

Prediction of relative pK_a values of amines by quantum chemical calculations

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Abstract An approach based on the cluster-continuum model is used to calculate some relative pK_a values. For this purpose, one and two explicit water molecules are combined with the polarizable continuum model (PCM), conductor-like polarizable continuum model (CPCM), and integral equation formalism polarizable continuum model (IEF-PCM) to accurately predict solvation free energies. Pure continuum model results are also presented for comparison. B3LYP/6-31+G* level of theory is used for prediction of both gas-phase and solvation free energies during all calculations. Atoms in molecules analyses are also presented to characterize the strength of intermolecular hydrogen bonds between the solvent molecules and the bases. Results are in line with previous studies and show that introducing explicit solvent molecules has a drastic effect on the prediction of acidity constants of amines.

Keywords PCM · CPCM · IEF-PCM · Continuum models · Acidity · Ab initio calculation

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Introduction

Compared with gas-phase results with high accuracy, quantum chemical calculations have fundamental problems for condensed-phase environments. However, many chemical and biological reactions occur in the solution phase. The solvent effect is an essential component of solution chemistry, and it is almost impossible to understand reactions in solution without considering these effects.

One of the important reactions is proton-transfer equilibrium, through which many chemical behaviors are understood. Acid–base reactions play a key role not only in chemistry but also in other branches of science such as medicine, biology, and food industry. A priori knowledge of pK_a values is crucially important in these fields.

Different approaches have been introduced to predict relative and/or absolute acidity constants. The oldest method is the Hammett equation [1]. This approach, which is known as the classical method, separates a compound into a parent molecule and a substituent section. The Hammett equation relates the property of the compound to the property of the parent molecule by considering the effect of the substituent section. The quantitative structure–property relationship (QSPR) method can be considered as a second approach. In this method a training set of molecules is considered, using which a model is built. This model is then used to predict acidity constants of molecules absent from the training set [2].

The other approaches use quantum chemical calculations in conjunction with semiclassical methods. Quantum chemical calculations involve gas-phase free energy estimation through energy minimization and frequency analyses, and semiclassical methods contain continuum models of solvent molecules. These models consider

solvent molecules as a continuum dielectric without considering their detailed structure. Reliable continuum model calculations should take account of different contributions to the solvation free energy such as the electrostatic, cavitation, and dispersion portions. These approaches try to create a detailed description of changes suffered by the solute molecule due to its interaction with the solvent. From this point of view, these changes form the cornerstone of studies in the solution phase. These two sets of calculations (gas and liquid phases) are combined by a thermodynamic cycle [3]. There is a vast amount of literature relating to this third approach. Some have used semiempirical methods, whereas other works have utilized *ab initio* or density functional theory [4, 5].

Some researchers have made an attempt to introduce alternative methods for liquid-phase calculations. Among these attempts, methods such as Monte Carlo [6], molecular dynamics [7], integral equation [8], and the Langevin dipole model [9] may be highlighted.

The aforementioned methods use classical approaches of force fields to model solvent molecules without considering any high-level quantum mechanics calculation, whereas continuum models take a perturbation approach based on the change of the Hamiltonian of the solute by introducing a solvent potential.

On the other hand, a particularly important problem in continuum models is their failure to include hydrogen bonds explicitly [10]. The implicit representation of the solvent molecules ignores their association with solute molecules through hydrogen-bond formation. Neglecting this crucial point leads to disagreement between calculated and experimental pK_a values.

To compensate for this deficiency in continuum models, Pliego and Riveros (PR) introduced explicit water molecules near the solute in the cavity, naming this the “cluster-continuum model” [11, 12]. Similar to this approach, some other works have been done by other researchers, but with different names such as microsolvation [13] or solvated supermolecules [14]. In this paper a method similar to the PR method is used with a slight difference in the calculation of the free energy change of the proton-transfer reaction.

Results and discussion

Table 1 presents the experimental pK_a values for the studied amines, containing primary, secondary, and tertiary amines, taken from Lange’s handbook [15]. Aliphatic cyclic and acyclic compounds are also found in the list. Clearly, the greater the variety of the compounds, the higher the mean absolute deviations (MADs) found in the corresponding works.

