# Density Functional Theory Calculation of pKa's of Thiols in Aqueous Solution Using Explicit Water Molecules and the Polarizable Continuum Model

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Ⓢ Supporting Information

ABSTRACT: The pK_a's of substituted thiols are important for understanding their properties and reactivities in applications in chemistry, biochemistry, and material chemistry. For a collection of 175 different density functionals and the SMD implicit solvation model, the average errors in the calculated pK_a's of methanethiol and ethanethiol are almost 10 pK_a units higher than for imidazole. A test set of 45 substituted thiols with pK_a's ranging from 4 to 12 has been used to assess the performance of 8 functionals with 3 different basis sets. As expected, the basis set needs to include polarization functions on the hydrogens and diffuse functions on the heavy atoms. Solvent cavity scaling was ineffective in correcting the errors in the calculated pK_a's. Inclusion of an explicit water molecule that is hydrogen bonded with the H of the thiol group (in neutral)

or S^- (in thiolates) lowers error by an average of 3.5 pK_a units. With one explicit water and the SMD solvation model, pK_a's calculated with the M06-2X, PBEPBE, BP86, and LC-BLYP functionals are found to deviate from the experimental values by about 1.5–2.0 pK_a units whereas pK_a's with the B3LYP, ωB97XD and PBEVWN5 functionals are still in error by more than 3 pK_a units. The inclusion of three explicit water molecules lowers the calculated pK_a further by about 4.5 pK_a units. With the B3LYP and ωB97XD functionals, the calculated pK_a's are within one unit of the experimental values whereas most other functionals used in this study underestimate the pK_a's. This study shows that the ωB97XD functional with the 6-31+G(d,p) and 6-311++G(d,p) basis sets, and the SMD solvation model with three explicit water molecules hydrogen bonded to the sulfur produces the best result for the test set (average error -0.11 ± 0.50 and $+0.15 \pm 0.58$, respectively). The B3LYP functional also performs well (average error -1.11 ± 0.82 and -0.78 ± 0.79, respectively).
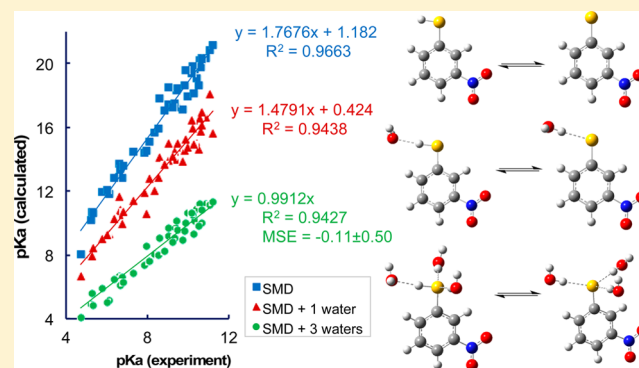
INTRODUCTION

Substituted thiols have a wide variety of uses and applications in chemistry, biochemistry, and material chemistry. In biochemistry, for example, thiols are known for antioxidant properties such as radical quenching.[1,2] In cell redox buffers, their role is to regulate the protein thiol/disulfide composition. The disulfide bonds are important in maintaining the structural stability of soluble proteins.[3,4] Some interesting examples from material science include the use of substituted benzenethiols in molecular electronics, surface-enhanced Raman spectroscopy, and quantum electronic tunneling between plasmonic nanoparticle resonators.[5–11] Understanding of the properties and reactivities of thiols as a function of pH requires a reliable set of measured or calculated acid dissociation constants. The experimental determination of pK_a's is not always easy because of problems such as interference from other solutes in the complex substrate environment, difficulties in isolation of specific residues, complexity due to the solvent system, etc. Hence, there is always a need to calculate pK_a's using quantum chemical techniques.

