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Predicting pK_a of Amines for CO_2 Capture: Computer versus Pencil-and-Paper

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Supporting Information

ABSTRACT: For pK_a prediction of aliphatic amines (amines relevant to industrial CO_2 capture), the performance of quantum-chemistry continuum-solvation methods is contrasted with the 1981 pencil-and-paper group-additivity method of Perrin, Dempsey, and Serjeant (PDS). We have optimized a quantum-chemistry continuum-plus-correction strategy, as well as updated the parameter values in the PDS method. The PDS method outperformed the continuum-based method: root-mean-square errors for a sample of 32 amines are 0.28 for the continuum-based method, 0.33 for the original PDS method, and 0.18 for the updated PDS method. Considering also that there is ambiguity in choice of cavity radii and molecular conformer for continuum-based methods, we recommend the pencil-and-paper PDS method over such methods.

1. INTRODUCTION

There is need for a simple procedure that can predict pK_a to within ±0.3 for a variety of amines important in CO_2 capture.[1,2] The pK_a of a compound has been estimated via quantum chemistry calculations using fairly routine continuum-solvation approximations, but the accuracy of these models is often unsatisfactory:[3,4] since 2005, most such procedures for studies of 10 or more amines have seen pK_a errors of ±1 or greater,[5−7] and the addition of correction terms, either constant[7,8] or proportional to the pK_a magnitude,[5,6,9−13] has reduced errors but not to ±0.3 accuracy. At the moment, the best of these methods have pushed accuracy to ±0.4 for selected amines[8,12] (±0.2 for the subclass of benzimidazoles[5]). Some researchers have bypassed continuum-solvation methods in favor of linear correlation formulas to other computable properties of the amine,[14,15] but to date have not improved upon ±0.4 accuracy.

We published in 2009 a general continuum-plus-correction procedure for pK_a computation, which produced rms errors of 0.68 for a test set of 17 amines.[7] It employed Gaussian 03[16] self-consistent reaction-field (SCRF) computations in a semi-continuum manner ("Model II"), in which an explicit water molecule is inside the cavity with the solute molecule: the H_2O is arranged to H-bond to the lone pair on N in the neutral amine, but to receive an H-bond from the protonated amine. The procedure, now labeled the KHE method, incorporated many terms in the calculation, including a statistical entropy effect for multiple conformations, in an attempt to get as much accuracy as one could out of the dielectric-continuum approximation. We have now simplified the procedure drastically, for both Gaussian 03 (G03)[16] and Gaussian 09 (G09)[17] users, and pushed its accuracy down to a root-mean-squared error of 0.28 for a training set of 32 CO_2-relevant amines (acyclic amines including alkanolamines, and substituted piperazines and morpholines). There remain problems, particularly with other classes of ringed amines. The new procedure is labeled SHE to distinguish it from our earlier one.

However, there is a computer-free group-additivity method for pK_a prediction, published in a book by Perrin, Dempsey, and Serjeant (PDS) in 1981,[18] that was known to provide accuracy to a few tenths for amines. Their ΔpK_a method was based on the knowledge that use of Taft parameters for organic substituents in an additive way can account for trends in equilibrium constants and free energies of reaction within classes of compounds.[19] This Article compares pencil-and-paper PDS results against those of the computer-based SHE method.

2. METHODS

2.1. SHE Method. The pK_a of a base B is a scaled version of $\Delta_r G_{(aq)}$, the free energy change of the acid-dissociation reaction $BH^+_{(aq)} \rightarrow B_{(aq)} + H^+_{(aq)}$. With energies in kcal mol^{-1}, the relation at T = 298.15 K is

$$\begin{aligned} pK_a &= \Delta_r G_{(aq)}/RT\ln 10 \\ &= \Delta_r G_{(aq)}/1.3643 \\ &= [G_{(aq)}(H^+) + G_{(aq)}(B) - G_{(aq)}(BH^+)]/1.3643 \end{aligned} \quad (1)$$

