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# Predicting Hydration Free Energies of Neutral Compounds by a Parametrization of the Polarizable Continuum Model

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A parametrization of the polarizable continuum model (PCM) is presented having the experimental hydration free energies of 215 neutral molecules as target. The cavitation and dispersion contributions were based on the Tuñón–Silla–Pascual–Ahuir (Tuñón; et al. *Chem. Phys. Lett.* **1993**, 203, 289) and Floris–Tomasi (Floris, F.; Tomasi, J. J. *Comput. Chem.* **1989**, 10, 616) expressions, respectively. Both the polar and nonpolar contributions were evaluated on the same solvent-excluding molecular surface that used unscaled Bondi atomic radii. The parametrization was provided for the HF, X $\alpha$ , LSDA, B3LYP, and mPW1PW91 methods at the 6-31G(d) basis set, and the results are in fair agreement with the experimental data. For the sake of comparison, the PCM(UAHF) and our parametrization (PCM2), both at HF level, have produced  $\Delta G_{\text{PCM(UAHF)}} = a\Delta G_{\text{exp}}$  ( $a = 1.02 \pm 0.02$ ,  $r = 0.945$ ,  $\text{sd} = 0.987$ ,  $F_{\text{test}} = 1778$ ) and  $\Delta G_{\text{PCM2}} = a\Delta G_{\text{exp}}$  ( $a = 0.95 \pm 0.02$ ,  $r = 0.952$ ,  $\text{sd} = 0.843$ ,  $F_{\text{test}} = 2070$ ), respectively. The mean absolute deviations from experimental data were 0.67 and 0.68 kcal/mol for PCM(UAHF) and PCM2, respectively.

## 1. Introduction

This work is focused on a special class of solvent models: the polarizable continuum model (PCM).<sup>1,2</sup> Briefly, the PCM describes a solute as a quantum mechanical object immersed in a continuum-dielectric solvent. It evaluates the reversible work necessary to turn on the electrostatic interactions between the solute and solvent in a self-consistent way. This reversible work is the polar component of the solvation free energy.

The PCM has recently been revised and improved concerning the definition and calculation of the “outlying charge”, stability and convergence of the self-consistent field procedure, definition and construction of the molecular cavity, analytical calculation of energy gradients, and linear scaling.<sup>3</sup>

For the prediction of solvation free energies, the polar term provided by PCM is combined with a nonpolar term.<sup>1</sup> Typically, the nonpolar term is modeled by contributions proportional to the molecular surface area.<sup>4–10</sup> However, deficiencies and inaccuracies of surface area models regarding properties of solute–solvent dispersion interactions have been shown recently.<sup>11–13</sup> Interestingly, the solvation free energy as calculated by PCM of Tomasi and co-workers<sup>1,2</sup> was originally formulated using a cavitation–dispersion partition of the nonpolar term.

Guided by these results, a new parametrization of the nonpolar term was attempted. The term was splitted in two contributions: an empirical expression for cavitation and dispersion term, both provided by *optimized* surface tension and solute–solvent interaction coefficients, respectively. The cavitation and dispersion terms were calculated on a solvent-excluding surface built from unscaled Bondi atomic radii instead of a typical solvent-accessible surface. The parametrization has used a dataset of

215 experimental hydration free energies compiled and grouped in different organic functions as proposed by Chambers et al.<sup>14</sup>

## 2. Computational Methodology

**Molecular Geometries.** Molecular geometries were fully optimized in the gas phase at HF, X $\alpha$ , LSDA, mPW1PW91,<sup>15</sup> and B3LYP<sup>16</sup> levels with the standard 6-31G(d) basis set (the LanL2DZ basis set was used for I atoms). Subsequently, frequency calculations were carried out on these optimized geometries and no saddle-points were found. All the ab initio calculations were done using Gaussian03 (Revision B.04).<sup>17</sup>

**Polarizable Continuum Model (PCM) in Gaussian03.** Single-point calculations in continuum-water model were done using the IEFPCM<sup>3,18</sup> at HF, X $\alpha$ , LSDA, mPW1PW91, and B3LYP levels with molecular cavities based on the united atom topological model applied on radii optimized for the HF/6-31G(d) and PBE0/6-31G(d) methods (i.e., the UAHF<sup>19</sup> and UAKS<sup>19</sup> radii, respectively). The hydration free energy was calculated by summing the polar contribution provided by the IEFPCM and the cavitation–dispersion contributions based on the Pierotti–Claverie<sup>1,20</sup> and Floris–Tomasi<sup>21</sup> expressions.

