IEF-PCM Calculations of Absolute pK_a for Substituted Phenols in Dimethyl Sulfoxide and Acetonitrile Solutions

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Absolute (nonrelative) pK_a calculations for substituted phenols were carried out in nonaqueous media, demonstrating the predictive power of the integral equation formalism PCM method with a mean unsigned error of 0.6 pK_a units for DMSO and 0.7 pK_a units for MeCN at the B3LYP/6-31+G** level of theory combined with the scaled B3LYP/6-311+G** gas-phase data. At the same time, the correlation between the calculated and experimental pK_a values yielded the value of the linear regression slope very close to unity for both DMSO and MeCN. Computation of pK_a of neutral acids in nonaqueous solutions with a reasonable precision obviously depends on carefully tuned cavities, optimized for nonaqueous solutions. The ability of continuum solvation model to compensate charge escape from the cavity, which is prominent in the case of anions, is also required. And finally, good quality gas-phase data is essential to achieve required pK_a precision.

Introduction

The ability to donate or accept the proton is a fundamental chemical property of a molecule defining it as an acid or a base. The acidity or basicity is therefore an important quantitative characteristic of chemical reactivity in acid−base equilibria. A number of well-established theoretical methods exist for calculating acidities and basicities of isolated molecules in the gas phase. The best of these methods reproduce absolute acidities and basicities well within the experimental error margin of around 8 kJ/mol.[1] The situation becomes, however, more complicated when acidity or basicity is calculated for a molecule in the solution, where the main source of uncertainty stems from the calculation of the energy of solvation. Several theoretical models exist for this case, including supermolecule-style calculations, variants of dielectric continuum theory, and cluster-continuum approach. The recent review by Tomasi et al.[2] provides extensive coverage of the modern solvation models. Our earlier article covered results of cluster-type computations for several anionic species in DMSO[3] where formation enthalpies of the complexes between anions and a single DMSO molecule fell in the range of 68.2−123.8 kJ/mol at the B3LYP/6-31+G* level of theory. The results indicate that, in addition to electrostatics, H-bonding is also responsible for binding anions to DMSO.

Typically, in the case of specific solvation, the dielectric continuum theory is improved by adding solvent molecules explicitly to the solute.[4] However, Liptak et al.[5] demonstrated an outstanding performance of the pure dielectric continuum theory applied to aqueous solutions with much stronger hydrogen bond interactions than in DMSO.

Several articles dedicated to pK_a calculations using various forms of the polarized continuum model (PCM) have been published recently. The results for H_2O and DMSO/MeCN solutions are presented below.

Case of H_2O. Liptak et al.[5] achieved promising results (accuracy within 0.4−0.5 pK_a units) with the CBS-QB3/CPCM method for carboxylic acids and substituted phenols in water. Murłowska and Sadlej-Sosnowska[6] followed the procedure proposed by Liptak et al. on tetrazoles and achieved a similar precision of 0.4 pK_a units. Da Silva et al.[7] used a combination of high-accuracy gas-phase methods and DPCM solvation procedure to calculate pK_a of HNO_2. The error margin was below 0.2 pK_a units. Kallies and Mitzner[8] studied aqueous solutions of aliphatic, alicyclic, and aromatic amines with DFT/SCI-PCM combination. The standard deviation of the calculated pK_a values amounted to 0.7 pK_a units. All these calculations employed an absolute thermodynamic cycle, whereas in the following references the relative thermodynamic cycle was applied. Takano and Houk[9] compared CPCM with other methods for calculating aqueous pK_a values. They found that the mean absolute deviation for CPCM is close to the cluster-continuum approach, within 2.19 and 2.06 pK_a units, respectively. Gutowski and Dixon[10] calculated pK_a values of some very strong acids using G3(MP2) and Cosmo solvation procedure with the error margin of ±2 pK_a units. Pliego and Riveros[11] used a cluster/IPCM method to calculate pK_a values of various acids and achieved a precision of 2.2 pK_a units. Klamt et al.[12] used COSMO-RS, combining dielectric continuum theory with a statistical thermodynamics treatment to predict pK_a values of organic and inorganic acids. The error of 0.5 pK_a units is reported to measure rms deviation between pK_a estimates from linear regression and corresponding experimental values. Chipman calculated pK_a values of several acids and bases in water, dimethyl sulfoxide, and acetonitrile from an absolute cycle and surface simulation with correction for volume polarization SSC(V)PE procedure.[13] For bases in the water medium, the results were reasonable with error about 2 pK_a units. For acids, however, the predictive power of the method in water was unsatisfactory.