These G_{aq} quantities can be approximated with dielectric-continuum models, by breaking each G_{aq} down into a sum of three components ($E_{el} + \Delta G_{nonel} + E_{nuc}$): Briefly, $E_{el} = \langle \Psi(f)|H + V/2|\Psi(f)\rangle$ is the internal energy of the solute in solution (including its electrostatic interaction with the solvent continuum), ΔG_{nonel} is the correction due to nonelectrostatic contributions to solvation (cavitation, dispersion, repulsion, solvent-structuring effects), and E_{nuc} is the nuclear-motion energy of the solute in solution. Such computations are

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problematic for $G_{(aq)}(H^+)$ due to the strong covalent nature of H^+ in solution (H_3O^+, $H_5O_2^+$, etc.), and hence $G_{(aq)}(H^+)$, a constant with respect to identity of base, should be estimated differently. For the other two free energies, we consider the half reaction free energy $\Delta_h G_{(aq)}(BH^+ \rightarrow B)$ and its components ($\Delta_h E_{el} + \Delta_h \Delta G_{nonel} + \Delta_h E_{nuc}$), leading to

$$pK_a = [G_{(aq)}(H^+) + \Delta_h E_{el} + \Delta_h \Delta G_{non\text{-}el} + \Delta_h E_{nuc}] /1.3643 \quad (2)$$

All four terms in eq 2 have been simplified in going from KHE to SHE, as follows.

$G_{(aq)}(H^+) = -270.3$ kcal mol^{-1}. The KHE method used this $G_{(aq)}(H^+)$ term as a fitting parameter, because it is difficult to predict ab initio. We now adopt a proper value, the sum of $G_{(g)}(H^+, 1\ atm) = -6.3$ kcal mol^{-1}, computed via a Sackur–Tetrode equation, with $\Delta_{solv}G(H^+, 1\ atm\ gas \rightarrow 1\ M\ aqueous) = -264.0$ kcal mol^{-1}, derived by Tissandier et al.[20] from experimental data. Using the Ben-Naim convention[21] for $\Delta_{solv}G$, one obtains the same value, summing $G_{(g)}(H^+, 1\ M) = -4.4$ kcal mol^{-1} with $\Delta_{solv}G(H^+, 1\ M\ gas \rightarrow 1\ M\ aqueous) = -265.9$ kcal mol^{-1}.

$\Delta_h E_{el}$ Now Employs MP2/6-31G(d). The KHE method used MP2/6-311++G(d,p), maximally trans conformers for acyclic amines, and UA0 radii for solute cavities. However, further basis set testing by us revealed that the removal of diffuse functions actually reduces errors for acyclic bases in both Model I and Model II calculations (without or with an explicit H_2O inside the cavity, respectively); Model II results are shown in Table 1. We also decided to reduce the basis set from triple- to double-ζ, possibly sacrificing some accuracy but gaining in speed for extension to larger amines. The UA0 radii are default in G03; in G09 they are requested by adding G03Defaults to the SCRF keyword.

Table 1. pK_a Errors from Uncorrected SHE Procedure: Basis Set Dependence[a]

amine	6-311++G(d,p)	6-311G(d,p)	6-31G(d)
NH_3	−4.24	−0.06	−0.49
$MeNH_2$	−2.81	0.78	0.52
Me_2NH	−2.14	1.14	0.67
Me_3N	−1.88	1.36	0.48
piperazine	−0.77	2.48	2.37

[a]SHE method as described in this work, but omitting empirical corrections and allowing for basis set substitution in the SCRF MP2 geometry optimizations. Piperazine calculations employed conformer choice of ref 7. Experimental pK_a values are 9.25, 10.66, 10.73, 9.80, and 9.73 for the five bases (CRC Handbook[23]).

$\Delta_h E_{nuc} = -9.4$ kcal mol^{-1}. We dramatically simplify this nuclear-motion energy term. E_{nuc} for a solute has an intrinsic term, $E_{nuc,int}$, and a statistical entropy term $-TS_{stat}$ due to multiple conformations and rotational symmetry.[7] In the KHE method, S_{stat} was derived for each solute (B and BH^+) from symmetry considerations and conformer counting, while $E_{nuc,int}$ was computed from vibrational frequencies of Model II gas-phase complexes (i.e., with solute·H_2O complexes). We now neglect TS_{stat} effects altogether, as the effects are less than 1 kcal mol^{-1} (Table 3 of ref 7), and are a hassle to incorporate for the nonspecialist. We also now replace $\Delta_h E_{nuc,int}$ with the constant −9.4 kcal mol^{-1} to eliminate the need for gas-phase opt+freq calculations. The value −9.4 was chosen to mimic previous Model I (no explicit water) gas-phase frequency values, which were consistently -9.4 ± 0.5 kcal mol^{-1} (Table 6 of ref 7). Closer inspection revealed that this amount is dominated by the zero-point vibrational energy (ZPVE) term: deprotonation generally resulted in the loss of a 3400 cm^{-1} NH stretch and two 1600 cm^{-1} HNC bend modes, and no net frequency shifts of other modes. Friesner and co-workers had already commented on how constant this term likely is for a particular class of compounds.[22]