**New Parametrization of the Cavitation–Dispersion Term.** The hydration free energy polar contribution was taken from the IEFPCM single-point calculations at HF, X $\alpha$ , LSDA, mPW1PW91, and B3LYP levels, but the calculations were done with molecular cavities based on *unscaled* Bondi atomic radii.<sup>22</sup> A value of 78.5 was used for the dielectric constant.

The free energy nonpolar contribution was calculated by

$$\Delta G_{\text{np}} = c_0 + c_1 \text{SES} + c_2 U_{\text{disp}}(\text{H}) + c_3 U_{\text{disp}}(\text{C}) + c_4 U_{\text{disp}}(\text{N}) + c_5 U_{\text{disp}}(\text{O}) + c_6 U_{\text{disp}}(\text{F}) + c_7 U_{\text{disp}}(\text{S}) + c_8 U_{\text{disp}}(\text{Cl}) + c_9 U_{\text{disp}}(\text{Br}) + c_{10} U_{\text{disp}}(\text{I}) \quad (1)$$

The  $c_0$  to  $c_{10}$  linear coefficients are optimized by multiple linear

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TABLE 1:  $c$  Coefficients Obtained by Multiple Linear Regression

coefficient <sup>a</sup>	method				
	HF	X $\alpha$	LSDA	mPW1PW91	B3LYP
$c_0$	$2.88 \pm 0.25$	$2.70 \pm 0.24$	$2.61 \pm 0.24$	$2.77 \pm 0.23$	$2.72 \pm 0.24$
$c_1$	$0.41 \pm 0.03$	$0.43 \pm 0.03$	$0.43 \pm 0.03$	$0.39 \pm 0.03$	$0.40 \pm 0.03$
$c_2$	$-69.25 \pm 5.39$	$-70.84 \pm 5.49$	$-71.10 \pm 5.51$	$-65.16 \pm 5.14$	$-66.92 \pm 5.34$
$c_3$	$-274.12 \pm 23.20$	$-296.00 \pm 23.93$	$-297.70 \pm 24.18$	$-265.85 \pm 22.26$	$-279.91 \pm 22.97$
$c_4$	$-217.44 \pm 18.80$	$-259.42 \pm 19.14$	$-258.52 \pm 19.29$	$-229.38 \pm 17.93$	$-238.93 \pm 18.63$
$c_5$	$-164.94 \pm 18.74$	$-229.97 \pm 19.03$	$-228.06 \pm 19.19$	$-194.96 \pm 17.90$	$-201.08 \pm 18.58$
$c_6$	$-188.97 \pm 17.35$	$-211.00 \pm 17.62$	$-212.40 \pm 17.76$	$-188.38 \pm 16.63$	$-194.56 \pm 17.27$
$c_7$	$-567.16 \pm 51.97$	$-591.56 \pm 52.36$	$-597.81 \pm 52.68$	$-539.53 \pm 49.12$	$-565.20 \pm 51.07$
$c_8$	$-549.32 \pm 46.17$	$-590.29 \pm 46.82$	$-596.59 \pm 47.24$	$-536.60 \pm 43.99$	$-550.22 \pm 45.67$
$c_9$	$-1136.89 \pm 93.91$	$-1212.65 \pm 95.19$	$-1226.10 \pm 96.08$	$-1106.93 \pm 89.41$	$-1138.62 \pm 92.77$
$c_{10}$	$-4017.83 \pm 323.86$	$-4212.51 \pm 329.13$	$-4256.60 \pm 332.27$	$-3849.77 \pm 308.23$	$-3960.44 \pm 318.85$

<sup>a</sup> Units are kcal mol<sup>-1</sup>, kcal mol<sup>-1</sup> Å<sup>-2</sup>, and kcal mol<sup>-1</sup> Å<sup>-6</sup> for  $c_0$ ,  $c_1$ , and  $c_2$  to  $c_{10}$ , respectively.