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Case of DMSO/MeCN. Almerindo et al.[14] applied PCM with their own parametrization when calculating pK_a values of organic acids in a DMSO solution with rms error of 2.2 pK_a units. Qi et al.[15] calculated pK_a values for transition-metal hydrides in MeCN with precision of 1.5 pK_a units by exploiting sophisticated ONIOM partitioning and CPCM. Klamt et al.[12] calculated pK_a values for seven acids with an rms error of 1.76 pK_a units and low regression slope value (0.70) in DMSO with the COSMO-RS procedure. Eckert et al.[16] also used COSMO-RS to calculate pK_a values for the different classes of organic acids in MeCN. The authors reported an rms error of 1.38 pK_a units for the entire data set after uniform correction was added to the calculated values of ΔG_{diss} for compounds forming anions with the localized charge. Kovačević and Maksić[17] applied a combination of DFT and IPCM to calculate pK_a values for various superbases in acetonitrile with the mean absolute deviation of 0.4 pK_a units. The theoretical pK_a values in the work of Klamt et al. and Kovačević and Maksić were calculated by using linear regression fit of either ΔG of the acid dissociation reaction (Klamt et al.) or proton affinity of the base (Kovačević and Maksić) with the experimental pK_a values. Magill et al.[18] combined CBS-QB3 and CPCM to calculate pK_a for nucleophilic carbenes in water, DMSO, and MeCN from absolute thermodynamic cycle. The errors for the two compounds with known experimental values in DMSO were 0.1 and 0.5 pK_a units, respectively. Chipman's SSC(V)PE results for DMSO and MeCN are very encouraging.[13] For DMSO and MeCN, the errors of the pK_a values, measured as deviations between the estimate from linear regression and corresponding experimental value, remain in the range of 0.3−0.6 and 0.1−0.7 pK_a units, respectively. However, the precision of calculated pK_a depends not only on the theoretical method and the basis set chosen for calculation, but also upon the chosen isodensity contour value. Our preliminary experience with SCI-PCM,[19] another continuum solvation method based on isodensity contour for cavity construction, was rather unsuccessful. The mean unsigned error of pK_a values for the series of substituted phenols in DMSO was 1.88 pK_a units at the B3LYP/6-311+G** level. The analysis of solvation energy dependence on the value of isodensity cutoff revealed significant deficiency of the method, which is caused by uncompensated charge escape from the solute cavity in case of anions. This deficiency seems to be responsible for the low slope value of the linear regression between the calculated and experimental pK_a values.

Fu et al.[20] presented several protocols to calculate pK_a values in DMSO and MeCN. Initially, the PCM-based cluster-continuum approach was used to calculate pK_a values of organic acids in DMSO with a precision of 1.7−1.8 pK_a units. In the follow up, an improved method based on pure integral equation formalism PCM (IEF-PCM) results with UA0 cavity model combined with B3LYP/6-311++G(2df,2p) gas-phase acidities predicted experimental pK_a values with the errors having standard deviation of 1.4 pK_a units. For MeCN, DPCM solvation method with Bondi cavity was selected to complement B3LYP/6-311++G(2df,2p) gas-phase acidities. The standard deviation of the resulting pK_a errors was 1.0 pK_a units. It is important to note that authors optimized the cavities for organic solvents, using nondefault scaling factors applied to the atomic radii. The values of 1.1 and 1.2 for DMSO and MeCN, respectively, resulted in the lowest standard deviation and the highest correlation coefficient.

For several types of cavity models, including UA0 and Bondi, the default scaling factors are specifically optimized for aqueous solutions. The results of Fu et al. confirm the requirement of cavity tuning as a prerequisite for calculation of solvation free energies in organic solvents.

The analysis of reference data suggests that integral equation formalism PCM,[21] the latest formulation of PCM model with carefully adjusted solute cavities, could be the method of choice (along with equivalent SSC(V)PE) if one is interested in absolute pK_a calculations in DMSO and MeCN with the precision close to 0.5 pK_a units, an important benchmark established for aqueous solutions. It is worth mentioning that both IEF-PCM and SSC(V)PE provide proper treatment of volume polarization, which is absolutely essential for pK_a calculation of neutral acids. The purpose of this work is to further test the performance of the IEF-PCM solvation procedure as implemented in Gaussian03[22] to calculate absolute pK_a values of substituted phenols in dimethyl sulfoxide and acetonitrile.