Table 1 Amines studied in this contribution

No.	Name	pK_a (exp.) ^a
1	Methylamine	10.62
2	Ethylamine	10.63
3	Propylamine	10.57
4	1,2-Ethanediamine	9.99
5	1,3-Propanediamine	10.47
6	Dimethylamine	10.77
7	Diethylamine	10.8
8	Piperidine	11.1
9	Dimethylcyclohexylamine	10.7

^a Data taken from Ref. [15]

Table 2 presents the results of computations using three solvation models: the polarizable continuum model (PCM), conductor-like polarizable continuum model (CPCM), and integral equation formalism polarizable continuum model (IEF-PCM). These data come from putting the molecules in the cavity alone without considering any water molecules. The solvation free energy of cations is much greater than that of neutral molecules. Comparing the three solvation models above shows that, in the absence of explicit hydrogen bonds between solute and solvent molecules, the results of CPCM are better than the results of the other solvation models. The MAD of CPCM is 1.21, while the MADs of PCM and IEF-PCM are 1.38 and 1.31, respectively.

Table 3 shows that introducing one water molecule into the cavity of the solute causes the results to be more reliable. For PCM, MAD reduces from 1.38 to 0.48. The result is nearly the same for the IEF-PCM model. However, for the CPCM model this is not the case. For the CPCM model, the MAD reduces from 1.21 to 0.38.

Introducing a second water molecule into the cavity, compared with the results with one explicit water molecule, increases the MAD for all three models (see the results of Table 4) even for the case of IEF-PCM. However, this change has little effect on the IEF-PCM results. This increase can be related to the bifunctional and tertiary molecules (4, 5, and 9) in the list. If we set aside these molecules, the MAD changes to 0.25 for the case of two explicit water molecules in the CPCM and IEF-PCM models. For the PCM, setting aside the above-mentioned molecules, the MAD becomes 0.23. This shows that, for relative methods, similarity between molecules is a very important point.

All the results above are based on the default cavity model in the G98 W program. Changing the cavity may cause the MADs to change. We have previously tested the role of cavity type in the prediction of relative pK_a values of some small amines [16]. Previous work showed that

Table 2 Calculated gas-phase standard Gibbs free energy (kJ/mol), solvation standard Gibbs free energy (kJ/mol), and calculated pK_a values using B3LYP/6-31+G*/B3LYP/6-31+G* without water molecules

	$G_{1,\text{gas}}^0$ (kJ/mol)	PCM		CPCM		IEF-PCM	
		$\Delta G_{1,s}$ (kJ/mol)	pK _a	$\Delta G_{1,s}$ (kJ/mol)	pK _a	$\Delta G_{1,s}$ (kJ/mol)	pK _a
1(A)	-251575.4	-21.1	11.03	-22.3	10.86	-22.3	10.78
1(AH ⁺)	-249841.0	-295.9		-296.2		-297.5	
2(A)	-354736.3	-20.3	11.05	-21.8	11.02	-21.8	10.93
2(AH ⁺)	-355641.5	-285.2		-282.4		-283.7	
3(A) ^a	-457888.2	-17.0	10.57	-18.7	10.57	-18.7	10.57
3(AH ⁺) ^a	-458797.7	-270.7		-272.8		-274.3	
4(A)	-500005.2	-42.1	11.28	-46.3	10.73	-46.5	11.22
4(AH ⁺)	-500911.5	-302.8		-304.1		-308.9	
5(A)	-603154.7	-43.4	11.31	-46.9	10.83	-47.1	11.27
5(AH ⁺)	-604067.6	-298.1		-298.9		-303.4	
6(A)	-354713.2	-18.8	11.92	-20.3	12.09	-20.2	12.09
6(AH ⁺)	-355631.3	-271.5		-274.1		-275.8	
7(A)	-561016.8	-16.0	15.48	-18.2	15.55	-18.2	15.59
7(AH ⁺)	-561975.4	-248.5		-251.2		-261.2	
8(A)	-661053.6	-22.1	13.69	-24.9	13.8	-25.0	13.88
8(AH ⁺)	-662001.4	-255.3		-258.9		-253.3	
9(A)	-970484.2	-8.7	9.69	-10.4	10.36	-10.3	10.37
9(AH ⁺)	-971442.1	-208.9		-214.6		-216.4	
MAD		1.38		1.21		1.31	

^a For reference**Table 3** Calculated gas-phase standard Gibbs free energy (kJ/mol), solvation standard Gibbs free energy (kJ/mol), and calculated pK_a values using B3LYP/6-31+G*/B3LYP/6-31+G* with one water molecule

