model for 1-octanol, one of the most important nonaqueous solvents. The combination of this model with the one for water allows a high accuracy quantum calculation of the partition coefficients ($\log P_{o/w}$) between 1-octanol and water, which is widely applicable to problems such as the membrane permeability.[9]

Our model is an extension of the PB model[10,11] implemented in Jaguar 4.1, an ab initio quantum chemistry software.[12] The solvation process is depicted hypothetically as two steps; (1) creating a cavity of the same size as the solute in solvent and then (2) charging the cavity to turn on the electrostatic interaction with the solvent. The solvation free energy, ΔG_{solv}, is composed of the electrostatic contribution, ΔG_{elec}, and the nonelectrostatic (or nonpolar) contribution, ΔG_{np}

$$\Delta G_{\text{solv}} = \Delta G_{\text{np}} + \Delta G_{\text{elec}}. \qquad (1)$$

ΔG_{np}, which is related to the energy cost of the cavity creation in solvent, is simply treated to depend linearly on the molecular surface area (MSA) of a solute in the solvent

$$\Delta G_{\text{np}} = \gamma \cdot \text{MSA} + b. \qquad (2)$$

ΔG_{elec} is the interaction of a charge distribution inside the solute (represented by a set of atom-centered electrostatic potential-fitted (ESP) charges) with the solvent medium of a dielectric constant 78 for water and 10.3 for 1-octanol.[13] The calculation procedure is as follows. A gas-phase quantum calculation with geometry optimization is carried out first to obtain the ESP charges of solute atoms. With these charges, the PB equation is solved to generate the reaction field of the solvent, which is represented as a set of polarization charges at the solute/solvent boundary. The Hamiltonian of the solute is then modified to include the solute-solvent interaction due to the reaction field. This leads to a new wavefunction and in turn a new set of ESP charges. This process is repeated self-consistently until convergence (0.1 kcal/mol of energy change) is reached, and the geometry is reoptimized along

the energy gradient. All calculations were performed at the HF/6-31G** level.

The solute/solvent boundary is built up as a van der Waals (vdW) envelope with a chosen set of vdW radii of solute atoms. The MSA of a solute is estimated by hypothetically rolling a solvent probe (of the radius estimated from the molecular weight and density;[12] 1.4 Å for water and 3.2 Å for 1-octanol) around the vdW envelope. The atomic radius parameters used to build the vdW envelope of a solute in water have been optimized in numerous studies such as the work of Marten and coworkers.[14] For solutes in nonaqueous solvents, however, there has been no consensus on which set of atomic radii should be used. Moreover, two parameters γ and b in Eq 2 have been optimized only for aqueous solution[10,11] and cyclohexane.[8] Here we determine the optimal set of atomic radii, γ, and b for 1-octanol by fitting them to experimental ΔG_{solv}'s in the same manner as for water. It is expected that the interactions of C and H with 1-octanol are not crucially different from those with water. Indeed the variations in their radii do not improve the quality of the model (results not shown). Thus, the values optimized for water[14] are used for C and H (1.15 Å for H, 1.9 Å for sp^3 C, 2.0 Å for sp^2 C, and 2.1 Å for sp C). In this letter, only the radius of O is optimized (to 2.0 Å; see below) for all types of O's in various solutes consisting of C, H, and O. This will be extended in future to a model covering a larger set of solutes containing C, H, O and N by optimizing the radius of N.

Experimental ΔG_{solv}'s of 127 solutes in water were from the collections of Hawkins et al.[15] and Wang et al.[16] Those of 112 solutes in 1-octanol were from the collections of Li et al.[15] and Wang et al.[16] or derived from the vast collection of experimental $\log P_{o/w}$ values by Hansch[9] in combination with ΔG_{solv}'s in water.[15,16] All data are defined with respect to the conventional standard states [1 mol/L(g) → 1 mol/L(sol)].

