pK\textsubscript{a} calculation for monoprotonated bipiperidine, bimorpholine and their derivatives in H\textsubscript{2}O and MeCN

Merle Uudsemaa, Tõnis Kanger, Margus Lopp, Toomas Tamm*  
Department of Chemistry, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia

1. Introduction

pK\textsubscript{a} is a fundamental value that characterizes not only the acidity of the compound but often determines its reactivity. Numerous studies aimed at prediction of accurate pK\textsubscript{a} values exist. Density-functional theory (DFT) has been utilized in many of these studies; examples of such research can be found in Refs. [1–3]. The calculation of pK\textsubscript{a} values is more complicated if several tautomers or conformers of the acid and/or base are present in the system simultaneously. However, some computations for systems of this type are known [4–6].

The present work was motivated by the explosive growth in the field of organocatalysis which has taken place during the last decade. One of the main branches of it is aminocatalysis where (di)amines are used as catalysts. Characterization of properties (including pK\textsubscript{a}) of amines is therefore of great interest. Several publications dealing with calculations or experimental measurements of pK\textsubscript{a} of diamines have been published [7].

However, no values of pK\textsubscript{a} are known for the efficient new catalysts, bimorpholines and bipiperidines (used in aldol reaction [8] and Michael addition [9], respectively). In this Letter we report the results of calculation of proton affinity (PA) and pK\textsubscript{a} values for monoprotonated bimorphidine, bimorpholine and their N-isopropyl (iPr) derivatives in water and in acetonitrile, based on density-functional theory simulation of the compounds.

Scheme 1 enumerates the unprotonated forms of all the compounds considered in this work. Compounds 1–4 are the title compounds, pK\textsubscript{a}'s of which are we are seeking to calculate. Compounds 5–7 were used for calibration of the method.

2. Theoretical procedure

The PA and pK\textsubscript{a} values of an amine can be computed from the corresponding gas-phase and solution energetic data. Proton affinity for the reaction B + H\textsuperscript{+} → BH\textsuperscript{+} is defined as the negative of the reaction enthalpy at standard conditions and can be calculated as

\[
PA = -\Delta H = -\Delta E_b - \Delta E_{ZH} + \frac{5}{2}RT
\]  

(1)

where \(\Delta E_b\) is the difference in total energy of BH\textsuperscript{+} and B, and \(\Delta E_{ZH}\) is the corresponding difference in zero point energies.

The calculations of pK\textsubscript{a} for the conjugated cation BH\textsuperscript{+} are based on the thermodynamic cycle shown in Scheme 2 [10]. pK\textsubscript{a} is directly related to the free energy of the deprotonation reaction in solution:

\[
pK_a = \frac{\Delta G_{aq}}{\sum 303RT}
\]  

(2)

where R is the gas constant, T is the temperature, and \(\Delta G_{aq}\) is the free energy of deprotonation of protonated amine in the solution. The standard temperature, 298 K was used in this work.

The equation for calculation of \(\Delta G_{aq}\) values is given by

\[
\Delta G_{aq} = \Delta G_b + \Delta G_{solb}^b + \Delta G_{solh}^h - \Delta G_{solh}^h
\]  

(3)

where \(\Delta G_b\) is the gas-phase free energy, and the \(\Delta G_{solb}^b\) values are the free energies of solvation of the corresponding species.

3. Method

Full DFT geometry optimization in the solution phases (H\textsubscript{2}O, MeCN) with the Becke-Perdew’86 [11,12] (BP86) exchange-correlation functional was performed. The functional was chosen due to its successful use in prior similar calculations [13],
Vibrational analysis was done in the gas phase at BP86/TZVPP level for gas-phase optimized minima for all amines. Lack of imaginary vibrational frequencies was verified. The gas-phase values for thermal corrections were added to the solution-phase electronic energies to get the Gibbs free energy. Use of gas-phase, rather than solution-phase, contributions is justified by the presence of the relevant contributions to the free energy components already in the solvation model. This approach avoids double counting of the corresponding terms which would occur if solution-phase contributions were used.

A conformational search for the compounds 1–4 and their protonated forms in gas phase and acetone has been performed by us earlier [20]. We used these conformations as a starting point for the optimizations in MeCN and H₂O for the purposes of the present work. The full conformational search was not performed for the derivatives (3 and 4) of bipiperidine and bimorpholine. Instead, the lower-energy conformations of the unsubstituted compounds (1 and 2) were used as templates to generate the initial conformations for the derivatives. The full range of conformations was then generated for the isopropyl groups and the lowest-energy conformations were selected for further work.

