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Theoretical Calculation of pK_a's of Selenols in Aqueous Solution Using an Implicit Solvation Model and Explicit Water Molecules

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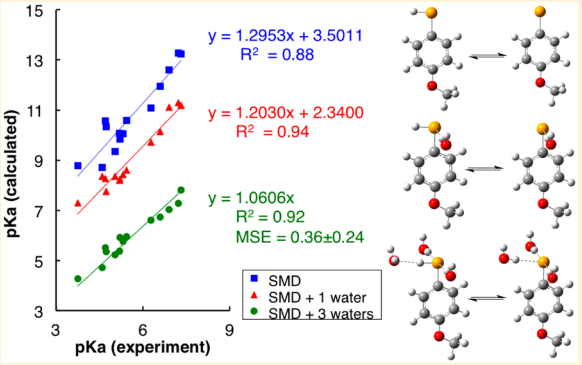
Supporting Information

ABSTRACT: A practical method for calculating the pK_a's of selenols in aqueous solution has been developed by using density functional theory with the SMD solvation model and up to three explicit water molecules. The pK_a's of 30 different organoselenols, 16 with known experimental pK_a's, have been calculated by using three different functionals (ωB97XD, B3LYP, and M06-2X) and two basis sets (6-31+G(d,p) and 6-311++G(d,p)). Calculations using ωB97XD and B3LYP with SMD solvation without explicit waters are found to have errors of 3−6 pK_a units; the errors with M06-2X are somewhat smaller. One explicit water interacting with the selenium reduces the calculated pK_a's by 1−2 pK_a units along with improving the slope and intercept of the fit of the calculated pK_a's to experiment. The best results for SMD/M06-2X/6-31+G(d,p) are with one explicit water (MSE = −0.08 ± 0.37 and MUE = 0.32 ± 0.37) whereas ωB97XD and B3LYP still have errors larger than 2 pK_a units. The best results for ωB97XD and B3LYP with 6-31+G(d,p) are obtained by using three explicit waters (MSE = 0.36 ± 0.24 and 0.34 ± 0.25, respectively) and a fit to experiment yields a slope of 1.06 with a zero intercept. The errors for M06-2X/6-31+G(d,p) with three explicit waters are significantly larger (−3.59 ± 0.45) because it overstabilizes the anions. On the basis of the molecules studied here, M06-2X/6-31+G(d,p) with one explicit water and ωB97XD/6-31+G(d,p) and B3LYP/6-31+G(d,p) with three explicit waters and the SMD solvation model can produce reliable pK_a's for the substituted selenols.



INTRODUCTION

Organoselenium compounds are essential compounds found in most major forms of life and perform vital functions in various biological processes. Selenocysteine, the selenium analogue of cysteine, is known as the 21st amino acid and is incorporated in various selenoproteins such as glutathione peroxidases, iodothyronine deiodinase, selenophosphatase synthase, etc.[1] Most of the selenoproteins are enzymes and are involved in redox reactions and various catalytic activities.[1−4] Because selenium has a number of isotopes, selenoproteins have applications in several biotechnological areas such as positron emission tomography (PET), residue-specific radiolabeling, protein crystallography, high-resolution NMR and EPR spectroscopy, protein folding studies, peptide conjugation, etc.[1] Substituted selenols also have roles in various biochemical functions as substrates for enzyme catalysis,[5,6] as integral component of antioxidants,[4,7−10] and as selenium-substituted nucleobases in RNA studies.[11−15] Because selenols have low pK_a's and the resulting selenolates are soft nucleophiles with highly reactivity, organoselenols are useful precursors in organic and biochemical synthesis.[16,17] Dietary deficiency in selenium can lead to various clinical problems including cardiovascular disease, viral infections, thyroid and reproduction dysfunction, asthma, carcinogenic effects, and neurodegenerative disorders,[10,18−21] whereas elevated levels of selenium lead to toxicity.

An important group of organoselenium compounds, organoselenols are similar to thiols in some of their physiochemical properties but are distinct in other aspects. The higher reactivity of selenium compared to that of sulfur and the lower pK_a's of the selenols compared to those of the thiols are some of the key factors for their importance and applicability in relation to their thiol analogues. Knowledge of the reactivity of selenols is essential to understand the chemistry of selenides, selenoxides, diselenides, selenyl sulfides, selenocyanates, etc. Only a few studies have reported experimental pK_a's of biologically relevant selenols.[17,22−29] Therefore, a reliable method for calculating pK_a's by quantum chemistry would be a valuable addition to our understanding of selenols.

