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Original Scientific Article

Simple Method for the Estimation of pK_a of Amines[†]

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Abstract. A simple and efficient model for the estimation of alkylamine basicities (through corresponding pK_a values) is developed. Model uses partial atomic charges of hydrogen and of neighboring nitrogen calculated by MNDO-PM6 semiempirical model, taking into account the order of the substitution on nitrogen.

Keywords: amine pK_a constants, partial atomic charges, MNDO-PM6 calculations

INTRODUCTION

Amines are a versatile and very frequently studied class of organic compounds. Their presence in biological tissues and importance in all aspects of biochemistry and natural product chemistry make them highly frequent subjects of physical- and (bio)chemical studies.

In a review[1] (2007), was stated: „Computational pK_a prediction tools are not yet sufficiently sophisticated to be of general practical value in the pharmaceutical industry, but this situation is expected to change in the future, as more experimental data become available, and continued efforts are spent to refine existing tools.“ On the other hand, a short time before the publication of that review, a comprehensive work[2] was published (in 2006) with very good prediction of amine pK_a. The method is rather computationally demanding, because for every amine it is needed to calculate at least two (up to four) optimized structures, using medium-sized basis set and DFT corrections.

The inspection of literature reveals that various other approaches were employed.

Frequently, only a specific class of amines was considered. One method is based on the study of hydrogen bonding of amine[3] as HBA (hydrogen bond acceptor) of 57 six-membered nitrogen heterocycles. They used a quite simple semiempirical QM method, selected 17 molecular descriptors, and finally used 4 of them for QSAR. Some of the proposed geometrical descriptors were not easy to derive.

On small sets of structurally similar amines the estimation of pK_a values was frequently done by the calculation of the free energy of proton exchange. Interesting are the DFT studies with emphasis on the simulation of solvent.[4–6] All these methods involve sophisticated computational method and the variations of Gibbs energy calculation schemes.

A comprehensive calculation of pK_a values was made on the basis of difference between the energies of free base and its protonated form. Calculations were done on OLYP/ 6-311G**//3-21G(d) with the conductor-like screening solvation model - water as solvent.[7] Method appears to be reliable and reasonably accurate. It was demonstrated that explicit inclusion of (several) water molecules in the calculation, may markedly improve the quality of calculation.[8]

Use of isodesmic approach for the calculation of pK_a values shoved a marked accuracy in study of organic superbases.[9] A similar scheme is used for description of the interaction of protein(s) and ligands.[10,11]

A marked improvement was done by introduction of more sophisticated scheme based on trichotomy paradigm, *i.e.* with recognition of the importance of the initial-, intermediate-, and final-state effects.[12,13] Along this line, the factors affecting the basicity of imines, conjugated imines, and pK_a values of proteins, were studied using high-level *ab initio* method(s).[14,15] These reviews were extended by inclusion of aromatic amines, too.[16] All described methods involved demanding *ab initio* calculations

A similar calculation was done on MP2/6-31G(d) level of theory, including the effect of solvent.[17] Method needs two empirical corrections and was outperformed with computer-free group-additivity-based scheme by Perrin, Dempsey, and Serjeant (PDS)[18] with updated parameters.

[†] Dedicated to Dr. Mirjana Eckert-Maksić on the occasion of her 70th birthday.

Molecular electrostatic potential (MEP) was recognized as an interesting molecular descriptor for the estimation of pK_a, and was tested on the set of 44 amines in tree classes, using now too unreliable semiempirical method (CNDO/2).[19] Apparently excellent result was obtained exploiting MEPs and NBO analysis.[20] The closer inspection of presented results reveals several flaws in the last paper. Among numerous declared amines (154) there are many repeated compounds under different names. The selection involves a moderate number of aliphatic amines, and majority of them are tertiary. It casts the shadow on the statement about the generality of the methodological approach. On the other hand the method comprises very demanding multi-step calculation: DFT optimization of structure, calculation of molecular electrostatic potential, and natural bonding analysis.

On the set of 36 anilines was shown that Hammett constants perform better than natural atomic charges in prediction of pK_a values.[21]

A rudimentary effort to use calculated partial atomic charges was done by Leite.[22] Study was done on 11 primary aromatic amines using AM1 semiempirical method. The work is of small value because of small set of amines and because of known problem of AM1 Hamiltonian for nitrogen.[23] On this line a study was done,[24] on various definitions of atomic charges as the descriptors for pK_a evaluation. Study was done on the set of 19 anilines and corresponding anilinium ions, using seven standard definitions of partial atomic charges, calculated from B3LYP/6-311G(d,p) wave functions.

