

## First-Principle Predictions of Absolute $pK_a$ 's of Organic Acids in Dimethyl Sulfoxide Solution

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**Abstract:** MP2/6-311++G(d,p) and B3LYP/6-311++G(2df,p) methods were found to be able to predict the gas-phase acidities of various organic acids with a precision of 2.2 and 2.3 kcal/mol. A PCM cluster-continuum solvation method was developed that could predict the solvation free energies of various neutral, cationic, and anionic organic species in DMSO with a precision of about 2.0 kcal/mol. Using these carefully tested methods, we successfully predicted the  $pK_a$ 's of 105 organic acids in DMSO with a precision of 1.7–1.8  $pK_a$  units. We also predicted the  $pK_a$ 's of a variety of organosilanes in DMSO for the first time using the newly developed methods. This study was one of the first that employed first-principle methods for calculating  $pK_a$ 's of unrelated compounds in organic solutions.

### 1. Introduction

The propensity of a compound to donate or accept a proton, as measured by its acidity or basicity, is fundamental to understanding many chemical and biochemical processes.<sup>1</sup> Consequently, considerable efforts have been devoted to developing experimental methods for the measurement of acidity/basicity.<sup>2</sup> Nevertheless, not all chemical species (e.g., reaction intermediates, very strong acids, very weak acids) are readily amenable to experimental characterization. As a result, there is also widespread interest in developing methods to calculate acidity/basicity from theoretical approaches. The ability to predict the acidity/basicity using a coherent, well-defined theoretical approach, without external approximations or fitting to experimental data, would be very useful to the chemical community.

Thanks to the rapid development of computational chemistry, the acidity/basicity of small molecules in the gas phase can currently be calculated with equivalent or greater accuracy than that obtained experimentally, provided that extended basis sets are used and that electron correlation effects are recovered through post-Hartree–Fock or density functional approaches.<sup>3</sup> However, the situation is much less satisfactory in solution, mostly due to the difficulty of quantitatively calculating solvation energies with adequate accuracy. Because an important objective of computational chemistry is to describe chemical events in solution, computation of acidity/basicity in solution is a rapidly growing topic for research.

To date, a few different approaches have been studied to deal with the solvation effects required for evaluation acidity/basicity

in solution. These include molecular simulations,<sup>4</sup> Langevin dipole models,<sup>5</sup> integral equation techniques,<sup>6</sup> and dielectric continuum methods.<sup>7</sup> Among them, the dielectric continuum methods are the most popular because they are easier to handle and more broadly applicable.<sup>8</sup> A good representative of the dielectric continuum methods is the polarized continuum model (PCM) developed by Tomasi and co-workers.<sup>9</sup> With the PCM model (or more specifically, PCM-UAHF), the mean error with

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respect to the experimental absolute solvation energies in water can be as small as about 0.2 and 1 kcal/mol for neutral molecules and ions, respectively.

Using Tomasi's PCM model, Schuurmann et al. calculated the  $pK_a$  values of 16 aliphatic carboxylic acids in 1998.<sup>10</sup> Good correlations between the experimental and theoretical results were obtained, although there is concern that the computational accuracy of the continuum solvation model may not be sufficient for predicting absolute proton-transfer energies in water. In 1999, Nascimento et al. also used the PCM model and calculated the absolute  $pK_a$ 's of a number of aliphatic alcohols, thiols, and carboxylic acids in aqueous solution.<sup>11</sup> A novel thermodynamic cycle was proposed in their study, and it was found that the theoretical predictions are in good agreement with the experimental  $pK_a$ 's. More recently, Shields et al. conducted excellent systematic studies on the  $pK_a$  values of carboxylic acids and phenols.<sup>12</sup> Complete Basis Set and Gaussian-n methods combined with CPCM continuum solvation methods were used in these studies. Remarkably, the predicted  $pK_a$  values were accurate to less than one-half of a  $pK_a$  unit. Very recent studies by Namazian<sup>13</sup> and Barone et al.<sup>14</sup> have also demonstrated the successful applications of the PCM methods for calculating  $pK_a$ 's in water.

In Shield's studies, a few closely related acids were considered. However, when more acids with a larger range of  $pK_a$ 's were taken into account, Pliego and Riveros found that the error of the PCM method in the predictions of acidities in water became as large as 7  $pK_a$  units.<sup>15</sup> It was proposed that the solvent-solute interactions (e.g., hydrogen bonding) in the first solvation shell might cause such a sizable error. A remedy for this problem was to use the cluster-continuum model developed by Pliego and Riveros.<sup>16</sup> This cluster-continuum model is a hybrid approach that combines gas-phase clustering by explicit solvent molecules and solvation of the cluster by the dielectric continuum. Using the cluster-continuum model,  $pK_a$ 's between -10 and 50 for 17 acids in aqueous solution were calculated with an error of 2.2  $pK_a$  units.<sup>15</sup>

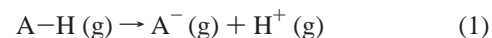
The above results have clearly demonstrated that, by using the PCM method, one is now able to predict the  $pK_a$ 's in aqueous solution with a precision of about 0.5–2.2  $pK_a$  units. This achievement is highly significant for the fields such as biophysics, biochemistry, and pharmaceutical science where a priori knowledge of  $pK_a$ 's of the biologically active compounds in water is crucial. Despite the great success in the prediction of  $pK_a$ 's in water, relatively little work has been done on the prediction of  $pK_a$ 's in organic solutions. The lack of study does

not mean that the  $pK_a$ 's in organic solutions are not important. In fact, a priori knowledge of  $pK_a$ 's of compounds in organic solutions is fundamental for the studies of a multitude of organic reactions such as aldol reactions and racemization reactions. Besides, the concept of carbon acidity in organic solutions is fundamental to a variety of structure-reactivity relationships in organic chemistry.<sup>17</sup>

In the present paper, we wish to report our recent systematic studies on the calculations of  $pK_a$ 's of various organic compounds in dimethyl sulfoxide (DMSO). The corresponding experimental values have been collected by Bordwell et al.<sup>18</sup> and have been intensively used in the organic chemical community for many years. Despite the enormous importance of these experimental data, up to now there has been little study about the calculation of the  $pK_a$ 's in DMSO from an ab initio approach.<sup>19,20</sup> Herein, we attempt to establish a coherent, simple, and first-principle method to predict these  $pK_a$  values without external approximations or fitting to experimental data. To test the performance of the theoretical method, we studied the  $pK_a$  values of over 100 organic compounds that possess various types of functional groups and structures.<sup>21</sup>

## 2. Results and Discussion

**2.1. Gas-Phase Acidities.** Before one considers the solution-phase energies, it is important to know the accuracy of the gas-phase calculations. Therefore, we calculated the gas-phase acidities of all of the compounds considered in this study as the free energy change of the following reaction in the gas phase at 298 K, 1 atm.



Both the B3LYP/6-311++G(2df,p)//B3LYP/6-31+G(d) and the MP2/6-311++G(d,p)//B3LYP/6-31+G(d) methods were used for the calculations of gas-phase acidities. In these two approaches, the geometry of each species was optimized using the B3LYP/6-31+G(d) method. The electronic energy of the species was then calculated either using the B3LYP/6-311++G(2df,p) or the MP2/6-311++G(d,p) method. The free energy of each species was calculated using the above electronic energy and zero-point vibrational energy, thermal corrections (0 → 298 K), and the entropy term all obtained at the B3LYP/6-31+G(d) level (unscaled).

