The DFT calculations of pK_a values
of the cationic acids of aniline and pyridine derivatives in common solvents

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Abstract: The theoretical pK_a values of the derivatives of anilinium and pyridinium ions in 7 solvents are presented. For this purpose, the usage of isodesmic reaction scheme using the DFT/B3LYP approach with IEFPCM solvation was evaluated. We have shown that the suitable selection of reference species has the primary influence on the resulting data. For the studied anilinium ion derivatives the nonsubstituted anilinium ion seems to be a satisfactory reference system. The calculated values are in good accordance with the available experimental data with the RMS error of 1.00 and 0.99 pK_a units in water and THF, respectively. The highest error in predicted pK_a value is less than 2.0 pK_a units in all cases. The chemical accuracy of the applied treatment is limited in the case of nitroaniline ions and the maximal therotetical uncertainty for derivatives of the pyridinium ion is within 2.1 pK_a units. Our theoretical results enable us to predict the values of pK_a for the solvents, where the experimental data are not completely available. Also the influence of the chemical structure on the accuracy of the applied method was discussed.

Keywords: pK_a, acid dissociation constant, DFT, B3LYP, IEFPCM, anilinium ion, pyridinium ion

Introduction

Proton transfer represents one of the most important elementary chemical reaction in the nature. Knowledge of acidity or basicity of compound expressed by logarithm of the acid dissociation constant (pK_a) is essential in a wide range of applications and research areas including chemical, food and pharmaceutical industry, biology and medicine (Graña et al. 2005, Murłowska and Sadlej-Sosnowska 2005). In biological systems, proton-transfer reactions are important for communication between the extracellular and intracellular environment (Remko and von der Lieth 2004). The pK_a value is one of the basic parameters determining the bioavailability of drugs since most of them are present in the solution as both the ionized and nonionized species while only the non-ionized species are able to cross the phospholipidic cellular membrane (Namazian and Halvani 2006). Therefore fast and reliable methods for determining the pK_a are of high interest (Shields and Seybold 2013, Schüürmann et al. 1998, Schüürmann 1996). Various experimental methods have been developed over the decades involving mainly the potentiometric titration, spectrophotometry, nuclear magnetic resonance, liquid chromatography, capillary electrophoresis, and several combined methods (Babić et al. 2007). The computational methods have been developed simultaneously providing fast estimation of the pK_a values, however their accuracy is often limited (Haiying et al. 2010). Contrary to the empirical quantitative structure-activity methods

(QSAR) (Shields and Seybold 2013), which rely on large databases, the methods of quantum mechanics (QM) are able to reliably predict the pK_a values using only a few experimental data. While the pK_a values predicted by the semiempirical AM1 method are rather worse than those of the QSAR (Haiying et al. 2010), the DFT and *ab initio* methods provide the pK_a values with reasonable accuracy in an arbitrary solvent (Charif et al. 2007, Namazian et al. 2006, Namazian et al. 2004, Dissanayake and Senthilnithy 2009). Furthermore, QM methods allow a better understanding of the structural and environmental factors that influence pK_a values and are essential for interpretation of experimental values in various systems (Schüürmann 1996). The importance of the theoretical determination of pK_a values has been discussed in a number of recent works (Magill et al. 2004, Schüürmann 1996, Schüürmann et al. 1998, Liptak and Shields 2001, Liptak et al. 2002, Topol et al. 2000, Chipman 2002).

The traditional approach in theoretical pK_a calculations is based on the use of thermodynamic cycles, that combine gas-phase deprotonation free energies (ΔG_{gas}) and the solvation free energies of the involved species (Pliego 2003, Namazian et al. 2004, 2006). The use of such cycles is due to the fact that it is not rigorously correct to obtain the free energy of deprotonation in solution (ΔG_{solv}) by calculating the free energies of the involved species according to the rigid rotor-harmonic approximation in the continuum solvent. In fact, the rigorous calculation would require costly simulation methods in which

the solvent is explicitly considered, together with a free energy calculation procedure (Sastre et al. 2013).