To optimize the parameters γ and b, we assume that ΔG_{elec}'s of alkane solutes are small enough to approximate ΔG_{solv} with ΔG_{np}.[10,11] Then, ΔG_{np}'s in Eq 2 are replaced by experimental ΔG_{solv}'s of a series of linear and branched alkanes (15 in water and 9 in 1-octanol), and their linear relationship with the calculated MSA's is determined for each solvent (Figure 1). The assumption of negligible ΔG_{elec} is quite valid since ΔG_{elec} is -0.4 kcal/mol on average ranging from -0.04 to -0.97 kcal/mol. The relationships
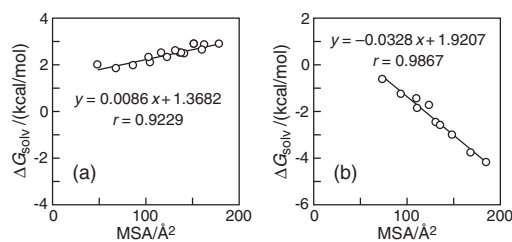

Figure 1. ΔG_{solv}(exptl) ($\approx \Delta G_{\text{np}}$) as a function of MSA for linear and branched alkanes in (a) water and (b) 1-octanol.

between ΔG_{np} (in kcal/mol) and MSA (in Å^2) are

$$\Delta G_{np}(\text{water}) = 0.0086 \times \text{MSA} + 1.368 (r = 0.9229), \quad (3)$$

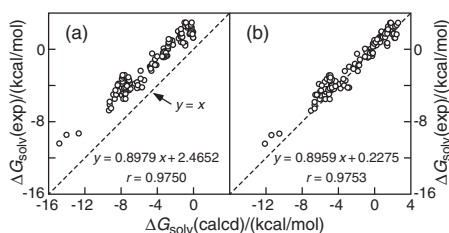$$\Delta G_{np}(\text{1-octanol}) = -0.0328 \times \text{MSA} + 1.921 (r = 0.9867), \quad (4)$$

with r the linear correlation coefficient. The linear correlation is better for less polar solvent 1-octanol, since ΔG_{elec} is smaller and the assumption $\Delta G_{solv} \approx \Delta G_{np}$ is more valid. The slope γ is related to the surface tension between the alkane solutes and the solvent. The surface tension between two liquids is positive when they are immiscible and negative when miscible. The positive γ in Eq 3 and the negative γ in Eq 4 indicate that hydrophobic alkane solutes favor solvation not in polar solvents (water) but in nonpolar solvents (1-octanol), which is in accord with the rule ''like dissolves like.''

Eqs 3 and 4 are then used to estimate ΔG_{np} of more general types of solutes (aliphatic and aromatic hydrocarbons, alcohols, ethers, ketones, aldehydes, and esters) in water (127 solutes) and in 1-octanol (112 solutes) from the calculated MSA values. This ΔG_{np} is combined with ΔG_{elec} calculated from the PB equation to give a complete ΔG_{solv}.

Figure 2a shows that ΔG_{elec} alone does not represent ΔG_{solv} well even in water, one of the most polar solvents. Although ΔG_{solv}(calcd)'s correlates well with ΔG_{solv}(exptl)'s with r of 0.9750, the calculation consistently overestimates the solubility, yielding a big RMS error of 3.0 kcal/mol. Adding ΔG_{np} of Eq 3 improves the match between the calculation and experiment significantly ($r = 0.9753$, RMS error = 0.87 kcal/mol; Figure 2b).

In 1-octanol, the correlation between ΔG_{solv}(exptl) and ΔG_{solv}(calcd) from the original PB model in Jaguar is not very good ($r = 0.7262$, RMS error = 1.9 kcal/mol; Figure 3a), since Jaguar uses a crude set of radii (1.9 Å for all types of C's, 1.6 Å for O, and 1.15 Å for H) and does not include ΔG_{np} for nonaqueous solvents. Adding ΔG_{np} of Eq 4 and using the radii optimized for aqueous solution improve the correlation significantly ($r = 0.8460$; Figure 3b). However, all the data are located above the $y = x$ line and the RMS error is even larger (2.8 kcal/mol).
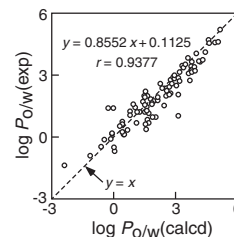
We then tune the O radius in solutes for the best correlation

Figure 2. ΔG_{solv}(exptl) versus ΔG_{solv}(calcd) in water. (a) ΔG_{solv}(calcd) = ΔG_{elec}. (b) ΔG_{solv}(calcd) = $\Delta G_{elec} + \Delta G_{np}$.
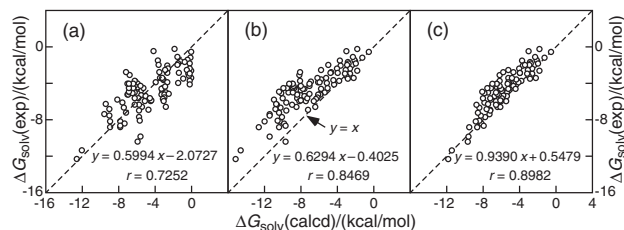
Figure 3. ΔG_{solv}(exptl) versus ΔG_{solv}(calcd) in 1-octanol. (a) ΔG_{solv}(calcd) = ΔG_{elec}. (b) ΔG_{solv}(calcd) = $\Delta G_{elec} + \Delta G_{np}$ with the same O radius as in water and (c) with the optimized O radius.