regression having the solvation experimental data as response variable:

$$\chi = \sum_{i=1}^N [\Delta G_{\text{exp}}(i) - \Delta G_{\text{pol}}(i) - \Delta G_{\text{np}}(i)]^2 \Rightarrow$$

$$\text{minimization of } \chi: \quad \frac{\partial \chi}{\partial c_0} = \frac{\partial \chi}{\partial c_1} = \dots = \frac{\partial \chi}{\partial c_{10}} = 0 \quad (2)$$

In eq 1, SES is the solvent-excluding molecular surface as calculated by GEPOL program<sup>24</sup> using a radius of 0.14 nm for the spherical-solvent probe.

The first two terms ( $c_0 + c_1 \text{SES}$ ) resemble the cavitation term as proposed by Tuñón et al.<sup>25–27</sup>

$$\Delta G_{\text{cav}} = \gamma \text{SES} - RT \ln(1 - V_S \rho_S) \quad (3)$$

where  $\gamma$  is a solvent surface tension,  $\rho_S$  and  $V_S$  are the number density and volume of a solvent molecule, respectively, at temperature  $T$ .  $c_1$  could be related to  $\gamma$  and  $c_0$  to the last term in eq 3. This last term is related to the reversible work required for the creation of a spherical cavity of radius  $(3V_S/4\pi)^{1/3}$ .

The  $U_{\text{disp}}$  terms are dispersion interactions between solute atomic types and solvent (here, atomic types are based on atomic number). The Floris–Tomasi expression<sup>1,21</sup> for the  $U_{\text{disp}}$  term was used in the uniform approximation:

$$U_{\text{disp}}(\text{Y}) = \rho_S \sum_{i=1}^{N_Y} \sum_k \Delta S_k \left[ \frac{\mathbf{r}_{ik}}{3r_{ik}^6} \circ \mathbf{n}_k \right] \quad (4)$$

The first summation is on the number of Y atomic types, and the second summation is on the tiles as defined by the GEPOL tessellation.<sup>24</sup>

### 3. Results and Discussion

A set of 215 neutral molecules having experimental hydration free energies was used in our parametrization (data and calculated values were at 298 K). These molecules were taken from the compilation of Chambers et al.<sup>14</sup> and includes different organic functions (i.e. alkanes, alkenes, alkynes, cycloalkanes, arenes, alcohols, aldehydes, ethers, ketones, esters, carboxylic acids, aromatic and aliphatic amines, nitriles, amides, nitro compounds, thiols, organic sulfides and disulfides, halo, and bifunctional compounds). [The full list of the molecules containing the experimental and calculated hydration free energies is found in the Supporting Information.]

The parametrization was carried out at HF, X $\alpha$ , LSDA, mPW1PW91, and B3LYP levels. “PCM2 at HF level”, “PCM-

UAKS at mPW1PW91”, ... will denote geometry optimization in the gas phase at HF and mPW1PW91 levels with the 6-31G(d) basis set and, subsequently, single-point calculations at HF/6-31G(d) or mPW1PW91/6-31G(d) levels in the PCM2 (our parametrization) and PCM(UAKS) solvation models, respectively.

For neutral molecules, the penetration effect of the solute charge density outside the cavity is not a very serious problem and the standard charge normalization procedure, the Miertus–Scrocco–Tomasi normalization procedure,<sup>2</sup> could be used instead of IEFPCM. Recent work of Soteras et al.<sup>4</sup> suggested the density-corrected charge normalization approach<sup>23</sup> as the preferred approach for comparison with IEFPCM calculations. Anyway, only a slight chance of coefficient values with the electrostatic treatment of the “outlying charge” is expected.

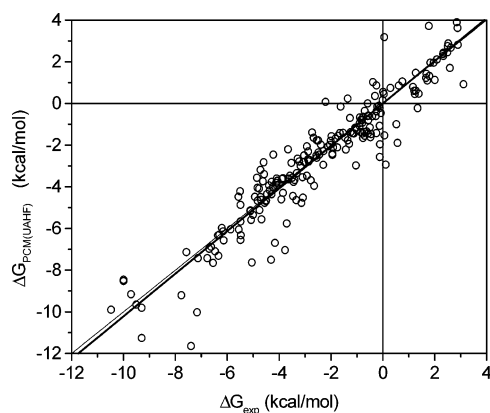
All the  $c$  coefficients obtained by multiple linear regression are shown in Table 1. Some trends can be noted:

- Fitted  $c$  coefficients are similar between the X $\alpha$  and LSDA methods and the mPW1PW91 and B3LYP methods.

