

# Comparative Study on Solvation Free Energy Expressions in Reference Interaction Site Model Integral Equation Theory

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The performance of the recently proposed partial wave (PW) free energy functional is compared with those of two previous expressions, Gaussian fluctuation (GF) and hypernetted chain (HNC), within the reference interaction site model framework. The applications to the calculations of ambient and supercritical water, solvation free energies of organic molecules, and partition coefficients clearly show that the PW and GF free energy expressions provide more reliable results than the HNC functional, indicating rather associative situations of geometry in ordinary liquids of medium-sized molecules.

## 1. Introduction

Most important chemical reactions go not in the gas phase but in liquids. For example, many biochemical reactions in the body take place in an aqueous environment. Thus it has been a challenge to assess the influence of solvent on thermodynamic properties and structures of molecules. Numerous theoretical studies have been performed to address this issue. Most of atomistic treatments are based on molecular simulation techniques and are capable of providing detailed information about microscopic properties. This class of treatments however contains the drawback of a large computational load required for a sufficient sampling. It is also difficult to estimate the absolute value of free energy because of the insufficient accuracy of sampling in the free energy perturbation technique. These problems have motivated the development of cost-effective models maintaining the microscopic description of solvent.

Integral equation theory based on classical statistical mechanics for equilibrium states has provided fast alternatives to molecular simulations.<sup>1</sup> The best feature of the theory is that free energies are expressed in closed form analytical expressions of distribution functions. In particular, the reference interaction site model (RISM) integral equation theory initiated by Chandler and Andersen<sup>2</sup> has drawn a lot of interest for the past three decades. The RISM theory focuses on site–site radial distribution functions for describing the solvation structures of molecular liquids. Thus the thermodynamic properties can be calculated with reasonable computational cost compared to molecular simulations. The extended version of the RISM theory for polar and charged solutes<sup>3,4</sup> typically associated with the hypernetted chain (HNC) closure relation for simple liquids has been applied to a variety of problems in solution chemistry.<sup>5–9</sup> Moreover, the introduction of RISM in quantum chemistry for a microscopic solvation model<sup>10,11</sup> has been highlighted as a chief improvement over the previous phenomenological models based on dielectric continuum.<sup>12</sup>

Although RISM was expected to be a promising alternative to molecular simulations, difficulties are encountered in its applications. The theory revealed to provide only rough agreement for solvation structures.<sup>5,7</sup> It also turned out that the accuracy of the calculated solvation free energies is not satisfactory.<sup>9</sup> A lot of effort has been devoted for circumventing these problems especially from the diagrammatically proper integral equation theory<sup>13–15</sup> and the density functional theory (DFT).<sup>16–20</sup> These theories have not been fully matured to provide useful computational methods in place of the original RISM. More recently, we have formulated another class of integral equation theory based on the distributed partial wave (PW) expansion.<sup>21–24</sup> The PW formulation bridges RISM and more rigorous theory based on the molecular OZ (MOZ) equation, because the MOZ equation in the partial form reduces to the RISM equation in the spherical expansion limit (i.e., each partial function is of only its site–site distance). Although there exists close resemblance between PW in the limit and DFT, PW is more systematic with angular correlations as higher components. Some specific studies based on RISM<sup>22</sup> and coupled RISM and simulation methods<sup>25–29</sup> have reported that the free energy expression of PW is more accurate than previous expressions derived with broader assumptions.

The objective of the present work is to study the performances of the energy expressions more extensively within the RISM framework to test the limitation of the method. We describe the theoretical background in the following section. Comparisons with molecular simulations for ambient and supercritical states of water are presented in section 3. We also examine solvation free energies and partition coefficients of organic molecules in sections 4 and 5. Conclusions are depicted in section 6.

## 2. Free Energy Expressions

We briefly review free energy expressions in the RISM theory. In the standard HNC theory, Helmholtz free energies can be calculated in closed form expressions of total and direct correlation functions.<sup>30</sup> Analogous formulas for solvation were derived within the RISM theory. One is the Chandler–