Most of the computational work on selenium containing molecules in the literature has focused on exploring the reactivity of biologically relevant organoselenium compounds. Despite the biologically importance of organoselenols,

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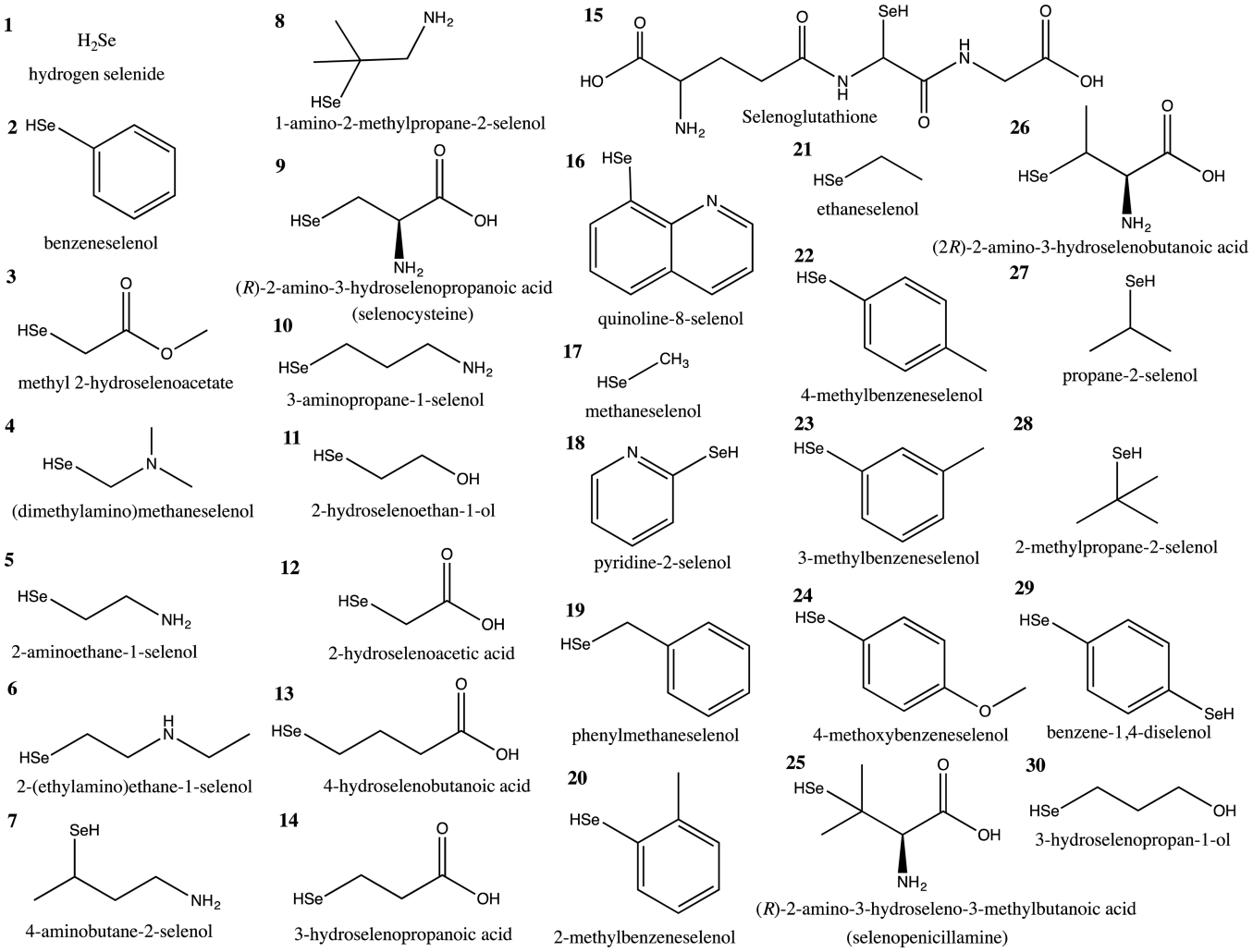

Figure 1. Organoselenols used in this study.

comparatively few computational studies have investigated their chemistry. In a series of papers,[30−33] Boyd and co-workers have tested various density functionals to find a reliable method of predicting the energetics and redox behavior of organoselenium compounds including some selenols, both in the gas phase and in solution. Nam and Nguyen[34] calculated the relationship between the bond dissociation enthalpy and spin density of various substituted benzeneselenols in the gas phase. However, these studies were not focused on acid dissociation constant (pK_a) calculations. Ali et al.[35] calculated the pK_a's of some of the selenol compounds that are relevant to the redox cycle of bovine glutathione peroxidase GPx1. Their study used the B3LYP and MP2 with IEFPCM and CPCM-COSMO-RS implicit solvation to calculate the pK_a's by using a thermodynamic cycle. With both implicit solvation models, the calculated pK_a's had significant errors compared to the experimental pK_a's. However, because the errors were found to be systematic, they employed a simple linear correlation method to obtain reasonable pK_a's. Byun and Kang[36] calculated the pK_a of selenocysteine in various conformations by using a thermodynamic cycle with the carefully selected B2PLYP-D/6-311++G(d,p)//M06-2X/6-31+G(d) level of theory and SMD solvation in the aqueous medium. Their study estimated the pK_a of selenocysteine to be 5.47, very close to the experimental reference value of 5.43 ± 0.02. To the best of our knowledge, no other studies have reported a reliable method to estimate the pK_a's of a larger group of selenols in the aqueous medium.

