Basicity of Some Organic Superbases in Acetonitrile
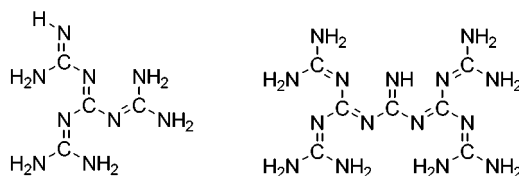
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ABSTRACT

It is shown that the pK_a values of strong neutral organic (super)bases in acetonitrile are well described by the density functional theory (DFT) employing the isodensity polarization continuum model (IPCM) for treating solvent–solute interactions. High pK_a values are predicted for two model compounds, and their synthesis is strongly recommended.

Considerable research efforts have been dedicated to the elucidation of the proton affinity (PA) and the related basicity (B) of organic molecules from both experimental[1] and theoretical standpoints.[2−4] Particular emphasis has been placed upon strong neutral organic bases and proton sponges.[5,6] The latter, compared to ionic bases, have distinct advantages in that they require milder reaction conditions and possess better solubility at the same time.[7] Consequently, the neutral bases have found a wider range of applications in organic synthesis as pivotal ingredients.[8] The most powerful organic neutral bases prepared as yet are Schwesinger proton sponges.[9,10] Recently, our research has been focused on the design of strong organic superbases, which span PAs between 250 and 300 kcal/mol in the gas phase.[11] For this purpose we developed a particular strategy consisting of several steps: (1) identification of the intrinsically strong basic functional groups, (2) selection of suitable molecular fragments serving as carriers of the functional group of choice, (3) use of the substituent effect by placing promising substituents on strategic positions, and (4) implementation of some additional structural groupings giving rise to special effects such as intramolecular hydrogen bonding, which stabilizes the conjugate acid more than the initial base. Examination of several functional groups has led to the conclusion that the imino moiety exhibits the largest inherent basicity. Suitable fragments serving as imino group carriers are provided by ring fragments such as 2,5-dihydro-pyrrolimine, cyclopropeneimine, and quinoneimine. An appropriate backbone is also given by the polyguanides, which

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(1) For reviews of the experimental data see: (a) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695. (b) Harrison A. G. *Chemical Ionization Mass Spectrometry*; CRC Press: Boca Raton, 1989. (c) Hunter, E. P.; Lias, S. G. *J. Phys. Chem. Ref. Data* **1998**, *27*, 413.

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exhibit a very strong resonance effect triggered by the protonation.[11] Substantially enhanced basicities are obtained by the aromatic tandem (two adjacent cyclic subunits in a row) or domino (several sequential cyclic fragments) effects induced by a π-electron density reorganization in the conjugate acid upon proton attack.[11] Substituents such as NH_2 and OCH_3 proved particularly useful in view of the pronounced n$-\pi$ resonance interaction in cationic conjugate bases, provided they are attached at proper sites on the molecular backbone. It also turned out that (poly)alkylation increases the electron density relaxation effect after protonation by providing additional reservoirs of the electron charge, thus increasing the basicity of the parent compound. Finally, amplification of the basicity can be achieved by the intramolecular hydrogen bond corona effect.[11]

All of these features of potentially strong organic neutral (super)bases are well established by sound theoretical models and lead to very high proton affinities, which in turn are good measures of the intrinsic basicity in the gas phase. However, the bulk of chemistry takes place in solutions, and consequently the influence of the solvent cannot be escaped. It is the aim of this paper to examine theoretically pK_a values of some available (super)bases in acetonitrile in order to make predictions regarding the basicity of some proposed systems (yet to be synthesized) in this particular solvent. The examined molecules are depicted in Figures 1 and 2. For
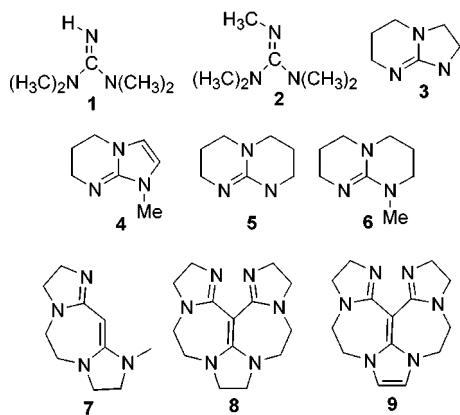

Figure 1. Schematic representation of gauge molecules enabling a correlation between theoretical PA(actn) and experimental pK_a values.

the inclusion of solvent effect we shall make use of the intuitively simple model in which the solvent is described by a polarized continuum.[12] Essentially, the physical picture is that of a homogeneous solvent characterized by a given dielectric constant, which surrounds a solute molecule embedded in a cavity, as put forward by Onsager[13] as early as 1936. The molecular electrostatic potential describing the interaction between such a solvent and a molecule of a solute
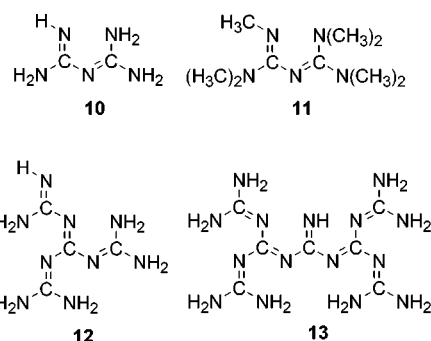
Figure 2. Highly basic polyguanides.

was developed by Miertuš et al.[14] Specifically, the charge distribution of the solute polarizes the infinite dielectric solvent and produces virtual charges on the cavity surface. The latter interact with the initial charge distribution of a molecule and enter the Hamiltonian of a solute as electrostatic perturbation.