Computational Methods

The gas-phase acidity (ΔG) is defined as the Gibbs free energy change of the following equilibrium:

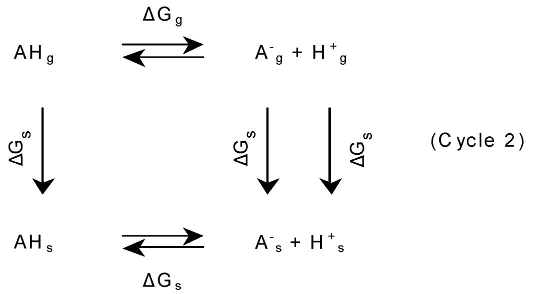
$$\mathrm{AH_g} \rightleftarrows \mathrm{A_g}^- + \mathrm{H_g}^+ \text{ (Cycle 1)}$$

$$\Delta G = G(\mathrm{A_g}^-) + G(\mathrm{H_g}^+) - G(\mathrm{AH_g})$$

Here, the value of Gibbs free energy of the proton in the gas phase is set to −26.32 kJ/mol using translational entropy calculated according to the well-known Sackur−Tetrode equation. The geometries of substituted phenols and corresponding phenoxide anions were fully optimized at the B3LYP/6-311+G** level of theory, and the values of Gibbs free energy were calculated for the standard state of 1 atm at 298.15 K. The second set of acidity values was based on B3LYP/6-311++G(2df,2p) single-point energies computed for B3LYP/6-311+G** optimized structures and corresponding B3LYP/6-311+G** thermal corrections. Finally, the B3LYP/6-311+G** gas-phase acidities were scaled according to the correlation with experimental acidities established previously[23] for the substituted phenols to produce the third set of gas-phase acidity values:

$$\Delta G_{\text{scaled}} = (\Delta G + 143.1)/1.091$$

Absolute pK_a calculations are based on the following thermodynamic cycle:



The following relations were applied to calculate pK_a:

$$K_a = [\mathrm{A_s}^-][\mathrm{H_s}^+]/[\mathrm{AH_s}]$$

$$\mathrm{p}K_a = -\log K_a$$

$$\Delta G_s = -RT \ln K_a$$

$$\mathrm{p}K_a = \Delta G_s/RT \ln 10$$

$$\Delta G_s = G(A_g^-) + G(H_g^+) - G(AH_g) + RT\ln(24.46) + \Delta G_s(A^-) + \Delta G_s(H^+) - \Delta G_s(AH)$$

The ΔG_s values in this study were determined from IEF-PCM/B3LYP/6-31+G** single-point calculations on gas-phase B3LYP/6-311+G** optimized geometry with either UA0 (DMSO, $\alpha = 1.1$) or Bondi (MeCN, $\alpha = 1.2$) cavity in SCFVAC mode using internally stored dielectric constants of 46.7 and 36.64 for dimethyl sulfoxide and acetonitrile, respectively. Both electrostatic and nonelectrostatic (i.e., cavitation, repulsion, and dispersion) terms were included in the calculation of ΔG_s values. $RT\ln(24.46)$ reflects the change in the standard conditions from 1 atm to moles per liter.

Initially, $\Delta G_s(H^+)$ was set to −1123.8 and −1058.1 kJ/mol for DMSO and MeCN, respectively. These values were derived from the free energy of solvation of proton in water as determined by Tissandier et al.[24] (−1104.5 kJ/mol) using the tetraphenylarsonium tetraphenylborate (TATB) assumption.[25] Later, the values of $\Delta G_s(H^+)$ were adjusted to provide the best correlation between calculated and experimental pK_a values.

All calculations were carried out with the Gaussian03 package using a SGI SMP computing server.

Results and Discussion

The calculated and experimental gas-phase acidities are presented in Table 1. All calculated values at the B3LYP-6-311+G** level are systematically lower (i.e., more acidic) than the corresponding experimental values. With the single exception of 2,4-dinitrophenol, the same holds true for B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** as well. The mean unsigned errors are 18.5 and 11.7 kJ/mol for B3LYP/6-311+G** and B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G**, respectively.