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- (14) Saracino, G. A. A.; Improta, R.; Barone, V. *Chem. Phys. Lett.* **2003**, *373*, 411. It is worthy to note that in this study the authors showed that geometry reoptimization in solution might lead to significant improvement for the solvation free energy calculations.
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- (19) Chipman recently has reported, to our knowledge, the first ab initio prediction of the  $pK_a$ 's in DMSO (Chipman, D. M. *J. Phys. Chem. A* **2002**, *106*, 7413). A total of nine closely related acids were considered in his study. Good correlation between the experimental and theoretical  $pK_a$ 's was obtained. However, it is noteworthy that the theoretical method developed in Chipman's study was not sufficient for the calculation of absolute  $pK_a$ 's, because the calculated  $pK_a$ 's were systematically lower than the experimental  $pK_a$ 's by several  $pK_a$  units.
- (20) A few theoretical predictions of  $pK_a$ 's in DMSO using certain correlation methods or extra experimental parameters have also been reported. See: (a) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513. (b) Kroeker, R. L.; Bachrach, S. M.; Kass, S. R. *J. Org. Chem.* **1991**, *56*, 4062. (c) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5754. (d) Choho, K.; van Lier, G.; van de Woude, G.; Geerlings, P. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1723. However, none of these studies has developed a truly ab initio and universally applicable method for the  $pK_a$  prediction.
- (21) All of the compounds that contain no more than 10 non-hydrogen atoms in Bordwell's review paper<sup>18</sup> were considered in the present study. Larger compounds are too resource demanding and, therefore, are not used.

It is worthy to mention that some acids (e.g., 1*H*-pyridin-4-one) are speciated over a few tautomers. Under this condition, we must employ a population-averaged free energy. This may be computed as

$$G^0 = -RT \ln \left( \sum_i e^{-G_i^0/RT} \right) \quad (2)$$

where  $R$  is the universal gas constant,  $T$  is the absolute temperature, and  $i$  runs over all tautomers.<sup>22</sup>

The gas-phase acidities calculated using the above two approaches are shown in Table 1. To evaluate their accuracy, the corresponding experimental data are also listed. Comparing the calculated and experimental gas-phase acidities, we obtain the following two regression equations (also see Figure 1). These equations indicate that the standard deviations ( $sd$ ) in the gas-phase acidity calculations are 2.2 and 2.3 kcal/mol for the MP2 and B3LYP methods,<sup>23</sup> while the mean errors ( $me$ ) are  $-1.0$  and  $+0.7$  kcal/mol for MP2 and B3LYP, respectively. As compared to the usual experimental error of the gas-phase acidities (i.e., 2.0 kcal/mol), the MP2 and B3LYP results are acceptable. Certainly, one may use higher level methods such as G3 and CBS-Q to improve the gas-phase acidity calculations.<sup>24</sup> However, these methods are too demanding for general applications. Moreover, the error of the G3 and CBS-Q calculations is about  $1-2$  kcal/mol,<sup>24</sup> which is not much smaller than the 2.2 and 2.3 kcal/mol seen for the MP2 and B3LYP methods.

$$\text{gas-phase acidity (exp.)} = 0.997 \text{ gas-phase acidity (MP2)}$$

$$(r = 0.998, sd = 2.2 \text{ kcal/mol}, me = -1.0 \text{ kcal/mol}, N = 77) \quad (3)$$

$$\text{gas-phase acidity (exp.)} =$$

$$1.002 \text{ gas-phase acidity (B3LYP)}$$

$$(r = 0.998, sd = 2.3 \text{ kcal/mol}, me = 0.7 \text{ kcal/mol}, N = 77) \quad (4)$$

**2.2. Solvation Energies. 2.2.1. Neutral Molecules and Anions.** With reliable theoretical gas-phase acidities in hand, the next crucial step for the  $pK_a$  calculation is the computation of solvation free energies. In the present study, we used the PCM solvation model developed by Tomasi and co-workers<sup>9</sup> to calculate the solvation free energies in DMSO.

A central idea in the PCM model is the construction of a solvent-inaccessible cavity in which the solute molecule resides. In practice, this solvent-inaccessible cavity is built as a union of overlapping spheres centered on the nuclei of atoms or chemical groups. The sphere radii are usually proportional to the atomic radii with a scale factor ( $f$ ). For aqueous solution, the scale factor was found to be  $f = 1.2$ .<sup>9</sup> However, for many

nonaqueous solutions, it remains unclear which scale factors one should use.

Nevertheless, Pliego et al. recently reported the first parametrization of the PCM model for calculating solvation free energies of anions in DMSO.<sup>25</sup> Only the electrostatic contribution to the solvent effect, however, was considered in this pioneering study. On the basis of 21 experimental solvation energies in DMSO, the scale factor for the atomic radii stored in Gamess program was suggested to be  $f = 1.35$ . The standard deviation with respect to the experimental absolute solvation energies of the 21 anions in DMSO was 2.2 kcal/mol.

Certainly, a model that can only deal with anions is not sufficient for the calculation of  $pK_a$ 's. Therefore, in the present study, we need to reparametrize the PCM model for solvation of both neutral molecules and cations in DMSO. Unlike Pliego's work where only the electrostatic contributions were considered, in our parametrization, we also took into consideration the nonelectrostatic contributions to the solvation effects to describe the solvent effects more completely. Furthermore, we choose Bondi radii<sup>26</sup> in our study because these radii obtained from crystallographic data appear more reasonable for the condensed phase. The good availability of Bondi radii is also advantageous. Although, in principle, the neutral and charged species should have different atomic radii,<sup>9</sup> in the present study we used the same Bondi radii for both neutral and charged species because this simple approach has been shown to be fairly good in the previous studies.<sup>25</sup>

Our calculations of the solvation free energies were conducted using the HF/6-31+G(d,p) method. This particular method, rather than any higher level method, was chosen because Tomasi's PCM model had been developed and parametrized using HF/6-31+G(d,p).<sup>9</sup> The solvation free energies were calculated as the sum of three terms according to the following equation.

$$\Delta G_{\text{sol}} = \Delta G_{\text{ele}} + \Delta G_{\text{cav}} + \Delta G_{\text{dis/rep}} \quad (5)$$

In eq 5, the first term stems from the electrostatic interaction of a charge distribution inside the solute with the solvent medium of a certain dielectric constant. This term was calculated using the PCM model that is based on the apparent surface charges (ASC) method. The second term is the cavitation energy, which originates from the formation of a sufficiently large cavity to accommodate the solute molecule in the solvent medium. This term was calculated using the scaled particle theory.<sup>28</sup> The third term comes from the dispersion/repulsion interactions between solute and solvent molecules. It was calculated using the atom-atom potential parameters proposed by Caillet and Claverie.<sup>29</sup>

Our theoretical solvation free energies using different scale factors ranging from 1.20 to 1.45 are summarized in Table 2. Totally, the solvation free energies of 23 anions and 9 neutral compounds in DMSO were considered.<sup>30</sup> It should be mentioned that the experimental and theoretical solvation free energies discussed in this paper are those as defined by Ben-Naim, which correspond to lead the solute from a fixed position in

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Table 1. Experimental and Theoretical Gas-Phase Acidities and  $pK_a$ 's in DMSO<sup>a</sup>