In the present study, we have calculated the pK_a's for a set of 30 organoselenols, 16 of which have known experimental pK_a's in aqueous solution. Most of the compounds have some biological significance. The pK_a's of these organoselenols have been computed with an implicit-explicit solvation model using SMD implicit solvation and up to three explicit waters. We developed and used this approach for the calculation of pK_a's for nucleobases and substituted thiols.[37,38] The free energy differences are calculated directly in solution without employing a thermodynamic cycle. The advantages of a direct approach for calculating pK_a's over using thermodynamic cycles are discussed and reviewed in detail by Ho, Coote and co-workers.[39−42] In the study of thiol pK_a's, we carefully compared the performance of numerous DFT functionals and SMD solvation with and without explicit waters for calculating pK_a's. At least one explicit water hydrogen bonded to the thiol/thiolate was needed to capture some of the short-range solute−solvent interactions not effectively treated by SMD. The best estimates of pK_a's for thiols were obtained with selected functionals and three explicit waters interacting with the sulfur atom undergoing protonation/deprotonation. Because the basic physiochemical properties of the organic selenols are similar to their thiol analogues, the set of the functionals that performed well for

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thiols has been selected for this study. As discussed in the literature, a more detailed treatment of short-range solvation interactions such as hydrogen bonding can be obtained by molecular dynamics simulations,[43−45] but such calculations require very careful calibration of the solute−solvent interactions and are costly because of long simulation times.

METHOD

All calculations were performed with the development version of the Gaussian series of programs.[46] A test set of 30 substituted organic selenols was used for the study—16 have known experimental pK_a's ranging from 3 to 8. In our previous paper,[38] a wide range of functionals was tested to calculate the pK_a's of 45 substituted thiols and the results were compared with experimental pK_a's. The three functionals that performed best in that study (B3LYP,[47−50] ωB97XD,[51] and M06-2X[52]) were chosen for the present work. Two basis sets (6-31+G(d,p) and 6-311++G(d,p))[53−57] along with these three functionals and the SMD[58] polarizable continuum solvation model were used to optimize the geometries in aqueous solution. All the geometries were confirmed to be the minima on the potential energy surface by harmonic vibrational frequency calculations and had no imaginary frequencies. If a structure has more than one conformer, the lowest energy conformers was used for the pK_a calculations (conformers within 1 kcal/mol have calculated pK_a's within 0.5 units of the lowest energy conformer). Preliminary calculations showed that it was difficult to optimize geometries with the larger basis set (6-311++G(d,p)) when the complex involved three explicit waters. Thus, only the 6-31+G(d,p) basis set was used for optimizations with three explicit waters.

The pK_a of RSeH ⇌ RSe^- + H^+ is calculated by using

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

where $\Delta G^*_{aq} = G^*_{aq,RSe^-} + G^*_{aq,H^+} - G^*_{aq,RSeH}$. The free energies of the selenols and selenates, G^*_{aq,RSe^-} and $G^*_{aq,RSeH}$, with thermal and entropy contributions at 298.15 K, were calculated directly in aqueous solution. For the proton, G^*_{aq,H^+} is calculated as

$$G^*_{aq,H^+} = G^\circ_{g,H^+} + \Delta G^*_{aq,solv,H^+} + \Delta G^{1atm\rightarrow 1M}$$

where $G^\circ_{g,H^+} = H^\circ_{gH^+} - TS^\circ_{gH^+}$ is obtained from $H^\circ_{g,H^+} = 5/2RT$ = 1.48 kcal/mol and S°_{g,H^+} = 26.05 cal/(mol·K). $\Delta G^*_{aq,solv,H^+}$ = −265.9 kcal/mol was taken from literature.[59−62] $\Delta G^{1atm\rightarrow 1M}$ = 1.89 kcal/mol is the correction that corresponds to the change in standard state from 1 atm to 1 mol/L. The * denotes a standard state of 1 mol/L and the ° denotes a standard state of 1 atm.

RESULTS AND DISCUSSION

The organoselenols used in this study are shown in Figure 1. Three functionals (B3LYP, ωB97XD, and M06-2X) and two basis sets (6-31+G(d,p) and 6-311++G(d,p)) were used to optimize the geometry and calculate pK_a's in aqueous solution with SMD solvation model. One and three explicit water molecules were placed near the selenium atom forming hydrogen bonds, as shown in Figure 2. For the one explicit water case, the H atom of the water forms a hydrogen bond with the Se atom (Se---HOH) of both the selenol and the selenolate. In contrast to the thiols, the Se---H−OH hydrogen bond in selenol is stronger than the Se−H---OH_2 hydrogen bond. When there are three explicit water molecules, two

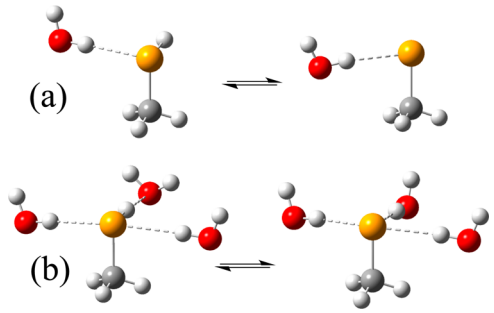

Figure 2. Arrangement of (a) one explicit water and (b) three explicit waters hydrogen bonded to methaneselenol and methaneselenolate.

waters form Se---HOH hydrogen bonds and the third water forms a SeH---OH_2 hydrogen bond. For selenolate, all three water molecules form Se---H−OH hydrogen bonds. The arrangement of explicit water molecules around the solute has to be matched as closely as possible in the selenol/selenolate pair to obtain the reliable pK_a's. The number of hydrogen bonds must be consistent for the neutral and anionic form to ensure that there is no bias in the calculated energy due to a difference in the number of hydrogen bonds. For larger systems with distributed charges or multiple sites for deprotonation, this may require a larger number of explicit water molecules.