This kind of methodological approach we have successfully already applied for the calculation of pK_a of carboxylic acids.[25–28] Basic idea was to take into consideration partial charges on all atoms in proton-releasing group. For study of pK_a values of amines we have calculated the charge distribution in corresponding protonated ammonium ions.

Chemical experience supports the judgment that the acidity of compound is a property localized on particular group inside the aliphatic non-conjugated molecule. The localized quantities that are relevant to the acidity of the given non-hydrogen acidic atom should be of either electrostatic or quantum nature, or both. In this work, we use a simple quantum-chemical descriptor to effectively estimate molecular pK_a values of balanced selection of primary, secondary, and tertiary (cyclo) alkylamines.

COMPUTATIONAL DETAILS

A total of 57 aliphatic amines (16 primary, 16 secondary, and 25 tertiary) in their protonated (ammonium) states were calculated as cations, using semiempirical PM6 Hamiltonian implemented in MOPAC2007 program package.[29] The effect of solvent was taken into account using COSMO model implemented in MOPAC. The water is simulated using the keyword ESP = 78.4.

For all flexible molecules a systematic conformational search was done (involving tautomers), and most stable conformers were selected as representative of particular ammonium ion. The Coulson's atomic charges of the optimized structures were used for statistical analysis.

RESULTS AND DISCUSSION

In the protonated amine (ammonium ion), the attached proton can be considered as a bearer of acidity defined by equation:

$$R_1R_2R_3NH^+ + :OH_2 \rightleftharpoons R_1R_2R_3N: + OH_3^+$$
$$K_a = \frac{[R_1R_2R_3N:]\cdot[OH_3^+]}{[R_1R_2R_3NH^+]\cdot[:OH_2]} \quad (1)$$

The pK_a values (–log K_a) of amines are extensively studied, and long ago was found that electronic factors are not a single feature which must be accounted for. A lot of effect could be assigned to steric hindrance, specific (conformation-dependent) electronic effects as rehybridization, hyperconjugation, *etc*. We have estimation that these additional influences mostly depend on the complexity of molecular structure, and there is clear distinction between primary, secondary, and tertiary amines. In our model, this additional effect is accounted through an index variable which is set equal to number of hydrogen atoms bound to nitrogen in ammonium ion. In Table 1 is given the list of compounds subjected to QM calculations and statistical analysis. We obtained the experimental pK_a values from the literature.[12,30–37]

Previous efforts[13] showed that the charge of 'acidic' hydrogen poorly correlates with pK_a values. It was the same in this work. Figure 1 shows the correlation of q_H with experimental pK_a.

The correlation with partial atomic charge on nitrogen, as presented on Figure 2, is slightly better but still is not good enough.

Therefore, we decided to include in correlation the charge on vicinal nitrogen atom (q_N) along with the partial atomic charge on hydrogen (q_H):

$$pK_{a(calc)} = A'q_H + B'q_N + C'I + D \quad (2)$$

Here, I is the index variable to distinguish between primary, secondary and tertiary amines. We didn't deeply analyze this variable, but it is clear that it must account for differences in steric hindrance, solvation, and other effectors for acidity of ammonium ions. For this

Table 1. Experimental pK_a values, atomic partial charges calculated by MNDO-PM6 semiempirical MO method, assigned index variable, and calculated pK_a values by Equation 2