	$G_{1,\text{gas}}^0$ (kJ/mol)	PCM		CPCM		IEF-PCM	
		$\Delta G_{1,s}$ (kJ/mol)	pK _a	$\Delta G_{1,s}$ (kJ/mol)	pK _a	$\Delta G_{1,s}$ (kJ/mol)	pK _a
1(A)	-452210.8	-35.2	9.75	-37.2	9.46	-36.9	9.56
1(AH ⁺)	-453153.1	-261.2		-262.2		-263.8	
2(A)	-555369.6	-33.8	10.45	-35.1	10.25	-34.9	10.39
2(AH ⁺)	-556323.4	-252.1		-253.0		-254.8	
3(A) ^a	-658521.5	-29.7	10.57	-30.1	10.57	-31.1	10.57
3(AH ⁺) ^a	-659478.5	-245.9		-247.0		-249.30	
4(A)	-700635.3	-54.2	10.71	-57.7	10.28	-57.4	10.82
4(AH ⁺)	-701588.4	-274.9		-276.6		-280.8	
5(A)	-803791.2	-59.0	11.29	-63.0	10.64	-63.1	11.24
5(AH ⁺)	-804794.2	-233.0		-234.1		-238.8	
6(A)	-555347.8	-30.3	9.92	-32.8	9.78	-32.7	9.85
6(AH ⁺)	-556309.0	-238.6		-241.0		-242.5	
7(A)	-761665.1	-24.9	10.55	-27.4	10.7	-27.7	10.82
7(AH ⁺)	-762643.4	-219.5		-223.6		-225.9	
8(A)	-862673.3	-35.1	11.59	-37.9	11.31	-37.9	11.53
8(AH ⁺)	-861687.7	-228.3		-230.2		-232.8	
9(A)	-1171114.3	-15.4	10.79	-18.1	10.74	-18.1	10.93
9(AH ⁺)	-1172113.4	-190.5		-193.7		-196.0	
MAD		0.48		0.38		0.51	

^a For reference

usage of one explicit water molecule in the cavity leads to better results for different cavity model types [16]. However, those data also noted that adding more than one water

molecule does not always lead to better results. It should be noted that this is not general; for example, for MP2/6-31G**, the model with two explicit water molecules gives

Table 4 Calculated gas-phase standard Gibbs free energy (kJ/mol), solvation standard Gibbs free energy (kJ/mol), and calculated pK_a values using B3LYP/6-31+G*/B3LYP/6-31+G* with two water molecules

	$G_{1,\text{gas}}^0$ (kJ/mol)	PCM		CPCM		IEF-PCM	
		$\Delta G_{1,s}$ (kJ/mol)	pK_a	$\Delta G_{1,s}$ (kJ/mol)	pK_a	$\Delta G_{1,s}$ (kJ/mol)	pK_a
1(A)	-652842.9	-30.2	10.69	-31.1	10.71	-30.8	10.67
1(AH ⁺)	-653823.5	-237.8		-238.1		-240.2	
2(A)	-756001.6	-27.7	10.89	-29.2	10.87	-28.8	10.84
2(AH ⁺)	-859154.4	-228.9		-229.6		-231.8	
3(A) ^a	-756989.6	-25.6	10.57	-27.2	10.57	-26.9	10.57
3(AH ⁺) ^a	-860143.9	-223.5		-224.4		-226.8	
4(A)	-901269.2	-62.7	8.69	-66.5	8.52	-66.1	8.83
4(AH ⁺)	-902257.2	-251.6		-253.8		-257.9	
5(A)	-1004423.2	-63.6	8.65	-67.1	8.37	-66.4	8.76
5(AH ⁺)	-1005432.2	-231.0		-232.3		-236.5	
6(A)	-755979.3	-23.1	11.29	-23.8	11.34	-23.5	11.48
6(AH ⁺)	-756978.3	-215.6		-216.0		-219.2	
7(A)	-962293.7	-14.8	11.21	-17.0	11.21	-16.7	11.15
7(AH ⁺)	-963301.4	-205.3		-199.8		-201.9	
8(A)	-1062322.4	-25.6	11.25	-27.9	11.3	-27.7	11.28
8(AH ⁺)	-1063334.2	-198.2		-207.1		-209.5	
9(A)	-1371745.7	-21.0	9.44	-24.3	9.44	-24.0	9.41
9(AH ⁺)	-1372766.7	-180.9		-183.6		-185.9	
MAD		0.64		0.70		0.62	

^a For reference

better results for both Bondi and united atom for Hartree–Fock (UAHF) cavities, but this is not the case for Pauling. On the other hand, all cavity models for HF/6-31G** show smaller MADs when two explicit water molecules are used in the cavity [16].