Table 1 summarizes the average pK_a's and standard deviations calculated by using the three different functionals with the 6-31+G(d,p) and 6-311++G(d,p) basis sets and the SMD solvation model with and without explicit waters. The pK_a values calculated with ωB97XD and B3LYP using the 6-31+G(d,p) basis set and SMD solvation have errors of 4−6 pK_a units compared to experimental values. This deviation in the calculated pK_a's is somewhat smaller than the 4−9 pK_a unit error found for thiols calculated at the same level of theory in our previous study.[38] The pK_a values calculated with M06-2X/6-31+G(d,p) and SMD implicit solvation have errors of only 1.39 ± 0.43 pK_a units. With the larger 6-311++G(d,p) basis set, the average error of calculated pK_a's changes by 1.2−1.8 pK_a units. The average deviations of the calculated pK_a's for ωB97XD and B3LYP are still about 3−4 pK_a units but the mean signed error for M06-2X is only −0.45 ± 0.52. Adding one explicit water molecule hydrogen bonded to Se improves the calculated pK_a's by about 1−2 pK_a units. This improvement is not as large as observed for the thiols (about 4.5 pK_a units). With one explicit water, pK_a values calculated with ωB97XD and B3LYP are still off by 2.5−4.5 pK_a units compared to experimental values. M06-2X with the 6-31+G(d,p) basis set is very close to experiment, with a mean signed error (MSE) of −0.08 ± 0.37, but M06-2X calculations with the 6-311++G(d,p) basis and one explicit water overstabilize the anion, resulting a larger deviation, −1.51 ± 0.52. Use of three explicit waters hydrogen bonded with Se changes the calculated pK_a by about 3 units. The improvement is rather impressive for ωB97XD and B3LYP with 6-31+G(d,p) basis set with a MSE of 0.36 ± 0.24 and 0.34 ± 0.25, respectively. In contrast, the average deviation for M06-2X becomes worse with three explicit waters (MSE = −3.59 ± 0.45).

Figure 3 shows plots of the calculated pK_a's with respect to the experimental values for three different functionals with the 6-31+G(d,p) basis set (similar plots with the 6-311+G(d,p) basis set are shown in Figure S1 of the Supporting Information). With SMD and no explicit waters, the slope of

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Table 1. Averages and the Standard Deviations of the Errors in the Calculated pK_a's for Different Levels of Theory

functional	basis set	SMD	SMD + 1 water	SMD + 3 waters
ωB97XD	6-31+G(d,p)	5.49 ± 0.57	4.34 ± 0.35	0.36 ± 0.24
	6-311++G(d,p)	4.21 ± 0.54	3.49 ± 0.55	
B3LYP	6-31+G(d,p)	5.15 ± 0.59	3.49 ± 0.37	0.34 ± 0.25
	6-311++G(d,p)	3.42 ± 0.50	2.76 ± 0.55	
M06-2X	6-31+G(d,p)	1.39 ± 0.43	−0.08 ± 0.37	3.59 ± 0.45
	6-311++G(d,p)	−0.45 ± 0.52	−1.51 ± 0.52	

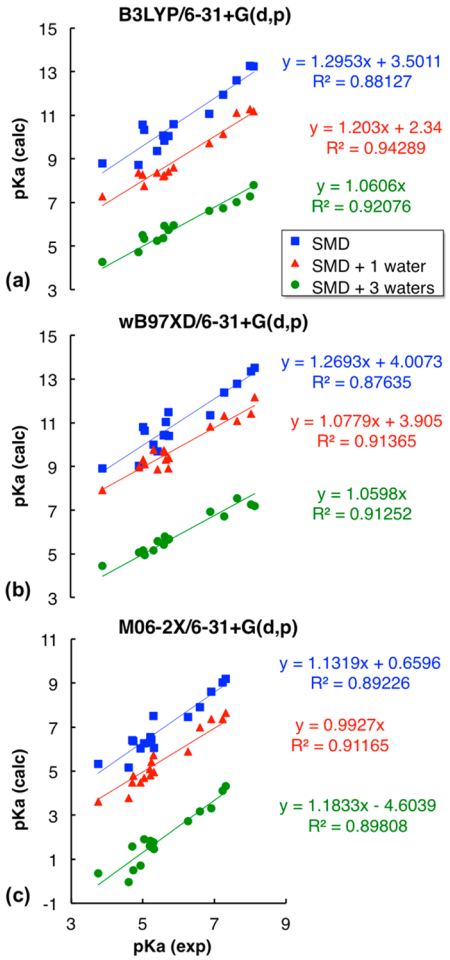

Figure 3. Linear correlation of experimental pK_a's and values calculated by using three different functionals, (a) B3LYP (b) ωB97XD, and (c) M06-2X, and the 6-31+G(d,p) basis set with SMD solvation and no explicit water molecules (blue squares), one explicit water (red triangles), and three explicit water molecules (green dots).