For the lowest-energy conformer of the compound 12 (Table 3 below), a gas-phase geometry and corresponding thermal corrections could not be obtained, since a spontaneous proton transfer to the other nitrogen (yielding compound 13) occurred during the geometry optimization. We therefore used the thermal correction for the latter also for the 12. Comparison with differences in ZPEs of similar isomer pairs of other conformers leads us to believe that the differences in final results are not larger than 2.5 kJ/mol or 0.5 pKₐ units. The solution-phase calculations did not suffer from this spontaneous proton transfer.

All calculations were performed with the program TurboMole [21,22], version 5.10.

### 4. Calibration of the model

We choses piperidine (5) and morpholine (6) as the reference compounds for calibration due to the similarity of the structures as well as the closeness of PA and pKₐ values with those of bipiperidine (1) and bimorpholine (2). Experimental pKₐ values for piperidine and morpholine are available in H₂O but only the piperidine PA and pKₐ have been measured in MeCN. To verify our approximations, pyrrolidine (7) was included in the test set as well. Relative pKₐ’s were calculated using piperidine as a standard in H₂O and in MeCN.

The value of the solvation free energy of the proton ΔG^H⁺_{solv} in Eq. (3) is difficult to measure or calculate accurately. Several different experimental and calculated values [17,23,24] for solvation free energy of the proton in H₂O and MeCN exist. In order to resolve the ambiguity and remove a potential source of error, we chose to eliminate the solvation free energy of the proton by using the relative basicity (ΔpKₐ) of the two bases B₁ and B₂:

\[
ΔpK_α = pK_α(B_1) - pK_α(B_2)
\]  (4)

First we calculated pKₐ for two bases B₁ and B₂ using Eqs. (2) and (3). In our case B₁ was the reference compound (piperidine) and B₂ was morpholine or pyrrolidine. Then we found the ΔpKₐ of B₁ and B₂ as the difference of the calculated pKₐ values (Eq. (4)). Finally, we calculated pKₐ for acid B₂ using the experimental value of pKₐ for piperidine (pKₐ = 11.22 in H₂O and pKₐ = 19.29 in MeCN) and the calculated value of ΔpKₐ.

The experimental and calculated PA and pKₐ values are presented in Table 2. In water, the absolute pKₐ values for morpholine are calculated to be higher than experimental. The values for pyrrolidine are lower than experimentally measured. The difference

\begin{table}
\centering
\caption{Absolute difference between calculated and experimental PA values (kJ/mol).}
\begin{tabular}{|c|c|c|}
\hline
   & \multicolumn{2}{c|}{p}  \\
   & SV & DZ & TZV & QZV \\
\hline
-  & 11.0 & 11.1 & 7.0 & 18.4  \\
\hline
P &  9.7 &  9.8 & 19.5 &  5.5  \\
\hline
PP & - & - & 6.3 & 5.5  \\
\hline
\end{tabular}
\end{table}
between the calculated and experimental proton affinities for piperidine and pyrrolidine is less than 7.9 kJ/mol. For pK_a calculations the difference is less than 0.6 pK_a units.

Since the proton affinity and pK_a in MeCN for morpholine appears not to be determined experimentally, we predict that these values should be about 920 kJ/mol and 16.8, respectively. The PA value has been rounded down since the method appears to overestimate this value for the compounds where experimental value is known.

5. Results and discussion

Different protonation forms of N-iPr derivatives (3 and 4) of bipiperidine and bimorpholine are possible. A single proton can be transferred according to Scheme 3.

In our previous work [20] we determined the lowest energy conformations for the compounds 1–4 and for the corresponding monoprotonated cations. Five different conformers for each species were found to have relatively close energies.

Due to simultaneous presence of several conformers in the solution, their Boltzmann probabilities need to be taken into account. We followed the procedure described by Jang et al. [4,5] to calculate the ‘global’ pK_a value for the configurations according to:

\[ pK_a = \sum K_{ij} \log f_i \]  

(5)

where pK_a^i and pK_a^j are the calculated pK_a values for protonated configurations i and deprotonated configurations j, and f_i and f_j are the Boltzmann probabilities of the configurations i and j, respectively. This approach is theoretically more correct than using just the lowest-energy conformer in the basicity calculations.

The calculated proton affinities and pK_a’s, using Eqs. (1)−(5) and piperidine (5) as the reference compound in Eq. (5), are presented in Table 3. Due to the account for different Boltzmann probabilities of the conformers via Eq. (5), a single value for this quantity is obtained for each compound in each solvent, even while each pair of protonated and deprotonated conformers has different value for pK_a^j.