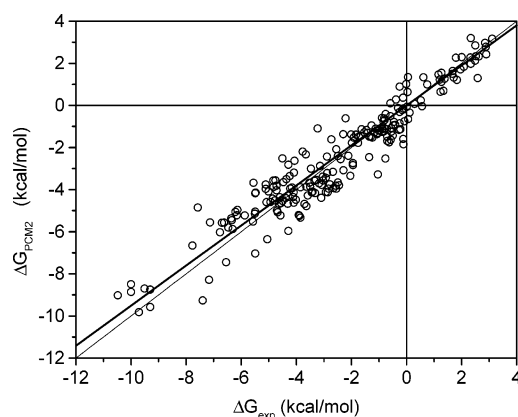
- The  $c_1$  coefficient has units of a surface tension, but all the values are 4-fold higher compared to water surface tension ( $\gamma_w \cong 0.1$  kcal mol<sup>-1</sup> Å<sup>-2</sup>). All  $c_1$  coefficients are higher and compensate a higher dispersion interaction between solute and water.

- The absolute values for  $c_2$  to  $c_{10}$  are concerned with the solute atom-water dispersion coefficients and they are ordered as follow:  $c_{10}(\text{I}) > c_9(\text{Br}) > c_7(\text{S}) > c_8(\text{Cl}) > c_3(\text{C}) > c_4(\text{N}) > c_5(\text{O}) > c_6(\text{F}) > c_2(\text{H})$  (at the HF level,  $c_5$  changes its position with  $c_6$ ). The  $c$  coefficients are taking into account shortcomings of the uniform approximation and the choice of molecular surface and may include an average charging parameter, allowing calculation of the dispersion free energy contribution from its interaction energy.<sup>1,28,29</sup>

Combining the nonpolar term of eq 1 with the PCM polar contribution produces hydration free energies of PCM2. In Figures 1–8, PCM2 is compared to PCM in Gaussian03 at HF and mPW1PW91 levels. Deviations between calculated and experimental values are shown. Figures 1 and 2 show PCM(UAHF) and PCM2 at the HF level compared to experimental data. Figures 1 and 2 suggest a better agreement of PCM(UAHF) with experiment than of PCM2, but it is not confirmed by linear regression: PCM2 is slightly better (see Table 2). Interestingly, the number of outliers from PCM(UAHF) (Figure 3) is around 2-fold higher than from PCM2 (Figure 4), and new linear regressions without outliers show a better performance of PCM(UAHF) (Table 2). This trend also appears when PCM(UAKS) is compared to PCM2 at the mPW1PW91 level. Again, PCM2 (Figure 6) works slightly better than PCM (Figure 5), as found in statistical analysis. The new linear regressions with exclusion



**Figure 1.** Hydration free energies as calculated by PCM(UAHF) at the HF level versus experimental data. The continuous thick line is the linear regression, and the thin line is the identity.



**Figure 2.** Hydration free energies as calculated by PCM2 at the HF level versus experimental data. The continuous thick line is the linear regression, and the thin line is the identity.

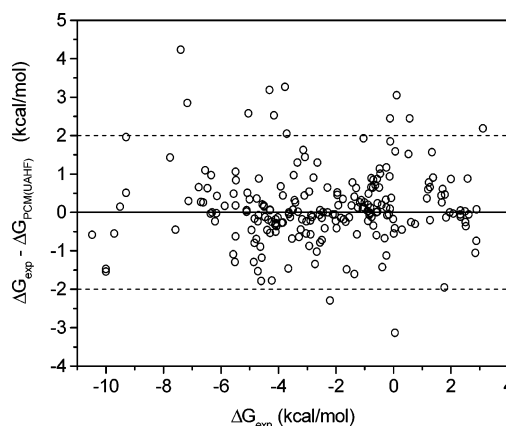
**TABLE 2: Linear Regression Parameters for PCM(UAHF), PCM(UAKS), and PCM2 at the HF and mPW1PW91 Levels<sup>a</sup>**