the linear correlation line is largest for B3LYP and ωB97XD (1.26−1.30) whereas the slope is smaller for M06-2X (1.13). Both the slope and the intercept of the line improve when the pK_a's are calculated with one explicit water and SMD solvation. The improvement of the slope is greatest for ωB97XD (from 1.27 to 1.08) and M06-2X (from 1.13 to 0.99). With three explicit waters, the slope of the line improves further and is close to 1 with zero intercept for B3LYP and ωB97XD but gets worse for M06-2X (from 0.99 to 1.18). For all the cases discussed here, the R^2 values are 0.89−0.95, indicating good correlations. The substantial improvement in the slope as explicit waters are added indicates that there are significant deficiencies in the SMD implicit solvation model for selenols/selenates, just as there are deficiencies in SMD solvation for thiols/thiolates.[38]

Table 2 summarizes the pK_a's calculated at the ωB97XD/6-31+G(d,p) level of theory for the compounds in Figure 1 that have experimental values. The linear correlation diagram of the calculated versus the experimental pK_a values is shown in Figure 3b. The errors are 5.49 ± 0.57 pK_a units with SMD and no explicit waters, 4.34 ± 0.35 with SMD and one explicit water, and 0.36 ± 0.24 with SMD and three explicit waters. For the thiols calculated at ωB97XD/6-31+G(d,p) with SMD and three explicit waters, the MSE was −0.11 ± 0.50.[38]

Table 3 lists the pK_a's calculated for 14 organoselenols in Figure 1 that do not have experimental pK_a's. The table includes the three methods that yield the best agreement for the cases where the experimental pK_a's are known, namely M06-2X with one explicit water, and ωB97XD and B3LYP with three explicit waters using the 6-31+G(d,p) basis set. The pK_a's calculated with these three methods are within 2 pK_a units with each other. For the compounds with known experimental pK_a's, the values calculated with M06-2X with one explicit water are often slightly lower than the experimental values, whereas the values calculated with the ωB97XD and B3LYP functionals with three explicit waters are usually slightly higher. This suggests that an improved estimate of the pK_a's might be obtained by taking an average of the values calculated by the three methods. For the test set with known experimental pK_a's, these estimated values are close to the experimental values with a mean signed error of 0.21 ± 0.15 and the linear correlation line has a slope of 0.96 and R^2 value of 0.98. The estimated pK_a's for the substituted organoselenols without experimental values are given in Table 3 along with the standard deviations.

SUMMARY

The aim of this study has been to obtain a practical method for calculating the pK_a's of selenols. The test set consists of 30 different organoselenols, 16 of which have known experimental pK_a's. The pK_a's were calculated in aqueous solution by three different functionals (ωB97XD, B3LYP, and M06-2X) and two basis sets (6-31+G(d,p) and 6-311++G(d,p)) with SMD solvation and one and three explicit water molecules. The density functionals were selected from a larger set of functionals on the basis of their performance in calculating the pK_a's of thiols in our previous study.[38] Without explicit waters, ωB97XD and B3LYP with SMD solvation had errors of 3−6 pK_a units. Smaller errors were found for the M06-2X functional with the 6-31+G(d,p) and 6-311++G(d,p) basis sets (−1.39 ± 0.43 and 0.45 ± 0.52, respectively). However, the linear correlations for the M06-2X calculations with experiment had larger slopes (1.13), and nontrivial intercepts (0.66 and −1.16, respectively). One explicit water interacting with the selenium lowered the calculated pK_a's by 1−2 pK_a units and improved the slope and intercept of the correlation with experiment. The best results for M06-2X were obtained with the 6-31+G(d,p)

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Table 2. Experimental pK_a's and Calculated pK_a's Using the ωB97XD/6-31+G(d,p) Level of Theory for Various Organoselenols

		SMD		SMD + 1 water		SMD + 3 waters	
structure	pK_a (exp)[a]	pK_a	ΔpK_a	pK_a	ΔpK_a	pK_a	ΔpK_a
1	3.75	8.91	5.16	7.92	4.17	4.44	0.69
2	4.60	9.04	4.44	8.95	4.35	5.06	0.46
3	4.70	10.79	6.09	9.31	4.61	5.16	0.46
4	4.74	10.63	5.89	9.09	4.35	4.95	0.21
5	5.31	10.40	5.09	9.38	4.07	5.67	0.36
6	5.04	9.69	4.65	8.85	3.81	5.59	0.55
7	5.19	10.41	5.22	9.74	4.55	5.41	0.22
8	5.21	10.44	5.23	9.66	4.45	5.79	0.58
9	5.24[b] (5.43[c])	11.04	5.80	9.31	4.07	5.63	0.39
10	6.27	11.35	5.08	10.82	4.55	6.93	0.66
11	6.60	12.39	5.79	11.32	4.72	6.72	0.12
12	6.91	12.79	5.88	11.09	4.18	7.54	0.63
13	7.23	13.35	6.12	11.43	4.20	7.25	0.02
14	7.32	13.52	6.20	12.17	4.85	7.18	−0.14
15	5.30	11.50	6.20	8.90	3.60	5.65	0.35
16	4.94	10.00	5.06	9.76	4.82	5.17	0.23
mean signed error (MSE)			5.49		4.34		0.36
mean unsigned error (MUE)			5.49		4.34		0.38
standard deviation (SD)			0.57		0.35		0.24

[a]References 17, 23−29. [b]Reference 22. [c]Reference 25.