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Singh–Richardson equation,<sup>31</sup> which assumes Gaussian fluctuations (GF) of solvent

$$\Delta\mu^{(\text{GF})} = -\frac{\rho}{2\beta} \sum_{\alpha i} \int 4\pi r^2 [2c_{\alpha i}^{uv}(r) + \tilde{h}_{\alpha i}^{uv}(r)c_{\alpha i}^{uv}(r)] dr \quad (1)$$

where  $\tilde{\mathbf{h}}^{uv}$  and  $\mathbf{c}^{uv}$  denote site–site total and direct correlation functions for solvation. We henceforth use the Greek and Roman subscripts,  $\alpha, \gamma, \dots$ , and  $i, j, \dots$ , for the interaction sites of the solute and solvent, respectively. The correlation functions are related by the Chandler–Andersen or the RISM equations<sup>2</sup>

$$\hat{\mathbf{h}}^{uv} = \hat{\omega}^u \hat{\mathbf{c}}^{uv} (\hat{\omega}^v + \rho \hat{\mathbf{h}}^{vv}) \quad (2)$$

$$\hat{\mathbf{h}}^{vv} = \hat{\omega}^v \hat{\mathbf{c}}^{vv} (\hat{\omega}^v + \rho \hat{\mathbf{h}}^{vv}) \quad (3)$$

In the equations,  $\hat{\mathbf{h}}^{vv}$  and  $\hat{\mathbf{c}}^{vv}$  are correlation functions for pure solvent, and the carets denote Fourier transforms. The RISM equations couple the contributions of different interaction sites in terms of the intramolecular correlation functions

$$\hat{\omega}_{\alpha\gamma}^u(k) = j_0(kL_{\alpha\gamma}^u) = \frac{\sin(kL_{\alpha\gamma}^u)}{kL_{\alpha\gamma}^u} \quad (4)$$

of the site–site distance  $L_{\alpha\gamma}^u$ , and analogous functions of  $L_{ij}^v$  for solvent. Another free energy expression was derived by Singer and Chandler based on the HNC closure relation<sup>32</sup>

$$\Delta\mu^{(\text{HNC})} = -\frac{\rho}{2\beta} \sum_{\alpha i} \int 4\pi r^2 \{2c_{\alpha i}^{uv}(r) - \tilde{h}_{\alpha i}^{uv}(r)[\tilde{h}_{\alpha i}^{uv}(r) - c_{\alpha i}^{uv}(r)]\} dr \quad (5)$$

Although  $\Delta\mu^{(\text{HNC})}$  includes a term which is absent in  $\Delta\mu^{(\text{GF})}$ , previous studies have found that  $\Delta\mu^{(\text{GF})}$  gives superior results in comparison with  $\Delta\mu^{(\text{HNC})}$ ,<sup>8,9</sup> indicating that the additional term in  $\Delta\mu^{(\text{HNC})}$  has a significant drawback in the calculations of molecular liquids.

More recently, we derived another free energy functional based on the PW expansion.<sup>21,22</sup> The expansion decomposes molecular correlation functions into distributed partial functions, each of which has an amplitude at the corresponding pair of interaction sites. Then the partial function is expanded into the rotational invariants of Blum.<sup>33,34</sup> The HNC functional of the PW theory in the spherical expansion limit, which is applicable in RISM, is

$$\Delta\mu^{(\text{PW})} = -\frac{\rho}{2\beta} \sum_{\alpha i} \int 4\pi r^2 \{c_{\alpha i}^{uv}(r) - \tilde{h}_{\alpha i}^{uv}(r)[h_{\alpha i}^{uv}(r) - c_{\alpha i}^{uv}(r)]\} dr \quad (6)$$

$$\hat{\mathbf{h}}^{uv} = \hat{\omega}^u \hat{\mathbf{h}}^{uv} \hat{\omega}^v \quad (7)$$

It is important to see the behaviors of the above expressions in the extended atom limit (EAL, in the infinite separation limit of distinct interaction sites) and the united atom limit (UAL, all interaction sites in a molecule coincides at the same position). In EAL, the exact free energy is that for simple liquid (SL) times the product of numbers of interaction site of solute and solvent,  $N_u$  and  $N_v$

$$\Delta\mu^{(\text{Exact})}(\text{EAL}) = N_u N_v \Delta\mu^{(\text{SL})} \quad (8)$$

Within the framework of HNC,  $\Delta\mu^{(\text{SL})}$  is given by

$$\Delta\mu^{(\text{SL})} = -\frac{\rho}{2\beta} \int 4\pi r^2 \{2c^{uv}(r) - h^{uv}(r)[h^{uv}(r) - c^{uv}(r)]\} dr \quad (9)$$