$\Delta_h \Delta G_{nonel} = 0$. We remind Gaussian users that three of the four nonelectrostatic effects (cavitation, dispersion, repulsion) are computed by default in G03 but must be requested in G09, and in G03 the values appear only in the middle of the logfile. Their effects are generally small. The sum of these three effects for the half-reaction, $\Delta_h \Delta G_{nonel}$, was computed (G03) to be small and nearly constant: 0.2 and 0.6 kcal mol^{-1} in Model I and Model II calculations, respectively (Tables 6 and 7 of ref 7). These small shifts tend to be swamped by remaining errors, and hence not of sufficient benefit for inclusion in a simple procedure.

Empirical Corrections. To make the errors uniformly small for multiple classes of compounds, class-dependent empirical corrections C are needed (see section 3.1). Also, in general, optimal values for C would depend on the choices made for computing $\Delta_h E_{el}$: level of theory, cavity radii, and molecular conformer. Attempts were made to find theoretical justification for a choice of cavity radii and molecular conformer, but these failed (section 3). Given the choices we have made for $\Delta_h E_{el}$, values for C deemed optimal for a training set of 32 amines (Table 5, section 4) are −0.7 for acyclic amines and −1.7 for cyclic amines.

In summary, the SHE procedure is to compute

$$pK_a = (1/1.3643)[-270.3 + E_{el}(B{\cdot}H_2O) - E_{el}(BH^+{\cdot}OH_2) - 9.4] + C \quad (3)$$

where the $E_{el}(B{\cdot}H_2O)$ and $E_{el}(BH^+{\cdot}OH_2)$ are MP2 energies, converted to kcal mol^{-1} (×627.50955), from the bottom of Gaussian logfiles ("MP2=") of SCRF=(PCM,G03Defaults) MP2/6-31G(d) geometry optimizations of maximally trans conformers. The C value is −1.7 for cyclic amines and −0.7 for acyclic amines.

2.2. PDS Method. The empirical pencil-and-paper Perrin–Dempsey–Serjeant method[18] uses only a table (Table 2 here) of pK_a "base" values and ΔpK_a additive functional-group corrections, thus offering much faster predictions. The original publication also offers some temperature correction formulas for pK_a. Because the parameter values in the PDS scheme were chosen before much alkanolamine data had been studied, we provide an updated set of these values ("new PDS"), obtained from a least-squares fit to experimental pK_a values of the same 33-amine training set used for SHE. Please note that we have only updated the parameter values relevant for CO_2-capture amines; the original method offers terms for other amines, and carboxylic acids as well.[18] Table 2 lists the old and new parameter values. Of the changes, note that (i) the base values for primary and tertiary amines are now equal, and (ii) the correction for cyclic amines is now zero. Our SHE results actually reveal a ring effect of −1.0 in the experimental pK_a values (section 3.1); in the PDS method, the effect is incorporated by counting a β group twice if it occurs in a ring.

Table 2. Terms in the Perrin–Dempsey–Serjeant Scheme for pK_a Prediction[a]

term		original[18]	updated
base value	primary amine NH_2R	10.77	10.6
	secondary amine NHR_2	11.15	11.1
	tertiary amine NR_3	10.50	10.6
ΔpK_a shifts	each CH_3 on N	−0.2	−0.2
	each β OR	−1.2	−1.4
	each β NHR or NR_2	−0.9	−1.0
	each β OH	−1.1	−1.0
	each β NH_2	−0.8	−0.9
	each γ group	$+0.4\Delta_\beta$	$+0.4\Delta_\beta$
	each δ group	$+0.4\Delta_\gamma$	$+0.4\Delta_\gamma$
	ring effect	+0.2	0
	if two equivalent N sites	+0.3	+0.3

[a]Terms for aliphatic N- and O-containing amines; for other groups and molecules, see the original method. The β effect is added twice for ringed compounds such as morpholine and piperazine. A γ effect is considered 40% the magnitude of a β effect; for example, for monopropanolamine, $pK_a = 10.6 + 0.4 \times (-1.0) = 10.2$ using updated parameters.