model	$a^d$	$r$	sd	$F_{\text{test}}$
PCM(UAHF)	$1.022 \pm 0.018$	0.945	0.987	1778
	( $0.989 \pm 0.013$ )	(0.968)	(0.720)	(2985)
PCM2 <sup>b</sup>	$0.951 \pm 0.015$	0.952	0.843	2070
	( $0.957 \pm 0.014$ )	(0.959)	(0.790)	(2311)
PCM(UAKS)	$0.981 \pm 0.016$	0.952	0.908	2058
	( $0.967 \pm 0.013$ )	(0.970)	(0.686)	(3225)
PCM2 <sup>c</sup>	$0.947 \pm 0.014$	0.959	0.765	2472
	( $0.955 \pm 0.013$ )	(0.969)	(0.693)	(3013)

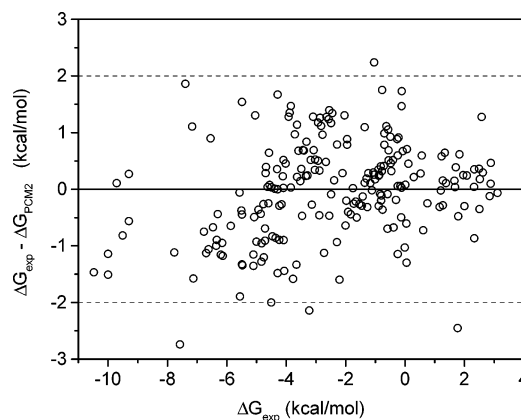
<sup>a</sup> Values in parentheses represent linear regression without the outliers. <sup>b</sup> At the HF level. <sup>c</sup> At the mPW1PW91 level. <sup>d</sup>  $\Delta G_{\text{model}} = a\Delta G_{\text{exp}}$ .

of outliers suggest an inversion of results (Table 2). Additional information about PCM2 performance appears in Table 3, with mean absolute deviations (MADs) from experimental values shown for all molecules in the set. As can be seen, PCM2 can be used to predict the hydration free energy of neutral molecules in any level of theory. Table 3 also includes calculated MADs of PCM using Bondi atomic radii. Clearly, PCM(Bondi) is in disagreement with experimental data and it should not be used for the estimative of hydration free energies.

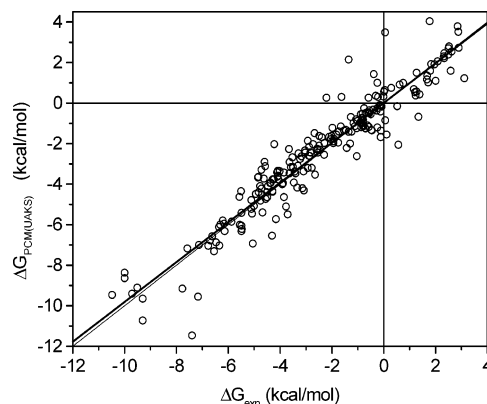
Inspection of deviation plots and results in Table 3 show that PCM2 works as well as PCM, at least taking into account the total number of molecules and functions. However, the performance of PCM2 taking into account each functional group as a distinct set must be analyzed. Thus, molecules were also



**Figure 3.** Deviations from experimental hydration free energies as calculated by PCM(UAHF) at the HF level. Thirteen values (outliers) are outside the  $[-2, 2]$  range.



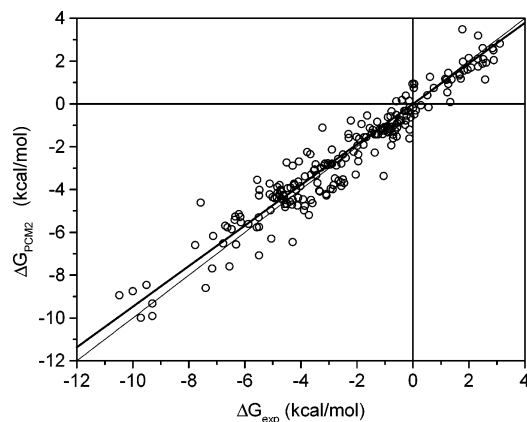
**Figure 4.** Deviations from experimental hydration free energies as calculated by PCM2 at the HF level. Four values are outside the  $[-2, 2]$  interval.