Figure 4. $\log P_{o/w}$(exptl) versus $\log P_{o/w}$(calcd).

between ΔG_{solv}(exptl) and ΔG_{solv}(calcd) in 1-octanol. The hydrogen bond between O-containing solutes and solvent would be as strong in 1-octanol as in water and the solute–solvent distance would be greater in 1-octanol. Thus, the O radius is increased to 2.0 Å for solutes in 1-octanol, which leads to a more positive ΔG_{elec}. Figure 3c shows a good correlation between ΔG_{solv}(exptl) and ΔG_{solv}(calcd) ($r = 0.8982$, RMS error = 1.3 kcal/mol).

Finally, $\log P_{o/w}$ values of 92 solutes common to both water and 1-octanol are calculated with the PB models developed for water and for 1-octanol (Figure 4):

$$\log P_{o/w} = [\Delta G_{solv}(\text{water}) - \Delta G_{solv}(\text{octanol})]/2.303RT \quad (5)$$

with R the gas constant and $T = 298$ K. These calculations also yield a good correlation with experiment[9] ($r = 0.9377$, RMS error = 0.57), which is better than the one for ΔG_{solv} in 1-octanol. It is probably due to partial cancellations of common errors in the evaluation of ΔG_{solv} for water and 1-octanol. Further studies are needed to confirm this cancellation effect.

In summary, a PB solvation model was developed for 1-octanol; the electrostatic part of the solvation free energy obtained from the PB equation was combined with the nonpolar part obtained from the linear relationship with the MSA's of solutes. The model was further improved by increasing the O radius of solutes in 1-octanol from that in water. The nonpolar contribution is expected to be even more drastic in a less polar solvent such as n-hexadecane and the development of a PB solvation model for n-hexadecane is in progress.

References
1   J. Tomasi and M. Persico, *Chem. Rev.*, **94**, 2027 (1994).
2   W. C. Still, A. Tempczyk, R. C. Hawley, and T. Hendrickson, *J. Am. Chem. Soc.*, **112**, 6127 (1990).
3   B. Honig, K. A. Sharp, and A.-S. Yang, *J. Phys. Chem.*, **97**, 1101 (1993).
4   B. Honig and A. Nicholls, *Science*, **268**, 1144 (1995).
5   Y. H. Jang, W. A. Goddard, III, K. T. Noyes, L. C. Sowers, S. Hwang, and D. S. Chung, *Chem. Res. Toxicol.*, **15**, 1023 (2002).
6   S. Hwang, Y. H. Jang, and D. S. Chung, *Chem. Lett.*, **2001**, 1182 (2001).
7   Y. H. Jang, S. Hwang, and D. S. Chung, *Chem. Lett.*, **2001**, 1316 (2001).
8   D. Sitkoff, N. Ben-Tal, and B. Honig, *J. Phys. Chem. B*, **100**, 2744 (1996).
9   C. Hansch and A. Leo, in "Exploring QSAR," American Chemical Society Publishers, Washington, DC. (1995).
10 D. Sitkoff, K. A. Sharp, and B. Honig, *J. Phys. Chem.*, **98**, 1978 (1994).
11 D. J. Tannor, B. Marten, R. Murphy, R. A. Friesner, D. Sitkoff, A. Nicholls, M. Ringnalda, W. A. Goddard, and B. Honig, *J. Am. Chem. Soc.*, **116**, 11875 (1994).
12 Jaguar 4.1, Schrödinger Inc., Portland, OR (2001).
13 "CRC Handbook of Chemistry and Physics," 80th ed., CRC Press, Boca Raton (1999-2000).
14 B. Marten, K. Kim, C. Cortis, R. A. Friesner, R. Murphy, M. Ringnalda, D. Sitkoff, and B. Honig, *J. Phys. Chem.*, **100**, 11775 (1996).
15 J. Li, T. Zhu, G. D. Hawkins, P. Winget, D. A. Liotard, and C. J. Cramer, *Theor. Chem. Acc.*, **103**, 9 (1999).
16 J. Wang, W. Wang, S. Huo, M. Lee, and P. A. Kollman, *J. Phys. Chem. B*, **105**, 5055 (2001).