Compounds	Gas-phase acidity (kcal/mol)			$pK_a$		
	Exp. <sup>a</sup>	MP2 <sup>b</sup>	B3LYP <sup>c</sup>	Exp. <sup>d</sup>	MP2 <sup>b</sup>	B3LYP <sup>c</sup>
CH <sub>3</sub> SO <sub>3</sub> -H	315.0 ± 2.0	314.0	312.2	1.6	-0.2 (-4.7) <sup>e</sup>	-1.4 (-5.9) <sup>e</sup>
H-Cl	328.10 ± 0.10	330.9	325.7	1.8	0.4 (-1.9) <sup>e</sup>	0.6 (-5.6) <sup>e</sup>
PhN <sup>+</sup> HMe <sub>2</sub>	217.3	219.1	215.6	2.45	4.6 (-4.8) <sup>e</sup>	2.2 (-7.2) <sup>e</sup>
CF <sub>3</sub> COO-H	317.4 ± 2.0	315.1	313.6	3.45	1.6 (-2.1) <sup>e</sup>	-0.6 (-3.1) <sup>e</sup>
Pyridine-H <sup>+</sup>	214.7	213.1	216.0	3.4	0.8 (-5.6) <sup>e</sup>	3.0 (-3.4) <sup>e</sup>
PhNH <sub>2</sub> -H <sup>+</sup>	203.3	203.6	202.7	3.6	2.0 (-6.5) <sup>e</sup>	1.4 (-7.1) <sup>e</sup>
PhCOS-H	-	326.0	325.0	5.2	4.6 (2.8) <sup>e</sup>	4.0 (2.2) <sup>e</sup>
Cl <sub>2</sub> CHCOO-H	321.9 ± 2.0	321.2	317.4	6.4	4.6 (1.8) <sup>e</sup>	1.9 (-0.8) <sup>e</sup>
PhSO <sub>2</sub> -H	-	326.9	323.6	7.1	9.2 (3.9) <sup>e</sup>	6.9 (1.7) <sup>e</sup>
H-ONO	333.70 ± 0.30	331.8	330.1	7.5	7.5	6.4
+H-NH <sub>2</sub> CH <sub>2</sub> COOH	-	210.0	209.0	7.5	0.9 (-1.3) <sup>e</sup>	0.3 (-1.9) <sup>e</sup>
CH <sub>2</sub> =CH-CH(-H)-NO <sub>2</sub>	-	333.7	333.1	7.7	8.3	8.0
H-N <sub>3</sub>	337.9 ± 2.3	337.2	339.1	7.9	7.7	9.2
+H-NH <sub>2</sub> CH <sub>2</sub> COOEt	203.7	209.3	209.6	8.7	6.6 (-3.1) <sup>e</sup>	7.0 (-2.7) <sup>e</sup>
CF <sub>3</sub> SO <sub>2</sub> NH-H	321.3 ± 2.0	321.7	320.2	9.7	5.8	4.9
1,3-cyclohexanedione	-	329.2	325.6	10.3	8.0	5.5
PhS-H	333.8 ± 2.0	333.8	332.2	10.3	7.3	6.3
NH <sub>3</sub> -H <sup>+</sup>	195.7	197.9	195.5	10.5	5.9 (1.6) <sup>e</sup>	4.3 (0.1) <sup>e</sup>
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> O-H	320.9 ± 2.0	320.5	315.7	10.8	8.5	5.1
PhCOO-H	333.0 ± 2.0	332.0	331.6	11.0	6.4	6.2
(NC) <sub>2</sub> CH-H	328.1 ± 2.0	331.2	330.9	11.0	12.2	12.1
	-	320.7	319.0	11.8	9.5	8.4
CH <sub>3</sub> COO-H	341.1 ± 2.0	339.8	337.9	12.3	8.9	7.6
PhCH <sub>2</sub> NO <sub>2</sub>	-	338.9	337.3	12.3	13.7	12.6
H-CN	343.60 ± 0.30	342.4	340.5	12.9	9.3	8.0
(CH <sub>3</sub> CO) <sub>2</sub> CH-H	-	335.6	334.7	13.3	11.9	11.4
PhCONHOH	-	338.6	339.3	13.65	11.6	12.2
1,2,3-triazole	339.1 ± 2.0	339.5	339.0	13.9	13.1	12.9
Uracil	-	338.7	338.3	14.1	12.3	12.2
CH <sub>3</sub> COCH <sub>2</sub> COOEt	-	340.8	336.5	14.2	13.5	10.5
Succinimide	338.0 ± 2.0	335.6	334.9	14.6	11.1	10.8
CH <sub>3</sub> C(=S)NHPh	-	334.3	333.8	14.7	11.9	11.7
1,2,4-triazole	336.9 ± 2.0	337.4	337.0	14.75	11.7	11.6
	-	335.3	336.1	14.75	11.6	12.3
	-	329.7	328.9	14.8	13.3	12.9
H-F	365.50 ± 0.20	365.9	364.9	15.0	15.6	15.0
CH <sub>3</sub> CH(COCH <sub>3</sub> ) <sub>2</sub>	-	347.7	342.7	15.05	17.3	13.8
PhCH <sub>2</sub> S-H	-	343.9	341.7	15.4	12.5	11.0
PhSO <sub>2</sub> NH-H	333.2 ± 2.0	335.0	334.0	16.1	12.1	11.5
NC-NH-H	344.1 ± 2.0	342.4	339.5	16.9	14.2	12.1
PhC(=S)NH-H	-	334.9	334.3	16.9	14.6	14.4
NO <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> -H	350.0 ± 2.0	353.6	345.4	16.9	18.6	12.6
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> S-H	347.4 ± 2.0	350.1	347.5	17.0	15.1	13.3
CF <sub>3</sub> CONH-H	336.7 ± 2.0	335.7	336.5	17.15	14.2	14.9
NO <sub>2</sub> CH <sub>2</sub> -H	349.7 ± 2.0	349.5	347.3	17.2	16.9	15.4
CH <sub>3</sub> SO <sub>2</sub> NH-H	338.8 ± 2.0	338.4	337.5	17.5	14.8	14.3
(CH <sub>3</sub> CO) <sub>2</sub> N-H	339.8 ± 2.0	342.0	341.1	17.9	15.6	15.1
PhO-H	342.3 ± 2.0	341.0	339.9	18.0	14.2	13.5
Cyclopentadiene	347.7 ± 2.0	348.9	346.1	18.0	17.8	15.9
(CH <sub>3</sub> ) <sub>3</sub> S <sup>+</sup>	-	257.8	254.1	18.2	20.5 (23.8) <sup>e</sup>	17.9 (21.2) <sup>e</sup>
CH <sub>3</sub> C(=S)-NH-H	339.4 ± 2.0	339.1	339.6	18.45	15.6	16.1
Imidazole	342.8 ± 2.0	343.6	342.8	18.6	17.6	17.1
CF <sub>3</sub> SO <sub>2</sub> CH <sub>2</sub> -H	339.8 ± 2.0	341.3	339.3	18.75	19.6	18.3
PhCONHNH <sub>2</sub>	-	341.2	341.4	18.9	14.9	15.2
Pyrazole	346.4 ± 2.0	344.3	347.6	19.8	14.5	17.0
PhCH <sub>2</sub> COCH <sub>3</sub>	344.5 ± 2.0	345.7	343.7	19.9	18.7	18.4
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -H	345.3 ± 2.0	345.1	342.6	20.4	23.2	21.5
Indole	344.1 ± 2.0	346.5	342.9	20.95	21.3	18.8
(H <sub>2</sub> N) <sub>2</sub> C=S	-	346.8	346.9	21.1	18.8	19.1
PhNHCOCH <sub>3</sub>	340.6 ± 2.0	343.6	343.2	21.45	17.7	17.6
CH <sub>3</sub> CONHNH <sub>2</sub>	-	349.9	350.7	21.8	19.5	20.2
4-acetylpyridine	-	349.3	349.2	21.8	21.8	21.8
PhCH <sub>2</sub> -CN	344.1 ± 2.0	345.5	344.2	21.9	22.5	21.7
Nicotinamide	-	342.0	342.9	22.0	18.5	19.3
pyrrole	350.9 ± 2.0	348.5	352.1	23.0	18.7	21.5
PhCHMeCN	-	347.3	347.0	23.0	23.9	23.8
PhCONH-H	347.0 ± 2.0	346.7	347.1	23.35	20.2	20.6
HCONH-H	359.8 ± 2.1	353.4	353.4	23.45	21.7	21.7
F <sub>3</sub> CCH <sub>2</sub> O-H	354.1 ± 2.0	353.9	351.0	23.45	21.6	19.6
MeOCH <sub>2</sub> CONH-H	351.5 ± 2.0	357.7	357.3	23.9	21.4	21.2
H-NHCOOEt	354.9 ± 2.2	360.3	358.9	24.6	24.0	23.2
NH <sub>2</sub> CH <sub>2</sub> CONH-H	-	356.0	356.5	24.7	23.7	24.2
PhCOCH <sub>2</sub> -H	354.5 ± 2.0	356.2	354.0	24.7	24.4	23.0
Cyclobutanone	359.0 ± 4.0	360.0	358.8	25.05	26.3	25.6
Cyclopentanone	360.3 ± 4.0	360.4	358.7	25.8	26.5	25.4
CH <sub>3</sub> CONH-H	355.0 ± 2.0	355.3	356.0	25.5	23.2	23.9
Cyclohexanone	358.7 ± 2.3	361.8	359.5	26.4	27.4	25.8