The calculation of pK_a's is the subject of a number of recent reviews.[12–14] The pK_a for a molecule is obtained from the solution phase free energy of the deprotonation reaction, AH $\rightleftharpoons$ A$^-$ + H$^+$. The quality of calculated pK_a's depends on the accuracy of the computed deprotonation energies and the reliability of the estimated solvation energies. Early studies showed that some implicit solvation models can lead to large errors in the calculated pK_a's.[12–14] However, these errors are often systematic for a given functional group, and suitable estimates of pK_a's can be obtained from linear correlations between calculated solvation free energies or pK_a's and known experimental values. Friesner and co-workers developed a protocol for predicting pK_a's for a wide range of functional groups that involved a linear correlation between experimental pK_a's and raw pK_a's computed by using free energies from density functional calculations and a continuum solvation model with radii optimized for each functional group.[15] Zhang
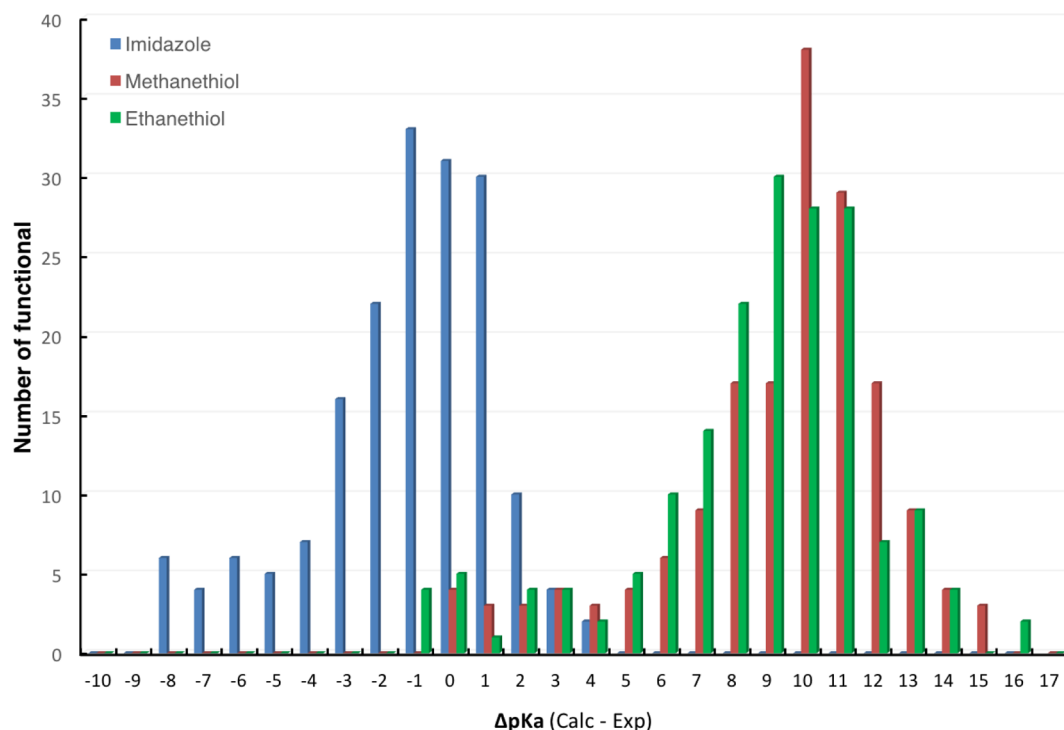
Figure 1. Comparison of the errors in the calculated pK_a's for imidazole, methanethiol, and ethanethiol computed with 175 different functionals and the 6-31+G(d,p) basis set using the SMD solvation model without explicit water molecules.

and Pulay[16,17] also developed an efficient method for estimating pK_a's for numerous functional groups using a linear correlation approach based on density functional calculations of deprotonation energies calculated in solution using the COSMO implicit solvation model. There are many other studies that use similar approaches to predict pK_a's for limited classes of molecules. The linear regression approach requires fitting the calculated values to a large and representative collection of experimental data. Although the predicted pK_a's can be quite good, different linear fits are needed for different functional groups. Often the linear fits have slopes that are very different from one and intercept that are nonzero. This indicates that some physical features of the deprotonation reaction in aqueous solution are not being captured by the calculations of the reaction energies and the solvation energies. Implicit solvation models do not include specific hydrogen bonding interactions, and these can be very important in aqueous solution, especially for ions. Explicit water molecules can be included to account for the specific hydrogen bonds. A number of studies have shown that this improves the calculation of pK_a's, especially for processes involving anions.[18−29]

In a series of papers, Junming Ho and Michelle Coote have published extensive comparisons of methods for calculating pK_a's directly and using various thermodynamic cycles.[13,30−33] The thermodynamic cycle approach involves free energy calculations in the gas phase and the computation of solvation free energies for individual reactants and products. In the direct approach, the free energies of the reactants and products are calculated directly in the solution.[32] The direct approach avoids geometry optimization in the gas phase and eliminates the possibility of differences in geometries optimized in the gas phase and in solution. Even though thermodynamic cycles have been employed more frequently to calculate pK_a's, the direct method is being used increasingly. Compared to the thermodynamic cycle approaches, the direct method is

computationally simpler and yields results of comparable accuracy.[32] In previous studies, we have used thermodynamic cycles and the direct approach to calculate pK_a's of DNA nucleobases and intermediates in the oxidative degradation of guanine.[29,34−36]