3. CONTINUUM-SOLVATION ISSUES

3.1. Choice of Radii. The accuracy of continuum-solvation computational methods is, unfortunately, very sensitive to the atomic radii used to define the solute cavity,[24,25] and we noted that the default radii choice changed (from unscaled "UA0" to "UFF" scaled by 1.1) when Gaussian upgraded its software from G03 to G09. In Figure 1, the change shifts pK_a predictions

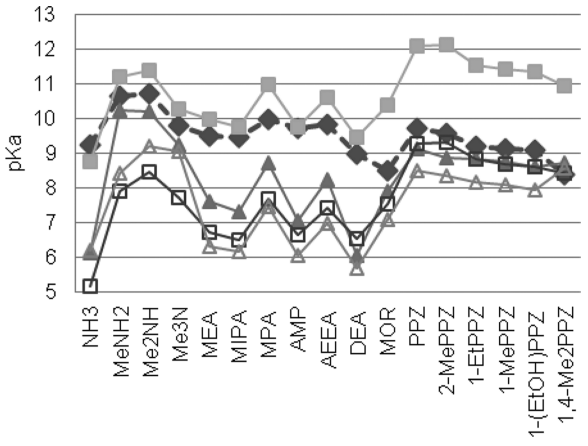

Figure 1. SHE results without empirical corrections (on conformers of ref 7), showing dramatic effects of cavity radii. ◆: experiment. ■: G03 (UA0). □: G09 radii=UA0(x1.1). ▲: G03 radii=UFF. △: G09 (UFFx1.1). Parentheses denote default effects.

down by an alarming amount: 3–4 units. (There was also a technical change in cavity and solute–solvent–surface construction in going from G03 to G09, which may have had a small effect upon predicted pK_a.[26,27]) In Figure 1, good estimates for trans conformers of all acyclic amines (NH_3 to DEA) were achieved with the unscaled UA0 radii, and hence this choice was incorporated into the SHE procedure.

Although the UA0 choice provides the highest pK_a estimates of the choices in Figure 1, it provides only moderate total molecular volumes (Figure 2); the key seems to be in the volume given to the reactive site, particularly primary and secondary N atoms, where the UA0 choice results in the

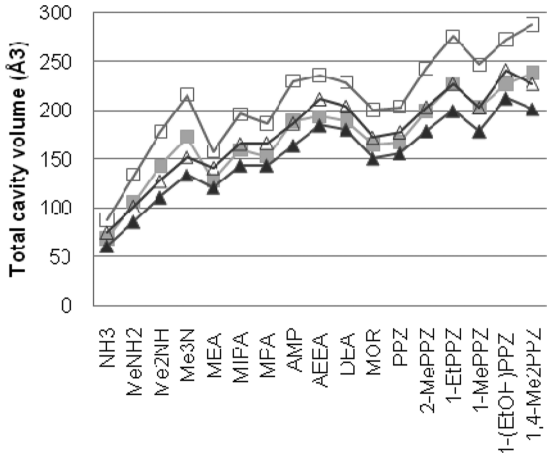

Figure 2. Cavity volumes of B·HOH complexes. See Figure 1 for legend.

smallest volumes (23 and 19 Å^3, respectively; the other procedures use volumes ≥26 and 21 Å^3, respectively).[28]

Regardless of choice of algorithm and radii, there are class-dependent errors evident in Figure 1, particularly the unique errors for cyclic compounds (morpholine and the piperazines in our case) that have been seen before.[7,29] Friesner and co-workers hypothesized[29] that the error shift for cyclic compounds is due to neglecting the fourth type of non-electrostatic effect: a solvent-structuring effect. Such solvent-structuring may be clathrate-like;[30] solid clathrate structures are known to be stable around cyclic ethers, for example.[31] This necessitated the use of separate values for the empirical shift C for cyclic versus acyclic amines (section 2).

