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Entropy contributions in pK_a computation: Application to alkanolamines and piperazines

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ABSTRACT

The pK_a values of 17 amines, alkanolamines, and piperazines have been computed using quantum chemistry techniques and the IEFPCM continuum solvation model. Several techniques were tested, including B3LYP and MP2 levels of electronic structure theory, the addition of an explicit water molecule inside the continuum cavity, and special scaling of cavity radii for ions. Entropy corrections for multiple conformers, often neglected in pK_a studies, are discussed and utilized. The use of explicit water inside the cavities reduced the pK_a rms error by 34%. As noted several years ago, ringed compounds do seem to be pathological cases for continuum solvation models, and the use of a second fitting parameter for these compounds dramatically lowered the overall rms error a further 42–45%, to below 0.9. Our best procedure reduces the errors found in a previous technique for similar compounds by 62%.

1. Purpose

Aqueous solutions of amines (particularly alkanolamines) have been used commercially in post-combustion CO_2 capture technologies for many years [1]. The most suitable amines would be ones with high capture capacity, fast reaction rate, and low heat of regeneration. A fundamental property of an alkanolamine is its basicity, quantified by the aqueous pK_a value of its conjugate acid. The basicity is important because it affects the kinetics and possibly the mechanism of the capture process [2–8].

An *a priori* means of predicting the aqueous pK_a of new alkanolamines would be useful. One possibility is direct calculation of such values using a widely popular quantum chemistry program (Gaussian [9]) with a continuum solvation model, in which the solvent is approximated as a dielectric continuum. The only such study of alkanolamines was reported by da Silva and Svendsen [10], but they deemed their results too inaccurate. Our main goal was to improve upon their technique, to calculate aqueous pK_a values to <1 pK_a accuracy for a similar set of industrially relevant CO_2-capture amines (including alkanolamines and substituted piperazines). The amines studied are listed in Table 1.

The second goal was to test, specifically for computation of amine pK_a values, some simple continuum modifications that have sporadically appeared in the literature: the reduction of cavities around cations (an electrostriction technique), and the use of explicit solvent molecules with solute molecules inside the cavities (a semicontinuum technique) (see Section 3).

The third goal was to recast the equations of pK_a calculation via continuum solvation methods more completely than has been done in the past, because pK_a calculation requires such accuracy that a number of small terms require attention, as we will demonstrate.

The fourth goal was to formalize an approximation for the entropy of multiple conformers, an effect usually neglected. Proper pK_a calculation requires an estimate of the entropy change of proton transfer between the base and water. East and Radom [14] discussed many aspects of molecular entropy computation in 1997, but for molecules with single conformers. Here we state the extension of the theory to molecules with several conformers, first summarized by DeTar [15], and an approximation employed by Rauk [16] and Guthrie [17] which we develop into a simple entropy correction formula for the effect of multiple conformers.

The fifth goal was to briefly summarize the historical problems with *ab initio* pK_a calculations in the past, as a guide to future workers in the field.

2. Theory

2.1. pK_a calculation

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:

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Table 1
Experimental pK_a values of the bases investigated in this study.

Base	Name or abbreviation	pK_a (25 °C)	Ref.
NH_3	Ammonia	9.25	[11]
$NH_2(CH_3)$	Methylamine	10.66	[11]
$NH(CH_3)_2$	Dimethylamine	10.73	[11]
$N(CH_3)_3$	Trimethylamine	9.80	[11]
$NH_2CH_2CH_2OH$	MEA (monoethanolamine)	9.50	[11]
$NH_2CH_2CH(CH_3)OH$	MIPA (monoisopropanolamine)	9.47	[12]
$NH_2CH_2CH_2CH_2OH$	MPA (monopropanolamine)	9.96	[12]
$NH_2C(CH_3)_2CH_2OH$	AMP (aminomethylpropanol)	9.70	[12]
$NH_2CH_2CH_2NHCH_2CH_2OH$	AEEA (aminoethylethanolamine)	9.82[a]	[12]
$NH(CH_2CH_2OH)_2$	DEA (diethanolamine)	8.97	[12]
$O(CH_2CH_2)_2NH$	Morpholine	8.50	[11]
$HN(CH_2CH_2)_2NH$	Piperazine	9.73[a]	[11]
$C_4H_9N_2(CH_3)$	2-Methylpiperazine	9.57[a]	[13]
$C_4H_9N_2(C_2H_5)$	1-Ethylpiperazine	9.20[a]	[13]
$C_4H_9N_2(CH_3)$	1-Methylpiperazine	9.14[a]	[13]
$C_4H_9N_2(C_2H_4OH)$	1-(2-Hydroxyethyl)piperazine	9.09[a]	[13]
$C_4H_8N_2(CH_3)_2$	1,4-Dimethylpiperazine	8.38[a]	[13]

[a] $pK_{a(1)}$.

$$BH^+_{(aq)} \rightarrow B_{(aq)} + H^+_{(aq)} \quad (1)$$

The relation is

$$pK_a = \Delta_r G_{(aq)}/RT \ln 10 \quad (2)$$

where R is the gas constant and T is temperature. Basicity increases with $\Delta_r G_{(aq)}$ and hence with pK_a. We write

$$\Delta_r G_{(aq)} = \Delta_h G_{(aq)}(BH^+ \rightarrow B) + G_{(aq)}(H^+) \quad (3)$$

because the half-reaction energy $\Delta_h G_{(aq)}$ ($BH^+ \rightarrow B$) is the quantity of interest in this work, and is hereafter denoted simply $\Delta_h G_{(aq)}$. It is computed as the difference of two free energies of compounds in solution:

$$\Delta_h G_{(aq)} = G_{(aq)}(B) - G_{(aq)}(BH^+) \quad (4)$$

The second term in Eq. (3), $G_{(aq)}(H^+)$, is independent of base. It is also notoriously difficult to calculate *ab initio*, probably because aqueous H^+ exists in several forms, like H_3O^+, $H_5O_2^+$, and $H_9O_4^+$ [18]. The best value for $G_{(aq)}(H^+)$ is −270.3 kcal mol^{-1}, which comes from summing $G_{(g)}(H^+)$ = −6.3 kcal mol^{-1} (1 atm pressure) [19] with $\Delta_{solv}G(H^+)$ = −264.0 kcal mol^{-1} (1 atm gas → 1 mol L^{-1} aqueous); the latter number was cleverly derived by Tissandier, Coe, and co-workers [20] from experimental data.