One may think that introducing water molecules into the cavity modifies the results because of enlarging the cavity, thereby reducing the escaped charge outside the cavity. Table 5 shows values of escaped charges for the PCM model with and without explicit water molecules. Data show that enlarging the cavity through the introduction of water molecules in it does not change the escaped charges. Therefore, it can be concluded that only hydrogen bonding affects the results of the solvation models and that the escaped charges are not very important.

Comparing the results of Tables 2 and 3 shows that the hydrogen bonds between explicit water molecules and solute in the cavity are too strong to be ignored. To test the strength of the hydrogen bond, the AIM2000 program was used. Table 5 presents three eigenvalues of the Hessian tensor, electron density, Laplacian, total energy density, and ellipticity at the critical bonds between water molecules and solute. The data show that nearly all hydrogen bonds are medium strength with positive Laplacian and negative total energy density. Topological properties show that cations form stronger hydrogen bonds with water than do neutral species. Atoms in molecules (AIM) molecular graphs, contour maps, shape of the molecules, and the distances of water molecules from solute in the optimized

geometries can be found in the Electronic Supplementary Material.

Conclusion

Acidity constants of simple amines have been predicted by a relative approach. Three continuum models (PCM, CPCM, and IEF-PCM) have been used to calculate solvation free energies. To investigate the role of hydrogen bonding between solutes and solvent molecules in the prediction, the cluster-continuum model of Pliego and Riveros has been used. Results show that, for some amines, introducing one water molecule into the cavity leads to better results than for two water molecules, while for some others introducing two water molecules is more important. In summary, it is fair to say that using more solvent molecules in the cavity does not always lead to better results. In addition, for the cases studied, enlarging the cavity due to the introduction of water molecules in it does not change the escaped charges (Table 6).

Methods

Calculation of pK_a

In this paper, as shown in Table 1, nine amines, including methylamine, ethylamine, propylamine, 1,2-ethanediamine,

Table 5 Calculated escaped charge for the PCM model with zero, one, and two water molecules

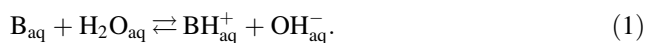
No.	PCM ^a		PCM/H ₂ O ^b		PCM/2H ₂ O ^c	
	Neutral	Cation	Neutral	Cation	Neutral	Cation
1	0.1829	0.0646	0.2604	0.1433	0.2232	0.1755
2	0.2359	0.1021	0.2966	0.1730	0.2972	0.2282
3	0.2528	0.1183	0.3175	0.1772	0.3369	0.2228
4	0.4251	0.2751	0.4206	0.3052	0.4384	0.4025
5	0.4854	0.3144	0.5098	0.3459	0.5429	0.3618
6	0.2396	0.1254	0.2900	0.1930	0.2799	0.2202
7	0.3521	0.1538	0.4347	0.2593	0.4177	0.3670
8	0.3942	0.2044	0.4646	0.2068	0.5073	0.3830
9	0.4898	0.2273	0.5540	0.3360	0.5314	0.3448

^a Without water molecule

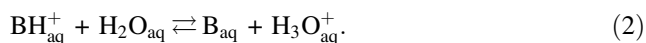
^b With one water molecule

^c With two water molecules

1,3-propanediamine, dimethylamine, diethylamine, piperidine, and dimethylcyclohexylamine, are considered for prediction of relative p*K*_a values. The list contains mono- and bifunctional groups in addition to primary, secondary, and tertiary amines. The above-mentioned compounds are bases, and in aqueous solution phase their neutral forms are in equilibrium with their protonated forms according to the following equation:



The equilibrium constant is known as the basicity constant, *K*_B. The reaction of the conjugated acid of B (that is BH⁺) is written as