3.2. Choice of Conformer. An additional unresolved issue is the choice of molecular conformer. This commonly ignored problem is important because pK_a results for alkanolamines are heavily dependent upon conformer choice (Table 3).[32] In the examples in the table, conformer effects are ∼0.5 for ethyl group rotation, but they are 2–4 for alkanolamine internal rotation. The large effect for alkanolamines is due to gauche XCCY conformations, which place the polar X and Y groups in close proximity; this preferentially stabilizes the BH^+ cation in a continuum-solvation calculation, and shifts up the pK_a prediction roughly 2 units per polar gauche interaction.

Note that these large pK_a variations with internal rotation of an XCCY unit are as large as the variations in switching default cavity radii in Figure 1. In fact, if G09 default radii (UFFx1.1) are used, Table 3 reveals that one gets the best agreement with experiment if gauche conformers are used instead of trans ones!

We chose the trans + UA0 combination over the gauche + UFFx1.1 combination mainly because UFF radii show less uniform errors than UA0 radii in Figure 1, which translates into worse rms errors as one tests more amines. It would have been better, of course, to choose the conformer based on which conformer dominates in aqueous solutions. Unfortunately, theory has been unable to predict this to date: (i) the rule of thumb that one should use the lowest-energy conformer in a conformer search cannot be employed, because although gas-phase and dielectric-continuum optimizations both predict the gauche forms of both B and BH^+ to be lower in energy than the trans forms, this prediction neglects the effects of explicit hydrogen bonding with solvating water molecules;[34] (ii) two nanosecond-scale classical dynamics simulations of aqueous monoethanolamine (MEA), which purported to demonstrate

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Table 3. pK_a Results from Uncorrected SHE Procedure: Conformer Dependence

amine[a]	conformer[b]	pK_a G03[c]	pK_a G09[c]
AMP 9.68	G	11.3	**7.9**
	T	**9.8**	6.1
DEA 8.88	GtgG	12.4	9.3
	GttG	11.9	**8.9**
	TtgG	11.2	7.6
	TgtG	10.8	7.4
	TttG	10.8	7.3
	TggT	9.6	5.8
	TgtT	9.5	5.7
	TttT	**9.5**	5.7
DIPA 8.84	GttG	12.5	**9.1**
	TttG	10.5	7.3
	TttT	**8.6**	5.3
MEA 9.5	G	11.7	**8.2**
	T	**10.0**	6.3
Et_2NH 10.84	gg	12.2	**9.4**
	tg	12.1	9.1
	tt	**11.9**	8.9
PPZ 9.73	GG	12.5	**9.2**
	TT ax/eq	12.1	8.5
	TT ax/ax	12.1	8.5
	TT eq/eq	11.7	8.0
	TT eq/ax	**11.6**	7.9
rms error		0.9	1.1

[a]Experimental pK_a values are listed: from Hamborg and Versteeg[33] for AMP, DEA, and DIPA, and from CRC Handbook[23] for MEA, Et_2NH, and piperazine. [b]Gauche and trans descriptors for NCCX dihedrals (G,T) and CNCC dihedrals (g,t) along the main atom chain. The HOCC and PNCC (P = lone pair) dihedrals are not specified in this notation; for T cases, we took them to be trans, but for G cases they were chosen to arbitrarily maximize NH···O hydrogen-bond interaction. For PPZ, the axial and equatorial descriptors are for the NH bonds of protonating and spectator N atoms, respectively. [c]Bold values represent the best single-conformer predictions; the difference between G03 and G09 calculations is the default cavity radii used (UA0 and UFFx1.1, respectively).

preference for gauche forms,[35,36] likely did not achieve full equilibration, because bizarrely asymmetric distributions of observed NCCO dihedral angles were reported in a third such study.[37,38] To our knowledge, the best relevant experimental study of this issue is a 1975 Raman spectrum study,[39] which demonstrated that both conformers of neutral MEA are present in solution; this calls into question the habit of choosing only one for quantum chemistry computation.

4. RESULTS

If one accepts the limitations inherent in a simple one-conformer procedure with a traditional continuum-plus-correction methodology, the SHE method constitutes an improvement within its class, as supported by a direct comparison of SHE results to those of other continuum-solvation procedures (Table 4).