2.2. Continuum solvation theory

The free energy of a compound in solution can be written as:

$$G_{(aq)} = E_{elec} + \Delta G_{el} + \Delta G_{non\text{-}el} + E_{nuc} \quad (5)$$

where E_{elec} is the electronic energy of the solute in solution, ΔG_{el} is electrostatic interaction between the solute and solvent, $\Delta G_{non\text{-}el}$ is the sum of non-electrostatic contributions (cavitation, dispersion and repulsion) to solvation energy, and E_{nuc} is the nuclear-motion energy of the solute in solution. Further expressions for these four terms are:

$$E_{elec} = \langle \Psi(f)|\hat{H}|\Psi(f)\rangle \quad (6)$$

$$\Delta G_{el} = \langle \Psi(f)|\frac{1}{2}\hat{V}|\Psi(f)\rangle \quad (7)$$

$$\Delta G_{non\text{-}el} = \Delta G_{cav} + \Delta G_{disp} + \Delta G_{rep} \quad (8)$$

$$E_{nuc} = ZPVE + E_{thermal} + PV - TS \quad (9)$$

where $\Psi(f)$ is the wavefunction for the solute after solvent-polarization, ZPVE is the zero-point vibrational energy, $E_{thermal}$ is the temperature correction $E(0 \rightarrow 298\ K)$, PV is the enthalpy term, and TS is the entropy term. Eq. (5) is based on Tomasi's theory [21], which is implemented as SCRF = PCM in the Gaussian 03 software program [9]. Under the Born–Oppenheimer approximation, these terms in Eq. (5) should be computed after the geometry has also been solvent-polarized; this is done in Gaussian 03 by minimizing $E_{elec} + \Delta G_{el}$, i.e., $\langle \Psi(f)|\hat{H} + \frac{1}{2}\hat{V}|\Psi(f)\rangle$, with respect to nuclear coordinates.

It is common (although not necessary) to talk of a solvation energy $\Delta_{solv}G$ for dissolving a solute into solution from the gas phase:

$$G_{(aq)} = G_{(g)} + \Delta_{solv}G \quad (10)$$

The projection of Eq. (10) onto Eq. (5) requires further partitioning of E_{elec} and E_{nuc} in Eq. (5). For this we propose a 7-term master equation which is more specific about the effects of geometry polarization than others that appear in the literature:

$$G_{(aq)} = E_{elec}(0)^{@g} + \Delta G_{gp} + \Delta G_{ep} + \Delta G_{el} + \Delta G_{non\text{-}el} + E_{nuc}(0)^{g@g} + \Delta E_{nuc}(g \rightarrow aq) \quad (11)$$

In Eq. (11), the first 3 terms are from partitioning E_{elec} in Eq. (5): $E_{elec}(0)^{@g}$ is the electronic energy of the unpolarized solute electron-density computed at gas-phase geometry, ΔG_{gp} is the shift of $E_{elec}(0)^{@g}$ to $E_{elec}(0)$ due to polarization of solute geometry by solvent, and ΔG_{ep} is the shift of $E_{elec}(0)$ to $E_{elec}(f)$ due to polarization of solute electron-density by solvent:

$$E_{elec}(0)^{@g} = \langle \Psi(0)|\hat{H}|\Psi(0)\rangle \quad (12)$$

$$\Delta G_{gp} = E_{elec}(0) - E_{elec}(0)^{@g} \quad (13)$$

$$\Delta G_{ep} = E_{elec}(f) - E_{elec}(0) \quad (14)$$

The last 2 terms in Eq. (11) are from partitioning E_{nuc} in Eq. (5): $E_{nuc}(0)^{g@g}$ is the nuclear-motion energy of the solute in gas-phase, and $\Delta E_{nuc}(g \rightarrow aq)$ is the correction needed for this term upon solvation. With these partitionings, Eq. (11) satisfies Eq. (10) because the 1st and 6th terms constitute $G_{(g)}$, while the remaining five terms constitute $\Delta_{solv}G$. There is a known effect (+1.9 kcal mol^{-1} at 298 K) of the change in standard state conventions from 1 atm to 1 mol L^{-1} upon solvation [19]; this would be part of the 7th term.

To denote the half-reaction energy of deprotonation of base (Eq. (4)) an additional Δ_h can be added in front of all terms in Eqs. (5)–(14). Thus, Eq. (10) becomes:

$$\Delta_h G_{(aq)} = \Delta_h G_{(g)} + \Delta_h \Delta_{solv} G \quad (15)$$

and master equation (11) becomes:

$$\Delta_h G_{(aq)} = \Delta_h E_{elec}(0)^{@g} + \Delta_h \Delta G_{gp} + \Delta_h \Delta G_{ep} + \Delta_h \Delta G_{el} + \Delta_h \Delta G_{non\text{-}el} + \Delta_h E_{nuc}(0)^{g@g} \quad (16)$$

where we have assumed $\Delta_h \Delta E_{nuc}(g \rightarrow aq) = 0$, i.e. $\Delta E_{nuc}(g \rightarrow aq)$ is the same for all solutes. In this work, the importance of the various terms in Eqs. (11) and (16) is investigated, before computed pK_a values are presented and examined.

2.3. Entropy contributions

Entropy calculation is needed for E_{nuc} in Eq. (9), $E_{nuc}(0)^{g@g}$ in Eq. (11), and $\Delta_h E_{nuc}(0)^{g@g}$ in Eq. (16). Let S_i be the entropy of the ith conformer of a molecule. The entropy of a system with d distinguishable conformers is:

$$S = \sum_{i=1}^{d} x_i S_i - R \sum_{i=1}^{d} x_i \ln x_i \quad (17)$$

where the first sum is the weighted average of the entropies of conformers, and the second sum is the entropy of mixing of conformers. Here x_i is the Boltzmann probability of conformer i;

$$x_i = \frac{\omega_i e^{-(H_i - H_1)/kT}}{\sum_{j=1}^{d} \omega_j e^{-(H_j - H_1)/kT}} \quad (18)$$

where H_1 is the energy (enthalpy) of the lowest-energy conformer and ω_i is the degeneracy of indistinguishable versions of the ith distinguishable conformer. The sum of these ω_i is the total number of configurations, n. For instance, for n-pentane, $d = 6$ (tt, g^+g^+, g^-g^-, tg^+, tg^-, g^+g^-), but n can be chosen to be either 9 or 81 (see below).

Computation of H_i for all conformers is problematic. First, the number of conformers may be large. Secondly, for the alkanolamines of the current project, single-molecule H_i calculations (even with continuum methods) will overweight the importance of closed (non-extended) conformers, where it can provide an intramolecular hydrogen-bond, and underweight the importance of open (extended) conformers, where it cannot describe intermolecular H-bonds with solvent water molecules. Although some recent molecular-mechanics simulations of aqueous ethanolamine reveal a preponderance of intramolecular hydrogen-bonded conformers [22,23], it is not clear if this result will be maintained when more accurate forces are used.