Despite their importance, the only models available for calculating pK_a's of thiols involve linear regression fits;[9,16,17,37] direct calculations thiols have been reported only for methanethiol and ethanethiol.[38] In the present paper, we have developed an explicit−implicit solvation model that can be used to calculate pK_a's of substituted thiols directly, without resorting to linear fits. We have compared the performance of different functionals using the SMD[39] implicit solvation model with and without explicit waters around the solute. The SMD model is parametrized to incorporate some of the short-range interactions between solute and solvent molecules such as dispersion and cavity formation contributions to the total solvation free energy. However, SMD does not adequately treat the hydrogen bonding interactions between thiols/thiolates and water. To account for these specific hydrogen bonds, we have included up to three explicit molecules of water hydrogen bonded to the sulfur. Some of the early work on implicit-explicit and cluster-continuum models has been discussed in a review by Cramer and Truhlar.[40] Often adding one to four explicit water molecules improves the solvation energies of ions and the calculation of pK_a's.[18−29] A more detailed treatment of pK_a's can be obtained by molecular dynamics calculations;[41−43] however, long simulations are needed to obtain accurate free energies. One of the goals of the present study is to establish a simple and inexpensive protocol for calculating pK_a's of thiols. A set of 45 substituted thiols with experimental pK_a's ranging from 4 to 12 has been used to assess the performance of different functionals and basis sets, and the effect of including explicit water molecules.
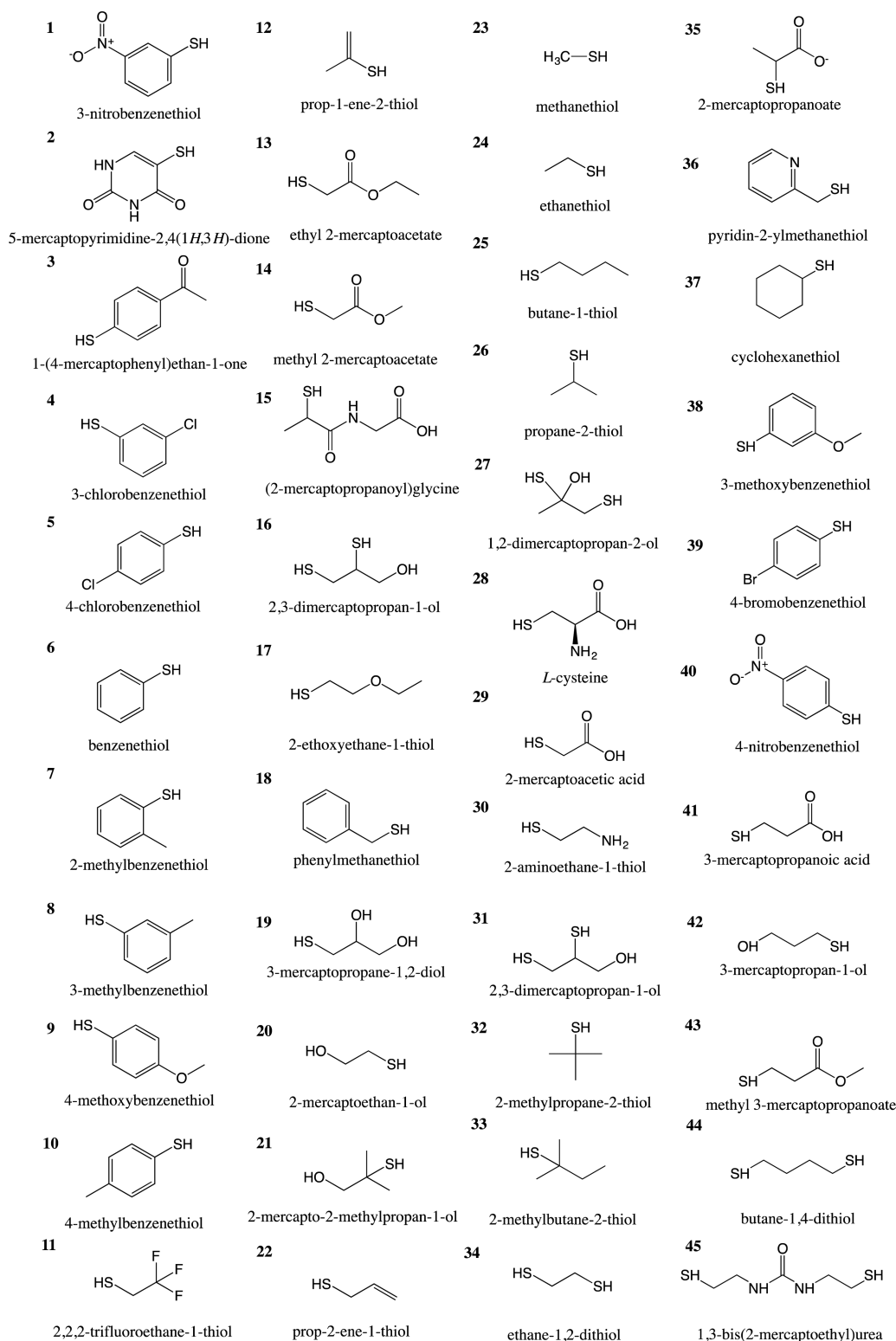
Figure 2. Molecules in this study.

■ COMPUTATIONAL METHODS

The pK_a for a molecule can be calculated from the solution phase free energy of the deprotonation reaction, AH $\rightleftharpoons$ A$^-$ + H$^+$

$$pK_a = \frac{\Delta G^*_{aq}}{2.303RT}$$

where $\Delta G^*_{aq} = G^*_{aq}(A^-) + G^*_{aq}(H^+) - G^*_{aq}(AH)$. The calculated Gibbs free energies include ZPVE, thermal corrections and entropies computed by standard statistical thermodynamic methods at 298.15 K using the unscaled frequencies and the ideal gas/rigid rotor/harmonic oscillator approximations. In the direct approach, the energy difference is calculated directly in solution rather than by a thermodynamic cycle involving gas phase energies. The aqueous phase proton free energy is

Table 1. Experimental pK_a's of the Substituted Thiols and Errors in pK_a's Calculated Using SMD Solvation and Three Explicit Water Molecules with Selected Density Functionals and the 6-311++G(d,p) Basis Set