In EAL,  $\hat{\omega}^u$  and  $\hat{\omega}^v$  are the identity matrixes, and the RISM equations reduce to the collections of decoupled OZ equations for simple liquids

$$\hat{h}^{uv} = \hat{c}^{uv}(1 + \rho \hat{h}^{vv}) \quad (10)$$

$$\hat{h}^{vv} = \hat{c}^{vv}(1 + \rho \hat{h}^{vv}) \quad (11)$$

Then  $\Delta\mu^{(\text{HNC})}$  consistent with the RISM/HNC theory reproduces the exact HNC free energy precisely

$$\Delta\mu^{(\text{HNC})} = \Delta\mu^{(\text{Exact})}(\text{EAL}) \quad (12)$$

$\Delta\mu^{(\text{PW})}$  is also identical to the exact HNC expression for simple liquids as there is no distinction between  $\tilde{\mathbf{h}}$  and  $\mathbf{h}$  in EAL

$$\Delta\mu^{(\text{PW})} = \Delta\mu^{(\text{Exact})}(\text{EAL}) \quad (13)$$

On the other hand, the term proportional to the square of the total correlation functions is missing in  $\Delta\mu^{(\text{GF})}$ , which does not lead to the exact HNC energy

$$\Delta\mu^{(\text{GF})} = \Delta\mu^{(\text{Exact})}(\text{EAL}) - N_u N_v \Theta \quad (14)$$

$$\Theta = \frac{\rho}{2\beta} \int 4\pi r^2 [h^{uv}(r)]^2 dr \geq 0 \quad (15)$$

Let us turn to UAL setting all bond lengths zero. This is identical to the case of an atomic molecule immersed in a simple liquid. We use the same notations,  $\Delta\mu^{(\text{SL})}$ ,  $h^{uv}(r)$ ,  $h^{vv}(r)$ ,  $c^{uv}(r)$ , and  $c^{vv}(r)$ , for the objects concerning the simple liquid as in EAL. The exact free energy in UAL is

$$\Delta\mu^{(\text{Exact})}(\text{UAL}) = \Delta\mu^{(\text{SL})} \quad (16)$$

In the site–site picture, the correlation functions are replicas of  $h^{uv}(r)$  and  $h^{vv}(r)$

$$\tilde{\mathbf{h}}^{uv}(r) = \begin{pmatrix} h^{uv}(r) & h^{uv}(r) & \cdots \\ h^{uv}(r) & h^{uv}(r) & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \quad (17)$$

and for  $\tilde{\mathbf{h}}^{vv}(r)$ . Since all elements of  $\hat{\omega}^u$  and  $\hat{\omega}^v$  are unity in UAL

$$\hat{\omega}(\text{UAL}) = \begin{pmatrix} 1 & 1 & \cdots \\ 1 & 1 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \quad (18)$$

$\mathbf{h}^{uv}(r)$  cannot be determined uniquely by eq 7. One of possible solutions is simply

$$\mathbf{h}^{uv}(r) = \begin{pmatrix} h^{uv}(r) & 0 & \cdots \\ 0 & 0 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \quad (19)$$

**TABLE 1: Errors of the Free Energy Expressions in EAL and UAL<sup>a</sup>**

	EAL	UAL
$\Delta\mu^{(\text{Exact})}$	$N_u N_v \Delta\mu^{(\text{SL})}$	$\Delta\mu^{(\text{SL})}$
$\Delta\Delta\mu^{(\text{HNC})}$	0	$(N_u N_v - 1)\Theta$
$\Delta\Delta\mu^{(\text{GF})}$	$-N_u N_v \Theta$	$-\Theta$
$\Delta\Delta\mu^{(\text{PW})}$	0	0

<sup>a</sup>  $\Delta\Delta\mu = \Delta\mu - \Delta\mu^{(\text{Exact})}$ .  $N_u$  and  $N_v$  are numbers of sites of solute and solvent.

Similarly, one can show that the matrix of the direct correlation functions

$$\mathbf{c}^{\text{uv}}(r) = \begin{pmatrix} c^{\text{uv}}(r) & 0 & \cdots \\ 0 & 0 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \quad (20)$$

suffices for the condition of the simple liquid from the RISM equation. It is noted that the choice of the weights of the correlation functions in  $\mathbf{h}^{\text{uv}}$  and  $\mathbf{c}^{\text{uv}}$  do not alter the result of the present analysis. Unlike EAL, the distinction between  $\tilde{\mathbf{h}}^{\text{uv}}$  and  $\mathbf{h}^{\text{uv}}$  is meaningful.  $\tilde{\mathbf{h}}^{\text{uv}}$  is an extensive object in the sense that the sum of the elements increases by the introduction of new interaction sites. Meanwhile,  $\mathbf{h}^{\text{uv}}$  is intensive. Substituting the above forms into the free energy expressions, we find