Table 1. (continued)

Compounds	Gas-phase acidity (kcal/mol)			Exp. <sup>d</sup>	pK <sub>a</sub>	
	Exp. <sup>a</sup>	MP2 <sup>b</sup>	B3LYP <sup>c</sup>		MP2 <sup>b</sup>	B3LYP <sup>c</sup>
2-piperidone	-	358.7	358.9	26.4	23.9	24.2
CH <sub>3</sub> COCH <sub>2</sub> -H	361.9 ± 2.0	364.2	361.2	26.5	27.4	25.4
4-Aminopyridine	349.8 ± 2.0	350.3	350.3	26.5	23.7	23.8
NH <sub>2</sub> CONH-H	355.7 ± 3.2	355.4	355.7	26.95	23.9	24.2
2-aminopyridine	355.8 ± 2.0	355.5	355.0	27.7	25.1	24.9
Cycloheptanone	360.0 ± 2.4	361.2	359.3	27.8	27.7	26.5
3-Aminopyridine	353.3 ± 2.0	354.5	354.0	28.5	25.9	25.8
PhC≡C-H	362.9 ± 2.0	362.8	362.6	28.7	27.2	27.1
CH <sub>3</sub> O-H	375.1 ± 1.1	375.9	371.7	29.0	29.9	26.9
Thiozole	-	360.8	352.7	29.4	30.8	25.0
(CH <sub>3</sub> ) <sub>2</sub> CHO-H	368.5 ± 1.1	369.7	366.7	30.25	28.7	26.7
PhNH-H	359.1 ± 2.0	360.3	359.5	30.6	28.5	28.0
CH <sub>3</sub> SO <sub>2</sub> CH <sub>2</sub> -H	358.2 ± 2.0	361.0	359.9	31.1	30.3	29.6
HO-H	383.70 ± 0.30	384.7	383.1	31.2	30.2	29.2
NCCH <sub>2</sub> -H	365.2 ± 2.0	368.5	363.3	31.3	32.2	28.5
(CH <sub>3</sub> ) <sub>3</sub> CO-H	368.1 ± 1.1	368.4	366.2	32.2	29.0	27.6
CH <sub>3</sub> SOCH <sub>2</sub> -H	366.4 ± 2.0	369.1	368.9	35	35.0	35.0
4-Methylpyridine	362.9 ± 5.0	366.7	363.0	35	35.3	32.7
	-	373.3	370.0	39	38.2	35.9
NH <sub>2</sub> -H	396.00 ± 0.20	398.1	396.6	41	39.8	38.8
PhSCH <sub>2</sub> -H	379.0 ± 5.0	378.1	374.8	42	41.5	39.2
2-Methylthiophene	373.0 ± 3.0	376.9	371.2	42	41.8	37.8
2-Methylfuran	377.0 ± 3.0	380.2	375.1	43	42.4	38.9
CH <sub>2</sub> =CH-CH <sub>2</sub> -H	382.5 ± 1.6	383.3	379.6	44	41.5	38.9
PhCH <sub>2</sub> -H	372.1 ± 2.0	377.7	373.9	43	42.4	39.7
CH <sub>3</sub> SCH <sub>2</sub> -H	383.0 ± 1.6	388.7	384.3	45	45.7	42.6
PhOCH <sub>2</sub> -H	394.0 ± 3.0	393.8	391.9	49	50.5	49.2
CH <sub>3</sub> -H	408.60 ± 0.80	414.0	411.2	56	55.4	53.4

<sup>a</sup> Gas-phase acidities are taken from NIST Standard Reference Database 69, March 1998 Release: *NIST Chemistry WebBook* (data compiled by J. E. Bartmess). <sup>b</sup> MP2/6-311++G(d,p). <sup>c</sup> B3LYP/6-311++G(2df,p). <sup>d</sup> The experimental pK<sub>a</sub>'s are taken from Bordwell's review (*Acc. Chem. Res.* **1988**, *21*, 456). <sup>e</sup> The values in the parentheses are calculated using the simple PCM method, whereas the values outside the parentheses are calculated using the cluster-continuum method.

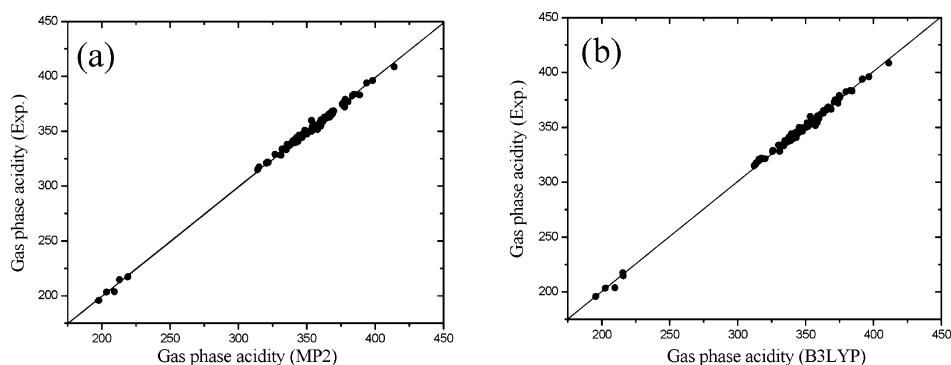


Figure 1. The correlation between the experimental and theoretical gas-phase acidities (unit: kcal/mol).

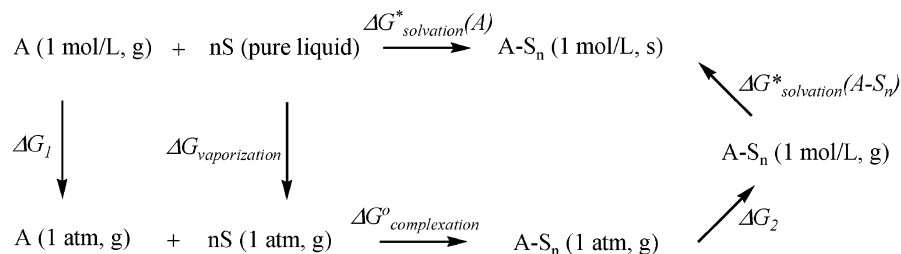


Figure 2. The thermodynamic cycle for the cluster-continuum solvation model.

the gas phase to a fixed position in solution. The corresponding standard state in both the gas and the solution phase is 1 mol/L.

Comparing the experimental and theoretical solvation free energies, we find that a scale factor of 1.35 is the most desirable for the species in DMSO. This result is in excellent agreement with Pliego's recent study on the solvation of anions in DMSO.<sup>25</sup> The standard deviation, mean error, and correlation coefficient

between the theoretical and experimental solvation free energies using this scale factor are 2.0 kcal/mol, 0.0 kcal/mol, and 0.997 for 32 species. Because the error of the gas-phase acidity calculation is about 2.2–2.3 kcal/mol, we concluded that the solvation model with a scale factor of 1.35 is sufficiently good for the present study.