Therefore, we make the approximation of equal weights, formalized as:

$$x_i \approx \frac{\omega_i}{n} \quad (19)$$

$$S_i \approx S_{int} - R \ln \sigma_i \quad (20)$$

which assumes each conformer has equal probability $1/n$, and that each conformer contributes an essentially constant intrinsic entropy, S_{int}. The intrinsic entropy is the entropy devoid of any rotational indistinguishability correction due to the rotational symmetry number, σ_i, which can be conformer-dependent (eg. 2 or 1 for n-pentane conformers) [15]. Both Rauk [16] and Guthrie [17], and probably Stull et al. [24], have used this approximation. With this approximation, Eq. (17) becomes

$$S \approx S_{int} - R \sum_{i=1}^{d} \frac{\omega_i}{n} \ln \frac{\sigma_i \omega_i}{n} \quad (21)$$

What has not been recognized to date is that, for many molecules,

$$\sigma_i \omega_i = \Omega \quad (22)$$

where Ω is an integer constant. Using this result, Eq. (21) simplifies to Eq. (23):

$$S \approx S_{int} - R \ln \frac{\Omega}{n} \quad (23)$$

Since Eq. (22) leads to a great simplification, it is worthwhile to devote some explanation to it. Reference here will be made to molecular symmetry group (MSG) theory [25]. Let $\mathcal{G}$ be the group containing all nuclear-permutation possibilities that are feasible, such as those arising from rotation and torsion (internal rotation). Woodman [26] proposed that, for molecules that can be described as internally rotating tops on a rigid frame, $\mathcal{G}$ can be factorized into a semidirect product of a torsion subgroup $\mathcal{H}$ and a frame subgroup $\mathcal{F}$. Although his torsion subgroup contained only indistinguishable torsions (e.g. methyl rotations), we will expand this group to include distinguishable torsions; this makes $\mathcal{G}$ not a symmetry group but a *conformer group* to represent all feasible conformers of a molecule. Hence in Table 2 we divide the total torsional subgroup $\mathcal{H}$ into 2 additional subgroups: distinguishable ones (group $\mathcal{D}$) and indistinguishable ones (group $\mathcal{I}$).

We have used the "small-n" convention: n = order of $\mathcal{D}$ (=9 for pentane), requiring Ω = order of $\mathcal{J}$ (=2 for pentane). Under the "large-n" convention, n = order of $\mathcal{I} \wedge \mathcal{D}$ (=81 for pentane) and Ω = order of $\mathcal{I} \wedge \mathcal{J}$ (=18 for pentane). The choice of convention does not affect the entropy-relevant Eq. (23) ratio Ω/n (=2/9 for pentane). Simply put, the "small-n" approach ignores the results of torsions that increase the degeneracy of all conformers equally: this means we ignore methyl rotations (which triple the values of ω_i and n), and the chair-to-chair conversions of piperazine and morpholine rings (which double the values of ω_i and n). One advantage with the "small-n" convention is that Ω becomes equal to the maximum rotational symmetry number $\sigma_{max} = \max\{\sigma_i\}$, for all the molecules studied here (and perhaps generally).

Eq. (22) arises as follows. Suppose a molecule has m plausible interconverting potential-minima geometrical structures that span a nonrigid-molecule symmetry subgroup $\mathcal{E}$ of order q. Then a theorem states that any symmetry-related subgroupings of these structures (such as a set of ω_i indistinguishable permutable conformers, represented by distinguishable conformer i) must contribute to a subgroup of $\mathcal{E}$, with an order p_i that is a subfactor of q [27]. Let $\mathcal{E}$ be $\mathcal{J}$, the rotation subgroup of the frame, so that $q = \Omega$ (=2 for pentane). Any rigid conformer i will have a rotation subgroup that will necessarily be a subgroup of $\mathcal{J}$ (either $\{E\}$ or $\{E,C_2\}$ for

Table 2
Conformer groups and subgroups.[a]

Group	Description	Factorized product (pentane)	Order of group (pentane)
$\mathcal{G} = \mathcal{H} \wedge \mathcal{F}$	Molecular conformer group	$[[C_3^a \wedge C_3^b] \otimes [C_3^d \wedge C_3^c]] \wedge [C_{2v}^F]$	324
$\mathcal{H} = \mathcal{I} \wedge \mathcal{D}$	Torsion subgroup	$[C_3^a \wedge C_3^b] \otimes [C_3^d \wedge C_3^c]$	81
$\mathcal{F} = \mathcal{J} \wedge \mathcal{V}$	Frame subgroup	$[C_{2v}^F]$	4
$\mathcal{I}$	Indistinguishable-torsion subgroup	$[C_3^a \otimes C_3^d]$	9
$\mathcal{D}$	Distinguishable-torsion subgroup	$[C_3^b \otimes C_3^c]$	9 (=n)
$\mathcal{J}$	Rotation subgroup of F	$[C_2^F]$	2 (=Ω)
$\mathcal{V}$	$\{E, V^*\}$	$\mathcal{V}$	2

[a] Four of these groups and the factorization technique are described in Ref. [26].

Table 3
Statistical entropy parameters and half-reaction free-energy corrections employed.

Base	$\sigma_{max}(B)$	$n(B)$	$\sigma_{max}(BH^+)$	$n(BH^+)$	$RT\ln\left(\frac{\sigma_{max}(B)n(BH^+)}{\sigma_{max}(BH^+)n(B)}\right)$
NH_3	3	1	12	1	$RT\ln(1/4) = -0.82$ kcal mol^{-1}
$NH_2(CH_3)$	1	1	3	1	$RT\ln(1/3) = -0.65$
$NH(CH_3)_2$	1	1	2	1	$RT\ln(1/2) = -0.41$
$N(CH_3)_3$	3	1	3	1	0
MEA	1	3^3	1	3^2	$RT\ln(1/3) = -0.65$
MIPA	1	3^3	1	3^2	$RT\ln(1/3) = -0.65$
MPA	1	3^4	1	3^3	$RT\ln(1/3) = -0.65$
AMP	1	3^3	1	3^2	$RT\ln(1/3) = -0.65$
AEEA	1	3^6	1	3^5	$RT\ln(1/3) = -0.65$
DEA	1	3^6	2	3^6	$RT\ln(1/2) = -0.41$
Morpholine	1	2	1	1	$RT\ln(1/2) = -0.41$
Piperazine	2	2^2	1	2	0
2-Methylpiperazine	1	2^4	1	$2^3 + 2^3$	0
1-Ethylpiperazine	1	$3^1 2^2$	1	$3^1 2^1 + 3^1 2^2$	$RT\ln(3/2) = +0.24$
1-Methylpiperazine	1	2^2	1	$2 + 2^2$	$RT\ln(3/2) = +0.24$
1-(2-Hydroxyethyl)piperazine	1	$3^3 2^2$	1	$3^3 2^1 + 3^3 2^2$	$RT\ln(3/2) = +0.24$
1,4-Dimethylpiperazine	2	2^2	1	2^2	$RT\ln(2) = +0.41$

pentane). The order of this rigid-conformer rotation subgroup is σ_i, the rotational symmetry number for *i*. Hence, by the theorem, Ω/σ_i = an integer.