structure	pK_a(exp)[a]	ΔpK_a (pK_a(calc) − pK_a(exp))							
		wB97XD	B3LYP	BLYP	PBEVWN5	M06-2X	BP86	PBEPBE	LC-BLYP
1	5.24	−1.16	−1.86	−2.56	0.42	−4.69	−3.59	−3.04	−4.37
2	5.30	−0.78	−2.03	−2.29	0.01	−3.07	−3.97	−4.04	−4.48
3	5.33	−0.06	−2.01	−3.32	0.32	−3.44	−5.90	−4.19	−3.88
4	5.78	0.05	−1.21	−0.65	1.29	−2.62	−2.84	−4.54	−4.36
5	6.14	−0.24	−1.48	−2.49	0.91	−4.28	−3.90	−4.20	−4.02
6	6.61	0.47	−1.22	−2.87	1.33	−4.17	−4.07	−4.54	−3.70
7	6.64	0.92	−0.05	−1.36	2.83	−2.72	−2.14	−2.55	−2.92[b]
8	6.66	0.67	−1.50	−2.44	2.08	−3.09	−3.46	−3.86	−4.38
9	6.78	−0.58	−0.07	−1.68	2.88	−1.35	−3.65	−3.80	−3.61
10	6.82	0.30	−1.62	−2.94	1.13	−3.71	−3.57	−4.03	−4.30
11	7.30	0.02	−0.43	−2.62	0.45	−5.39	−4.11	−3.93	−5.18
12	7.86	0.32	−1.34	−1.94	2.14	−3.64	−3.50	−2.66	−4.28
13	7.95	1.06	−0.68	−1.20	0.83	−3.16	−3.27	−3.76	−4.30
14	8.08	−0.17	−0.82	−3.41	1.87	−3.44	−3.00	−4.21	−3.41
15	8.33	−0.19	0.14	−0.94	2.53	−4.95	−2.99	−3.88	−5.29
16	8.62	0.44	−0.33	−1.44	3.19	−1.46	−2.58	−2.63	−2.32
17	9.38	0.04	−0.19	−1.42	2.44	−2.31	−3.61	−4.13	−3.69
18	9.43	0.75	0.04	−1.56	2.52	−4.56	−3.33	−4.03	−2.64
19	9.51	0.77[b]	−1.01	−2.10	2.66	−2.69	−3.15	−2.60	−3.26
20	9.72	−0.37	−1.88	−2.67	1.11	−4.17	−3.79	−4.13	−4.08
21	9.85	0.22	−0.88	−1.61	2.37	−2.69	−3.71	−3.83	−4.82
22	9.96	0.74	−0.83	−2.07	2.73	−3.17	−4.22	−4.44	−4.22
23	10.33	−0.66	−0.61	−1.70	2.32	−1.70	−3.68	−3.95	−4.06
24	10.61	0.51	−0.50	−1.24	3.47	−3.60	−3.10	−3.70	−3.80
25	10.67	−0.25	−0.01	−1.48	3.93	−2.72	−3.93	−4.29	−4.34
26	10.86	0.57	0.21	−1.76	2.56	−3.27	−3.54	−2.59	−2.94
27	9.04	−0.05	−0.42	−0.85	2.20	−2.72	−3.95	−3.72	−3.39
28	8.55	0.38	−0.70	−2.19	2.02	−2.16	−3.05	−4.09	−3.42
29	10.40	1.01[b]	−0.37	−0.27	2.64	−2.33	−2.12	−2.40	−5.27
30	10.53	−1.03	−0.54	−2.13	1.87	−3.10	−3.59	−3.10	−4.86
31	10.57	0.69	0.76	−0.01	4.34	−3.07	−2.48	−2.61	−3.34
32	11.05	0.56	0.04	−1.02	3.68	−2.40	−4.12	−3.02	−2.06
33	11.22	0.76	−0.94	−1.81	2.69	−3.20	−3.94	−4.05	−3.01
34	9.05	−0.02	−1.13	−2.54	1.64	−2.89	−3.83	−3.89	−3.42
35	10.22	1.13	−0.14	−1.32	2.51	−2.42	−2.02	−3.06	−3.64
36	8.82	0.50	−0.57	−1.91	1.32	−3.78	−2.82	−3.43	−3.32
37	10.69	0.70	0.06	−1.32	3.18	−3.12	−4.21	−3.65	−3.51
38	6.39	0.33	−0.95	−2.12	2.20	−3.32	−3.28	−3.95	−3.76
39	6.02	−0.27	−1.44	−1.80	0.20	−3.14	−4.29	−3.89	−5.05
40	4.72	−0.63	−3.26	−5.66	−3.03	−4.70	−5.76	−5.91	−5.51
41	10.27	−0.86	−1.37	−3.35	0.96	−4.71	−4.06	−3.93	−4.39
42	10.19	0.63	0.74	−0.85	2.23	−2.71	−2.60	−2.93	−3.41
43	9.33	−0.24	−0.64	−2.10	2.50	−3.86	−3.88	−3.13	−3.15
44	9.88	0.62	−0.43	−0.73	3.74	−2.33	−3.76	−3.82	−3.19
45	9.26	0.12	−1.65	−2.84	1.11	−2.22	−4.55	−4.41	−2.18
mean signed error (MSE)		0.17	−0.78	−1.92	1.96	−3.20	−3.58	−3.70	−3.83
mean unsigned error (MUE)		0.51	0.87	1.92	2.10	3.20	3.58	3.70	3.83
standard deviation (SD)		0.58	0.79	0.98	1.29	0.92	0.78	0.70	0.82

[a]References 65−76. [b]6-311++G(d,p)//6-31+G(d,p).

$$G_{aq}^{*}(H^+) = G_g^o(H^+) + \Delta G_{aq,solv}(H^+) + \Delta G^{1atm \rightarrow 1M}$$

$\Delta G_{aq,solv}(H^+)$ = −265.9 kcal/mol was taken from the literature[44−47] and $G_g^o(H^+)$ was calculated using $G_g^o = H_g^o − TS_g^o$ where $E_{0K} = 0$, $H_g^o = 5/2RT = 1.48$ kcal/mol, and $S_g^o = 26.05$ cal/(mol·K). $\Delta G^{1 atm \rightarrow 1M} = 1.89$ kcal/mol corresponds to

the free energy change due to changing the standard state from 1 atm to 1 M.