However, SHE is outperformed by the "New PDS" method. First, Table 5 presents PDS and SHE results for the 32-amine training set. Both SHE and the "New PDS" methods were trained on this set and give rms errors of 0.28 and 0.18, respectively. Second, Table 6 presents further comparisons of SHE and New PDS results, for 11 amines outside of the training set, and while the New PDS method is still performing very well, the SHE method shows further weaknesses, particularly with piperidine and 1-methylpyrrolidine. Looking more closely, the SHE0 calculation (without empirical shifts) reveals an error that is dependent on the class of ringed compound: +1.9 for piperazines, +1.4 for morpholines, +1.2 for piperidines, and +0.8 for pyrrolidines. It seems that the entropy change of the surrounding water upon protonation of the amine (the only term not in the calculation) is important in an ab initio calculation of pK_a for ringed compounds. Rather than introducing more empirical shifts onto a continuum-solvation electronic structure procedure, one should turn to a simpler procedure that has only empirical shifts and abandons the electronic structure calculation altogether, that is, the empirical PDS methods.

5. CONCLUSION

For predicting aqueous pK_a values of CO_2-relevant amines, we have pushed the continuum-plus-correction method about as far as we can push it, producing a method (SHE) whose pK_a predictions have a root-mean-square error of 0.28 for 32 such amines. This appears to be an improvement over all other known computer-based methods. However, the method employs two empirical corrections, which would need to be expanded to accommodate other classes of ringed compounds. The 30-year-old computer-free group-additivity-based scheme by Perrin, Dempsey, and Serjeant (PDS) produced an rms error of 0.33 for the same amine set, and with updated

Table 4. pK_a Results: Comparison of Continuum-Solvation Procedures

			COSMO	Jaguar	COSMO-RS			
amine	expt.[a]	SHE	2010[b]	2002[c]	2010-1[d]	2010-2[e]	2006-1[f]	2006-2[g]
methylamine	10.66	10.52	10.52	10.5	11.97	11.09	11.71	11.71
dimethylamine	10.73	10.74	10.71	10.9	10.94	9.64	10.67	11.67
trimethylamine	9.80	9.66	10.12	10.1	8.93	7.73	8.63	10.63
MEA	9.50	9.32		9.8			10.29	10.29
morpholine	8.50	8.25		9.5			8.36	9.36
rms error		0.2	0.2	0.5	0.9	1.4	0.8	0.9

[a]Reference 23. [b]Reference 12. [c]Reference 22. [d]Reference 11. Table 3 "bare" data. [e]Reference 11. Table 3 "H_2O" data. [f]Reference 10. Table 2 "pK_a calc" data. [g]Reference 10. Table 2 "pK_a corrected" data.

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Table 5. SHE versus PDS Predictions for pK_a of 32 CO_2-Relevant Amines