In the present work, Eq. 2 is used to determine the p*K*_a values of the studied compounds. By this equation, acidity constants for the conjugated acids are determined by using the following equation:

$$pK_a(BH^+) = \frac{\Delta G_{aq}^0}{2.303RT} - 1.74, \quad (3)$$

where 1.74 comes from the logarithm of the concentration of water (log 55.5), and Δ*G*_{aq}⁰ is the standard Gibbs free energy change of the reaction (2) in the aqueous phase. To estimate this quantity, a thermodynamic cycle is used (Fig. 1). According to this scheme, Δ*G*_{aq}⁰ is equal to the sum of two terms, namely the free energy change in gas phase (Δ*G*_{gas}⁰) and the free energy change of solvation (ΔΔ*G*_s⁰). The relation between Δ*G*_{aq}⁰ and the two terms above, and the equations defining Δ*G*_{gas}⁰ and ΔΔ*G*_s⁰ are as follows:

$$\Delta G_{aq}^0 = \Delta G_{gas}^0 + \Delta \Delta G_s^0, \quad (4)$$

Table 6 Topological properties (in a.u.) for hydrogen-bond critical points

Compound	BCP	ρ(<i>r</i>)	∇ ² ρ(<i>r</i>)	<i>H</i> (<i>r</i>)	Ellipticity
1 ^a	1	0.0350	0.0936	−0.0019	0.0132
1 ^b	1	0.0327	0.1032	−0.0011	0.0271
	2	0.0153	0.0532	0.0003	0.0651
	3	0.0411	0.1060	−0.0027	0.0299
1 ^c	1	0.0415	0.1380	−0.0002	0.0751
1 ^d	1	0.0363	0.1216	−0.0001	0.0831
	2	0.0369	0.1236	−0.0001	0.0800
2 ^a	1	0.0351	0.0933	0.0019	0.0135
2 ^b	2	0.0397	0.1027	−0.0025	0.0304
	3	0.0149	0.0518	−0.0003	0.0491
	4	0.0328	0.1033	−0.0011	0.0277
2 ^c	1	0.0400	0.1332	−0.0002	0.0792
2 ^d	1	0.0355	0.1192	−0.0001	0.0837
	2	0.0348	0.1164	−0.0001	0.0824
3 ^a	1	0.0352	0.0936	−0.0019	0.0138
3 ^b	1	0.0187	0.0784	0.0000	0.0919
	2	0.0119	−0.0336	0.0000	0.4548
	3	0.0192	0.0796	0.0002	0.1545
3 ^c	1	0.0396	0.1136	−0.0002	0.0794
3 ^d	1	0.0327	0.132	0.0001	0.0812
	2	0.0293	0.1092	0.0007	0.0752
4 ^a	1	0.0049	0.0196	0.0010	0.8923
	2	0.0347	0.0920	−0.0019	0.0065
4 ^b	1	0.0062	0.0240	0.0010	0.4204
	2	0.0346	0.0920	−0.0019	0.0040
	3	0.0346	0.0240	−0.0019	0.0040
	4	0.0062	0.1288	0.0010	0.4203
4 ^c	1	0.0387	0.1196	−0.0002	0.0781
4 ^d	1	0.0357	0.1160	−0.0001	0.0084
	2	0.0347	0.0924	−0.0002	0.0082
5 ^a	1	0.0343	0.0924	−0.0017	0.0065
5 ^b	1	0.0354	0.0940	−0.0020	0.0120
	2	0.0055	0.0220	0.0010	0.6982
	3	0.0055	0.0220	0.0011	0.7046
	4	0.0354	0.0940	−0.0020	0.0120
5 ^{c,e}	1	0.0339	0.0764	−0.0021	0.0144
	2	0.0346	0.1164	−0.00005	0.0909
5 ^{c,f}	1	0.0394	0.1312	−0.00005	−0.0002
5 ^{d,e}	1	0.0526	0.1708	−0.0017	0.0497
	2	0.0473	0.1184	−0.0039	0.0068
	3	0.0343	0.1148	−0.0002	0.0814
5 ^{d,f}	1	0.0286	0.1048	0.0005	0.0922
	2	0.0531	0.0952		
	3	0.0099	0.0504	−0.0055	0.0282
6 ^a	1	0.0356	0.0928	0.0006	0.1154
6 ^b	1	0.0327	0.1032	−0.0012	0.0267
	2	0.0155	0.0532	0.0003	0.0528