To assess the performance of various DFT methods, pK_a's were calculated for imidazole, methanethiol, and ethanethiol using a set of 175 density functionals (listed in the Supporting Information) with the 6-31+G(d,p) basis set. From this set of 175 functionals, eight functionals that performed well were

selected for the second part of the study: B3LYP,[48−51] M06-2X,[52] ωB97XD,[53] BLYP,[48−50] PBEPBE,[54,55] PBEVWN5,[54−56] BP86,[50,57] and LC-BLYP.[48,50,58] Three different basis sets (6-31G(d), 6-31+G(d,p), and 6-311++G(d,p))[59−63] were used to optimize the geometry with each of the functionals in aqueous solution with SMD solvation model. Frequency calculations were used to confirm that all of the structures were minima on the potential energy surface. A set of 45 different organic thiols was used to assess the performance and accuracy of the various functionals. Some of the structures used in this study may have more than one conformer; the ones with the lowest energy have been used for the pK_a calculations. Conformers having the energies within 1 kcal/mol are found to have calculated pK_a within 0.5 pK_a units of the lowest energy conformers. The pK_a calculations were carried out using the SMD[39] polarizable continuum solvation model without explicit water molecules, and using SMD with one and three explicit waters around the sulfur atom involved in deprotonation/protonation reaction. The development version of Gaussian series of programs was used to perform the calculations.[64]

■ RESULTS AND DISCUSSION

The performance of a set of 175 density functionals in the calculation of the pK_a's of imidazole, methanethiol, and ethanethiol is shown in Figure 1. The difference between the calculated and experimental pK_a's for imidazole−imidazolium forms a rather broad distribution but is peaked near zero. This shows that a large fraction of the functionals yield quite good values for the pK_a of imidazole when used with the SMD implicit solvation model. The shape of the distribution of calculated pK_a values for methanethiol and ethanethiol is very similar to that for imidazole, but the peak in the calculated pK_a's for the thiols is almost 10 pK_a units higher than the experimental values. This deviation in ΔpK_a is fairly consistent for each of the 175 density functionals for both the methanethiol and the ethanethiol. The ΔpK_a for the thiols is 8.5 ± 3.4 units higher than ΔpK_a for imidazole when averaged over the 175 density functionals. From this set of 175 DFT functionals, eight functionals were selected for the study of the pK_a's of substituted organic thiols: four pure functionals (BLYP, PBEPBE, PBEVWN5, and BP86), a long-range corrected pure functional (LC-BLYP), two hybrid functionals (B3LYP, M06-2X), and a range-separated hybrid functional (ωB97XD).

The set of 45 different organic thiols used to assess the performance of the various functionals is shown in Figure 2. The experimental pK_a's for this set of organic thiols are listed in Table 1 and range from 4 to 12 pK_a units.[65−76] The test calculations in Figure 1 indicate that there is a large error in the calculation of the pK_a's for simple thiols. In previous studies on nucleobases, we found that the methods that performed well for pK_a's of cation−neutral pairs often performed poorly for pK_a's of neutral−anion pairs.[29,34−36] Earlier studies of thiol pK_a's involving linear fits of the solvation free energy or linear correlations of the calculated pK_a's with respect to the experimental values show that there are systematic errors in the calculated solvation energy for the anions.[15,17] Aside from reparametrizing the solvation model specifically for thiol pK_a's, there are two viable ways to correct these errors: (a) scaling the solvent cavity and (b) including explicit solvent molecules in addition to implicit solvation.

a. Solvent Cavity Scaling. Even though implicit solvation models are highly parametrized, the calculated aqueous solvation free energies for anionic species still tend to have

larger errors than for neutral species. A simple way to compensate for the effect of missing charge density and short-range interactions is by scaling the solvent cavity or by scaling individual atomic radii. In an earlier study of the calculation of pK_a's and reduction potentials of nucleobases,[34,35] we scaled the solvation cavity to successfully correct for errors in the solvation energy. The cavity scaling approach was particularly useful for the anions with the negative charged localized on nitrogen or oxygen atoms. The applicability of cavity scaling for charged species was also noted in some other studies.[34,77−80] Scaling the solvent cavity was used in an attempt to correct for the systematic errors in the solvation free energy of thiolates. Even with an unreasonably small cavity scaling factor of 0.70, the calculated pK_a's were still 3 units higher than the experimental values. This indicates that scaling the solvent cavity does not sufficiently compensate for the errors in solvation free energy for thiolates.

b. Inclusion of Explicit Waters. By their very nature, implicit solvation models do not include a direct treatment of specific short-range solute−solvent interactions such as hydrogen bonds. Those short-ranged interactions are particularly strong for charged species in polar solvents like water. One way to account for these interactions is to use a cluster-continuum or explicit-implicit solvent model.[18−29] In the present study, we have placed one and three explicit water molecules near the sulfur atom undergoing deprotonation/protonation. The general arrangement of hydrogen bonds between the thiol/thiolate and the explicit water molecules is shown in Figure 3a,b. For the one explicit water case, the orientation of the
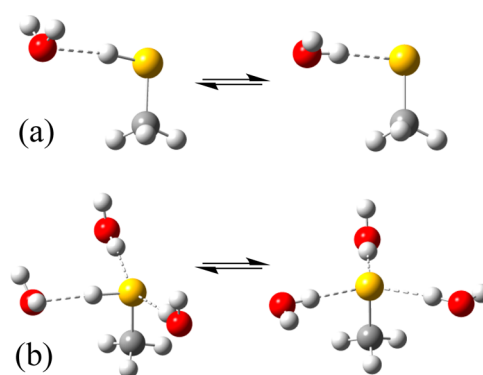

Figure 3. Placement of (a) one explicit water and (b) three explicit waters hydrogen bonded to methanethiol and methanethiolate.

water changes from a hydrogen bond acceptor with thiol to a hydrogen donor for thiolate. For three explicit water molecules, the two additional waters form S···HOH hydrogen bonds with both the thiol and the thiolate. With this arrangement, the total number of hydrogen bonds is the same for the thiol and the thiolate, ensuring that the contributing to the energy difference comes from change in the strength of hydrogen bonds and not from a change in the number of hydrogen bonds.