**2.2.2. Cations.** The solvation energies include not only the bulk polarization effects, which can be described by continuum-

**Table 2.** Comparison between the Experimental and Theoretical Solvation Free Energies (kcal/mol) for Neutral and Anionic Compounds in DMSO

species	$\Delta G_{\text{sol}}^{\text{exp}^a}$	$\Delta G_{\text{sol}}^{\text{PCM}}$					
		$f=1.20$	$f=1.25$	$f=1.30$	$f=1.35$	$f=1.40$	$f=1.45$
F <sup>-</sup>	-82.6	-89.29	-86.01	-82.92	-80.01	-77.26	-74.68
Cl <sup>-</sup>	-65.0	-73.89	-71.61	-69.37	-67.19	-65.09	-63.07
Br <sup>-</sup>	-62.1	-69.54	-67.52	-65.51	-63.54	-61.63	-59.79
OH <sup>-</sup>	-79.0	-90.02	-86.38	-83.09	-79.98	-77.07	-74.17
CH <sub>3</sub> O <sup>-</sup>	-72.1	-77.25	-74.16	-71.34	-70.19	-66.31	-64.06
EtO <sup>-</sup>	-67.6	-73.69	-70.66	-67.84	-65.20	-62.75	-60.53
<i>i</i> -PrO <sup>-</sup>	-63.7	-70.41	-67.27	-64.47	-61.86	-59.44	-57.31
<i>t</i> -BuO <sup>-</sup>	-59.4	-67.22	-63.78	-61.41	-58.61	-56.33	-54.20
PhO <sup>-</sup>	-56.7	-61.32	-58.85	-56.68	-54.69	-52.69	-50.91
CH <sub>3</sub> COO <sup>-</sup>	-62.7	-69.72	-67.00	-64.47	-62.13	-59.94	-57.93
CH <sub>3</sub> SO <sub>3</sub> <sup>-</sup>	-56.0	-67.23	-64.67	-62.32	-60.13	-58.11	-56.23
CH <sub>2</sub> NO <sub>2</sub> <sup>-</sup>	-61.9	-67.83	-65.61	-63.19	-60.93	-58.78	-56.93
CH <sub>3</sub> COCH <sub>2</sub> <sup>-</sup>	-60.9	-65.39	-62.87	-60.58	-58.40	-56.41	-54.54
HCONH <sup>-</sup>	-58.9	-69.97	-67.35	-64.89	-62.59	-60.49	-58.42
CH <sub>2</sub> CN <sup>-</sup>	-57.2	-64.03	-61.97	-60.00	-58.14	-56.37	-54.76
CH <sub>3</sub> CONH <sup>-</sup>	-59.2	-68.77	-66.01	-63.38	-61.05	-60.85	-56.68
CH <sub>3</sub> SOCH <sub>2</sub> <sup>-</sup>	-57.6	-65.98	-63.32	-60.78	-58.50	-56.29	-54.35
NH <sub>2</sub> <sup>-</sup>	-74.3	-87.58	-84.16	-81.20	-76.91	-75.72	-72.91
CN <sup>-</sup>	-58.0	-69.60	-67.48	-65.41	-62.11	-61.50	-59.67
N <sub>3</sub> <sup>-</sup>	-65.6	-65.48	-63.60	-61.77	-63.02	-58.34	-56.74
PhNH <sup>-</sup>	-55.3	-61.09	-58.82	-56.54	-54.48	-52.83	-50.74
PhS <sup>-</sup>	-54.9	-61.74	-59.83	-57.87	-56.04	-54.14	-52.21
PhCH <sub>2</sub> <sup>-</sup>	-50.9	-53.66	-51.99	-50.39	-48.83	-47.34	-45.97
CH <sub>3</sub> OH	-5.08	-6.02	-5.41	-4.95	-4.40	-4.01	-3.34
C <sub>2</sub> H <sub>5</sub> OH	-5.19	-5.86	-5.49	-4.81	-4.23	-3.81	-3.34
(CH <sub>3</sub> ) <sub>2</sub> CHOH	-5.12	-5.88	-5.09	-4.56	-4.05	-3.33	-3.15
CH <sub>3</sub> COCH <sub>3</sub>	-3.76	-6.32	-5.58	-4.94	-4.41	-3.98	-3.65
CH <sub>3</sub> SOCH <sub>3</sub>	-7.68	-10.45	-9.12	-7.93	-6.86	-5.93	-5.25
HF	-5.89	-6.97	-6.70	-6.09	-5.78	-5.34	-4.48
HCN	-3.15	-6.66	-6.05	-5.51	-5.03	-4.61	-4.24
H <sub>2</sub> O	-6.30	-8.74	-8.08	-7.38	-6.83	-6.28	-5.06
PhCH <sub>3</sub>	-4.42	-2.80	-2.48	-2.19	-1.92	-1.68	-1.49
$r^b$		0.996	0.996	0.996	0.997	0.996	0.996
$sd^c$		3.8	3.1	2.6	2.0	2.5	2.7
$me^d$		5.7	3.6	1.7	0.0	-1.7	-3.4

<sup>a</sup> The experimental solvation free energies are taken from ref 30.  
<sup>b</sup> Correlation coefficient between the experimental and theoretical data.  
<sup>c</sup> Standard deviation (kcal/mol) between the experimental and theoretical data.  
<sup>d</sup> Mean error (kcal/mol) between the experimental and theoretical data.

solvation models, but also the first-layer solvation effects, which are caused by the short-range solvent–solute interactions (i.e., hydrogen bonding). For neutral and anionic species, it is expected that their hydrogen bonding interactions with DMSO are not very strong. Therefore, it may be sufficient to use the continuum-solvation model to depict their solvation energies. Indeed, the results in section 2.2.1 are in agreement with this argument.

However, because the oxygen in DMSO carries a significant amount of negative charge, a cationic species (e.g., a quaternary ammonium ion) may form a strong hydrogen bond with DMSO. Consequently, it may not be sufficient to use the continuum-solvation model to depict the solvation energies of cations in DMSO. As shown in Table 3, using the PCM method ( $f=1.35$ ), we determined that the calculated solvation free energies for six cations are in poor agreement with the experimental data. The correlation coefficient and standard deviation between the experimental and theoretical solvation free energies are 0.971 and 16.0 kcal/mol.

Therefore, we need to develop a better model to depict the solvation free energies of cations. For this purpose, let us consider a general solvation process. Consider that the solvation of a species (A) in a solution (S) undergoes the following thermodynamic cycle in which the solute (A) forms a tight complex (A–S<sub>n</sub>) with a certain number ( $n$ ) of solvent molecules in the solution (Figure 2). In the cycle,  $\Delta G_{\text{solvation}}^*$  is the

**Table 3.** Comparison between the Experimental and Theoretical Solvation Free Energies (kcal/mol) for Cationic Compounds in DMSO<sup>a</sup>

cations	exp.	PCM	cluster-continuum
(DMSO)H <sup>+</sup>	-69.6	-53.5	-65.1 ( $n=1$ )
NH <sub>4</sub> <sup>+</sup>	-89.2	-78.4	-84.3 ( $n=1$ )
Et <sub>3</sub> NH <sup>+</sup>	-56.0	-40.0	-54.2 ( $n=1$ )
<i>n</i> -BuNH <sub>3</sub> <sup>+</sup>	-75.2	-54.6	-70.3 ( $n=1$ )
PhNH <sub>3</sub> <sup>+</sup>	-77.0	-60.5	-76.3 ( $n=1$ )
pyridine–H <sup>+</sup>	-65.3	-51.2	-60.1 ( $n=1$ )
$r^b$		0.971	0.986
$sd^c$		16.0	4.1
$me^d$		-15.7	-3.7

<sup>a</sup> The experimental solvation free energies are taken from ref 30.  
<sup>b</sup> Correlation coefficient between the experimental and theoretical data.  
<sup>c</sup> Standard deviation (kcal/mol) between the experimental and theoretical data.  
<sup>d</sup> Mean error (kcal/mol) between the experimental and theoretical data.