Table 3. Calculated pK_a's of Some of the Organoselenols with the 6-31+G(d,p) Basis Set and SMD Solvation for Various Levels of Theory

structure	ωB97XD (SMD + 3 waters)	B3LYP (SMD + 3 waters)	M062X (SMD + 1 water)	best estimate[a]
17	7.93	8.18	7.74	7.95 ± 0.22
18	3.39	4.43	3.02	3.61 ± 0.73
19	5.93	7.98	6.38	6.76 ± 1.08
20	4.11	5.10	4.17	4.46 ± 0.55
21	8.22	8.16	7.73	8.04 ± 0.27
22	4.08	4.86	3.67	4.20 ± 0.60
23	4.64	4.98	3.58	4.40 ± 0.73
24	4.84	4.35	3.78	4.32 ± 0.53
25	7.42	7.88	6.24	7.18 ± 0.85
26	6.88	6.34	5.68	6.30 ± 0.60
27	7.48	8.89	7.79	8.05 ± 0.74
28	8.87	8.12	7.68	8.22 ± 0.60
29	3.81	4.29	3.89	4.00 ± 0.26
30	8.33	7.27	6.76	7.45 ± 0.80

[a]The best estimates are obtained by taking an average of the pK_a's calculated with the three different functionals. The error in best estimates is the standard deviation of three pK_a values used to obtain the estimated value.

basis set and one explicit water (MSE = −0.08 ± 0.37 and MUE= 0.32 ± 0.37). With one explicit water, the ωB97XD and B3LYP errors were 3−4 pK_a units. The best results for ωB97XD and B3LYP were obtained with the 6-31+G(d,p) basis and three explicit waters. The calculated mean deviations for these two functionals are 0.36 ± 0.24 and 0.34 ± 0.25, respectively, with a slope of 1.06 when the intercept is set to zero. M06-2X/6-31+G(d,p) has much larger errors with three explicit waters (−3.59 ± 0.45) because it overstabilizes the anions. The ωB97XD/6-31+G(d,p) level of theory with SMD solvation and three explicit waters also produced the best results for the substituted thiols (MSE = −0.11 ± 0.50).[38] Even though this study provides a reliable method for predicting selenol pK_a's, this study and our previous work on pK_a's of thiols[38] suggest that improvements in the parametrization of the SMD solvation model are necessary to obtain better solvation energies for thiolates and selenolates without explicit waters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.6b09520.

Linear correlation plots of calculated and experimental pK_a's and coordinates for the optimized geometries of protonated and deprotonated selenols with three explicit waters (PDF)

Absolute free energy of the various compounds and the detail of the calculation of the pK_a's (XLSX)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Johansson, L.; Gafvelin, G.; Arnér, E. S. Selenocysteine in proteins—properties and biotechnological use. *Biochim. Biophys. Acta, Gen. Subj.* **2005**, *1726*, 1−13.

(2) Papp, L. V.; Lu, J.; Holmgren, A.; Khanna, K. K. From selenium to selenoproteins: Synthesis, identity, and their role in human health. *Antioxid. Redox Signaling* **2007**, *9*, 775−806.