Figure 4 shows a linear correlation between the experimental pK_a's of the thiols and the pK_a's calculated using the SMD implicit solvation model with zero, one and three explicit waters at the ωB97XD/6-31+G(d,p) level of theory. The performance of the other seven density functionals is similar (Figure S1 in the Supporting Information). The R^2 values are 0.94−0.96, indicating a good correlation in all three cases. However, without an explicit water, the intercept is greater than 0 and the slope is significantly greater than 1, indicating a systematic error
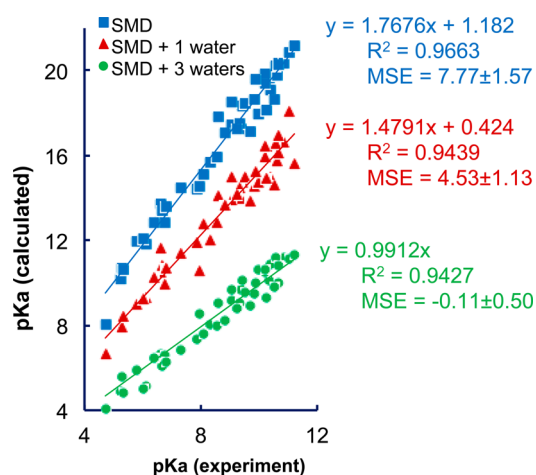
Figure 4. Linear correlation of experimental pK_a's and values calculated using ωB97XD/6-31+G(d,p) with SMD and no explicit water molecules (blue squares), one explicit water (red triangles), and three explicit waters (green dots).

that increases with the pK_a. Adding one explicit water reduces the slope from 1.76 to 1.48 and the intercept from 1.18 to 0.42. The average error in the pK_a's is reduced from 7.77 to 4.53 pK_a units (Table 2). This implies that the lack of short-range hydrogen bonding interactions is a major factor in the poor performance of SMD for calculating thiol pK_a's. When three waters are placed around the sulfur, the correlation between the experimental pK_a's and the ones calculated at the ωB97XD/6-31+G(d,p) level of theory has a slope of 0.991 when the intercept is set to zero, and the average error in the pK_a's is only -0.11. This demonstrates that the short-range interactions

needed for the calculation of pK_a's for thiols are treated very well by the inclusion of three waters.

Table 1 compares the errors in the pK_a's for individual molecules calculated with the selected eight functionals using the 6-311++G(d,p) basis and SMD solvation with three explicit waters. The ωB97XD functional performs the best, with the lowest mean signed error (MSE), mean unsigned error (MUE), and standard deviation (SD); the largest maximum positive and negative errors are $+1.13$ and -1.16, respectively. The B3LYP functional has the second best performance, whereas M0-62X, PBEPBE, BP86, BLYP, and LC-BLYP show systematic deviations, underestimating the pK_a's on average by more than 3 units.

Table 2 summarizes the performance of the eight selected functionals and three different basis sets for calculating pK_a's of substituted thiols using SMD solvation with zero, one, and three explicit waters. As expected, the basis set needs to include polarization functions on the hydrogen; the pK_a's calculated with the 6-31G(d) basis set and no explicit waters deviate from experimental values by 8–14 pK_a units. With the 6-31+G(d,p) basis set, the mean unsigned error in the calculated pK_a's is reduced to 5–9 pK_a units. M06-2X has the smallest deviation (4.8 ± 1.7 pK_a units) and ωB97XD has the largest deviation (7.8 ± 1.6 pK_a units). Enlarging the basis set and adding diffused functions on the hydrogens (6-311++G(d,p) basis set) changes the average errors in the calculated pK_a values by only about ±0.2 pK_a units. This change is insignificant compared to the deviation from the experimental values. Because of the large errors in the pK_a values calculated with 6-31G(d) basis set, only the 6-31+G(d,p) and 6-311++G(d,p) basis sets were used for calculations with explicit water molecules.

The error in the calculated pK_a's is reduced impressively by an average of 3.0 pK_a units when one explicit water molecule is