Table 6 continued

Compound	BCP	$\rho(r)$	$\nabla^2\rho(r)$	$H(r)$	Ellipticity
	3	0.0424	0.1060	-0.0032	0.0306
6^c	1	0.0381	0.1268	-0.0003	0.0787
6^d	1	0.0344	0.1148	-0.0002	0.0839
	2	0.0344	0.1148	-0.0003	0.0842
7^a	1	0.0363	0.0940	-0.0022	0.0
7^b	1	0.0131	0.0464	0.0005	0.0491
	2	0.0414	0.1028	-0.0030	0.0276
	3	0.0325	0.1020	-0.0012	0.0280
7^c	1	0.0340	0.1128	-0.0003	0.0834
7^d	1	0.0305	0.1012	-0.0003	0.0852
	2	0.0306	0.1016	-0.0003	0.0851
8^a	1	0.0366	0.0952	-0.0022	0.0087
8^b	1	0.0439	0.1092	-0.0034	0.0259
	2	0.0324	0.1036	-0.0010	0.0270
	3	0.0146	0.0512	0.0005	0.0593
8^c	1	0.0357	0.1192	-0.0003	0.0812
8^d	2	0.0325	0.1084	-0.0002	0.0883
	3	0.0317	0.1060	-0.0002	0.0828
9^a	1	0.0357	0.0908	-0.0023	0.0090
9^b	1	0.0071	0.0248	0.0009	0.0589
9^b	2	0.0347	0.1092	-0.0012	0.0400
9^b	3	0.0436	0.1052	-0.0037	0.0037
9^c	1	0.0320	0.1056	-0.0004	0.0903
9^d	1	0.0396	0.1308	-0.0005	0.0807
9^d	2	0.0360	0.1216	-0.0003	0.0633

^a Neutral species with one water molecule

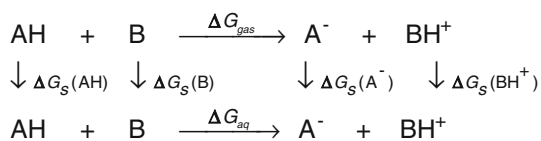
^b Neutral species with two water molecules

^c Cationic species with one water molecule

^d Cationic species with two water molecules

^e Cyclic

^f Linear

**Fig. 1** The proposed thermodynamic cycle

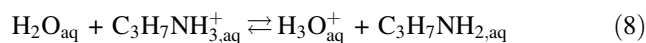
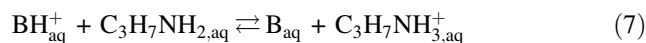
$$\Delta G_{\text{gas}}^0 = G_{\text{gas,B}}^0 + G_{\text{gas,H}_3\text{O}^+}^0 - G_{\text{gas,BH}^+}^0 - G_{\text{gas,H}_2\text{O}}^0 \quad (5)$$

$$\Delta \Delta G_{\text{s}}^0 = \Delta G_{\text{s,B}}^0 + \Delta G_{\text{s,H}_3\text{O}^+}^0 - \Delta G_{\text{s,BH}^+}^0 - \Delta G_{\text{s,H}_2\text{O}}^0 \quad (6)$$

Standard states in the equations above are 1.013 bar and 298.15 K for the gas and 1 M and 298 K for the solution phase. Converting the ΔG_{gas}^0 reference from 1.013 bar to 1 M requires the introduction of $R\ln(24.46)$ into the above

equations. However, because in relative methods this quantity is the same for both test and reference molecule, we have omitted this value. The above discussion is the same for both relative and absolute $\text{p}K_{\text{a}}$ calculations; however, the differences start from the next step. Methods calculating absolute acidity constants either use experimental data for the standard Gibbs free energy of hydronium ion (or hydroxide ion for bases) or estimate it from simulation approaches, while relative methods use an experimental acidity constant as a reference and calculate other $\text{p}K_{\text{a}}$ values by comparing their free energies to the free energy of the reference. So, it can be concluded that both absolute and relative methods are not fully theoretical approaches. An error of 4–8 kJ/mol leads to 1.5–3 units shift in $\text{p}K_{\text{a}}$. Experimental data for $\Delta G_{\text{solv}}^0(\text{H}^+)$ used in absolute methods differ over a range of -1,062.7 to -1,098.3 kJ/mol [17]. Almost all absolute works have used a value in the above range to reduce their MAD errors.