$$\Delta\mu^{(\text{HNC})} = \Delta\mu^{(\text{Exact})}(\text{UAL}) + (N_u N_v - 1)\Theta \quad (21)$$

$$\Delta\mu^{(\text{GF})} = \Delta\mu^{(\text{Exact})}(\text{UAL}) - \Theta \quad (22)$$

$$\Delta\mu^{(\text{PW})} = \Delta\mu^{(\text{Exact})}(\text{UAL}) \quad (23)$$

The errors of the free energy expressions in EAL and UAL are summarized in Table 1. The error in  $\Delta\mu^{(\text{HNC})}$  increases positively as the numbers of associated (interacting) interactions sites increase, while that of  $\Delta\mu^{(\text{GF})}$  also increases negatively according to the numbers of dissociated (noninteracting) sites. The present analysis in EAL and UAL indicates that the free energies are in the order,  $\Delta\mu^{(\text{HNC})} \geq \Delta\mu^{(\text{PW})} > \Delta\mu^{(\text{GF})}$ . The real situations will be mostly between the two limits. Thus it is anticipated that  $\Delta\mu^{(\text{HNC})}$  and  $\Delta\mu^{(\text{GF})}$  will give upper and lower bounds of the true free energy of solvation in many applications.

### 3. Result for Water

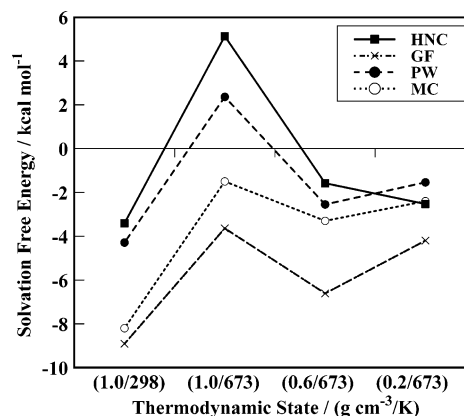
We calculate solvation free energies of a water molecule in water for several thermodynamic conditions using the SPC/E model<sup>35</sup> and compare the results with those of computer simulation.<sup>36</sup> Four thermodynamic states are examined, i.e., one ambient state of 1.0 g/cm<sup>3</sup> at 298 K and three supercritical states of 1.0, 0.6, and 0.2 g/cm<sup>3</sup> at 673 K. The additional van der Waals parameters for the hydrogen sites are taken from ref 37. These parameters do not change the molecular interaction physically but are necessary for convergences in RISM calculations. The site–site interactions are determined by the standard combination rules. The RISM/HNC method is used for site–site correlation functions throughout this paper. The direct iterative inversion space (DIIS) accelerator as used in refs 38 and 39 provides fast convergences in RISM calculations.

We show the result in Table 2 and Figure 1. All energy expressions give qualitatively correct results for the alternation of temperature; i.e., the free energy increases as the temperature becomes higher.  $\Delta\mu^{(\text{PW})}$  is always more positive than  $\Delta\mu^{(\text{GF})}$  as anticipated in the last section. The result of MC simulation shows an irregularity for the alternations of density.  $\Delta\mu^{(\text{GF})}$  and  $\Delta\mu^{(\text{PW})}$  reproduce this feature qualitatively while such an

**TABLE 2: Solvation Free Energies of a Water Molecule in Water (kcal/mol)**

expression	thermodynamic state (g cm <sup>-3</sup> /K)			
	(1.0/298)	(1.0/673)	(0.6/673)	(0.2/673)
$\Delta\mu^{(\text{HNC})}$	-3.41	5.13	-1.58	-2.53
$\Delta\mu^{(\text{GF})}$	-8.91	-3.64	-6.61	-4.20
$\Delta\mu^{(\text{PW})}$	-4.29	2.36	-2.55	-1.54
MC <sup>a</sup>	-8.2	-1.5	-3.3	-2.4

<sup>a</sup> MC simulation, ref 36.