The correlation between experimental and calculated gas-phase acidities resulted in the following equations:

$$\Delta G_{\mathrm{expt}} = 0.9062\,\Delta G_{\mathrm{calcd}} + 145.0179,\ R^2 = 0.9905$$

and

$$\Delta G_{\mathrm{expt}} = 0.9365\,\Delta G_{\mathrm{calcd}} + 97.1437,\ R^2 = 0.9904$$

representing B3LYP/6-311+G** and B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** methods, respectively. It is evident that B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** results are closer to the experimental acidity values; however, the value of the slope still deviates from unity. A closer look at individual errors in Table 1 reveals that 2,4,6-trinitrophenol, pentakis(trifluoromethyl)phenol, and 2,4,6-tris(trifluoromethanesulfonyl)phenol have the largest errors, which on average are 2 times higher than MUE. These enormous errors for the three outer points of the linear regression lower the value of the slope and together represent the root cause of its deviation from unity. Unfortunately, both B3LYP/6-311+G** and B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** methods have severe difficulties in predicting the gas-phase acidities of these highly acidic phenols. To resolve this situation, the results of B3LYP/6-311+G** calculations were scaled according to the expected correlation with experimental acidities. The scaled B3LYP/6-311+G** results predict experimental acidities with the mean unsigned error of 3.5 kJ/mol.

The results of correlation between scaled B3LYP/6-311+G** and experimental gas-phase acidities are presented in Figure 1. The slope of the regression line is very close to unity, and the intercept is reasonably small. However, 2,4-dinitrophenol with the error of 22.2 kJ/mol is a clear outlier.

Both B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** and scaled B3LYP/6-311+G** gas-phase results were used in the following pK_a calculations. Table 2 includes calculated pK_a values in DMSO with mean unsigned error of 1.2 pK_a units for B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** results and 1.3 pK_a units for scaled B3LYP/6-311+G** results.

TABLE 1: Experimental and Calculated Gas-Phase Acidities; All Values Are Given in Kilojoules per Mole

		B3LYP/6-311+G**		B3LYP/6-311++G(2df, 2p)//B3LYP/6-311+G**		B3LYP/6-311+G**, scaled	
substituted phenols	expt[23,26]	calcd	error	calcd	error	calcd	error
phenol	1432.2	1419.5	−12.7	1423.9	−8.3	1432.2	0.0
4-NH_2-phenol	1446.0	1434.7	−11.3	1440.8	−5.2	1446.2	0.3
3-NH_2-phenol	1438.0	1427.1	−11.0	1432.0	−6.0	1439.2	1.2
2-NH_2-phenol	1428.0	1413.8	−14.2	1418.0	−10.0	1427.0	−1.0
4-F-phenol	1422.1	1405.7	−16.4	1412.6	−9.6	1419.6	−2.6
2-F-phenol	1418.4	1404.9	−13.4	1410.7	−7.7	1418.9	0.5
3-F-phenol	1409.2	1393.0	−16.2	1399.5	−9.7	1408.0	−1.2
3-Cl-phenol	1401.6	1384.7	−16.9	1390.2	−11.4	1400.3	−1.3
2-NO_2-phenol	1378.6	1369.5	−9.1	1376.3	−2.3	1386.5	7.8
3-NO_2-phenol	1370.3	1354.1	−16.2	1360.3	−10.0	1372.3	2.0
4-CN-phenol	1361.1	1341.8	−19.2	1346.6	−14.4	1361.1	0.0
3,4,5-Cl_3-phenol	1355.2	1340.8	−14.4	1347.5	−7.7	1360.2	5.0
4-NO_2-phenol	1342.6	1316.6	−26.0	1323.2	−19.5	1338.0	−4.7
2,4-$(NO_2)_2$-phenol	1291.2	1289.8	−1.3	1298.5	7.4	1313.4	22.2
2,3,4,5,6-F_5-phenol	1342.2	1320.8	−21.4	1333.9	−8.3	1341.9	−0.4
2,4,6-$(NO_2)_3$-phenol	1266.9	1228.3	−38.7	1238.6	−28.3	1257.0	−10.0
4-CF_3-phenol	1381.1	1360.6	−20.5	1368.7	−12.4	1378.3	−2.8
3-CF_3-phenol	1390.8	1373.2	−17.6	1379.9	−10.8	1389.8	−1.0
2-CF_3-phenol	1389.9	1368.6	−21.3	1375.3	−14.6	1385.6	−4.4
3,5-$(CF_3)_2$-phenol	1351.0	1331.8	−19.2	1341.2	−9.8	1351.9	0.8
2,3,4,5,6-$(CF_3)_5$-phenol	1249.8	1214.2	−35.6	1229.8	−20.0	1244.1	−5.7
2,4,6-Tf_3-phenol[a]	1220.9	1186.2	−34.6	1197.0	−23.9	1218.5	−2.4
2,4,6-$(FSO_2)_3$-phenol		1172.4		1191.8		1205.8	
mean error			−18.5		−11.0		0.1
mean unsigned error			18.5		11.7		3.5
rms error			20.4		13.2		6.0

[a] Tf denotes CF_3SO_2.