		PM6/COSMO				
Amine	pK_a	q_H	q_N	I	p*K*a(calc)	Δp*K*a
Ethylamine	10.98	0.277	-0.043	3	10.5	–0.4
n-propylamine	10.53	0.278	-0.037	3	10.4	–0.1
Isopropylamine	10.63	0.279	-0.105	3	11.0	0.4
n-butylamine	10.59	0.278	-0.038	3	10.3	–0.3
Isobutylamine	10.15	0.278	-0.028	3	10.1	–0.1
sec-butylamine	10.56	0.279	-0.102	3	10.9	0.3
t-butylamine	10.68	0.280	-0.157	3	11.4	0.7
Neo-pentylamine	10.21	0.278	-0.020	3	10.1	–0.1
Methoxyamine	5.59	0.290	0.153	3	6.4	0.8
Ethanolamine	9.5	0.284	-0.019	3	9.2	–0.3
Allylamine	9.49	0.281	-0.028	3	9.8	0.3
Benzylamine	9.34	0.281	-0.025	3	9.7	0.4
Cyclohexylamine	10.49	0.280	-0.099	3	10.7	0.2
Hydrazine	8.1	0.283	0.083	3	8.1	0.0
Ethylenediamine	9.98	0.282	-0.031	3	9.7	–0.3
Hydroxylamine	5.97	0.284	0.198	3	6.7	0.7
N-Methylhydroxylamine	5.96	0.288	0.286	2	6.3	0.3
Diethylamine	10.98	0.285	-0.024	2	10.4	–0.4
Di-*n*-propylamine	11	0.285	-0.011	2	10.2	–0.8
Diisopropylamine	11.05	0.288	-0.135	2	11.3	0.2
Di-*n*-butylamine	11.25	0.286	-0.009	2	10.2	–1.0
Diisobutylamine	10.5	0.277	0.009	2	11.2	0.7
Di-sec-butylamine	11.01	0.290	-0.132	2	11.0	–0.0
Pyrrolidine	11.27	0.285	0.0085	2	10.1	–1.2
Piperidine	11.22	0.285	0.009	2	10.0	–1.2
Morpholine	8.36	0.295	0.040	2	8.3	–0.1
Diallylamine	9.29	0.291	0.004	2	9.2	–0.1
Allylmethylamine	10.11	0.285	0.057	2	9.5	–0.6
Benzylmethylamine	9.58	0.281	0.061	2	9.9	0.4
Benzylethylamine	9.68	0.286	-0.008	2	10.0	0.3
Cyclohexylmethylamine	10.49	0.287	-0.011	2	9.9	0.4
N-carbethoxypiperazine	8.28	0.297	0.030	2	8.0	–0.3
Dimethyl-*n*-propylamine	9.99	0.286	0.162	1	9.3	–0.7
Triethylamine	10.65	0.285	0.031	1	11.1	0.4
Tri-*n*-propylamine	10.65	0.280	0.051	1	11.5	0.9
Benzyldimethylamine	8.93	0.284	0.176	1	9.5	0.4
Dimethylethylamine	9.99	0.288	0.153	1	9.1	–0.9
Methyldiethylamine	10.29	0.288	0.091	1	9.9	–0.4
Dimethyl-isopropylamine	10.3	0.286	0.097	1	10.0	–0.3
Dimethyl-*n*-butylamine	10.02	0.286	0.163	1	9.3	–0.7
Dimethyl-isobutylamine	9.91	0.283	0.168	1	9.6	–0.3
Dimethyl-sec-butylamine	10.4	0.287	0.101	1	9.9	–0.5
Dimethyl-t-butylamine	10.52	0.286	0.051	1	10.6	0.1
Tri-*n*-butylamine	10.89	0.280	0.053	1	11.4	0.5
Allyldimethylamine	8.72	0.288	0.168	1	9.0	0.3
Diallylmethylamine	8.79	0.287	0.122	1	9.6	0.8
Benzyldiethylamine	9.48	0.288	0.047	1	10.5	1.0
triethanolamine	7.77	0.297	0.099	1	8.6	0.8
N,N-dimethylmethoxyamine	3.65	0.311	0.353	1	3.5	–0.1
N,N-dimethylhydroxylamine	5.2	0.298	0.391	1	4.9	–0.3
N-Methylpyrrolidine	10.46	0.290	0.117	1	9.3	–1.2
N-methylmorpholine	7.41	0.294	0.145	1	8.4	1.0
N-ethylmorpholine	7.7	0.298	0.077	1	8.6	0.9
N-Allylmorpholine	7.05	0.299	0.191	1	7.2	0.1
N-methylpiperidine	10.08	0.288	0.118	1	9.5	–0.6
N-ethylpiperidine	10.4	0.286	0.055	1	10.6	0.2
N-Allylpiperidine	9.68	0.287	0.070	1	10.3	0.6

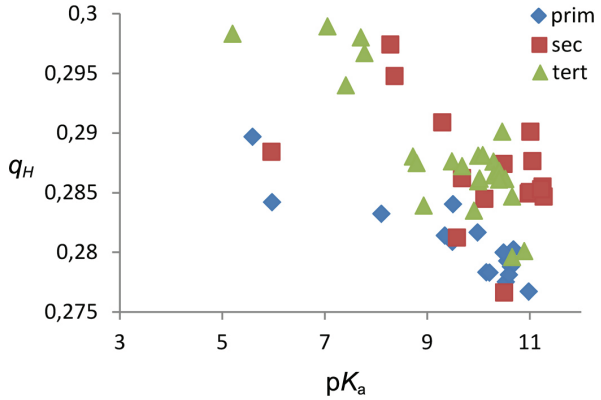

Figure 1. Correlation of partial atomic charges on amonium hydrogen of 57 aliphatic amines, with experimental pK_a values.