The use of thermodynamic cycles shows problems for those species that are gas-phase unstable or undergoes major conformational changes between gas-phase and solution-phase. However, it is possible to calculate the approximate free energies of deprotonation in solution by using the isodesmic reaction, since gas-phase energies are not required for the pK_a calculation (Eq. 1).

$$AH_{(solv)}^{q} + B_{(solv)}^{m-1} \xrightarrow{\Delta G_{(solv)}} A_{(solv)}^{q-1} + BH_{(solv)}^{m} \quad (1)$$

Additionally, this equation, also known as relative pK_a calculation or proton exchange reaction, benefits from the absence of the proton free energy of solvation, which is a potential source of error in the calculated free energies (Ho et al. 2010). The pK_a of the acid AH can be calculated from Eqs. 2—4 and the experimental pK_a value of the reference species BH.

$$\Delta G_{\text{solv}} = G_{\text{solv}}\left(BH^{m}\right) + G_{\text{solv}}\left(A^{q-1}\right) - \\ - G_{\text{solv}}\left(AH^{q}\right) - G_{\text{solv}}\left(B^{m-1}\right) \quad (2)$$

$$G_{\text{solv}} = E_{\text{solv}} + G_{\text{ssi}} + \Delta G_{\text{corr}} \quad (3)$$

$$pK_a\left(AH^{q}\right) = \frac{\Delta G_{\text{solv}}}{2,303RT} + pK_a\left(BH^{m}\right) \quad (4)$$

The exact free energies in solution cannot be calculated, since partition function of the involved species in solution is unknown. However, Casasnovas et al. (Casasnovas et al. 2011) have proposed to calculate approximate free energies in solution under the assumption that gas-phase vibrational partition functions of the solutes is an approximation for the solution-phase. Secondly, the values of rotational and translational contributions to the free energies corresponding to conjugate acid and base are of same magnitude, so according to Eg. 2, they mostly cancel out. According to Eg. 3, the approximate free energies of each species in solution (G_{solv}) are calculated as the sum of the potential energy of the solute (E_{solv}) which includes the electric response of the continuum solvent, all the non-electrostatic contributions to the solute–solvent interaction (namely dispersion, repulsion and cavitation energies) which are all included in the term G_{ssi}, and the contribution to the free energies from the vibrational motion of the nuclei at 298 K (ΔG_{corr}). So far the isodesmic reaction has mainly been used for calculation of the enthalpies of formation (Wang et al. 2008) but, concerning pK_a calculations, it has been less used than the thermodynamic cycles. Li

et al. (Li et al. 1997) reported that relative instead of absolute pK_a values are predicted with higher precision when combining ab initio methods and continuum solvent models for the study of methylimidazoles in aqueous solution. A recent combined experimental and theoretical study performed by Derbel et al. (Derbel et al. 2012) also shows that remarkably low errors are obtained when using the isodesmic reaction for diprotic species. Govender and Cukrowski (Govender and Cukrowski 2009, 2010) have employed this scheme, together with PCM solvent model and UA0 cavities for the calculation of the successive dissociation constants of nitrilopropanoic and nitrilotriacetic acids, obtaining errors of 0.2—3 pK_a units. The results obtained for substituted pyridines by Casasnovas et al. (Casasnovas et al. 2011) were equivalent to results obtained from thermodynamic cycle, but no explicit water molecules were needed to increase the accuracy. Although the errors of the calculated pK_a values are actually causing a change of one or two orders of magnitude of the K_a values, the results can be considered satisfactory. It should be noted that the error of 5.7 kJ mol⁻¹ of determination of Gibbs free energy at standard temperature means one order of magnitude of the K_a value.

The derivatives of aniline and pyridine are important substances in wide-range of applications from chemical and pharmaceutical industry to medicine, chemical and biological sciences and knowledge of the pK_a values of their conjugate acids is essential for their further utilization.

Therefore the theoretical calculations of these molecules have the own relevance and they enable us to understand their basic chemical processes and reactivity.

The main objective in this work is to evaluate the robustness of the isodesmic reaction in the calculation of pK_a values of substituted anilinium and pyridinium ions in various organic solvents and to examine the precision of the DFT/B3LYP with the integral equation formalism variant of polarizable continuum model (IEFPCM) (Chipman 2000).

Computational details

All calculations were performed using Gaussian 03 program package (Frisch et al. 2003). The geometry of both the neutral molecule and cationic acid was optimized in the gas phase using density functional theory (DFT) method with B3LYP (Becke's three parameter Lee-Yang-Parr) (Becke 1988, Lee et al. 1988, Frisch et al. 2003) functional without any constraints (energy cut-off of 10⁻⁵ kJ mol⁻¹, final RMS energy gradient under 0.01 kJ mol⁻¹ Å⁻¹). B3LYP functional represent widely applied approach for