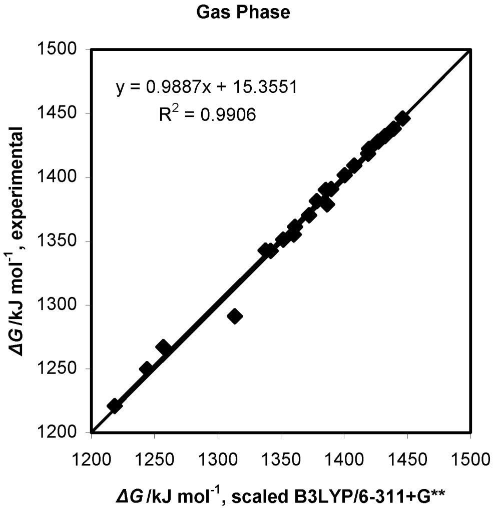


Figure 1. Correlation between the experimental and calculated gas-phase acidities of phenols in the gas phase (all values in kilojoules per mole). The $y = x$ line is added for comparison.

To assess performance of theoretical methods, the correlations between calculated and experimental pK_a values should also be examined. These correlations are characterized by the following parameters:

$$\mathrm{p}K_{\mathrm{a\ expt}} = 0.8299\ \mathrm{p}K_{\mathrm{a\ calcd}} + 3.1322,\ R^2 = 0.9627$$

and

$$\mathrm{p}K_{\mathrm{a\ expt}} = 0.8894\ \mathrm{p}K_{\mathrm{a\ calcd}} + 0.7496\ R^2 = 0.9559$$

based on B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** and scaled B3LYP/6-311+G** methods, respectively. The regression line slope for both methods is significantly lower than the expected value of 1. This deviation is obviously connected with the large error in pK_a value of pentakis(trifluoromethyl)phenol. After excluding this compound from the data set, the mean unsigned errors decrease to 1.0 and 1.2 pK_a units for B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** and scaled B3LYP/6-311+G** methods, respectively, while the corresponding values of the regression line slopes become 0.90 and 0.98. It appears that the former slope value is lower than the latter one because of a rather large error in gas-phase acidity of the picric acid at the B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** level of theory. The scaled B3LYP/6-311+G** method eliminates that distortion, and the corresponding slope value is very close to unity.

It is also important to note that the value of the intercept strongly depends on the value of the solvation free energy of the proton. The error in this value is a source of systematic error component of the pK_a series in the case of the slope being close to unity. As solvation free energies of the proton in DMSO and MeCN are estimated from the TATB assumption and are not established thermodynamic values, it is reasonable to optimize these values to minimize the mean unsigned error for the series. It was found that the value of −1129.7 kJ/mol for DMSO provides the best fit with the mean unsigned error of 0.6 pK_a units. The corresponding linear regression is presented in Figure 2. The work of Westphal and Pliego[33] suggested a more negative value of $\Delta G_s(H^+)$ in DMSO than the value based on TATB assumption. The solvation free energy of the proton in DMSO has been recently determined from the cluster-pair approach by Kelly et al.,[34] who obtained even more negative value (−1143.5 kJ/mol).

The results of pK_a calculations in MeCN are given in Table 3. Unfortunately, there are no experimental pK_a values available in acetonitrile for many phenols in our series, especially in the less acidic range. Instead, experimental pK_a values are available for 2,4,6-tris(trifluoromethanesulfonyl)phenol and 2,4,6-tris(fluorosulfonyl)phenol at the acidic end of the scale. The mean unsigned error for the B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** method is larger for MeCN as compared