**Table 4.** Calculation of Solvation Free Energy (kcal/mol) of DMSO, (DMSO)H<sup>+</sup>, and MeSOCH<sub>2</sub><sup>-</sup> Using the Cluster-Continuum Approach

$n$	$\Delta G_{\text{complexation}}^{\circ}$	$n\Delta G_{\text{vaporization}}$	$\Delta G_{\text{solvation}}^*$ (A–S <sub>n</sub> )	$\Delta G_{\text{solvation}}^*$ (A) <sub>n</sub>
DMSO (Exp: -7.68)				
0	0.0	0.0	-6.9	<b>-6.9</b>
1	1.6	4.0	-5.8	-0.3
2	0.5	8.0	1.8	10.3
(DMSO)H <sup>+</sup> (Exp: -69.6)				
0	0.0	0.0	-55.7	-55.7
1	-25.5	4.0	-44.9	<b>-66.4</b>
2	-35.5	8.0	-28.5	-56.0
MeSOCH <sub>2</sub> <sup>-</sup> (Exp: -57.6)				
0	0.0	0.0	-58.5	<b>-58.5</b>
1	-10.0	4.0	-49.4	-55.4
2	-15.4	8.0	-48.6	-56.0

solvation free energy as defined by Ben–Naim, which corresponds to lead the solute from a fixed position in the gas phase to a fixed position in solution. The “\*” symbol is used for a standard state of 1 mol/L in any phase.  $\Delta G_1$  and  $\Delta G_2$  are the free energy changes due to the concentration change.  $\Delta G_{\text{vaporization}}$  is the vaporization free energy under the standard conditions (i.e., from pure liquid to 1 atm gas).  $\Delta G_{\text{complexation}}^{\circ}$  is the free energy change in the complexation between A and S in the gas phase under standard conditions (i.e., 1 atm).

Presumably, we can consider A and A–S<sub>n</sub> to be an ideal gas in the gas phase, which means that  $\Delta G_1 + \Delta G_2 = 0$ . As a result, using the thermodynamic cycle in Figure 2, we are left with eq 6.

$$\Delta G_{\text{solvation}}^* (\text{A}) = n\Delta G_{\text{vaporization}} + \Delta G_{\text{complexation}}^{\circ} + \Delta G_{\text{solvation}}^* (\text{A}\cdot\text{S}_n) \quad (6)$$

In eq 6, the number of solvent molecules ( $n$ ) has not been determined. However, we can assume that to get a stable solution,  $n$  must be the value at which the solvation free energy  $\Delta G_{\text{solvation}}^*$  reaches the lowest value. Thus, starting with  $n=0$ , we can perform a sequence of computation until we find the lowest  $\Delta G_{\text{solvation}}^*$ . This lowest  $\Delta G_{\text{solvation}}^*$  can be used as the best estimate of the real solvation free energy.

In Table 4, we briefly show how to use the above cluster-continuum method to calculate the solvation free energies of DMSO, (DMSO)H<sup>+</sup>, and MeSOCH<sub>2</sub><sup>-</sup> in DMSO. In each step of the sequence, the term  $\Delta G_{\text{solvation}}^* (\text{A}\cdot\text{S}_n)$  is calculated using

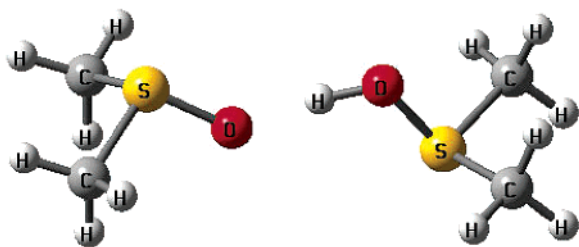


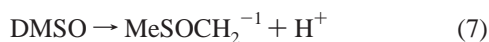
Figure 3. Optimized geometry for the (DMSO)H<sup>+</sup>...DMSO complex.

the PCM model. The experimental value for  $\Delta G_{\text{vaporization}}$  (4.0 kcal/mol, 298 K) is employed.<sup>30</sup> The term  $\Delta G_{\text{complexation}}^{\circ}$  is calculated using the MP2/6-311+G(2d,p) method (corrected with zero point energy and basis set superposition error).

As seen in Table 4, the lowest solvation free energies (−6.9 and −58.5 kcal/mol) are obtained at  $n = 0$  for DMSO and  $\text{CH}_3\text{SOCH}_2^-$ . These values are in good agreement with the experimental data (−7.68 and −57.6 kcal/mol). However, for (DMSO)H<sup>+</sup>, the lowest solvation free energy (−66.4 kcal/mol) is obtained at  $n = 1$ . This value, but not the value for  $n = 0$  (−55.7 kcal/mol), is in agreement with the experimental result (−69.6 kcal/mol). The structure of the  $n = 1$  solute–solvent complex for (DMSO)H<sup>+</sup> is shown in Figure 3. This solute–solvent complex should be a tightly tied species in the DMSO solution due to the relatively large hydrogen bonding energy (25.5 kcal/mol).

Using the cluster-continuum method, we recalculate the solvation free energies of the six cations whose experimental data are available. We find that all of these cations should form tight solute–solvent complexes ( $n = 1$ ) in DMSO (see Table 3). The solvation free energies calculated using the solute–solvent complexes are in much better agreement with the experimental data. The correlation coefficient is improved to 0.986, and the standard deviation is reduced to 4.1 kcal/mol. Therefore, the cluster-continuum method is sufficient for calculating the solvation free energies of cations in DMSO.

**2.3. Theoretical  $pK_a$ 's in DMSO. 2.3.1.  $pK_a$  of DMSO in DMSO.** The  $pK_a$  of DMSO in DMSO is of special importance because it is related to the autoionization of DMSO. It can be calculated from the free energy change of the following reaction in DMSO at 298 K.



The gas-phase free energy change of the above reaction (i.e., gas-phase acidity) is calculated to be +369.1 kcal/mol. The solvation free energies of DMSO and  $\text{CH}_3\text{SOCH}_2^-$  in DMSO are calculated to be −6.9 and −58.5 kcal/mol, respectively. The solvation free energy of a proton in DMSO can be calculated using the solvation free energy of (DMSO)H<sup>+</sup> (i.e., −66.4 kcal/mol) using the following equation.<sup>30</sup>

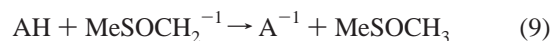
$$\Delta G_{\text{solvation}}(\text{H}^+) = \Delta G_{\text{solvation}}[(\text{DMSO})\text{H}^+] - \Delta G_{\text{basicity}}(\text{DMSO}) - \Delta G_{\text{solvation}}(\text{DMSO}) - RT \ln(\check{R}T) - RT \ln[\text{DMSO}] \quad (8)$$

In eq 8,  $\Delta G_{\text{basicity}}(\text{DMSO})$  is the gas-phase basicity of DMSO, which is 204.0 kcal/mol,<sup>30</sup>  $\check{R} = 0.082053 \text{ K}^{-1}$ ,  $[\text{DMSO}] = 14.0 \text{ mol/L}$ . Using eq 8, we predict that the solvation free energy of proton in DMSO is −267.0 kcal/mol, which compares well to the experimental value of −270.5 kcal/mol.<sup>30</sup>

Thus, the free energy change the reaction depicted by eq 7 in DMSO is +53.4 kcal/mol.<sup>31</sup> The corresponding  $pK_a$  value is 39.1. This predicted value is higher than the experimental  $pK_a$  of DMSO in DMSO (i.e., 35) by 4.1 units.<sup>18</sup> The major reason for the overestimation is that the solvation free energy of proton is underestimated by 3.5 kcal/mol and the gas-phase acidity of DMSO is overestimated by 2.7 kcal/mol.