the theoretical study of the reaction energetics. For mono-substituted phenols, thiophenols and anilines, it has been found that B3LYP functional provided the energetics of both the homolytic and heterolytic bond cleavage in very good accordance with available experimental and/or theoretical results (Klein et al. 2006, Klein and Lukeš 2006a, 2006b, 2006c, Rimarčík et al. 2011, Vagánek et al. 2011, 2013, Najafi et al. 2012). The pK_a values of carboxylic acids calculated using the same functional are also in acceptable accordance with experiment (Charif et al. 2007, Namazian et al. 2004, Dissanayake and Senthilnithy 2009, Sastre et al. 2013). Calculations were performed in the 6-311++G** (Krishnan et al. 1980, McLean and Chandler 1980, Curtiss et al. 1995) basis set. The optimized structures of anilines, pyridines and their conjugate acids, without fixing any internal coordinates, were confirmed to be real minima by vibrational analysis (no imaginary frequency). The sum of the potential energy of the solute in solvent was calculated for the gas-phase optimal geometry using the IEFPCM (Chipman 2000). The cavities were built up using radii from the universal force field (UFF) with explicit hydrogen spheres. The solute-solvent boundary was defined by the Van der Waals surface. Gibbs free energies of all structures were calculated for 298.15 K. Applying an isodesmic reaction for the pK_a calculation requires an experimental value of similar molecule in the same solvent (Sastre et al. 2013). In our work, we have choosen anilinium and pyridinium ions as a reference species for their derivatives.

Results and discussion

The calculated values of pK_a compared with experimental values (Garrido et al. 2008) are summarized in Table 1. For the most of the studied substituted anilinium ions, the deviations are within 1 pK_a unit. Unfortunatelly, the highest error of the calculated pK_a value is of 11.50 pK_a units for 2,4-dinitroanilinium ion in tetrahydrofuran (THF) and 4.89 pK_a units in water. However, errors higher than 2 pK_a units were observed for all nitroanilinium ions in almost all studied solvents, while a limited accuracy is achieved for 3-nitroanilinium ion. Moreover, only a minor improvement in accuracy can be observed when using own reference species for nitroanilinium ions. With 4-nitroanilinium ion applied as the reference species, the highest absolute deviation in water is as high as 2.41 pK_a units for 2,4-dinitroanilinium ion, however in THF this error has unacceptable value of 7.61 pK_a units. In nitromethane, the calculated pK_a of 3-nitroanilinium ion in respect of reference 4-nitroanilinium ion differs by 5.16 pK_a units from experimental value, thus the nitroanilinium ions

pose a problematic set of acids, when trying to predict their pK_a in various solvents using the isodesmic reaction. The calculated pK_a values of the remaining species are within the 2 pK_a units from the experimental values in every solvent, therefore the anilinium ion can be used as the reference for calculation of pK_a values of derivatives of the anilinium ion except the nitroanilinium ions which were excluded from the evaluation of method in our work. The high deviations of the calculated pK_a of 2-nitroanilinium ions are possibly caused by the structure of the reaction site, which differs remarkably from that of anilinium ion. According to DFT calculations, the proton of 2-nitroanilinium and 2,4-dinitroanilinium ion is bound between the nitrogen atom of —NH$_2$ functional group and oxygen atom of —NO$_2$ functional group. Comparing with 4-nitroanilinium ion, the N—H in 2,4-dinitroanilinium ion is elongated by 0.036 Å towards the oxygen atom of —NO$_2$ functional group. Other major difference between the anilinium ion and nitroanilinium ions is the strong π-electron withdrawing nature of the NO$_2$ group leading to the push–pull character of the H$_2$N—phenylene—NO$_2$ system. The defect in the cavity of the PCM model around the reaction site could also contribute significantly to the deviations. Furthermore, some structural changes or other effects of the solvent, which cannot be caught by the used methods, are possible. Unfortunately, the exact proportion of each contribution on the total deviation is not known, however we expect the defective cavity to be the main source of the deviation. For these reasons the reference species have to be chosen carefully.

Consequently, the applied scheme can be considered reliable for pK_a calculations of derivatives of the anilinium ion in any of studied solvent with root mean square (RMS) error 1.00 in water and 0.99 in THF with the highest absolute deviation of 1.91 and 1.94 respectively, all RMS errors are given in pK_a units. RMS error in other solvents are lower, however due to lack of some of the experimental values, it cannot be compared with calculations of water and THF solutions in this work.