DOI: 10.1021/acs.jpca.6b09520
J. Phys. Chem. A 2016, 120, 8916−8922

(3) Steinbrenner, H.; Sies, H. Protection against reactive oxygen species by selenoproteins. *Biochim. Biophys. Acta, Gen. Subj.* **2009**, *1790*, 1478−1485.
(4) Steinbrenner, H.; Speckmann, B.; Klotz, L.-O. Selenoproteins: Antioxidant selenoenzymes and beyond. *Arch. Biochem. Biophys.* **2016**, *595*, 113−119.
(5) Zhao, R.; Masayasu, H.; Holmgren, A. Ebselen: A substrate for human thioredoxin reductase strongly stimulating its hydroperoxide reductase activity and a superfast thioredoxin oxidant. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 8579−8584.
(6) Fang, J.; Zhong, L.; Zhao, R.; Holmgren, A. Ebselen: A thioredoxin reductase-dependent catalyst for α-tocopherol quinone reduction. *Toxicol. Appl. Pharmacol.* **2005**, *207*, 103−109.
(7) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. A novel biologically active seleno-organic compound—1: Glutathione peroxidase-like activity in vitro and antioxidant capacity of PZ 51 (ebselen). *Biochem. Pharmacol.* **1984**, *33*, 3235−3239.
(8) Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. A novel biologically active seleno-organic compound—II: Activity of PZ 51 in relation to glutathione peroxidase. *Biochem. Pharmacol.* **1984**, *33*, 3241−3245.
(9) Nakamura, Y.; Feng, Q.; Kumagai, T.; Torikai, K.; Ohigashi, H.; Osawa, T.; Noguchi, N.; Niki, E.; Uchida, K. Ebselen, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant implication for inflammation-associated carcinogenesis. *J. Biol. Chem.* **2002**, *277*, 2687−2694.
(10) Tapiero, H.; Townsend, D. M.; Tew, K. D. The antioxidant role of selenium and seleno-compounds. *Biomed. Pharmacother.* **2003**, *57*, 134−144.
(11) Brandt, G.; Carrasco, N.; Huang, Z. Efficient substrate cleavage catalyzed by hammerhead ribozymes derivatized with selenium for X-ray crystallography. *Biochemistry* **2006**, *45*, 8972−8977.
(12) Moroder, H.; Kreutz, C.; Lang, K.; Serganov, A.; Micura, R. Synthesis, oxidation behavior, crystallization and structure of 2′-methylseleno guanosine containing RNAs. *J. Am. Chem. Soc.* **2006**, *128*, 9909−9918.
(13) Salon, J.; Sheng, J.; Jiang, J.; Chen, G.; Caton-Williams, J.; Huang, Z. Oxygen replacement with selenium at the thymidine 4-position for the Se base pairing and crystal structure studies. *J. Am. Chem. Soc.* **2007**, *129*, 4862−4863.
(14) Salon, J.; Jiang, J.; Sheng, J.; Gerlits, O. O.; Huang, Z. Derivatization of DNAs with selenium at 6-position of guanine for function and crystal structure studies. *Nucleic Acids Res.* **2008**, *36*, 7009−7018.
(15) Sheng, J.; Huang, Z. Selenium derivatization of nucleic acids for X-ray crystal-structure and function studies. *Chem. Biodiversity* **2010**, *7*, 753−785.
(16) Mugesh, G.; du Mont, W.-W.; Sies, H. Chemistry of biologically important synthetic organoselenium compounds. *Chem. Rev.* **2001**, *101*, 2125−2180.
(17) Krief, A.; Hevesi, L. *Organoselenium chemistry I: Functional group transformations*; Springer Science & Business Media: Berlin, Germany, 2012.
(18) Rayman, M. P. The importance of selenium to human health. *Lancet* **2000**, *356*, 233−241.
(19) Brown, K.; Arthur, J. Selenium, selenoproteins and human health: A review. *Public Health Nutr.* **2001**, *4*, 593−599.
(20) Oropeza-Moe, M.; Wisløff, H.; Bernhoft, A. Selenium deficiency associated porcine and human cardiomyopathies. *J. Trace Elem. Med. Biol.* **2015**, *31*, 148−156.
(21) Cardoso, B. R.; Roberts, B. R.; Bush, A. I.; Hare, D. J. Selenium, selenoproteins and neurodegenerative diseases. *Metallomics* **2015**, *7*, 1213−1228.
(22) Huber, R. E.; Criddle, R. S. Comparison of the chemical properties of selenocysteine and selenocystine with their sulfur analogs. *Arch. Biochem. Biophys.* **1967**, *122*, 164−173.
(23) Yokoyama, A.; Sakurai, H.; Tanaka, H. Syntheses of related compounds of selenocysteamine and their complex formation with metal ions. *Chem. Pharm. Bull.* **1971**, *19*, 1089−1094.
(24) Serjeant, E. P.; Dempsey, B. *Ionisation constants of organic acids in aqueous solution*; Pergamon: New York, USA, 1979; Vol. 23.
(25) Arnold, A. P.; Tan, K. S.; Rabenstein, D. L. Nuclear magnetic resonance studies of the solution chemistry of metal complexes. 23. Complexation of methylmercury by selenohydryl-containing amino acids and related molecules. *Inorg. Chem.* **1986**, *25*, 2433−2437.
(26) Tan, K.-S.; Arnold, A. P.; Rabenstein, D. L. Selenium-77 nuclear magnetic resonance studies of selenols, diselenides, and selenenyl sulfides. *Can. J. Chem.* **1988**, *66*, 54−60.
(27) Huang, J.; Li, C.; Nolan, S. P.; Petersen, J. L. Solution calorimetric investigation of oxidative addition of HEAr (E= O, S, Se; Ar= C_6H_4X, X= CH_3, H, Cl, NO_2) to (PMe_3) 4Ru (C_2H_4): Relationship between hear acidity and enthalpy of reaction. *Organometallics* **1998**, *17*, 3516−3521.
(28) Sokolov, M. N.; Abramov, P. A.; Peresypkina, E. V.; Virovets, A. V.; Fedin, V. P. In situ generation of H_2Se and hydrothermal synthesis of new polynuclear rhenium carbonyl polyselenides. *Polyhedron* **2008**, *27*, 3259−3262.
(29) Beld, J.; Woycechowsky, K. J.; Hilvert, D. Selenoglutathione: Efficient oxidative protein folding by a diselenide. *Biochemistry* **2007**, *46*, 5382−5390.
(30) Pearson, J. K.; Ban, F.; Boyd, R. J. An evaluation of various computational methods for the treatment of organoselenium compounds. *J. Phys. Chem. A* **2005**, *109*, 10373−10379.
(31) Heverly-Coulson, G. S.; Boyd, R. J. Systematic study of the performance of density functional theory methods for prediction of energies and geometries of organoselenium compounds. *J. Phys. Chem. A* **2011**, *115*, 4827−4831.
(32) Heverly-Coulson, G. S.; Boyd, R. J. Mechanism of the reduction of an oxidized glutathione peroxidase mimic with thiols. *J. Chem. Theory Comput.* **2012**, *8*, 5052−5057.
(33) Bushnell, E. A.; Burns, T. D.; Boyd, R. J. The one-electron reduction of dithiolate and diselenolate ligands. *Phys. Chem. Chem. Phys.* **2014**, *16*, 10897−10902.
(34) Nam, P. C.; Nguyen, M. T. The Se−H bond of benzeneselenols (ArSe-H): Relationship between bond dissociation enthalpy and spin density of radicals. *Chem. Phys.* **2013**, *415*, 18−25.
(35) Ali, S. T.; Jahangir, S.; Karamat, S.; Fabian, W. M. F.; Nawara, K.; Kóňa, J. Theoretical study on the redox cycle of bovine glutathione peroxidase GPx1: pKa calculations, docking, and molecular dynamics simulations. *J. Chem. Theory Comput.* **2010**, *6*, 1670−1681.
(36) Byun, B. J.; Kang, Y. K. Conformational preferences and pKa value of selenocysteine residue. *Biopolymers* **2011**, *95*, 345−353.
(37) Thapa, B.; Schlegel, H. B. Calculations of pKa's and redox potentials of nucleobases with explicit waters and polarizable continuum solvation. *J. Phys. Chem. A* **2015**, *119*, 5134−5144.
(38) Thapa, B.; Schlegel, H. B. Density functional theory calculation of pKa's of thiols in aqueous solution using explicit water molecules and the polarizable continuum model. *J. Phys. Chem. A* **2016**, *120*, 5726−5735.
(39) Ho, J.; Coote, M. L. A universal approach for continuum solvent pKa calculations: Are we there yet? *Theor. Chem. Acc.* **2010**, *125*, 3−21.
(40) Ho, J. Predicting pKa in implicit solvents: Current status and future directions. *Aust. J. Chem.* **2014**, *67*, 1441−1460.
(41) Ho, J. Are thermodynamic cycles necessary for continuum solvent calculation of pKas and reduction potentials? *Phys. Chem. Chem. Phys.* **2015**, *17*, 2859−2868.
(42) Ho, J.; Ertem, M. Z. Calculating free energy changes in continuum solvation models. *J. Phys. Chem. B* **2016**, *120*, 1319−1329.
(43) Mangold, M.; Rolland, L.; Costanzo, F.; Sprik, M.; Sulpizi, M.; Blumberger, J. Absolute pKa values and solvation structure of amino acids from density functional based molecular dynamics simulation. *J. Chem. Theory Comput.* **2011**, *7*, 1951−1961.
(44) Chen, Y.-L.; Doltsinis, N. L.; Hider, R. C.; Barlow, D. J. Prediction of absolute hydroxyl pKa values for 3-hydroxypyridin-4-ones. *J. Phys. Chem. Lett.* **2012**, *3*, 2980−2985.
(45) Uddin, N.; Choi, T. H.; Choi, C. H. Direct absolute pKa predictions and proton transfer mechanisms of small molecules in