In this work, a relative approach is used, and propylamine is considered as the reference. By Eq. 3, its ΔG_{aq}^0 is determined from the experimental acidity constant. In relative methods, hydronium ion (for acids) or hydroxide ion (for bases) is replaced by the reference molecule. In the present work, the following equations are used instead of Eq. 2:



The sum of the two equations above leads to Eq. 2, therefore $\Delta G_{2,\text{aq}}^0 = \Delta G_{7,\text{aq}}^0 + \Delta G_{8,\text{aq}}^0$. The free energy of Eq. 7 is calculated by a hybrid method defined in the next section, and for $\Delta G_{8,\text{aq}}^0$, experimental $\text{p}K_{\text{a}}^{\text{ref}}$ is used in conjunction with Eq. 3. All above attempts are made to avoid calculation of the free energy of the hydronium ion, because the ion has a large charge density and it has been concluded that the common methods cannot estimate its solvation free energy accurately.

Gas-phase calculations

It was found that, when a molecule becomes large, a more complex potential energy surface (PES) results. Among the many minimum points in the PES, it is important to find the global minimum or a conformation near to it. One approximate way to do this is by surfing the PES via semiempirical or even molecular mechanics methods. After that, a high level of theory such as ab initio or DFT is used to calculate the energy more accurately. In this work, the PM3 semiempirical method (by HyperChem 7.0 software [18]) is used for pre-optimization and finding the global minimum for each of the structures studied without or with water molecules. Then, all of the geometries are fully

optimized at the B3LYP/6-31+G(d) level of theory in vacuum using the Gaussian98 program [19]. The optimized structures are confirmed to be real minima on the potential energy surface by frequency analysis at the same level and finding no negative frequencies (NIMAG = 0) in the output of keyword FREQ.

Solvation calculations

Solvation free energy estimation is the main task in prediction of the acidity constant in the thermodynamic cycle. Several methods have been introduced in the literature for calculating solvation free energy, including Monte Carlo, molecular dynamics, free energy perturbation, continuum models, and so on.

In this paper we used a modified version of the continuum model, named by Pliego and Riveros (PR) as the cluster-continuum model. In fact, our model is somewhat different from the PR model. In this work, microsolvation has been considered for both neutral and ionic species, while in the cluster-continuum model of PR [12] only ionic species form clusters.

The polarizable continuum model (PCM), conductor-like polarizable continuum model (CPCM), and integral equation formalism polarizable continuum model (IEF-PCM) are used with zero, one, and two water molecules. Gas-phase optimized geometries are used as input for all calculations in solution. It must be noted that reoptimization in solution may lead to better results; however, due to central processing unit (CPU) time restrictions we have not reoptimized geometries in solution.

AIM analyses

The “atoms in molecules” (AIM) theory of Bader is a very useful method for evaluation and classification of hydrogen bonds [20, 21]. Bader’s theory is based on the topological properties at bond critical points (BCP) containing the electron density (ρ_{BCP}), the Laplacian of the electron density ($\nabla^2_{\rho_{\text{BCP}}}$), and the total energy density (H_{BCP}). In this work, we used the AIM2000 program with all its default options to calculate BCPs and their properties [22]. Bader and Essen have reported different categories of critical points [23]. For shared (covalent) interactions, the electron density at bond critical point is of order $>10^{-1}$ a.u. The Laplacian of the electron density [$\nabla^2\rho(r_c)$] is a measure of local concentration of electron density and may be positive or negative. The Laplacian is the sum of two negative curvatures perpendicular to the bond path (λ_1 , λ_2) and a positive curvature (λ_3) tangent to it. A negative Laplacian value denotes electron concentration, while a positive value

shows depletion of electron density. It has been reported that, for noble-gas dimers and ionic systems, electron density is of order $\sim 10^{-2}$ a.u. and for van der Waals complexes, it is of order $\sim 10^{-3}$ a.u. and the Laplacian is positive [20]. Another parameter for characterization of hydrogen-bond strength is bond ellipticity. The ellipticity is taken as a measure of the extent to which ρ is accumulated in the plane defined by the axes of curvature λ_1 and λ_2 , both perpendicular to the bond path. It is defined as $\left[\varepsilon = \left(\frac{\lambda_1}{\lambda_2}\right) - 1\right]$. Weak hydrogen bonds show both positive Laplacian and total energy density; medium-strength hydrogen bonds show positive Laplacian but negative total energy density; and strong hydrogen bonds exhibit both negative Laplacian and total energy density [24].

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