**Figure 1.** Computed profiles of free energies of hydration for a water molecule at several thermodynamic states.

**TABLE 3: The Solvation Free Energy in Water (kcal/mol)**

solute	$\Delta\mu^{(\text{HNC})}$	$\Delta\mu^{(\text{GF})}$	$\Delta\mu^{(\text{PW})}$	expt
ethylene	10.49	0.40	3.75	1.3 <sup>a</sup>
benzene	20.56	-2.48	3.08	-0.87 <sup>a</sup>
toluene	26.40	-3.65	3.10	-0.89 <sup>a</sup>
methoxybenzene	26.18	-6.12	1.40	
phenol	13.60	-12.57	-3.80	-6.62 <sup>a</sup>
pyridine	16.03	-6.00	0.30	-4.7 <sup>a</sup>
pyradine	14.06	-6.40	-0.32	
pyrimidine	11.52	-9.53	-2.30	
cyclohexane	36.15	-1.78	4.29	1.2 <sup>a</sup>
acetone	13.12	-7.50	-1.21	-3.8 <sup>a</sup>
dimethylformamide	19.64	-12.23	-4.01	-8.54 <sup>a</sup>
diethyl ether	25.99	-2.21	4.31	-1.75 <sup>b</sup>

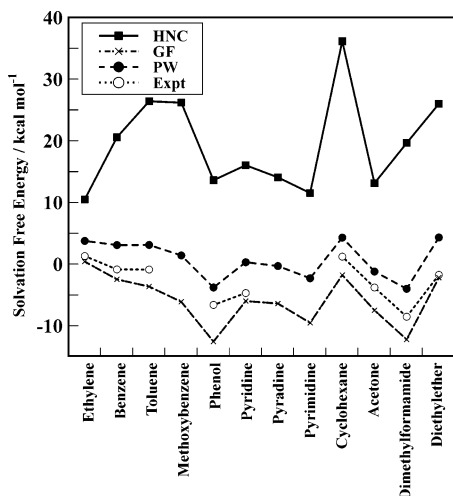
<sup>a</sup> Reference 46. <sup>b</sup> Reference 47.

irregularity cannot be found in  $\Delta\mu^{(\text{HNC})}$ .  $\Delta\mu^{(\text{PW})}$  is above  $\Delta\mu^{(\text{HNC})}$  at 0.2 g cm<sup>-3</sup>/673 K. This is an exceptional case which is unexpected by the previous observation in UAL and EAL. The term proportional to  $(\tilde{h}_{\text{ui}}^{\text{uv}})^2$  in  $\Delta\mu^{(\text{HNC})}$  is considered to give unbalanced contribution to the solvation free energies for different coordination numbers of water molecules.

### 4. Solvation Free Energies of Organic Molecules

We calculate the solvation free energies of 12 organic molecules, ethylene, benzene, toluene, methoxybenzene, phenol, pyridine, pyradine, pyrimidine, cyclohexane, acetone, dimethylformamide, and diethyl ether, in chloroform and water at 298 K. All of the geometrical parameters are optimized at the Hartree–Fock (HF)/6-311+G\*\* level. Partial charges are determined by the charges from electrostatic potentials using the grid based (CHELPG) method<sup>40,41</sup> to the HF wave functions. The OPLS all atom parameter set<sup>42,43</sup> is employed for the other force field parameters. We follow the minor modification of the parameter set.<sup>7</sup> The TIP3P<sup>44</sup> and OPLS<sup>45</sup> models are adopted for the solvents water and chloroform, respectively. The van der Waals parameters for the hydrogen sites of the TIP3P water are taken from ref 22.

The calculated free energies in water are shown in Table 4 and Figure 2. The corresponding result for the solvation in



**Figure 2.** Solvation free energies of 12 organic molecules in aqueous solution.

**TABLE 4: The Solvation Free Energy in Chloroform (kcal/mol)**

solute	$\Delta\mu^{(\text{HNC})}$	$\Delta\mu^{(\text{GF})}$	$\Delta\mu^{(\text{PW})}$	expt
ethylene	4.60	-3.13	-0.37	
benzene	7.42	-7.48	-2.75	-4.64 <sup>a</sup>
toluene	10.35	-8.67	-3.06	-5.48 <sup>a</sup>
methoxybenzene	10.09	-10.57	-4.29	
phenol	6.70	-9.64	-3.87	-7.14 <sup>a</sup>
pyridine	5.82	-8.71	-3.61	-6.45 <sup>a</sup>
pyrindine	4.77	-9.03	-3.97	
pyrimidine	4.60	-9.32	-4.13	
cyclohexane	16.78	-6.78	-1.75	-4.48 <sup>a</sup>
acetone	6.84	-7.09	-2.06	-4.96 <sup>a</sup>
dimethylformamide	9.58	-10.84	-4.15	
diethyl ether	12.75	-5.49	-0.29	