Table 2. Averages and Standard Deviations for the Errors in the Calculated pK_a's for Different Levels of Theory

functional	basis set	ΔpK_a (pK_a(calc) $-$ pK_a(exp))		
		SMD	SMD + 1 water	SMD + 3 waters
ωB97XD	6-31G(d)	11.04 ± 2.23		
	6-31+G(d,p)	7.77 ± 1.58	4.53 ± 1.13	-0.11 ± 0.50
	6-311++G(d,p)	8.02 ± 1.54	4.99 ± 1.05	0.17 ± 0.58
B3LYP	6-31G(d)	11.25 ± 2.50		
	6-31+G(d,p)	7.16 ± 1.85	3.74 ± 1.33	-1.11 ± 0.82
	6-311++G(d,p)	7.21 ± 1.82	3.87 ± 1.31	-0.78 ± 0.79
BLYP	6-31G(d)	11.65 ± 2.77		
	6-31+G(d,p)	6.43 ± 1.93	2.77 ± 1.26	-2.17 ± 1.01
	6-311++G(d,p)	6.49 ± 1.89	2.88 ± 1.34	-1.92 ± 0.98
PBEVWN5	6-31G(d)	14.18 ± 2.69		
	6-31+G(d,p)	9.23 ± 1.95	6.16 ± 1.37	1.71 ± 1.24
	6-311++G(d,p)	9.36 ± 1.98	6.27 ± 1.33	1.96 ± 1.29
MO62X	6-31G(d)	8.06 ± 2.34		
	6-31+G(d,p)	4.76 ± 1.74	1.63 ± 1.22	-3.21 ± 1.04
	6-311++G(d,p)	4.84 ± 1.67	1.54 ± 1.24	-3.20 ± 0.92
BP86	6-31G(d)	10.17 ± 2.85		
	6-31+G(d,p)	6.04 ± 2.01	1.81 ± 1.20	-3.78 ± 0.77
	6-311++G(d,p)	6.12 ± 1.98	1.97 ± 1.36	-3.58 ± 0.78
PBEPBE	6-31G(d)	10.21 ± 2.89		
	6-31+G(d,p)	6.00 ± 2.02	1.49 ± 1.42	-3.92 ± 0.78
	6-311++G(d,p)	6.17 ± 2.00	1.76 ± 1.43	-3.70 ± 0.70
LC-BLYP	6-31G(d)	8.88 ± 2.00		
	6-31+G(d,p)	5.22 ± 1.48	1.43 ± 1.07	-4.00 ± 0.82
	6-311++G(d,p)	5.21 ± 1.48	1.53 ± 0.98	-3.83 ± 0.82

Table 3. Experimental pK_a's and Values Calculated with the ωB97XD/6-31+G(d,p) Level of Theory for Various Substituted Thiols

structure	pK_a(exp)[a]	SMD		SMD + 1 water		SMD + 3 waters	
		pK_a	ΔpK_a	pK_a	ΔpK_a	pK_a	ΔpK_a
1	5.24	10.18	4.94	8.02	2.78	4.86	−0.38
2	5.30	10.68	5.38	7.93	2.63	5.58	0.28
3	5.33	10.65	5.32	8.39	3.06	4.80	−0.53
4	5.78	11.97	6.19	9.00	3.22	5.88	0.10
5	6.14	11.80	5.66	9.27	3.13	5.13	−1.01
6	6.61	12.89	6.28	10.49	3.88	6.63	0.02
7	6.64	13.74	7.10	11.61	4.97	6.66	0.02
8	6.66	13.43	6.77	10.82	4.16	6.06	−0.60
9	6.78	12.84	6.06	9.93	3.15	6.56	−0.22
10	6.82	13.58	6.76	10.70	3.88	6.25	−0.57
11	7.30	14.46	7.16	11.37	4.07	6.87	−0.43
12	7.86	14.43	6.57	11.87	4.01	7.38	−0.48
13	7.95	14.56	6.61	10.58	2.63	8.57	0.62
14	8.08	15.11	7.03	12.78	4.70	7.62	−0.46
15	8.33	15.65	7.32	12.01	3.68	8.05	−0.28
16	8.62	17.81	9.19	14.10	5.48	9.05	0.43
17	9.38	17.27	7.89	13.99	4.61	9.67	0.29
18	9.43	18.34	8.91	14.70	5.27	10.11	0.68
19	9.51	18.43	8.92	14.97	5.46	9.58	0.07
20	9.72	17.12	7.40	13.82	4.10	8.93	−0.79
21	9.85	18.64	8.79	14.51	4.66	9.48	−0.37
22	9.96	17.93	7.97	14.73	4.77	10.63	0.67
23	10.33	19.63	9.30	16.42	6.09	10.13	−0.20
24	10.61	19.76	9.15	15.73	5.12	11.15	0.54
25	10.67	20.35	9.68	16.09	5.42	9.99	−0.68
26	10.86	20.32	9.46	16.64	5.78	11.17	0.31
27	9.04	18.52	9.48	14.98	5.94	9.67	0.63
28	8.55	15.94	7.39	12.81	4.26	7.99	−0.56
29	10.40	19.11	8.71	14.99	4.59	10.88	0.48
30	10.53	18.63	8.10	14.60	4.07	9.78	−0.75
31	10.57	20.22	9.65	16.54	5.97	11.19	0.62
32	11.05	20.87	9.82	18.07	7.02	11.13	0.08
33	11.22	21.18	9.96	15.59	4.37	11.32	0.10
34	9.05	17.46	8.41	13.94	4.89	9.20	0.15
35	10.22	19.84	9.62	15.91	5.69	10.50	0.28
36	8.82	17.09	8.27	13.68	4.86	8.25	−0.57
37	10.69	20.27	9.58	16.97	6.28	10.83	0.14
38	6.39	12.82	6.43	10.23	3.84	6.46	0.07
39	6.02	12.06	6.04	9.26	3.24	5.01	−1.01
40	4.72	8.03	3.31	6.67	1.95	4.06	−0.66
41	10.27	18.11	7.84	14.92	4.65	9.31	−0.96
42	10.19	19.39	9.20	16.46	6.27	10.63	0.44
43	9.33	17.53	8.20	14.47	5.14	9.03	−0.30
44	9.88	19.56	9.68	15.25	5.37	10.01	0.13
45	9.26	17.23	7.97	14.15	4.89	8.77	−0.49
mean signed error (MSE)			7.77		4.53		−0.11
mean unsigned error (MUE)			7.77		4.53		0.43
standard deviation (SD)			1.58		1.13		0.50