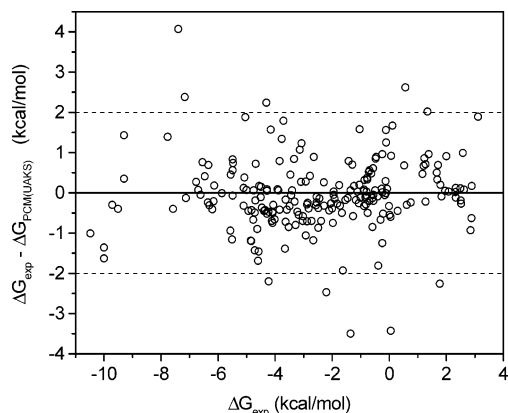
**Figure 5.** Hydration free energies as calculated by PCM(UAKS) at the mPW1PW91 level versus experimental data. The continuous thick line is the linear regression, and the thin line is the identity.

divided and analyzed into groups as proposed by Chambers et al.<sup>14</sup>

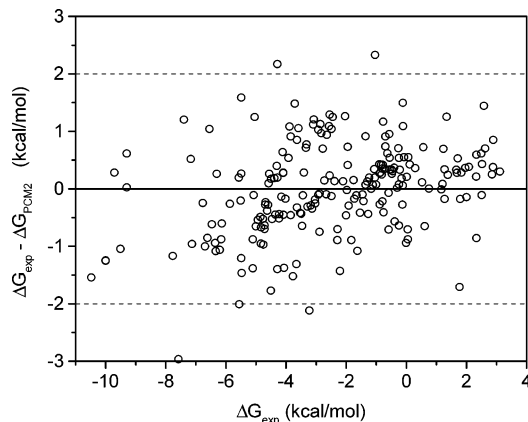
Table 4 contains apolar functional groups (alkanes, alkenes, and alkynes), arenes, alcohols, ethers, aldehydes, ketones, carboxylic acids, esters, water, H<sub>2</sub>, and bifunctional compounds (2-propen-1-ol, 2-methoxyethanol, butenyne, *m*-hydroxybenzaldehyde, and *p*-hydroxybenzaldehyde). Comparison between PCM2 and PCM(UAHF) or PCM(UAKS) MADs of unbranched alkanes show that PCM in Gaussian03 is better. It is clearly so because hydration free energies from unbranched alkanes (methane, ethane, and propane) were used in the UAHF (UAKS)



**Figure 6.** Hydration free energies as calculated by PCM2 at the mPW1PW91 level versus experimental data. The continuous thick line is the linear regression, and the thin line is the identity.



**Figure 7.** Deviations from experimental hydration free energies as calculated by PCM(UAKS) at the mPW1PW91 level. Ten outliers are outside the  $[-2, 2]$  interval.



**Figure 8.** Deviations from experimental hydration free energies as calculated by PCM2 at the mPW1PW91 level. Five outliers are outside the  $[-2, 2]$  range.

parametrization.<sup>19</sup> The next result is not so obvious: PCM2 MADs of branched alkanes, cycloalkanes, alkenes, alkynes, and arenes were less than PCM(UAHF) and PCM(UAKS) MADs. Actually, UAHF aliphatic and aromatic carbon radii (hydrogens are included in the heavy atom sphere) have been determined by hydration free energies of alkanes. Also ethylene, ethyne, and benzene were considered in the adjust process. Therefore, PCM(UAHF) and PCM(UAKS) should respond better but they do not. This result (and following results) may be pointing out limitations of the united atom topological model regarding transferability.