**2.3.2.  $pK_a$  of Various Molecules in DMSO.** Certainly, one can use the reaction  $\text{HA} \rightarrow \text{H}^+ + \text{A}^-$  to calculate the  $pK_a$  of HA. However, the computational error for the solvation free energy of proton (3.5 kcal/mol) is significantly higher than the standard deviation for the solvation free energies of other species, which is about 1.8–2.0 kcal/mol. Therefore, we need to develop a better method for the  $pK_a$  calculations in which the solvation free energy of a proton is not used.

Therefore, we focus on the free energy change ( $\Delta G_{\text{exchange}}$ ) of the following reaction (eq 9) in DMSO at 298 K, which can be easily calculated using the gas-phase acidities and the solvation free energies aforementioned.



On the basis of eq 9, we have

$$e^{-\Delta G_{\text{exchange}}/RT} = \frac{[\text{A}^-][\text{MeSOCH}_3]}{[\text{AH}][\text{MeSOCH}_2^-]} \quad (10)$$

If we use the experimental  $pK_a$  value of DMSO in DMSO (i.e., 35),<sup>18</sup> we also have

$$\frac{[\text{H}^+][\text{MeSOCH}_2^-]}{[\text{MeSOCH}_3]} = 10^{-35} \quad (11)$$

Using eqs 10 and 11, we obtain

$$K_a(\text{HA}) = \frac{[\text{H}^+][\text{A}^-]}{[\text{AH}]} = 10^{-35} \times e^{-\Delta G_{\text{exchange}}/RT} \quad (12)$$

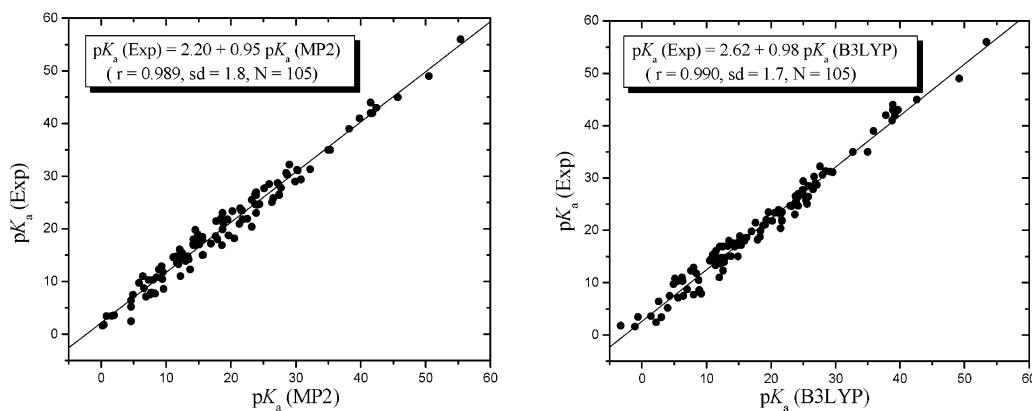
Thus,

$$pK_a(\text{HA}) = 35 + \frac{\Delta G_{\text{exchange}}}{2.303 \times RT} \quad (13)$$

The major advantage of using eq 13 to calculate  $pK_a$ 's is that we do not need to use the solvation free energy of proton. Furthermore, computational error for an exchange reaction such as that depicted by eq 9 is usually very small due to the error cancellation. Using eq 13, we calculate the  $pK_a$ 's of 105 organic acids in DMSO. The detailed results are listed in Table 1.

To our satisfaction, the results in Table 1 clearly show that the predicted  $pK_a$ 's are usually in good agreement with the experimental data for neutral and relatively weak organic acids. However, for cationic or relatively strong acids, the predictions are fairly poor. As mentioned in section 2.2.2, the simple PCM method cannot accurately predict the solvation free energies of

(31) The gas-phase free energy change of the reaction  $\text{DMSO} \rightarrow \text{MeSOCH}_2^- + \text{H}^+$  is +369.1 kcal/mol (reference state: 1 atm, 298 K). The solvation free energies for DMSO, proton, and  $\text{CH}_3\text{SOCH}_2^-$  in DMSO are −8.5, −265.4, and −58.5 kcal/mol. Therefore, the solute-phase free energy (reference state: 1 mol/L, 298 K) of the reaction is  $369.1 + 8.5 - 265.4 - 58.5 + RT \ln(\check{R}T) = 55.6 \text{ kcal/mol}$ .



**Figure 4.** Correlation between the experimental and theoretical  $pK_a$ 's.

cations. Interestingly, here we also find that the simple PCM method cannot reasonably predict the solvation free energies of some strongly acidic molecules (e.g.,  $\text{CH}_3\text{SO}_3\text{H}$ ,  $\text{HCl}$ ), either. This failure is due to the strong hydrogen bonding interaction between the strongly acidic molecules and DMSO that leads to strong first-layer solvation effects. As a result, we have to use the cluster-continuum method for these strongly acidic compounds.

The  $pK_a$ 's predicted by the simple PCM method are shown in the parentheses in Table 1, whereas the  $pK_a$ 's predicted by the cluster-continuum method are shown outside the parentheses. Evidently, the values predicted by the cluster-continuum method are superior, indicating that the use of the cluster-continuum method is necessary. Plotting all of the predicted  $pK_a$ 's against the experimental data, we obtain two straight regression lines for the MP2 and B3LYP methods (see Figure 4). The slopes of these lines are close to unity, the correlation coefficients ( $\sim 0.99$ ) are very high, and the standard deviations are 1.8 and 1.7 units. It is worthy to note that a total of 105 organic acids are considered in the present study. Their  $pK_a$ 's range from about 0 to 50. Given the highly diverse structures and properties of these 105 compounds, we can conclude that both the MP2/6-311++G(d,p) and the B3LYP/6-311++G(2df, p) methods are very successful in predicting the  $pK_a$ 's of organic acids in DMSO.

### 3. Applications: $pK_a$ 's of Organosilanes in DMSO

As mentioned in the Introduction, although considerable efforts have been devoted to developing experimental methods for the measurement of  $pK_a$ 's, not all chemical species are readily amenable to experimental characterization. Under this circumstance, it would be very helpful if one can use a reliable theoretical method to predict the  $pK_a$ 's.

In the present study, we used the theoretical method developed above to calculate the  $pK_a$ 's of organosilanes. We believe that this computational work should be important because nucleophilic silyl anions such as  $\text{Ph}_3\text{Si}^-$ ,<sup>33</sup>  $\text{Ph}_2\text{MeSi}^-$ ,<sup>34</sup>  $\text{PhMe}_2\text{Si}^-$ ,<sup>34</sup>  $\text{Me}_3\text{Si}^-$ ,<sup>35</sup>  $(\text{Me}_3\text{Si})_3\text{Si}^-$ ,<sup>36</sup> and  $\text{Cl}_3\text{Si}^-$ <sup>37</sup> have drawn considerable attention recently in synthetic chemistry.<sup>38</sup> However, due to the myriad of reactions that organosilanes can undergo (e.g., isomerization, polymerization) in the presence of bases, silyl anions are much harder to obtain in solution than carbanions. Therefore, up to now, the solution acidity of organosilanes remained almost entirely unknown<sup>39</sup> except for

triphenylsilane ( $pK_a \approx 35.1$  in THF)<sup>40</sup> and tris(trimethylsilyl)silane ( $pK \approx 29.4$  in ether),<sup>41</sup> which were determined very recently.