This integer can be used as ω_i, the degeneracy of conformer *i* in internal-rotation space (and therefore the weight in the Boltzmann formula Eq. (18)). Suppose there is a reference structure $i = 1$ such that $\sigma_1 = \Omega$. If a particular torsion generates structure $i = 2$ with half this rotational symmetry ($\sigma_2 = \sigma_1/2$), then by symmetry there must be an opposing torsion that will make a degenerate copy of this structure (hence $\omega_2 = 2*\omega_1$), and hence these degeneracies ω_i are in direct proportion to the integers Ω/σ_i.

Eq. (23) allows one to compute the intrinsic entropy of only one conformer (in C_1-symmetry, to avoid automatic application of σ_i by programs like Gaussian 03), and make two "statistical entropy" corrections: an increase $+R\ln n$ for conformer uncertainty, and a decrease $-R\ln\Omega$ for internal- and overall-rotation indistinguishability. Furthermore, the rotational symmetry numbers σ_i (inside Ω) properly take into effect the possibility of protonating two identical base sites of a molecule (like piperazine), obviating the need for an ad hoc correction for this.

Strictly speaking, for Eq. (23), *n* should be the number of low-energy (populated) conformers, for the equal-weights approximation (Eq. (19)) to be valid. Indeed, we neglect the twist-boat conformers of morpholines and piperazines for this reason. However, for the computation of $\Delta S(BH^+ \rightarrow B)$ for pK_a determinations, it is the ratio $n(BH^+)/n(B)$ that is needed, and this ratio will be fairly well estimated regardless of energy range allowed.

Table 3 shows the values used for σ_{max} (*i.e.*, Ω) and the choices made for *n*. In the small-*n* convention, *n* was built from factors of 3 for internal rotations about C–C, C–N, and C–O bonds (except indistinguishable $-CH_3$ or $-NH_3$ rotations), and factors of 2 for (i) axial-vs-equatorial positions and (ii) the enantiomers of neutral and protonated 2-methylpiperazine. Furthermore, for four of the last five $n(BH^+)$ entries in Table 3, we have summed conformer counts for two distinguishable protonation-site possibilities, since our conformer checks revealed that both nitrogen sites yield similar protonation energies. Table 3 also lists the total correction applied to $\Delta G_{(aq)}$ half-reactions; the largest correction, for $NH_4^+ \rightarrow NH_3$, is -0.8 kcal mol^{-1}, or a pK_a shift of -0.6. For S_{int} in Eq. (23), the rigid-rotor/harmonic oscillator approximation was used.

3. Previous pK_a studies

There is, in fact, a long history of pK_a computation using continuum solvation techniques. They began to look promising in 1992, when Tomasi and co-workers [28] used MP4/6-31G(d) and an early version of their continuum solvation model PCM to reproduce the peculiar $\Delta_r G_{(aq)}$ basicity ordering of the methylated amines, despite a relatively systematic absolute error of +2 to +3 kcal mol^{-1}. Unfortunately, simple continuum solvation models are poor approximations for systems in which the solute molecules interact strongly with the solvent molecules around them, with the worst cases being aqueous solvation of hydrogen-bonding solutes and solute ions. In the late 1990s, research teams at the University of Minnesota (Cramer/Truhlar) [29] and Columbia University (Friesner/Honig) [30] were already aware of one such difficulty: nitrogen-containing solutes in water. Ensuing research has shown that this breakdown of the approximation results in a host of systematic errors, many of which depend on class of solute compound. In continuum-based pK_a calculations, the systematic errors appear either as (i) constant-shift errors or (ii) errors proportional to pK_a itself. A variety of strategies have been applied in the past to deal with these problems, as described below.

Constant-shift errors can be due to erroneous choices for $G_{(aq)}(H^+)$ or terms within, such as $\Delta_{solv}G(H_3O^+)$ or $\Delta_{solv}G(H^+)$ [28,31,32] or the standard-state shift within $\Delta E_{nuc}(g \rightarrow aq)$ [19]. Constant-shift errors that depend on class of compound could be due to poor electronic-structure treatment of certain atoms and the point charges generated around the cavity, or in poor choices of radius for certain atoms or functional groups. Techniques for improving these errors include extensive element-dependent parametrization of the continuum model (the SMx series of Cramer/Truhlar [33]), consideration of electrostriction by making cavity radii dependent on partial charge [33,34] (a simpler scaling idea is tried in this work), or least-squares fitting vs. experiment to determine $\Delta_{solv}G(H^+)$ [35] or all of $G_{(aq)}(H^+)$ (tried in this work).

Errors proportional to pK_a itself have been revealed in plots of experimental vs. computed pK_a, in studies of compounds over a wide pK_a range [36–41]. They can also be seen in the data of Liptak/Shields [42] and Nascimento and co-workers [43], when plotted. Tomasi [38] originally thought the problem lay in poor $\Delta G_{(g)}$ computation, but Chipman [44] elegantly showed that the problem was with $\Delta_{solv}G_{(aq)}$, by demonstrating that this error virtually disappears when the alternative solvents DMSO and MeCN were considered. Friesner and co-workers [39] explained that the incorrect slope arises because the error due to ignoring local hydrogen-bonding effects should be proportional to the partial charge at the hydrogen-bonding site, and thus dependent on the acidity/basicity of this site. Three groups [45–47] have had success in reducing this pK_a-proportional error with a semicontinuum technique

[34] by adding explicit water molecules inside the solute cavity (tried in this work). Other groups have suggested a more empirical approach, relying on a known systematic error to build class-dependent empirical relations

$$pK_a(\text{expt}) = m * pK_a(\text{theo}) + b \quad (24)$$

for predictive uses [37–39]. Some, such as Adam [46] and Tao [48], have found phenomenal accuracy for single classes of compounds (<0.2 pK_a errors) by taking this approach further, replacing pK_a(theo) in Eq. (24) with some other computable property of the solute molecule.

Of the direct-pK_a-computation studies (i.e. not based on linear regressions like Eq. (24)), the few that have reported computed pK_a accuracy of better than ±1 were studies of a handful of compounds within a single class and small pK_a ranges [35,42,43,49], where slope errors are hard to observe and constant-shift errors may have fortuitously cancelled them. A good example would be the work of Nascimento and co-workers, whose results for carboxylic acids looked very good [43], but whose ensuing results for three other classes of compounds showed large class-dependent errors [50]. We will demonstrate that similar success can be achieved for alkanolamines or piperazines of pH range 8–11.