DOI: 10.1021/acs.jpca.6b09520
J. Phys. Chem. A 2016, 120, 8916−8922

aqueous solution by QM/MM-MD. *J. Phys. Chem. B* **2013**, *117*, 6269−75.
(46) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; et al. *Gaussian development version*, Revision H.35; Gaussian, Inc.: Wallingford, CT, 2014.
(47) Becke, A. D. Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098−3100.
(48) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.
(49) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(50) Stephens, P.; Devlin, F.; Chabalowski, C.; Frisch, M. J. Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(51) Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom−atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620.
(52) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(53) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-consistent molecular-orbital methods. IX. An extended Gaussian-type basis for molecular-orbital studies of organic molecules. *J. Chem. Phys.* **1971**, *54*, 724−728.
(54) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-consistent molecular orbital methods. XII. Further extensions of Gaussian-type basis sets for use in molecular orbital studies of organic molecules. *J. Chem. Phys.* **1972**, *56*, 2257−2261.
(55) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta* **1973**, *28*, 213−222.
(56) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-consistent molecular orbital methods. XXIII. A polarization-type basis set for second-row elements. *J. Chem. Phys.* **1982**, *77*, 3654−3665.
(57) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. Efficient diffuse function-augmented basis sets for anion calculations. III. The 3-21+G basis set for first-row elements, Li-F. *J. Comput. Chem.* **1983**, *4*, 294−301.
(58) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(59) Camaioni, D. M.; Schwerdtfeger, C. A. Comment on "Accurate experimental values for the free energies of hydration of H^+, OH^-, and H_3O^+. *J. Phys. Chem. A* **2005**, *109*, 10795−10797.
(60) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. Aqueous solvation free energies of ions and ion−water clusters based on an accurate value for the absolute aqueous solvation free energy of the proton. *J. Phys. Chem. B* **2006**, *110*, 16066−16081.
(61) Isse, A. A.; Gennaro, A. Absolute potential of the standard hydrogen electrode and the problem of interconversion of potentials in different solvents. *J. Phys. Chem. B* **2010**, *114*, 7894−7899.
(62) Marenich, A. V.; Ho, J.; Coote, M. L.; Cramer, C. J.; Truhlar, D. G. Computational electrochemistry: Prediction of liquid-phase reduction potentials. *Phys. Chem. Chem. Phys.* **2014**, *16*, 15068−15106.

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J. Phys. Chem. A 2016, 120, 8916−8922