A total of 33 organosilanes are considered in the present study. The B3LYP/6-311++G(2df,p) method is used to calculate the gas-phase acidity of each organosilane (see Table 5). The results show that the theoretical gas-phase acidities are in excellent agreement with the experimental data. The same PCM model as described above is then utilized to calculate the solution-phase  $pK_a$ 's using eq 13 (also see Table 5).

The accuracy of the calculated  $pK_a$ 's can only be evaluated with the two available experimental data. The calculated  $pK_a$  for triphenylsilane in DMSO is 34.8, as compared to the experimental  $pK_a$  (35.1) in THF.<sup>40</sup> Because Streitwieser et al.

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**Table 5.** Gas-Phase Acidities and  $pK_a$  Values in DMSO for a Variety of Organosilanes

Compound	Gas-phase acidity (kcal/mol)		$pK_a$ DMSO
	Exp.	B3LYP <sup>b</sup>	
SiH <sub>3</sub> -H	365.7 ± 2.0 <sup>a</sup>	365.2	29.5
MeSiH <sub>2</sub> -H	369.0 ± 2.0 <sup>a</sup>	372.0	36.1
Me <sub>2</sub> SiH-H	377.0 ± 4.0 <sup>a</sup>	376.7	41.4
Me <sub>3</sub> Si-H	380.0 ± 2.2 <sup>a</sup>	379.1	44.9
CH <sub>3</sub> CH <sub>2</sub> -SiH <sub>2</sub> -H	368.1 ± 2 <sup>a</sup>	370.5	36.0
CH <sub>2</sub> =CH-SiH <sub>2</sub> -H	365.7 ± 2 <sup>a</sup>	365.5	32.4
CH <sub>2</sub> =CH-SiMe <sub>2</sub> -H	-	374.6	42.3
CH≡C-SiH <sub>2</sub> -H	360.2 ± 2 <sup>a</sup>	368.8	33.7
CH≡C-SiMe <sub>2</sub> -H	-	368.7	32.2
Ph-SiH <sub>2</sub> -H	362.1 ± 2 <sup>a</sup>	361.5	31.6
PhMe <sub>2</sub> Si-H	370.5 ± 2.0 <sup>a</sup>	371.2	41.2
Ph <sub>2</sub> SiH-H	-	360.3	33.9
Ph <sub>2</sub> MeSi-H	-	365.3	37.9
Ph <sub>3</sub> Si-H	-	360.0	34.8
Me <sub>2</sub> N-SiH <sub>2</sub> -H	-	371.5	36.7
(Me <sub>2</sub> N) <sub>2</sub> SiH-H	-	373.0	41.4
(Me <sub>2</sub> N) <sub>3</sub> Si-H	-	379.7	46.9
MeO-SiH <sub>2</sub> -H	-	367.3	32.8
(MeO) <sub>2</sub> SiH-H	-	370.6	36.1
(MeO) <sub>3</sub> Si-H	-	368.7	37.1
F-SiH <sub>2</sub> -H	-	363.8	29.9
F <sub>2</sub> SiH-H	-	358.7	27.3
F <sub>3</sub> Si-H	350.4 ± 5.3 <sup>a</sup>	345.7	18.5
Me <sub>3</sub> Si-SiH <sub>2</sub> -H	-	358.1	31.1
(Me <sub>3</sub> Si) <sub>2</sub> SiH-H	352 ± 6 <sup>a</sup>	352.8	30.3
(Me <sub>3</sub> Si) <sub>3</sub> Si-H	346 ± 3 <sup>a</sup>	348.9	27.6
ClSiH <sub>2</sub> -H	-	352.6	24.1
Cl <sub>2</sub> SiH-H	-	339.6	17.1
Cl <sub>3</sub> Si-H	< 351.1 ± 1.2 <sup>a</sup>	325.2	8.3
	-	358.2	27.5
	-	369.5	37.3
	-	371.7	38.9
	-	372.6	40.2

<sup>a</sup> Gas-phase acidities are taken from NIST Standard Reference Database 69, March 1998 Release: *NIST Chemistry WebBook* (data compiled by J. E. Bartmess). <sup>b</sup> B3LYP/6-311++G(2df,p).

has reported that there is an excellent correlation between the  $pK_a$ 's in THF with the absolute  $pK_a$ 's in DMSO ( $pK(\text{THF}) = -0.963 + 1.046 pK_a(\text{DMSO})$ ,  $r^2 = 0.998$ ),<sup>42</sup> we can conclude that the calculated  $pK_a$  for triphenylsilane in DMSO is in good agreement with the experimental measurement. Moreover, the calculated  $pK_a$  for tris(trimethylsilyl)silane in DMSO is 27.6, as compared to the experimental value (29.4) in ether.<sup>41</sup> Thus, all of the evidence we have suggests that the calculated  $pK_a$ 's for organosilanes are reasonably reliable.

The results in Table 5 suggest that the  $pK_a$ 's of most organosilanes in DMSO are distributed in the range from 30 to 40. Many functional groups such as alkyl, alkenyl, aryl, amino, and alkoxy groups generally show very small effects on the

$pK_a$ 's of organosilanes. However, the effects of halogen atoms on the  $pK_a$ 's of organosilanes are dramatic. From SiH<sub>4</sub> to F<sub>3</sub>-SiH, the  $pK_a$  of the Si-H bond changes from 29.5 to 18.5. Furthermore, the  $pK_a$  of Cl<sub>3</sub>SiH is 8.3, suggesting that this species should be a fairly strong acid.

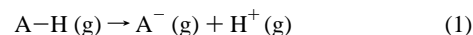
#### 4. Summary

MP2/6-311++G(d,p) and B3LYP/6-311++G(2df,p) methods were found to be able to predict the gas-phase acidities of various organic acids with a precision of 2.2 and 2.3 kcal/mol. A PCM cluster-continuum solvation method was developed that could predict the solvation free energies of various neutral, cationic, and anionic organic species in DMSO with a precision of 1.9–2.0 kcal/mol. Using these carefully selected methods, we successfully predicted the  $pK_a$ 's of 105 organic acids in DMSO with a precision of 1.7–1.8  $pK_a$  units. We also predicted the  $pK_a$ 's of a variety of organosilanes in DMSO for the first time using the newly developed methods.

#### 5. Computational Methodology

All of the calculations were conducted using Gaussian 98 programs.<sup>32</sup> The geometry of each species was optimized using the B3LYP/6-31+G\* method. For those molecules or complexes which have more than one possible conformation, the conformation with the lowest electronic energy was singled out and used in the ensuing calculations. Each final optimized geometry was confirmed by the B3LYP/6-31+G\* frequency calculation to be a real minimum on the potential energy surface without any imaginary frequency.

Harmonic vibrational frequencies were calculated using the B3LYP/6-31+G\* method for the optimized geometries. Zero-point vibrational energy (ZPE) corrections were obtained using unscaled frequencies. Single-point electronic energies were calculated at the B3LYP/6-311++G(2df,p) and MP2/6-311++G(d,p) levels. Gas-phase acidity was calculated as the free energy of reaction 1 at 298 K and 1 atm in the gas phase.



This free energy change was corrected with ZPE, thermal corrections (0 → 298 K), and the entropy term obtained at B3LYP/6-31+G\* level. It should be noted that all of the gas-phase free energies reported in the paper correspond to the reference state of 1 atm, 298 K.

To calculate  $pK_a$ 's, we used the PCM method at the HF/6-31+G(d,p) level (version = MATRIX INVERSION, cavity PENTAKISDODECAHEDRA, Icomp = 4, TSNUM = 60, TSARE = 0.4, radii = bondi, alpha = 1.35). The gas-phase geometry was used for all of the solution-phase calculations, as it has been demonstrated that the change of geometry by the solvation effect is usually not significant.<sup>11–16</sup> All of the solution-phase free energies reported in the paper correspond to the reference state of 1 mol/L, 298 K.

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**Supporting Information Available:** Tables of experimental data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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