<sup>a</sup> Reference 48.

chloroform is given in Table 5 and Figure 3. The experimental free energies are taken from the previous works.<sup>46–48</sup> The present results reproduce the ordering of the free energy expressions predicted in section 2 precisely. In either case of the solvations in water and chloroform, the results of  $\Delta\mu^{(\text{GF})}$  and  $\Delta\mu^{(\text{PW})}$  are almost parallel with respect to the change of solute. The experimental free energies always lie between them. Such a systematic profile is not observed in  $\Delta\mu^{(\text{HNC})}$ . To see it more closely, we show the statistical measures

$$\bar{\Delta} = N^{-1} \sum_u^{\text{solute}} [\Delta\mu_u^{(\text{Calc})} - \Delta\mu_u^{(\text{Expt})}] \quad (24)$$

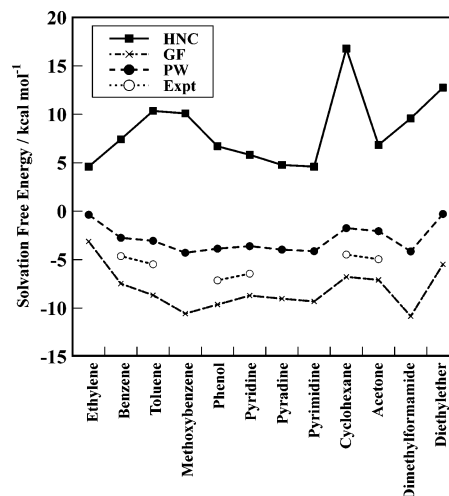
$$\bar{\Delta}_{\text{STD}} = (N^{-1} \sum_u^{\text{solute}} [\Delta\mu_u^{(\text{Calc})} - \Delta\mu_u^{(\text{Expt})} - \bar{\Delta}]^2)^{1/2} \quad (25)$$

$$\bar{\Delta}_{\text{MAX}} = \max_u |\Delta\mu_u^{(\text{Calc})} - \Delta\mu_u^{(\text{Expt})}| \quad (26)$$

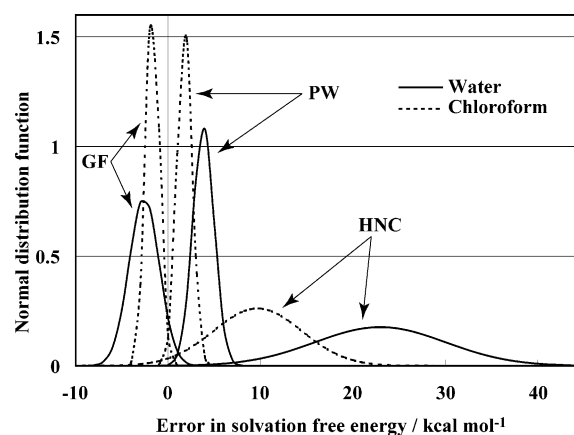
in Table 5, where  $N$  is the number of solute molecules in each data set. On the basis of the mean errors  $\bar{\Delta}$  and standard deviations  $\bar{\Delta}_{\text{STD}}$ , we plot the normal distribution functions

$$\rho(\epsilon) = \frac{1}{\bar{\Delta}_{\text{STD}}} \left( \frac{\pi}{2} \right)^{1/2} \exp \left[ -\frac{1}{2} \left( \frac{\epsilon - \bar{\Delta}}{\bar{\Delta}_{\text{STD}}} \right)^2 \right] \quad (27)$$

of error  $\epsilon$  in Figure 4. For each of the free energy expressions, the resulting measures for the solvation in chloroform are more accurate than those for water. This might be mainly attributed to the difference of the polarity of the solvents. The partial



**Figure 3.** Solvation free energies of 12 organic molecules in  $\text{CCl}_4$  solution.



**Figure 4.** Normal distribution functions for the errors between theoretical and experimental free energies of solvation.