4. Computational methods in this work

4.1. Procedures

All the calculations were done using the Gaussian 03 software program and the 6-311++G** basis set [9]. Solvent effects were computed using the continuum solvation method IEFPCM [18] with UA0 radii for spherical cavities [9]. The electronic structure levels of theory tested for IEFPCM calculations (including geometry optimization) were B3LYP and MP2 [9], although we note that in the MP2 calculation the $\Delta G_{\text{non-el}}$ term is only computed at the Hartree–Fock level of theory. Geometry optimizations with IEFPCM minimize $E_{\text{elec}} + \Delta G_{\text{el}}$ in Eq. (5). All $E_{\text{nuc}}(0)^{g@g}$ terms were computed only with B3LYP at B3LYP gas-phase-optimized geometries.

We tested the semicontinuum [34] technique of Kelly et al. [47] of monohydrating the solute ions inside the continuum cavity, but we consistently hydrated all solute ions, and went another step further by also monohydrating the neutral bases. For neutral amine, a hydrogen atom of the explicit water molecule was hydrogen-bonded to the nitrogen atom in amine, while for protonated amine the new proton attached to nitrogen atom was hydrogen-bonded to the oxygen of water molecule. The alcohol group of alkanolamine could also hydrogen-bond to the solvent molecules, but the error in $\Delta_{\text{solv}}G$ caused by not providing explicit H_2O here should cancel well when the half- reaction $\Delta\Delta_{\text{solv}}G$ is considered. We will designate the use of one explicit water molecule as Model II, to distinguish from Model I, where no explicit water is used.

To accommodate electrostriction in a simple manner, we decided to test the utility of a constant scale factor to contract the radii of charged "united atoms:" 0.9 instead of the default factor of 1.0 for the NH_x groups of protonated amines [51]. This will be referred to as "special scaling."

4.2. Conformer choices

Some conformer testing was done in order to ensure that the ones we chose were among the lowest-energy ones for each base B and conjugate acid BH^+. In gas-phase calculations on alkanolamines we assumed intramolecular hydrogen-bonds; from the –OH hydrogen to the N atom of neutral ones, and from a $-NH_3^+$ hydrogen to the O atom of the protonated forms. In aqueous solution, other structures become competitive in energy, due to intermolecular H bonding with the solvent (see Section 2.3), but the IEFPCM could not provide such interactions. Hence, In Model I (no explicit water), these same intramolecular-H-bonded configurations were used. However, in Model II calculations with one explicit H_2O molecule, all-*trans* conformers could be maintained and hence were used for alkanolamines (Fig. 1).

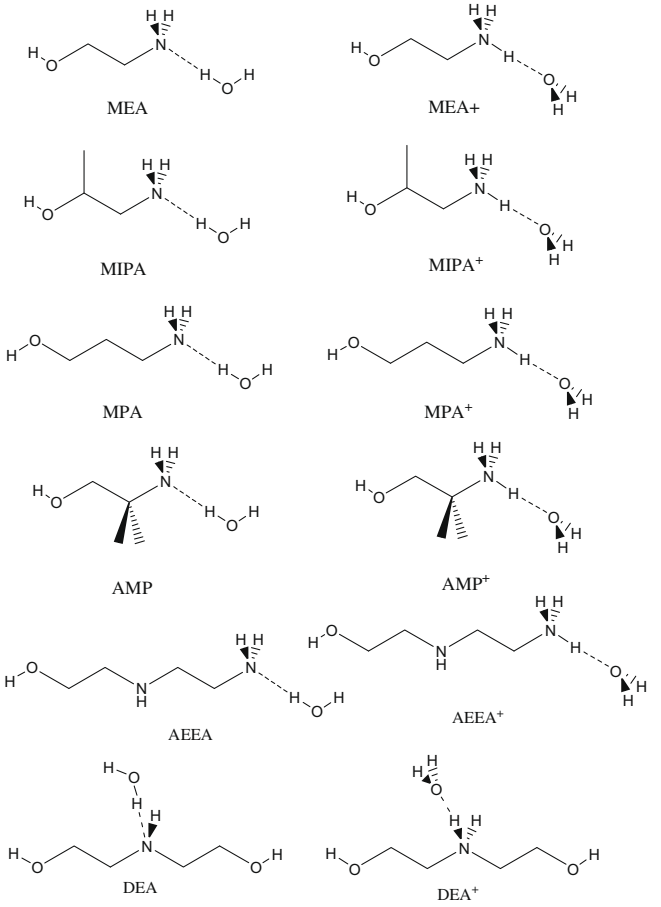

Fig. 1. Conformers of alkanolamines used in Model II.

For the monohydrated cyclic amines piperazine and morpholine, different axial-vs-equatorial positions for the NH groups were tested with chair conformers (Fig. 2), and the differences were within 1 kcal mol^{-1}. The most stable conformers at B3LYP/IEFPCM were used: structures II in Model I, but structures I in Model II.

Fig. 3 shows the conformers used for the substituted piperazines. The substituents were added at equatorial positions, these being the most stable positions in piperazine. For the four cases where the two N atoms were inequivalent, both protonation sites were tested. Interestingly, for 1-methylpiperazine and 2-methylpiperazine, protonating the N atom in position 1 was preferred in gas-phase calculations, but not in IEFPCM calculations. The conformers used (shown in Fig. 3) were the ones lowest in energy in IEFPCM/B3LYP calculations.

5. Results and discussion

5.1. Free energies

First we perform a component analysis, via Eq. (11), of the solvation energies of individual compounds. Tables 4 and 5 present results for the solvation of bases and protonated bases, respectively.