TABLE 2: Experimental and IEF-PCM Calculated pK_a Values in DMSO

		B3LYP/6-311++G(2df, 2p)// B3LYP/6-311+G**		B3LYP/6-311+G** scaled		B3LYP/6-311+G** scaled, optimized	
substituted phenols	expt[23,27−32]	calcd	error	calcd	error	calcd	error
phenol	18.0	18.0	0.0	19.4	1.4	18.4	0.4
4-NH_2-phenol	20.8	21.8	1.0	22.8	2.0	21.7	0.9
3-NH_2-phenol	19.5	19.3	−0.2	20.5	1.0	19.5	0.0
2-NH_2-phenol	18.2	18.6	0.4	20.2	2.0	19.2	0.9
4-F-phenol	18.0	17.5	−0.5	18.7	0.7	17.7	−0.3
2-F-phenol	15.6	14.8	−0.8	16.3	0.7	15.2	−0.4
3-F-phenol	15.9	15.7	−0.2	17.2	1.3	16.2	0.3
3-Cl-phenol	15.8	15.2	−0.6	16.9	1.1	15.9	0.1
2-NO_2-phenol	11.0	11.1	0.1	12.9	1.9	11.9	0.9
3-NO_2-phenol	14.4	12.9	−1.5	15.0	0.6	14.0	−0.4
4-CN-phenol	13.2	11.6	−1.6	14.1	0.9	13.1	−0.1
3,4,5-Cl_3-phenol	12.6	11.7	−0.9	13.9	1.3	12.9	0.3
4-NO_2-phenol	10.8	8.3	−2.5	10.8	0.0	9.8	−1.0
2,4-$(NO_2)_2$-phenol	5.1	4.4	−0.8	7.0	1.9	5.9	0.8
2,3,4,5,6-F_5-phenol	8.9	7.3	−1.6	8.7	−0.2	7.7	−1.2
2,4,6-$(NO_2)_3$-phenol	−1.0	−2.3	−1.3	0.9	1.9	−0.1	0.9
4-CF_3-phenol	14.6	14.0	−0.6	15.7	1.1	14.7	0.1
3-CF_3-phenol	15.1	14.9	−0.2	16.7	1.6	15.7	0.6
2-CF_3-phenol	14.4	11.2	−3.2	13.0	−1.4	12.0	−2.4
3,5-$(CF_3)_2$-phenol	13.2	12.0	−1.2	13.9	0.7	12.8	−0.4
2,3,4,5,6-$(CF_3)_5$-phenol	3.1	−3.1	−6.2	−0.6	−3.7	−1.7	−4.8
mean error			−1.1(−0.8)[a]		0.8(1.0)		−0.2(0.0)
mean unsigned error			1.2(1.0)		1.3(1.2)		0.8(0.6)
rms error			1.8(1.3)		1.5(1.3)		1.3(0.8)

[a] The values in parentheses exclude 2,3,4,5,6-$(CF_3)_5$-phenol.

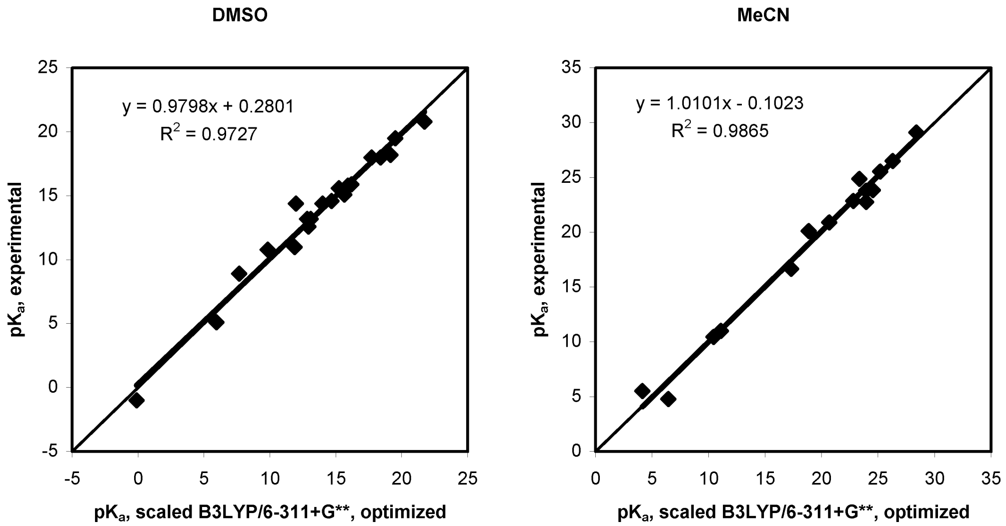


Figure 2. Correlation between the experimental and calculated pK_a values of phenols in DMSO. The $y = x$ line is added for comparison.