amine	amine label	SHE0[a]	SHE	old PDS	new PDS	expt.	ref[b]
$NH(C_2H_5)_2$	diethylamine	11.88	11.18	11.15	11.10	10.84	23
$NH_2(CH_2)_4NH_2$	1,4-butanediamine	11.42	10.72	10.94	10.76	10.80	23
$NH(CH_3)_2$	dimethylamine	11.39	10.69	10.75	10.70	10.73	23
$N(C_2H_5)_3$	triethylamine	11.78	11.08	10.50	10.60	10.75	23
$NH_2C(CH_3)_3$	*tert*-butylamine	10.90	10.20	10.77	10.60	10.68	23
$NH_2CH_2CH_3$	ethylamine	11.28	10.58	10.77	10.60	10.65	23
$NH_2CH(CH_3)_2$	iso-propylamine	11.13	10.43	10.77	10.60	10.63	23
$NH_2CH_2CH_2CH_2CH_3$	butylamine	11.48	10.78	10.77	10.60	10.56	23
$NH_2CH_2CH_2CH_3$	propylamine	11.39	10.69	10.77	10.60	10.54	23
$NH_2(CH_2)_3NH_2$	1,3-propanediamine	11.34	10.64	10.75	10.54	10.55	23
NH_2CH_3	methylamine	11.17	10.47	10.57	10.40	10.66	23
$NH_2CH_2CH_2CH_2OH$	MPA	10.90	10.20	10.33	10.20	9.96	43
$N(CH_3)_3$	trimethylamine	10.31	9.61	9.90	10.00	9.80	23
$NH_2(CH_2)_2NH_2$	1,2-ethanediamine	10.99	10.29	10.27	10.00	9.92	23
$NH(CH_3)CH_2CH_2OH$	MMEA	10.75	10.05	9.85	9.90	9.85	33
$N(C_2H_5)_2CH_2CH_2OH$	DEMEA	10.66	9.96	9.40	9.60	9.75	33
$NH_2C(CH_3)_2CH_2OH$	AMP	9.76	9.06	9.67	9.60	9.68	33
$NH_2CH_2CH_2OH$	MEA	9.97	9.27	9.67	9.60	9.50	23
$NH_2CH_2CH(CH_3)OH$	MIPA	9.76	9.06	9.67	9.60	9.45	33
$N(CH_3)_2CH_2CH_2OH$	DMMEA	9.76	9.06	9.00	9.20	9.22	33
$NH(CH_2CH_2OH)_2$	DEA	9.47	8.77	8.95	9.10	8.88	42
$N(CH_3)(CH_2CH_2OH)_2$	MDEA	8.64	7.94	8.10	8.40	8.56	41
$N(CH_2CH_2OH)_3$	TEA	8.53	7.83	7.20	7.60	7.78	23
$HN(CH_2CH_2)_2NH$	PPZ (piperazine)	11.69	9.99	9.85	9.40	9.73	23
$C_4H_9N_2(CH_3)$	2-MePPZ (H+ on 4)	11.60	9.90	9.55	9.10	9.57	40
$C_4H_9N_2(C_2H_5)$	1-EtPPZ	11.12	9.42	9.55	9.10	9.20	40
$C_4H_9N_2(CH_3)$	1-MePPZ	11.17	9.47	9.55	9.10	9.14	40
$C_4H_9N_2(C_2H_4OH)$	1-(2-EtOH)PPZ	10.96	9.26	9.55	9.10	9.09	40
$C_4H_8N_2(CH_3)_2$	1,4-Me_2PPZ	9.94	8.24	9.00	8.70	8.38	40
$HN(CH_2CH_2)_2O$	MOR (morpholine)	9.95	8.25	8.95	8.30	8.50	23
$C_2H_5N(CH_2CH_2)_2O$	4-EtMOR	9.16	7.46	8.30	7.80	7.67	23
$CH_3N(CH_2CH_2)_2O$	4-MeMOR	8.76	7.06	8.10	7.60	7.38	23
	rms error	1.11	0.28	0.33	0.18		

[a]SHE procedure without empirical corrections C in eq 3. [b]Reference for experimental value.

Table 6. pK_a Errors in SHE versus PDS Predictions Outside the Training Set

amine	pK_a(expt)[a]	SHE error	old PDS error	new PDS error
piperidine	11.12	−0.49	0.23	−0.02
1-methylpyrrolidine	10.46	−0.88	0.04	−0.06
cis-2,5-dimethylpiperazine	9.66	0.09	0.19	−0.26
2-methoxyethylamine	9.40	−0.57	0.17	−0.20
2-(ethylamino)ethanol	9.99	−0.01	0.06	0.11
2-(proylamino)ethanol	9.90	0.18	0.15	0.20
2-(butylamino)ethanol	9.92	0.26	0.13	0.18
pentylamine	10.63	0.18	0.14	−0.03
hexylamine	10.56	0.27	0.21	0.04
diethylmethylamine	10.35	−0.05	−0.05	0.05
3-methyl-1-butylamine	10.60	0.27	−0.10	0.00
rms error		0.39	0.15	0.14

[a]Reference 23, except reference 13 for entries 5−7.

parameter values it produced an rms error of only 0.18. The updated PDS method outperforms the best continuum-solvation methods in both speed and accuracy, can extend to other ringed amines, and has no conformer or cavity-radii issues, and hence should be the method of choice for aliphatic amines. Future work should aim at updating the values of other PDS parameters for application to other bases and to acids.

■ ASSOCIATED CONTENT

Supporting Information

Images of all conformers used for data in Tables 3, 5, and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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