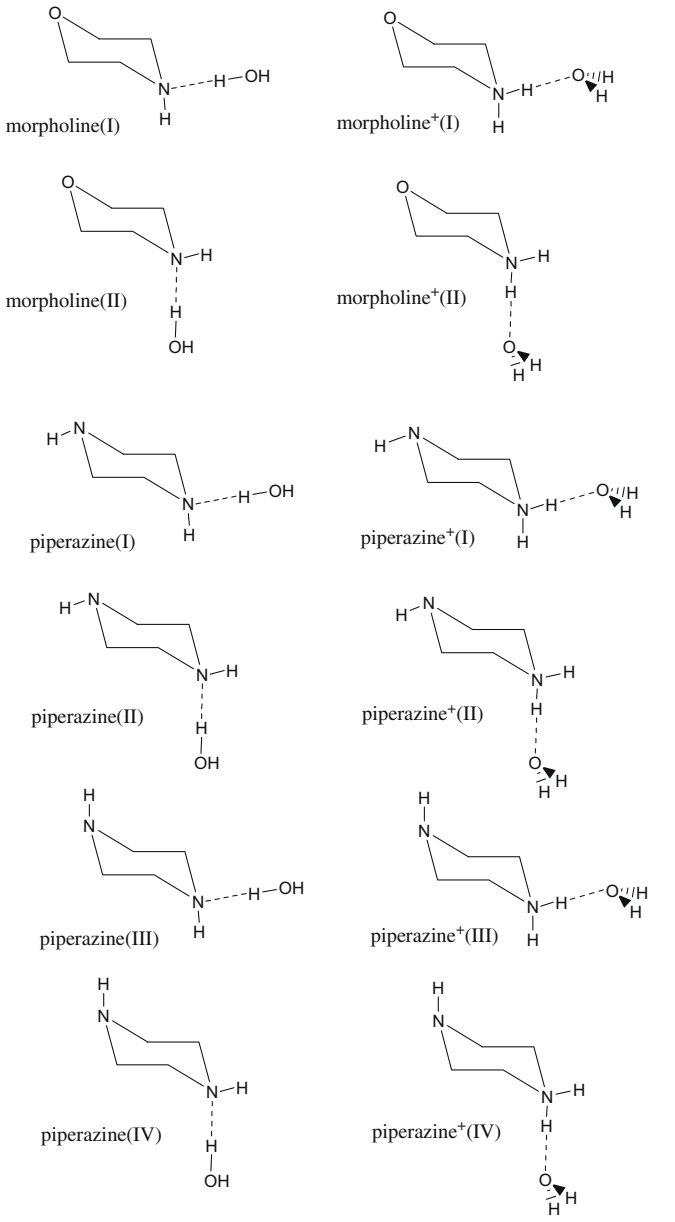

Fig. 2. Possible conformers of morpholine and piperazine in Model II.

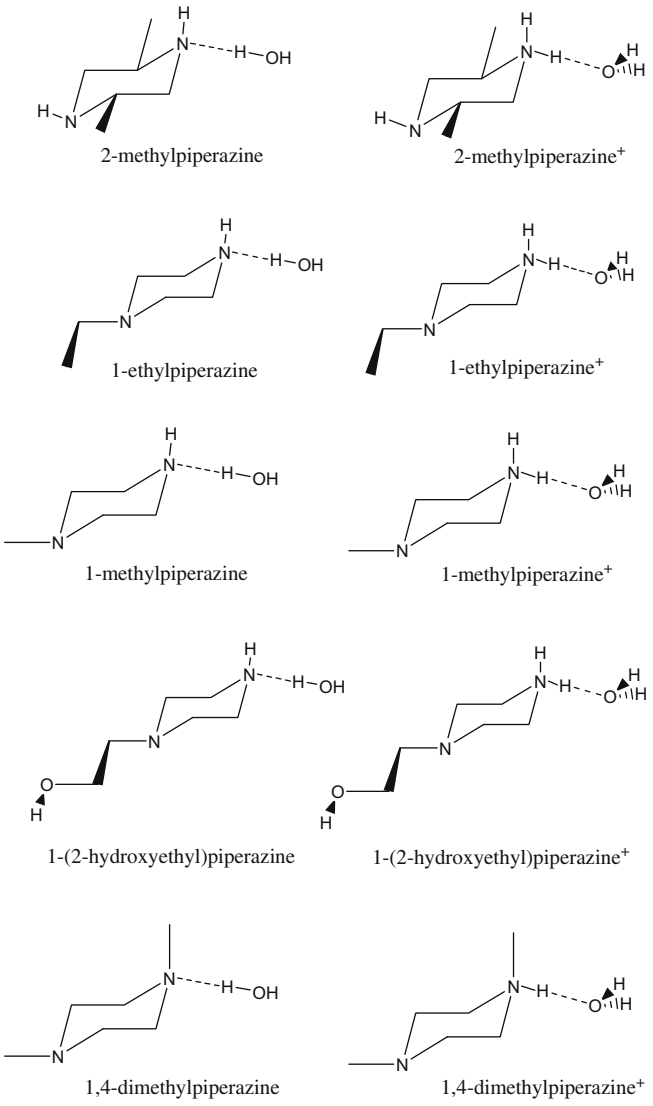

Fig. 3. Conformers of cyclic amines (piperazine family) used in Model II.

The last column of Table 4 predicts that the methylamines are actually destabilized by aqueous solvation ($\Delta_{solv}G > 0$), with aversion increasing monotonically with methylation. This prediction is in line with other theoretical studies that have disagreed with the negative values from experimental work [52,53]. The trend with methylation is due to the hydrophobicity of methyl groups, which reduces electrostatic benefits ($|\Delta G_{el}| < 6$ kcal mol^{-1}), while increasing the energy spent on making the cavity (ΔG_{cav}, a term in $\Delta G_{non\text{-}el}$). The three alkanolamines are the most stabilized by solvation effects, due to two polar sites (amine and hydroxyl group) which can stabilize quite well in the polar solvent and can benefit from electrostatic interactions ($\Delta G_{el} = -10$ kcal mol^{-1}).

Comparing Table 5 to Table 4, the $\Delta G_{non\text{-}el}$ term changes very little upon protonating the amines, but the ΔG_{el} term is greatly amplified (much more negative) due to the positive charge from the added H^+. As a result, solvation energies ($\Delta_{solv}G$) are much lower. The ammonium ion is the most stabilized by solvation because of its high charge-to-volume ratio and lack of hydrophobic groups.

Next we move to the half-reactions ($BH^+ \rightarrow B$) and Eq. (16). Tables 6 and 7 show computed components of half-reaction free energies of the seven bases using Model I and Model II respectively. The energies were calculated using the IEFPCM continuum model and the B3LYP/6-311++G** level of theory.

In Table 6, the gas-phase terms ($\Delta_h E_{elec}(0)^{@g}$) span a 23 kcal mol^{-1} range (212–235 kcal mol^{-1}). Addition of one explicit H_2O reduces this span to a 17 kcal mol^{-1} range (227–244 kcal mol^{-1}, first column of Table 7). With the continuum model of full solution,

Table 4
Computed components of $\Delta_{solv}G$ for bases (kcal/mol), Model I/PCM/B3LYP.[a]

Base	ΔG_{gp}	ΔG_{ep}	ΔG_{el}	$\Delta G_{non\text{-}el}$	Sum[b]
NH_3	0.05	0.61	−5.48	2.71	−2.11
$NH_2(CH_3)$	0.08	0.63	−5.14	4.55	0.13
$NH(CH_3)_2$	0.10	0.51	−4.08	6.46	2.98
$N(CH_3)_3$	0.07	0.18	−1.75	7.89	6.39
MEA	0.67	1.21	−10.43	3.93	−4.62
MIPA	0.36	1.22	−9.70	5.48	−2.63
MPA	0.38	1.44	−9.93	4.48	−3.62

[a] IEFPCM calculations; no explicit water or special scaling used.
[b] Sum is equal to $\Delta_{solv}G$ but without the $\Delta E_{nuc}(g \rightarrow aq)$ term.