**TABLE 3: Mean Absolute Deviations, MADs (kcal mol<sup>-1</sup>), of PCM(Bondi) and PCM2 at the HF, X $\alpha$ , LSDA, B3LYP, and mPW1PW91 Levels, PCM(UAHF) at the HF Level, and PCM(UAKS) at the mPW1PW91 Level from the Experimental Data**

model	HF	X $\alpha$	LSDA	B3LYP	mPW1
PCM(UAHF)	0.67				
PCM(UAKS)					0.63
PCM(Bondi)	2.05	2.04	1.90	2.00	1.87
PCM2	0.68	0.62	0.62	0.64	0.62

For alcohol, aldehyde, ketone, carboxylic acid, ether, ester, and so on, the superiority of PCM against PCM2 can be observed, but it must be noted that ethers and ketones are better predicted by PCM2.

Table 5 contains aliphatic and aromatic amines, nitriles, nitrohydrocarbons, amides, ammonia, hydrazine, and bifunctional compounds (2-methoxyethanamine, morpholine and *N*-methylmorpholine). Inspections of Table 5 have shown a better prediction by PCM(UAHF) or PCM(UAKS) for aliphatic amines than by PCM2. On the other hand, PCM2 is better for aromatic amines. For nitriles, PCM(UAHF) and PCM(UAKS) have MADs of 0.23 and 0.58, respectively, in comparison to 1.12 and 0.78 provided by PCM2. Nitrohydrocarbons, amides, and bifunctional compounds are better described by PCM2. Ammonia is an outlier in PCM2 at the mPW1PW91 level, being well described by PCM(UAHF) and PCM(UAKS). Hydrazine is better in PCM2 at the HF level.

Table 6 contains hydration free energy results related to the following sulfur compounds: thiols, organic sulfides, H<sub>2</sub>S, and organic disulfides. PCM2 was slightly better than PCM(UAHF) or PCM(UAKS) for all these functions.

Table 7 contains halo compounds (fluorinated, chlorinated, brominated, and iodinated molecules) plus mixed functions (bromotrifluoromethane, chlorofluoromethane, chlorodifluoromethane, tetrafluoromethane, 1-bromo-1-chloro-2,2,2-trifluoromethane, 1-bromo-2-chloroethane, 1-bromo-1,2,2,2-tetrafluoroethane, tetrachloroethene, 1-chloro-2,2,2-trifluoroethane, 1,1,2-trichloro-1,2,2-trifluoroethane, 2,2,2-trifluoroethanol, 1-chloro-2,2,2-trifluorethyl difluoromethyl ether, 1,1,1-trifluoropropan-2-ol, 1,1,1,3,3,3-hexafluoropropan-2-ol, bis(2-chloroethyl) sulfide, 2,2,2-trifluorethyl vinyl ether, *p*-bromophenol). PCM(UAHF) or PCM(UAKS) had high MADs (greater or equal than 0.9 kcal/mol) in fluorinated (0.9 at HF level) chloroarenes (1.2 at mPW1 level) and mixed functions (1.1 at mPW1 level). In PCM2, high MADs were found in fluorinated (1.0) and mixed function (0.95) compounds at HF level.

Overall, PCM2 at the mPW1PW91 level seems slightly better than PCM2 at the HF level by inspection of numbers in Tables 2 and 3.

The PCM(UAHF) or PCM(UAKS) work better predicts the solvation of homologous series (e.g., water  $\rightarrow$  methanol  $\rightarrow$  dimethyl ether and ammonia  $\rightarrow$  methylamine  $\rightarrow$  dimethylamine  $\rightarrow$  trimethylamine). As known, water in its first solvation shell can be specifically interacting with the solute, and in these cases the interactions are not well correlated with classical electrostatic interactions.<sup>30,31</sup> A short-range empirical correction based on solvent accessibility was applied for amines, reducing the discrepancy between experimental and calculated values.<sup>30</sup> The united atom topological model is doing a similar work for PCM by changing the atomic radius and thus solvent accessibility. It would be more interesting to include explicit waters when and where they are doing specific interactions with solute, as exemplified in the recent work of Yu et al.<sup>31</sup>

As a final remark, this work paid attention *only to the parametrization of hydration free energy* and nothing was said