The accuracy of results obtained for pyridinium ions in water are similar to those presented in the work of Sastre et al. (Sastre et al. 2013), however the mean absolute deviation (MAD) in our work is 1.01 pK_a units in water and 1.50 pK_a units in THF comparing to their value 0.75 pK_a units. While in their work the same functional and basis set were used, they have applied conductor-like polarizable continuum model (CPCM) with the UAKS (Frisch et al. 2003) cavities instead. Furthermore a slightly different set of molecules was studied, which comprise the main contribution to pK_a value difference. From the nature
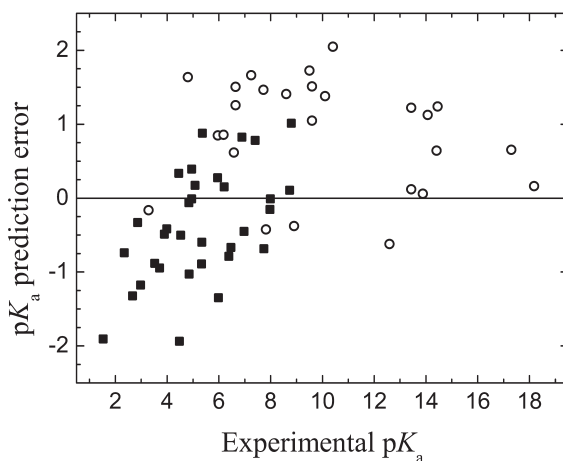
Tab. 1. Experimental and calculated pK_a values of the cationic acids of aniline and pyridine derivatives.

	Acetone		Acetonitrile		DMSO		Methanol		Nitromethane		THF		Water	
	Exp	Calc	Exp	Calc	Exp	Calc	Exp	Calc	Exp	Calc	Exp	Calc	Exp	Calc
Anilinium	**5.92**[a]		**10.56**[a]		**3.60**[a]		**6.05**[a]		**9.07**[a]		**7.97**[a]		**4.60**[a]	
2,4-dinitroanilinium		–8.25		–3.40		–10.31		–7.95		–4.88	4.61[a]	–6.89	–4.33[a]	–9.22
2,5-dichloroanilinium		0.78		5.52		–1.42		0.98		4.03	4.47[a]	2.53	1.53[a]	–0.38
2-chloroanilinium		2.62		7.28		0.32	3.71[a]	2.76	6.46[a]	5.79	5.98[a]	4.63	2.66[a]	1.34
2-methylanilinium		6.10		10.74		3.78	5.95[a]	6.23		9.25	7.40[a]	8.18	4.45[a]	4.79
2-nitroanilinium	3.77[a]	–2.79	4.85[a]	1.88		–5.09	0.20[a]	–2.65		0.38	5.12[a]	–0.79	–0.25[a]	–4.08
3,4-dichloroanilinium		2.87		7.65		0.73		3.12		6.17	5.33[a]	4.44	2.97[a]	1.79
3-chloroanilinium	4.85[a]	3.82		8.54	2.34[b]	1.60	4.52[a]	4.02	7.74[a]	7.06	6.38[a]	5.59	3.52[a]	2.64
3-nitroanilinium	3.97[a]	2.07	7.60[a]	6.92		0.01		2.38	6.62[a]	5.44	5.81[a]	3.37	2.46[a]	1.10
4-bromoanilinium		4.58		9.31		2.37	4.84[a]	4.78	7.97[a]	7.82	6.20[a]	6.35	3.89[a]	3.40
4-chloroanilinium	5.34[a]	4.74		9.47	2.86[b]	2.53	4.95[a]	4.94	7.99[a]	7.98	6.97[a]	6.52	3.98[a]	3.56
4-methoxyanilinium		7.61		12.22	5.08[b]	5.25	6.89[a]	7.71		10.73	8.80[a]	9.81	5.36[a]	6.24
4-nitroanilinium	3.52[a]	–0.45		4.37		–2.54	1.55[a]	–0.17	5.18[a]	2.89	4.82[a]	0.93	1.02[a]	–1.46
4-tertbutylanilinium		6.71		11.32		4.35		6.81		9.83	8.73[a]	8.84	4.95[a]	5.34
Pyridinium	**5.77**[a]		**12.33**[a]		**3.40**[a]		**5.44**[a]		**11.95**[a]		**8.25**[a]		**5.23**[a]	
2,4,6-trimethylpyridinium		9.60		16.09		7.12	7.72[a]	9.19	14.45[a]	15.69	10.40[a]	12.45	7.25[a]	8.91
2,6-dimethylpyridinium	8.90[a]	8.52	14.41[a]	15.05		6.09	6.64[a]	8.14	13.43[a]	14.65	9.50[a]	11.23	6.64[a]	7.90
2-methoxypyridinium		3.73		10.26		1.31		3.35		9.87	4.80[a]	6.44	3.28[a]	3.12
2-methylpyridinium	7.82[a]	7.40	13.88[a]	13.94		4.99	6.18[a]	7.04	13.43[a]	13.55	8.60[a]	10.01	5.96[a]	6.81
4-dimethylaminopyridinium	12.59[a]	11.97	18.18[a]	18.34		9.36	10.10[a]	11.48	17.30[a]	17.95	14.07[a]	15.20	9.60[a]	11.11
4-methoxypyridinium		7.87		14.35		5.39		7.48		13.97	9.60[a]	10.65	6.58[a]	7.19