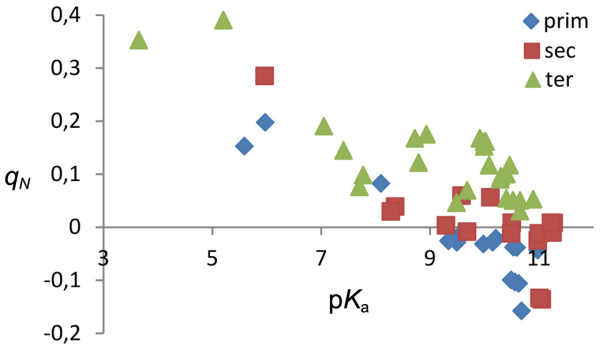

Figure 2. Correlation of partial atomic charges on amonium nitrogen of 57 aliphatic amines, with experimental pK_a values.

purpose it is set to have integer values. Polylinear regression of data in Table 1 gives the following statistics:

$$A = -140.878;\ B = -11.775;\ C = -1.250;\ D = 52.773$$
$$n = 57;\quad r = 0.937;\quad sd = 0.604;\quad F = 126.306$$

The correlation between pK_a and p$K_{a(calc)}$ is presented on Figure 3

This simple model works equally accurate as various other very sophisticated approaches (mentioned in Introduction), and can be valuable aid in estimation of pK_a values of aliphatic amines. In Figure 3 is obvious that the scattering of data is minimal for primary amines. A likely reason for it is that among secondary and tertiary amines the cyclic amines (with N atom in the ring) are included, which can have markedly reduced steric hindrance. We didn't checked quinuclidine, because its peculiar structure (bridgehead tricyclic amine) will set it as outlier. We have ammonia from the start in our list, too, and found it to be an outlier. After short consideration, we understood that there is no point of keeping it on the list because of known bias in the MNDO methods regarding electronegativity of carbon. (For example, in these semiempirical methods carbon is

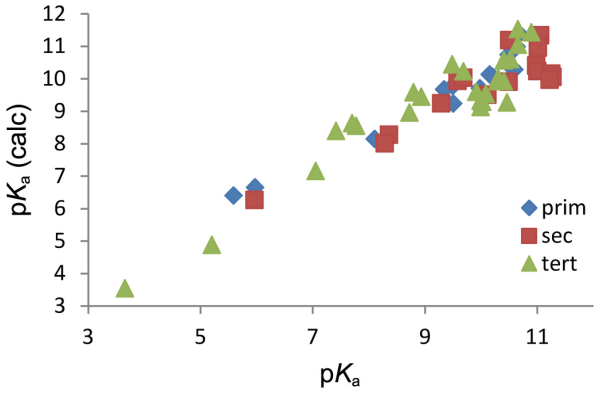

Figure 3. Correlation of experimental and calculated (Equation 2) pK_a values for 57 aliphatic amines. Standard deviaton of estimate is 0.593.

more electronegative than chlorine.) So, organic amines can't be computationally treated by applied method together with ammonia which lacks carbon substituent on nitrogen.

The additional research on constant I can enable the inclusion of other amines into the statistics. At this stage we can state that partial atomic charges, derived from semiempirical calculations, can be guidance for the estimation of pK_a values of organic bases.

CONCLUSION

A simple and efficient model for the estimation of alkylamine basicities (through corresponding pK_a values) is developed. Model uses partial atomic charges of hydrogen and neighboring nitrogen calculated by MNDO-PM6 semiempirical model, taking account of the order of the substitution on nitrogen.

It is demonstrated that statistically weighted partial atomic charges of two atoms involved in proton dissociation can very well predict extent of such dissociation.

An index variable is introduced, and the model can be made more precise and more general with further elaboration of the (now) integer index variable.

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