**TABLE 5: Statistical Measures of the Calculated Free Energies of Solvation (kcal/mol)**

solvent	measure	$\Delta\mu^{(\text{HNC})}$	$\Delta\mu^{(\text{GF})}$	$\Delta\mu^{(\text{PW})}$
water	$\bar{\Delta}$	23.0	-2.6	3.8
	$\bar{\Delta}_{\text{STD}}$	7.1	1.6	1.1
	$\bar{\Delta}_{\text{MAX}}$	35.0	6.0	6.1
chloroform	$\bar{\Delta}$	9.7	-1.7	1.8
	$\bar{\Delta}_{\text{STD}}$	4.8	0.8	0.8
	$\bar{\Delta}_{\text{MAX}}$	21.3	3.2	3.3

charges of solute are fixed at the gas-phase electronic structures in the present calculations. The absent polarization effects of the solute molecules will be more prominent in the water case. It is noted that the mean error of  $\Delta\mu^{(\text{GF})}$  for water is more negative than that for chloroform.

## 5. Partition Coefficients

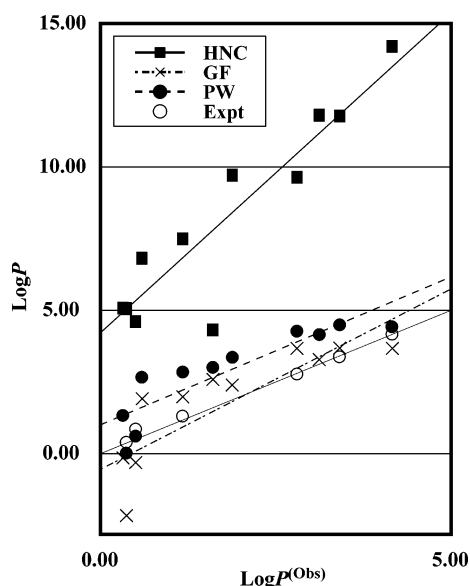
The partition coefficient  $\log P$  between aqueous and organic solvent phases has been one of the most significant molecular indices that nicely correlate with biological activities. For instance, the one based on the solvents water and *n*-octanol is the primary selection for hydrophobicity in quantitative structure–activity relationship (QSAR) studies of bioactive compounds. The chloroform–water partition coefficient is related with the solvation free energies by

$$\log P_{\text{CHCl}_3/\text{H}_2\text{O}} = -(\Delta\mu_{\text{CHCl}_3} - \Delta\mu_{\text{H}_2\text{O}})/(2.303RT) \quad (28)$$



**TABLE 6: Comparison of Partition Coefficients  $\log P_{\text{CCl}_3/\text{H}_2\text{O}}$** 

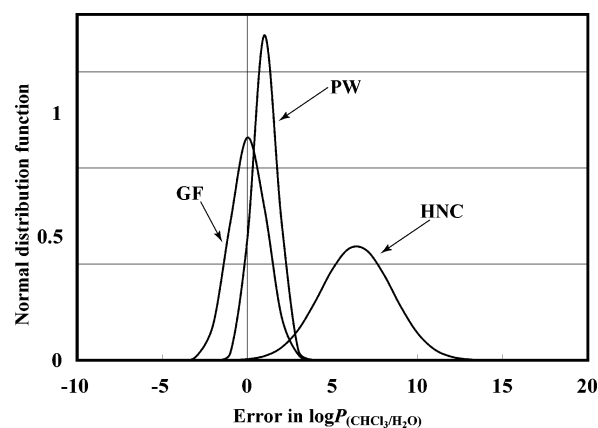
solute	$\log P^{(\text{HNC})}$	$\log P^{(\text{GF})}$	$\log P^{(\text{PW})}$	$\log P^{(\text{Expt})a}$	$\log P^{(\text{Obs})}$
ethylene	4.32	2.59	3.02		1.60 <sup>b</sup>
benzene	9.64	3.67	4.28	2.77	2.80 <sup>c</sup>
toluene	11.77	3.68	4.51	3.37	3.41 <sup>c</sup>
methoxybenzene	11.80	3.27	4.17		3.12 <sup>b</sup>
phenol	5.06	-2.16	0.05	0.38	0.37 <sup>b</sup>
pyridine	7.49	1.99	2.87	1.28	1.17 <sup>d</sup>
pyridine	6.82	1.93	2.68		0.59 <sup>d</sup>
pyrimidine	5.07	-0.15	1.35		0.32 <sup>d</sup>
cyclohexane	14.20	3.67	4.43	4.17	4.16 <sup>b</sup>
acetone	4.61	-0.30	0.63	0.85	0.50 <sup>b</sup>
diethyl ether	9.71	2.41	3.38		1.88 <sup>b</sup>