TABLE 3: Experimental and IEF-PCM Calculated pK_a Values in MeCN

		B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G**		B3LYP/6-311+G** scaled		B3LYP/6-311+G** scaled, optimized	
substituted phenols	expt[16,23,31,35]	calcd	error	calcd	error	calcd	error
phenol	29.1	26.2	−2.9	27.7	−1.4	28.4	−0.7
2-NO_2-phenol	22.9	20.3	−2.6	22.1	−0.8	22.8	−0.1
3-NO_2-phenol	23.9	21.7	−2.1	23.8	−0.1	24.5	0.7
4-CN-phenol	22.8	20.7	−2.1	23.2	0.4	24.0	1.2
4-NO_2-phenol	20.9	17.4	−3.6	19.9	−1.0	20.7	−0.2
2,4-$(NO_2)_2$-phenol	16.7	14.0	−2.7	16.6	−0.1	17.3	0.6
2,3,4,5,6-F_5-phenol	20.1	16.7	−3.4	18.1	−2.0	18.9	−1.3
2,4,6-$(NO_2)_3$-phenol	11.0	7.2	−3.9	10.4	−0.6	11.1	0.1
4-CF_3-phenol	25.5	22.8	−2.8	24.5	−1.1	25.2	−0.3
3-CF_3-phenol	26.5	23.8	−2.7	25.6	−0.9	26.3	−0.2
2-CF_3-phenol	24.9	20.8	−4.1	22.6	−2.3	23.3	−1.6
3,5-$(CF_3)_2$-phenol	23.8	21.3	−2.4	23.2	−0.6	23.9	0.2
2,3,4,5,6-$(CF_3)_5$-phenol	10.5	7.2	−3.3	9.7	−0.8	10.4	0.0
2,4,6-Tf_3-phenol[a]	4.8	2.0	−2.9	5.7	0.9	6.4	1.6
2,4,6-$(FSO_2)_3$-phenol	5.5	1.0	−4.6	3.4	−2.1	4.1	−1.4
mean error			−3.1		−0.8		−0.1
mean unsigned error			3.1		1.0		0.7
rms error			3.1		1.2		0.9

[a] Tf denotes CF_3SO_2.

with that for DMSO, while for the scaled B3LYP/6-311+G** a slight improvement over DMSO results is observed. The regression line slopes are slightly higher as compared to those of DMSO. The resulting equations for B3LYP/6-311++G(2df,2p)//B3LYP/6-311+G** and scaled B3LYP/6-311+G** methods are:

$$pK_{a\ expt} = 0.9522\ pK_{a\ calcd} + 3.8261,\ R^2 = 0.9940$$

and

$$pK_{a\ expt} = 1.0100\ pK_{a\ calcd} + 0.6407,\ R^2 = 0.9864$$

Finally, using previously described arguments, we optimized the value of solvation free energy of the proton for MeCN as done for DMSO. The optimized value of −1054.0 kJ/mol resulted in the mean unsigned error of 0.7 pK_a units. The corresponding regression plot is presented in Figure 2. Kelly et al.[34] recently determined the solvation free energy of the proton in MeCN from the cluster-pair approach and obtained a more negative value (−1088.7 kJ/mol) compared to our optimized value.

It was also found that an appropriately optimized UA0 cavity model (α = 1.05) performed less satisfactorily in terms of regression line slope in MeCN than the cavity based on Bondi radii.

Table 4 provides comparison of the results of pK_a calculations from this study with the results published by Eckert et al., Chipman, and Fu et al.

From the data in Table 4, it follows that achieving both reasonably low mean unsigned error and regression line slope value close to unity at the same time might be a complicated task. In this regard, IEF-PCM, the default solvation method implemented in Gaussian03, combined with the scaled B3LYP/6-311+G** gas-phase data performs rather well in both DMSO and MeCN. This good performance is obviously associated with the quality of underlying gas-phase results. Unfortunately, there is no analysis available about the gas-phase performance of the B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G* method on compounds studied by Fu et al., and therefore, it is impossible to conclude whether the method might introduce excessive errors for any compounds that could translate into the low slope value in pK_a correlations.