For the case of proton affinities, we considered the lowest-energy gas-phase conformer of both the protonated and unprotonated form to calculate the PA. Furthermore, since the energies of the protonated forms 9 and 12 are higher than these protonated at the alternative sites, 10 and 13, respectively, protonation at these sites in the gas phase is unlikely and the corresponding PA values are not reported. This leads to a single PA value for each of the compounds 1–4.

The PA values were analyzed according to the method proposed in Ref. [27] which divides the protonation process into initial-, intermediate- and final-stage components. By performing a calculation of the corresponding molecular cation of the base at the geometry of the neutral molecule, as well as with geometry optimization, the effects of ionization, geometric relaxation, and proton-base bond formation can be discerned. Due to limitations of software, our approach differs from the referred one by not using a frozen orbitals approximation, therefore our vertical ionization energies include an orbital relaxation energy.

The results of the calculations are presented in Table 4. Here IE (vert) is the vertical ionization energy (including orbital relaxation of the molecular radical cation), E_relax is the energy of geometric relaxation of the molecular radical ion B^+, and BAE is the bond association energy between the relaxed cation and a hydrogen atom. The reader is referred to the paper [27] for a detailed description and justification of these terms.

The vertical ionization energies of all four compounds are very similar and do not appear to lead to dissimilarities of the PA’s. The differences are rooted in the various relaxation effects. For the pairs 8–10 and 10–13 it is primarily the relaxation of the molecular cation (intermediate-state effect), while for 8–11 and 11–13, the

![Scheme 3. X = –CH2– N-iPr–(2R,2’R)-2,2’-bipiperidine (3) X = –O– N-iPr–(3R,3’S)-3,3’-bimorpholine (4).](image)
relaxation associated with base-hydrogen bond formation is the leading term.

The transition from proton affinities to pKₐ’s involves the process of solvation. The ΔG_{obs} values for the unprotonated compounds here are −12...−25 kJ/mol for bipiperidine and −32...−44 kJ/mol for bimorpholine. The corresponding values for protonated forms are much more negative due to the charge-solvant interactions, and are −188...−235 kJ/mol and −205...−272 kJ/mol, respectively, across all conformers considered.

A comparison of the ionization and solvation energies reveals a compensation effect. For example, when 8 and 10 are compared, the increase of solvation energies associated with protonation, for the lowest-energy conformers, is 188 kJ/mol for 8 and 165 kJ/mol for 10. The 23 kJ/mol difference of these values is almost exactly canceled by the corresponding drop in proton affinity. As a result, the compounds 8 and 10 have a difference of ΔG_{obs} of only 2 kJ/mol (0.35 pKₐ units), once the influence of other conformers has been included.

Comparison between bimorpholines 11 and 13 leads to similar results, even though the compensation is not exact and the therefore the substituted form has higher pKₐ than the unsubstituted one, opposite from the case of bipiperidines 8 and 10.

The protonated bimorpholines have lower pKₐ values than protonated bipiperidines. Higher polarity of the former makes the ΔG_{obs} more negative (from −12...−25 kJ/mol for 8...10 to −32...−44 kJ/mol for 11...13), but a similar drop occurs for the protonated forms and the influence of the sum of these terms on the ΔG_{obs} is 6...13 kJ/mol. It is of opposite sign with the difference in proton affinities: 30 kJ/mol between 8 and 11, and 24 kJ/mol between 10 and 13. These counteracting influences again lead to numerically very similar differences of the calculated pKₐ’s by 3...4 pKₐ units between the bipiperidines and the corresponding bimorpholines.

Although we have shown that the protonation of the N-isopropyl derivatives 3 and 4 has remarkable influence on their conformations [20], the relative location of the protonation site does not have a significant influence on the calculated pKₐ values. The differences are comparable to the accuracy of the model determined in the calibration (approx. 0.5 pKₐ units according to Table 2), and the basicities can be considered equal within these ramifications.

We conclude that the similarities in pKₐ’s within the triples of bipiperidines and bimorpholines considered here are due to a cancellation of opposite but nearly equal terms rather than due to parallel trends in the corresponding components of free energy. The differences of pKₐ’s between the triples of bipiperidines and bimorpholines can be traced back to the corresponding difference in proton affinities, with the solvation effects playing a minor role.

6. Summary

In this work we have calculated the proton affinities and pKₐ values for useful organocatalysts – bipiperidine (1), bimorpholine (2) and their N-isopropyl derivatives (3 and 4). We have used a model where the solvation free energy of the proton was eliminated using relative basicity of two bases. The equilibrium between different conformers of the compounds in solution was also taken into account. While experimental evidence suggests that the isopropyl substituents have an influence on the reactivity of the compounds, the underlying cause apparently is not the corresponding difference in the pKₐ values. The latter can be considered independent of the presence and location of the substituent within the accuracy of the computational model.

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References