Table 5
Computed components of $\Delta_{solv}G$ for protonated bases (kcal/mol), Model I/PCM/B3LYP.[a]

Base	ΔG_{gp}	ΔG_{ep}	ΔG_{el}	$\Delta G_{non\text{-}el}$	Sum[b]
NH_4^+	0.02	0.03	−75.45	2.79	−72.60
$NH_3(CH_3)^+$	0.16	0.97	−70.49	4.32	−65.03
$NH_2(CH_3)_2^+$	0.26	1.36	−64.72	6.20	−56.91
$NH(CH_3)_3^+$	0.32	0.92	−57.16	7.76	−48.16
$MEAH^+$	1.62	1.56	−72.16	3.65	−65.34
$MIPAH^+$	1.98	2.48	−71.86	5.26	−62.13
$MPAH^+$	0.96	1.37	−65.56	4.16	−59.07

[a] IEFPCM calculations; no explicit water or special scaling used.
[b] Sum is equal to $\Delta_{solv}G$ but without the $\Delta E_{nuc}(g \rightarrow aq)$ term.

the ranges of $\Delta G_{(aq)}$ get remarkably narrow: 8.6 kcal mol^{-1} with Model I, and 5.5 kcal mol^{-1} with Model II. If NH_3 is omitted from this list, the other 6 bases have tightly clustered $\Delta G_{(aq)}$ values, making the prediction of correct ordering a nearly impossible task, and making all six components of the energy important.

5.2. pK_a results

In order to calculate the pK_a values using Eq. (2), we must convert $\Delta G_{(aq)}$ to $\Delta_r G_{(aq)}$ via Eq. (3), by adding the contribution $G_{(aq)}(H^+)$. Direct computational estimates of this term have been attempted, but the resulting pK_a values tend to be sufficiently poor that most scientists [28,35,42,44,47] have resorted to taking an empirical choice for $\Delta_{solv}G(H^+)$, the dominant component of $G_{(aq)}(H^+)$. We simplify this by taking empirical choices for $G_{(aq)}(H^+)$ itself. We used it as the fitting parameter in minimizing the root mean square (rms) of calculated pK_a values vs. experimental values. Fitting was done for each model and level of theory. It was also done to convert the results of da Silva and Svendsen [10] from relative $\Delta G_{(aq)}$ values into best possible pK_a values.

The results are displayed in Table 8. The rms errors reveal that the best results are obtained from Model II with default radii scaling. For B3LYP calculations, Model II reduced the errors of Model I (no explicit water) by 34%. Although the specialized scaling (reducing the radii of charged "united atoms" by 10%) did improve the pK_a of ammonia considerably, it made results for other amines worse. Closer inspection of the data (naively assuming the pK_a values vary linearly with scaling factor) suggests that a more optimal scaling would have been 3% instead of 10%, with a potential improvement of only 10% for the rms errors of the default-scaling techniques.

We used the best 2 techniques of Table 7 to compute the pK_a values of the last 5 compounds in Table 1 (the substituted piperazines). This included refitting of $G_{(aq)}(H^+)$ to minimize rms error. In doing so, we noticed that the errors for cyclic compounds tended to be unique, as Friesner and co-workers had found years ago [30], so we also did separate fittings for the 10 acyclic bases and the 7 cyclic ones. This resulted in two fitting parameters for each modelling technique, and improved the rms errors by 42–45% compared to single-parameter results (Table 9). A large error is still seen for NH_3 (2 pK_a units), due to the high charge-to-volume ratio which amplifies the imperfections of the cavity.

Friesner and co-workers had speculated that the problem with ringed compounds might be with the changing structure of water around them [30]. The ensuing years has revealed that continuum solvation models generally produce systematic errors for different classes of compounds. It would appear that simple continuum solvation models are simply too crude to provide greater accuracy across several classes of compounds, and the models that try (SMx [33], Jaguar [39], and COSMO [54]) have been forced to use extensive (and continually upgraded) empirical parametrization.

Our most accurate procedure for the calculation of the pK_a of bases studied in this work is a Model II (explicit water) technique employing IEFPCM/MP2/6-311++G** for the optimized geometries and ensuing energies, with $E_{nuc}(0)^{g@g}$ terms computed with B3LYP/6-311++G** at a C_1-symmetry gas-phase conformer geometry, statistical entropy corrections from Eq. (23), and $G_{(aq)}(H^+)$ values of −266.96 kcal mol^{-1} for acyclic bases and −269.63 kcal mol^{-1} for cyclic bases. It produced an rms error of 0.68 for the pK_a of the 17 compounds studied here.

We mentioned in Section 2 that the best experimental value for $G_{(aq)}(H^+)$ is −270.3 kcal mol^{-1}. Interestingly, the fitted values in our computational work are close to this value for (i) cyclic molecules with no electrostriction scaling, and (ii) acyclic molecules with

Table 6
Half-reaction energies $\Delta_h G_{(aq)}$ and their components (kcal/mol), Model I/PCM/B3LYP.[a]

Base	$\Delta_h E_{elec}(0)^{@g}$	$\Delta_h \Delta G_{gp}$	$\Delta_h \Delta G_{ep}$	$\Delta_h \Delta G_{el}$	$\Delta_h \Delta G_{non\text{-}el}$	$\Delta_h E_{nuc}(0)^{g@g}$	$\Delta_h G_{(aq)}$
NH_3	211.87	0.03	0.58	69.97	−0.08	−9.19	272.36
$NH_2(CH_3)$	222.87	−0.08	−0.34	65.35	0.23	−9.47	277.91
$NH(CH_3)_2$	230.05	−0.16	−0.85	60.64	0.26	−9.70	279.83
$N(CH_3)_3$	234.41	−0.25	−0.74	55.41	0.13	−9.79	279.18
MEA	227.88	−0.94	−0.35	61.73	0.28	−9.02	278.92
MIPA	229.51	−1.62	−1.26	62.16	0.22	−8.91	279.45
MPA	235.15	−0.58	0.08	55.63	0.31	−9.00	280.95

[a] IEFPCM calculations; no explicit water or special scaling used. The statistical entropy corrections (Table 3) were not included in the $\Delta_h E_{nuc}(0)^{g@g}$ values, but are included in the $\Delta_h G_{(aq)}$ values.