**TABLE 4: Mean Absolute Deviations, MADs (kcal mol<sup>-1</sup>), of PCM(UAHF), PCM(UAKS), and PCM2 at the HF and mPW1PW91 Levels by Function (Compounds Containing at Most C, H, and/or O)**

functional group	no. of molecules	MAD at HF level		MAD at mPW1PW91 level	
		PCM(UAHF)	PCM2	PCM(UAKS)	PCM2
unbranched alkanes	8	0.16	0.36	0.20	0.49
branched alkanes	5	0.49	0.16	0.41	0.28
cycloalkanes	5	0.63	0.50	0.69	0.55
alkenes	9	0.79	0.34	0.90	0.44
alkynes	5	0.38	0.31	0.41	0.34
arenes	8	0.39	0.21	0.44	0.32
alcohols	16	0.39	0.99	0.36	0.67
ethers	9	1.06	0.91	0.98	0.85
aldehydes	6	0.16	0.56	0.42	0.33
ketones	12	0.59	0.37	0.70	0.28
carboxylic acids	5	0.24	0.98	0.27	0.90
esters	12	0.31	1.20	0.33	1.05
bifunctional	5	0.46	0.82	0.53	0.73
water, H <sub>2</sub>	2	0.05	0.65	0.22	0.56

**TABLE 5: Mean absolute deviations, MADs (kcal mol<sup>-1</sup>), of PCM(UAHF), PCM(UAKS) and PCM2 at the HF and mPW1PW91 Levels by Function (Compounds Containing N)**

functional group	no. of molecules	MAD at HF level		MAD at mPW1PW91 level	
		PCM(UAHF)	PCM2	PCM(UAKS)	PCM2
aliphatic amines	15	0.78	1.12	0.74	1.17
aromatic amines	10	0.97	0.43	0.92	0.52
nitriles	4	0.23	1.12	0.58	0.78
nitrohydrocarbons	6	1.14	0.51	1.01	0.91
amides	3	1.19	0.92	1.10	0.93
bifunctional	3	1.64	0.97	1.28	0.88
ammonia, hydrazine	2	0.29	0.97	0.22	1.39

**TABLE 6: Mean Absolute Deviations, MADs (kcal mol<sup>-1</sup>), of PCM(UAHF), PCM(UAKS), and PCM2 at the HF and mPW1PW91 Levels by Function (Compounds Containing S, H, and/or C)**

functional group	no. of molecules	MAD at HF level		MAD at mPW1PW91 level	
		PCM(UAHF)	PCM2	PCM(UAKS)	PCM2
thiols	4	0.42	0.30	0.33	0.19
organic sulfides, H <sub>2</sub> S	5	0.63	0.52	0.49	0.42
organic disulfides	2	0.81	0.47	1.10	0.99

**TABLE 7: Mean Absolute Deviations, MADs (kcal mol<sup>-1</sup>), of PCM(UAHF), PCM(UAKS), and PCM2 at the HF and mPW1PW91 Levels by Function (Compounds Containing Halogens)**

functional group	no. of molecules	MAD at HF level		MAD at mPW1PW91 level	
		PCM(UAHF)	PCM2	PCM(UAKS)	PCM2
fluorinated hydrocarbons	3	0.86	0.99	0.71	0.61
chloroalkanes	8	0.55	0.84	0.42	0.63
chloroalkenes	5	0.65	0.58	0.79	0.53
chloroarenes	3	0.73	0.10	1.22	0.07
brominated hydrocarbons	10	0.41	0.53	0.35	0.36
iodinated hydrocarbons	8	0.38	0.19	0.39	0.18
other halo compounds	17	1.72	0.95	1.10	0.67

about hydration entropy and enthalpy modeling. Actually, hydration free energy calculation by implicit solvent models<sup>32,33</sup> or even explicit solvent model<sup>34</sup> has a smaller discrepancy with experimental data due to a canceling effect between hydration entropy and enthalpy. Thus, a reliable model for hydration free energy prediction does not necessary lead to a reliable model for hydration entropy and/or enthalpy calculation.

#### 4. Conclusions and Perspectives

A parametrization of the cavitation-dispersion term was performed for organic functions containing H, C, N, O, F, S, Cl, Br, and I atoms. Results are in fair agreement with experimental data and suggest that this parametrization is competitive with the PCM(UAHF) or PCM(UAKS) parametrization. Future work will address parametrization of others solvents (methanol, ethanol, hexadecane, ...) and ionic molecules in PCM2.

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**Supporting Information Available:** Table containing experimental and calculated hydration free energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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