[a](Garrido et al. 2008).
[b](Cox 2013).

of the isodesmic reaction and the approximations applied while using solvation models, it should be expected, that the electronic and structure properties of the reacting species have to be similar to acquire reliable results. While the errors for nitroanilinium ions were significant and hard to expect, the highest absolute deviation of calculated values for pyridine ions is only 2.05 pK_a units for 2,4,6-trimethylpyridinium ion in THF, however the RMS errors are higher for pyridines in both the solvents, where experimental data for all the studied species are available, namely 1.14 in water and 1.54 in THF. Since continuum solvent models do not reproduce the solvent structure around the solute, it is not possible to model the steric effects on the solvation of the amino group caused by its substituents (Sastre et al. 2013). Thus the structural difference of 2,4,6-trimethylpyridine and its conjugate acid could be considered as the source of the highest absolute deviation, since the nitrogen lone electron pair is sterically hindered. However, the chemical structure should not be the only criterion when choosing the reference molecule, since the cancellation of errors due to similarities in the solute–continuum interactions is not always trivial (Sastre et al. 2013).

Remaining derivatives of the pyridinium ion are structurally more similar to pyridinium ion, therefore their pK_a values are estimated more accurately. Nevertheless, as shown on the Fig. 1, the pK_a values

Fig. 1. The dependence of the error of the calculated pK_a values on the experimental pK_a values of cationic acids of aniline derivatives (solid squares) and pyridine derivatives (open circles). Nitroanilines are excluded.

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predicted by this method for both the anilinium and pyridinium ions are in plausible agreement overall and are similar to data obtained using the thermodynamic cycles (Casasnovas et al. 2009). It can be seen, that the deviations of anilinium ions' pK_a predictions are well distributed around zero, however the deviations for pyridinium ions are mostly positive. This fact could have risen from the choice of the reference species. While the reference species for anilinium-like compounds is roughly the middle in respect to the pK_a values of the studied anilinium ions, the pK_a value of reference species of pyridinium-like compounds is almost the lowest. Unfortunately, due to the lack of the experimental data for the studied species dissolved in acetone, acetonitrile, dimethylsulfoxide (DMSO), methanol and nitromethane, we were not able to evaluate the isodesmic reaction scheme in these solvents. We highly expect, that the proposed data can serve as accurate estimation of unknown pK_a values, since the calculated data are in good agreement with available experimental values except the nitroanilines. The measurement of unknown values and further validation of the isodesmic reaction scheme in these solvents and on the larger set of compounds is the object of our future studies.

Conclusion

In this work, the pK_a values of anilinium and pyridinium ions in various solvents have been calculated through the isodesmic reaction scheme using the DFT/B3LYP approach with IEFPCM solvation. We have shown, that in most cases, the calculated values are in good accordance with the available experimental data. However, it should be kept in mind that the application of the isodesmic reaction scheme is very sensitive to the selection of reference experimental pK_a value. As revealed in our work, the choice of reference species is not trivial and wrong choice can lead to almost meaningless data. Namely the anilinium ion acts very well as reference species for many derivatives of the anilinium ion including alkylanilinium ions and halogenated anilinium ions, however the errors of the calculated pK_a values of nitroanilinium ions are exceptionally high. Moreover, only a minor improvement in accuracy is observed, if some of the nitroanilinium ions is picked as their own reference molecule. On the other hand, the pyridinium ion poses a satisfactory reference species for the calculation of pK_a values of derivatives of the pyridinium ion studied in this work and the used method can be considered reliable for this type of chemical compounds. The influence of the molecular properties on the accuracy of the

applied method was discussed. Last but not least, our results represent a plausible estimation of unknown pK_a values of derivatives of the anilinium and pyridinium ions in acetone, acetonitrile, DMSO, methanol and nitromethane. These data are useful in many fields of chemical applications including organic synthesis and drug development.

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