Table 7
Half-reaction energies $\Delta G_{(aq)}$ and their components (kcal/mol), Model II/PCM/B3LYP.[a]

Base	$\Delta_h E_{elec}(0)^{@g}$	$\Delta_h \Delta G_{gp}$	$\Delta_h \Delta G_{ep}$	$\Delta_h \Delta G_{el}$	$\Delta_h \Delta G_{non\text{-}el}$	$\Delta_h E_{nuc}(0)^{g@g}$	$\Delta_h G_{(aq)}$
NH_3	226.61	−0.85	0.76	58.47	0.28	−9.36	275.08
$NH_2(CH_3)$	234.79	−0.76	0.21	54.70	0.61	−8.33	280.57
$NH(CH_3)_2$	240.31	−0.89	0.06	50.51	0.69	−9.71	280.55
$N(CH_3)_3$	243.67	−0.08	0.55	45.06	0.57	−10.43	279.33
MEA	234.64	−0.90	0.39	53.38	0.58	−7.78	279.66
MIPA	235.96	−0.98	0.02	52.47	0.60	−8.86	278.56
MPA	236.84	−1.09	−0.41	53.72	0.54	−10.33	279.27

[a] IEFPCM calculations; no explicit water or special scaling used. The statistical entropy corrections (Table 3) were not included in the $\Delta_h E_{nuc}(0)^{g@g}$ values, but are included in the $\Delta_h G_{(aq)}$ values.

Table 8
Comparison of theoretical[a] and experimental pK_a results.

Base	B3LYP Model I Ref. [9][b]	B3LYP Model I Def. sc.[c]	B3LYP Model II Sp. sc.[c]	MP2 Model II Sp. sc.[c]	B3LYP Model II Def. sc.[c]	MP2 Model II Def. sc.[c]	Expt.[d]
NH_3	9.03	4.52	8.24	8.74	6.29	6.81	9.25
$NH_2(CH_3)$	8.64	8.61	10.96	11.43	10.33	10.76	10.66
$NH(CH_3)_2$	10.60	10.02	9.09	9.52	10.32	10.76	10.73
$N(CH_3)_3$	10.65	9.54	5.92	6.15	9.42	9.78	9.80
MEA	12.15	9.36	10.58	10.60	9.66	9.67	9.50
MIPA	7.33	9.74	9.53	9.37	8.85	8.70	9.47
MPA	7.86	10.85	10.18	10.12	9.38	9.30	9.96
AMP	7.75	9.78	10.94	10.49	10.14	9.73	9.70
AEEA[e]	9.49	10.58	11.01	10.95	10.20	10.04	9.82
DEA	9.13	11.25	9.17	8.89	9.68	9.37	8.97
Morpholine	10.97	9.61	9.21	8.97	9.81	9.56	8.50
Piperazine[e]	12.49	12.21	11.26	10.87	12.02	11.61	9.73
Rms error	1.79	1.85	1.47	1.30	1.22	1.00	

[a] Obtained via $\Delta_h G_{(aq)}(BH^+ \rightarrow B)$ computation and single-parameter least-squares fitting of $G_{(aq)}(H^+)$, whose optimized values (kcal/mol) were: −12.27, −266.20, −271.35, −272.28, −266.52, −267.36. The parameter value for the first column (−12.27) represents $G_{(aq)}(H^+)$ plus a large term to shift the relative $\Delta_r G_{(aq)}$ data of Ref. [10] to absolute data.
[b] Values we have optimally converted from relative $\Delta_r G_{(aq)}$ values of Ref. [10] (their Tables 4 and 7, B3LYP/6-311++G** gas-phase plus PCM/B3LYP/3-21G* solvent effects). Their technique is similar to our B3LYP/PCM/Model I/default-scaling. Their particularly good value for NH_3 arises from suspicious anchoring.
[c] "Def. sc." means default radii scaling. "Sp. sc." means special scaling (Section 4.1).
[d] For references see Table 1.
[e] p$K_{a(1)}$.

Table 9
Comparison of theoretical[ab] and experimental pK_a results, including extra piperazines.

Base	One fitting parameter		Two fitting parameters		Expt.[c]
	B3LYP	MP2	B3LYP	MP2	
NH_3	5.61	6.29	6.65	7.10	9.25
$NH_2(CH_3)$	9.65	10.25	10.69	11.05	10.66
$NH(CH_3)_2$	9.64	10.25	10.68	11.05	10.73
$N(CH_3)_3$	8.74	9.27	9.78	10.07	9.80
MEA	8.98	9.15	10.02	9.96	9.50
MIPA	8.18	8.19	9.21	9.00	9.47
MPA	8.70	8.79	9.74	9.59	9.96
AMP	9.47	9.22	10.50	10.03	9.70
AEEA[d]	9.52	9.53	10.56	10.34	9.82
DEA	9.00	8.86	10.04	9.67	8.97
Morpholine	9.13	9.04	7.65	7.89	8.50
Piperazine[d]	11.34	11.10	9.86	9.95	9.73
2-Methylpiperazine[d]	11.01	10.46	9.53	9.31	9.57
1-Ethylpiperazine[d]	10.95	10.60	9.47	9.45	9.20
1-Methylpiperazine[d]	10.40	10.02	8.92	8.87	9.14
1-(2-Hydroxyethyl)piperazine[d]	10.49	10.08	9.01	8.93	9.09
1,4-Dimethylpiperazine[d]	10.65	10.37	9.17	9.21	8.38
Rms error	1.48	1.18	0.81	0.68	

[a] Obtained via $\Delta_h G_{(aq)}(BH^+ \rightarrow B)$ computation and least-squares fitting of $G_{(aq)}(H^+)$, whose optimized values (kcal/mol) were: −267.44 (B3LYP), −268.06 (MP2), −266.04 (acyclic B3LYP), −269.46 (cyclic B3LYP), −266.96 (acyclic MP2), −269.63 (cyclic MP2).
[b] Model II (explicit water) calculations with default radii scaling.
[c] For references see Table 1.
[d] p$K_{a(1)}$.

electrostriction scaling. In our future work, we will investigate whether this observation can lead to a chemically meaningful *ab initio* procedure in which the empirical fitting of $G_{(aq)}(H^+)$ is replaced by properly fixing this quantity at its experimental value.

6. Conclusions

The pK_a values of 17 amines, alkanolamines, and piperazines have been computed using quantum chemistry techniques and the IEFPCM continuum solvation model. Of several techniques tested, the best ones involved incorporation of an explicit water molecule inside the continuum cavity (Model II). The incorporation of 10% smaller cavity radii for charged "united atoms" did not improve the Model II results, but a 3% shrinkage would have provided small improvements. Proper entropy corrections, often neglected in pK_a studies, were presented. The use of explicit water inside the cavities reduced the pK_a rms error (12 cases) by 34%. As noted several years ago [30], ringed compounds do seem to be pathological cases for continuum solvation models, and the use of a second fitting parameter for these compounds dramatically lowered the overall rms error (17 cases) by 42–45%, to below 0.9. Our best technique reduces the errors found in a previous technique for similar compounds [10] by 62%.

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