[a]References 65−76.

hydrogen bonded to the sulfur atom (Table 2). The largest improvement is seen for BP86 and PBEPBE (more than 4 pK_a units). The best performances with one explicit water are for LC-BLYP (MSE 1.4−1.5 pK_a units), M06-2X (MSE 1.5−1.6 pK_a units), PBEPBE (MSE 1.5−1.8 pK_a units), and BP86 (MSE 1.8−2.0 pK_a units). For the popular B3LYP hybrid functional, the calculated pK_a values still deviate from experiment by about 3.7−3.8 pK_a units with one explicit water and SMD solvation,

even though there is more than 3.3 pK_a units improvement compared to SMD with no explicit waters. With three explicit waters, the M06-2X, PBEPBE, BLYP, and LC-BLYP functionals are found to overstabilize thiolates (Tables 1 and 2), resulting in calculated pK_a's that are much lower than the experimental values (MSE of −3.2 to −4.0 pK_a units). By contrast, PBEVWN5 underestimates the stability of anions even with three explicit waters, resulting pK_a's that are higher than the

experimental values. The average error in the pK_a's calculated with the B3LYP/6-31+G(d,p) level of theory is -1.11 ± 0.82 pK_a units. An accuracy of better than 1 pK_a unit is obtained with B3LYP and the larger 6-311++G(d,p) basis set (MSE -0.78 ± 0.79). The performance of ωB97XD is rather impressive; with the three explicit water molecules, the average error is -0.11 ± 0.50 and $+0.17 \pm 0.58$ pK_a units with the 6-31+G(d,p) and 6-311++G(d,p) basis sets, respectively. The pK_a's calculated for the individual thiols with the ωB97XD/6-31+G(d,p) level of theory are compared with the experimental values in Table 3. Adding one explicit water reduces the average error from 7.78 to 4.53 pK_a units. With three explicit waters the MSE and MUE are -0.11 and $+0.43$, respectively, and the standard deviation is 0.50 pK_a units.

The present study demonstrates that including explicit waters near the sulfur is essential for obtaining reasonable pK_a's for thiols with the SMD solvation model. With one explicit water, the M06-2X and LC-BLYP functionals can give pK_a's within 2 units of the experimental values. To achieve an error of less than 1 pK_a unit, three explicit waters hydrogen bonded to the sulfur atom and the ωB97XD functional with a 6-31+G(d,p) basis set or better are recommended.

■ SUMMARY

A survey of 175 different density functionals showed that the average pK_a's of methanethiol and ethanethiol calculated with the SMD implicit solvation model are almost 10 pK_a units higher than the experimental values. To probe the nature of this discrepancy, we selected a test set of 45 substituted thiols with experimental values ranging from 4 to 12. Eight different density functionals with three different basis sets were used for calculations with the SMD implicit solvation model with and without explicit water molecules. Without explicit waters, the SMD solvation model had large errors in the solvation energy of thiolate anions, with calculated pK_a's deviating from the experimental values by 5 to 10 pK_a units depending upon the level of theory used. Solvent cavity scaling for the anions was found to be ineffective in producing reasonable pK_a's for the thiols, indicating that the error in the SMD solvation energy of thiolates cannot be corrected simply by scaling the cavity. The calculation of pK_a's with three different basis sets (6-31G(d), 6-31+G(d,p), and 6-311++G(d,p)) showed that polarization functions on the hydrogens and diffuse functions on the heavy atoms are needed. Inclusion of one explicit water hydrogen bonded with the H of the thiol group (in thiols) or S⁻ (in thiolates) lowered the error of the pK_a's by an average of 3.5 units. With one explicit water and SMD solvation, pK_a's calculated with M06-2X, PBEPBE, BP86, and LC-BLYP functionals have a MUE of 1.5–2.0 pK_a units whereas pK_a's calculated with PBEVWN5, B3LYP, and ωB97XD are still in error by more than 3 pK_a units. The inclusion of three explicit water molecules around sulfur lowered the calculated pK_a's further by as much as 4.5 pK_a units but had mixed effects on the accuracy. With the B3LYP and ωB97XD functionals and three explicit waters, the calculated pK_a's are within 1 pK_a unit of the experimental value whereas most of the other functionals used in this study underestimate the pK_a's because they overstabilize the anions. B3LYP with 6-311++G(d,p) basis set and three explicit waters has average error of -0.78 ± 0.79. The ωB97XD/6-31+G(d,p) level of theory with SMD and three explicit water molecules hydrogen bonded to the sulfur produced best result (average error of -0.11 ± 0.50 compared to the experiment). This study demonstrates that the SMD

implicit solvation model seriously underestimates the stabilization of thiolates in aqueous solution, but that the inclusion of three explicit water molecules can correct this shortcoming in the calculation of pK_a's.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.6b05040.

> Linear correlation plots of pK_a(calc) vs pK_a(exp) and coordinates for the protonated and deprotonated thiols (PDF)
> Absolute free energies for various compounds and details of the calculation of the pK_a's along with the 175 functionals used for imidazole, methanethiol and ethanethiol (XLSX)

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Notes

The authors declare no competing financial interest.

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