<sup>a</sup>  $\log P$  calculated from experimental solvation free energies.<sup>b</sup> Experimental  $\log P$  in ref 49. <sup>c</sup> Experimental  $\log P$  in ref 50.<sup>d</sup> Experimental  $\log P$  in ref 51.**Figure 5.** Comparison of  $\log P$  obtained from the RISM calculations and experiment. “Expt” denotes  $\log P$  calculated from experimental solvation free energies.**TABLE 7: Statistical Measures of Partition Coefficients**

measure	$\Delta\mu^{(\text{HNC})}$	$\Delta\mu^{(\text{GF})}$	$\Delta\mu^{(\text{PW})}$
$\bar{\Delta}$	6.42	0.06	1.04
$\Delta_{\text{STD}}$	2.11	1.08	0.74

With this formula, we calculate  $\log P^{(\text{HNC})}$ ,  $\log P^{(\text{GF})}$ , and  $\log P^{(\text{PW})}$  of the corresponding free energy expressions and compare the result with observed partition coefficients  $\log P^{(\text{Obs})}$ <sup>49–51</sup> in Table 6. Dimethylformamide, whose  $\log P$  is unavailable, is excluded from the original set of molecules. The partition coefficients  $\log P^{(\text{Expt})}$  are also obtained from the experimental free energies of solvation. We plot the calculated coefficients versus  $\log P^{(\text{Obs})}$  in Figure 5.  $\log P^{(\text{Expt})}$  agrees almost perfectly with  $\log P^{(\text{Obs})}$ . Among the three theoretical results,  $\log P^{(\text{HNC})}$  deviates significantly from  $\log P^{(\text{Obs})}$ , meaning that the errors in  $\Delta\mu^{(\text{HNC})}$  do not cancel out between the solvation environments to lead to the worse result for the free energy differences.

The statistical measures for  $\log P$  are given in Table 7. We show the resulting normal distribution functions in Figure 6. The standard deviation of  $\log P^{(\text{PW})}$  is the smallest among the three energy expressions. Although, the absolute value of the mean error of  $\log P^{(\text{PW})}$  is larger than that of  $\log P^{(\text{GF})}$ , the polarity effects of solute absent in the present calculations will decrease  $\log P$ . Chuman and co-workers estimated the electro-

**Figure 6.** Normal distribution functions for the errors between theoretical and experimental  $\log P$ .

static contribution to  $\log P$  of pyridine<sup>52</sup> to be 1.86 using the polarizable continuum model.<sup>53</sup> This amount corresponds to ca. 1.3 in  $\log P$ . As a molecule is largely polarized in aqueous environments, it is anticipated that a RISM self-consistent field treatment<sup>10,11</sup> will not better the standard error of  $\log P^{(\text{GF})}$ .

## 6. Conclusion

We have investigated the free energy expressions in the RISM integral equation theory comparatively. The theoretical analysis indicates that the error in  $\Delta\mu^{(\text{HNC})}$  increases according to the number of associated interactions sites, while  $\Delta\mu^{(\text{GF})}$  becomes inaccurate as the number of dissociated interaction sites increases. The numerical comparisons clearly show that  $\Delta\mu^{(\text{HNC})}$ , which has been used widely in the past applications, provides a more ambiguous result than the others,  $\Delta\mu^{(\text{GF})}$  and  $\Delta\mu^{(\text{PW})}$ , within the RISM framework. Thus the ordinary situations as those for the molecules in the present study are rather associative to worsen the profile of  $\Delta\mu^{(\text{HNC})}$ . It is also shown that the functional is not competent even for differences of solvation free energies.

Among the three expressions examined here,  $\Delta\mu^{(\text{PW})}$  is the most sophisticated theoretically. However, the performance of  $\Delta\mu^{(\text{PW})}$  is only comparable with  $\Delta\mu^{(\text{GF})}$  in the present numerical results. One of the main reasons will be the correlation functions we have used are based on RISM/HNC. In this case, the correlation functions are optimized with respect to the functional  $\Delta\mu^{(\text{HNC})}$ , and accordingly there is room to lower the free energy of  $\Delta\mu^{(\text{PW})}$ . The recent works of Freedman and Truong<sup>25–29</sup> using correlation functions of molecular simulations support this aspect strongly. In addition, the solute polarization effects are not included in the present model. To address these issues, a quantum mechanical treatment under the solvent reaction field of a more reliable solvent structure is required. As the PW theory is parallel to the integral equation theory of MOZ, it is considered that there exists a closure relation consistent with  $\Delta\mu^{(\text{PW})}$ .

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