TABLE 4: Mean Unsigned Errors (MUE), RMS Errors, Values of Slope, and R^2 Coefficients for the Series of pK_a Calculations in DMSO and MeCN; IC Is Isodensity Cutoff in Atomic Units

	DMSO				MeCN			
methods	MUE	rms	slope	R^2	MUE	rms	slope	R^2
IEF-PCM/B3LYP/6-31+G**//B3LYP/6-311+G**, scaled B3LYP/6-311+G**//B3LYP/6-311+G**[a]	0.6	0.8	0.980	0.973	0.7	0.9	1.010	0.987
IEF-PCM/B3LYP/6-31+G**//B3LYP/6-31+G*, B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G*[b]	1.2	1.5	0.893	0.988				
DPCM/B3LYP/6-31+G**//B3LYP/6-31+G*, B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G*[c]					0.9	0.9	0.791	0.953
DPCM/B3LYP/6-31+G**//B3LYP/6-31+G*, B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G*[c,d]					0.8	0.9	0.853	0.937
SSC(V)PE/HF/6-31+G*, IC = 0.001[e]	0.3[g]		0.764	0.998	0.7[g]		0.904	0.978
SSC(V)PE/B3LYP/aug-cc-pVTZ, IC = 0.001[e]	0.6[g]		0.776	0.992	0.1[g]		0.848	0.998
COSMO-RS/BP/TZP[f]					3.2	3.3	0.926	0.983
COSMO-RS/BP/TZP[f]					0.8[g]	1.0[g]	1.060	0.983

[a] This work. [b] Reference 20b. [c] Reference 20c. [d] With the latest experimental pK_a value for phenol. [e] Reference 13. [f] Reference 16 values for the group of phenols. [g] Based on results predicted by correlations.

Chipman's SSC(V)PE method demonstrates good performance in terms of mean unsigned error. It is important to note, however, that these MUE values are based on the results predicted by correlations between experimental and calculated pK_a values and should not be directly compared with other results. The performance of the method depends heavily on the chosen isodensity cutoff value and the choice of quantum chemical method and basis set. By modifying the isodensity contours it is possible to achieve the slope value of 1; however, the default and recommended cutoff value of 0.001 au resulted in a lower value of slope. Klamt et al.'s COSMO-RS method predicts pK_a of substituted phenols in MeCN with the mean unsigned error of 0.8 pK_a units. However, this quite good precision is achieved only after applying the results of the correlation between calculated $\Delta G_{\mathrm{diss}}/RT \ln 10$ and the respective experimental pK_a values, which were established for the large set of diverse compounds. The raw ab initio pK_a values deviate more substantially from the corresponding experimental values with the mean unsigned error and rms error of 3.2 and 3.3 pK_a units, respectively. The rms error of ab initio pK_a values for the subset of CH acids is much lower, being 0.9−1.1 pK_a units. The authors give the following explanation to the differences in performance: the anionic charge is more delocalized in the case of CH acids as compared to phenols, and therefore, the phenoxide anions exhibit stronger interaction with solvent molecules, which is not fully accounted for by the solvation model.

Conclusions

The combination of scaled B3LYP/6-311+G** gas-phase acidities with the IEF-PCM method provided reliable nonrelative pK_a values for a diverse set of substituted phenols in the widely used DMSO and MeCN solvents despite the fact that it is not granted for sure that the developed protocols will be simply extensible to the other classes of molecules or even other solvent systems. Thus far, however, the good predictive power of such an IEF-PCM approach is characterized with a mean unsigned error of 0.6 pK_a units for DMSO and 0.7 pK_a units for MeCN. The corresponding correlations between the calculated and experimental pK_a values resulted in regression line slopes very close to the expected value of 1. This performance compares well with the series of Fu et al. (MUE equal to 1.2 pK_a units in DMSO and 0.8 pK_a units in MeCN), Klamt et al. (rms error of 1.76 pK_a units in DMSO and 1.38 pK_a units in MeCN), and Pliego et al. (rms error of 2.2 pK_a units in DMSO) and approaches the important benchmark of 0.5 pK_a units achieved in water by Liptak et al.

Our approach binds the scaled gas-phase acidities with optimized solute cavity formation and solvent interactions addressing the charge leak problem.

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Supporting Information Available: B3LYP/6-311+G(2df,2p) energies, B3LYP/6-311+G** energies, free energies, and structures of the studied acids and corresponding anions, IEF-PCM/B3LYP/6-31+G** solvation free energies of the acids and anions. This material is available free of charge via the Internet at http://pubs.acs.org.

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