Obviously, the solution of the quantum mechanical problem is to be found by an iterative procedure. In determining the cavity we follow the suggestion of Wiberg et al.,[15] who defined it by isodensity surface (shell) encompassing the solute molecule, possessing a charge of 0.0004 e/B^3. The latter was selected because it gave good agreement with the observed molar volumes. This approach is termed as the isodensity polarized continuum model (IPCM).[15] It involves two calculations for each studied organic base: one for the neutral molecule and the other for its conjugate acid in solution. Having said that, it should be mentioned that the ZPVE is taken over from HF/6-31G* calculation of free molecules. The difference in the total energies gives the proton affinity (PA) in acetonitrile simulated by the permittivity constant $\epsilon = 36.64$. The theoretical method of choice was the economical B3LYP/6-311+G**//HF/6-31G*, which takes into account the electron correlation energy. The latter is important for a quantitative description of molecular properties solvated in solvents.[15,16] In addition, it is important to note that the correlation energy affects the proton affinity in the gas phase to an appreciable extent also, particularly in planar molecules.[17] Two important points should be stressed here. Unlike some other authors[18,19] we use the proton affinity as a measure of basicity instead of the free energy, because of the following reasons: (a) Occam's razor

(12) For authoritative reviews on the subject see: Tomasi, J.; Perisco, M. *Chem. Rev.* **1994**, *94*, 2027. Orozco, M.; Luque, F. *J. Chem. Rev.* **2000**, *100*, 4187.

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Table 1. Total Molecular Energies at the B3LYP/6-311+G**//HF/6-31G* Level (in shorthand B3LYP) in Gas Phase (g) and Acetonitrile (actn)[a]

molecule	B3LYP(g)	ZPVE[b]	B3LYP(actn)	PA(actn)	pK_a(exp)	pK_a(theor)
NH$_3$	−56.58219	20.6	−56.58702			
NH$_4^+$	−56.91979	29.7	−57.04055	275.5	16.5	16.7
CH$_3$CH$_2$NH$_2$	−135.22077	55.7	−135.22412			
CH$_3$CH$_2$NH$_3^+$	−135.58112	64.6	−135.68058	277.5	18.4	17.7
aniline	−287.68649	70.1	−287.69230			
anilineH$^+$	−288.03323	78.9	−288.12676	263.8	10.6	10.9
1	−362.69768	113.5	−362.70319			
1H$^+$	−363.10533	121.4	−363.17725	289.6	23.3	23.7
2	−402.00527	129.7	−402.00919			
2H$^+$	−402.42065	138.7	−402.48869	291.1	25.0	24.4
3	−383.57171	112.9	−383.57812			
3H$^+$	−383.98253	121.5	−384.05330	289.6	23.79	23.7
4	−437.71683	108.4	−437.72356			
4H$^+$	−438.13095	116.9	−438.20061	290.8	24.55	24.3
5	−438.94041	124.1	−438.94696			
5H$^+$	−439.35949	132.2	−439.42946	294.7	25.96	26.2
6	−478.25547	140.8	−478.26021			
6H$^+$	−478.67604	149.2	−478.74173	293.7	25.43	25.7
7	−609.83175	158.2	−609.84297			
7H$^+$	−610.26744	166.4	−610.32836	296.4	26.95	27.1
8	−874.20057	208.2	−874.21820			
8H$^+$	−874.65365	217.1	−874.71377	302.1	29.2	29.8
9	−872.98536	194.0	−873.00447			
9H$^+$	−873.44399	203.0	−873.50531	305.2	31.94	31.4
10	−354.31962	69.9	−354.33185			
10H$^+$	−354.71946	77.1	−354.80235	288.0		22.9
11	−629.48793	187.2	−629.49187			
11H$^+$	−629.92232	196.0	−629.98204	298.8		28.1
12	−652.04154	117.5	−652.06562			
12H$^+$	−652.48307	123.7	−652.56164	305.1		31.3
13	−1098.62741	188.9	−1098.66856			
13H+	−1099.10191	195.3	−1099.17205	309.5		33.5

[a] The total molecular energies are given in au; the proton affinity in acetonitrile and ZPVEs are given in kcal/mol. [b] ZPV energies are calculated at the HF level for free molecules being subsequently scaled by 0.89 (in kcal/mol).[22]

criterion should be employed whenever possible, and (b) the polarized infinite continuum model of solvent is so crude that other refinements are not appropriate. Moreover, the PA values of amino nitrogens are considerably smaller, implying that their statistical contribution to the experimental pK_a data is negligible.[11] Our approach is justified a posteriori by a good accordance with experiment. To establish a relationship between PA(actn) and pK_a we examined NH$_3$, CH$_3$CH$_2$NH$_2$, aniline, and systems **1−9** depicted in Figure 1 as gauge molecules. Results of present calculations are given in Table 1, together with available experimental pK_a data taken from the work of Kolthoff et al.[20] and Schwesinger.[21] The proton affinities in acetonitrile PA(actn) are correlated with the experimental data, yielding the linear relationship

$$pK_a(\text{theor}) = 0.4953\,PA(\text{actn}) - 119.7 \qquad (1)$$

with the regression coefficient $R = 0.997$ and average

(20) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1967**, *90*, 23.

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absolute error as low as 0.4, which reflect high correlativity of theoretical results with observed pK_a values. It is of interest to compare the gas-phase results free of solvent "contamination" with those in acetonitrile, since this kind of information will shed some light on an interplay of various interactions contributing to the solvent effect. We defer a more detailed discussion to a later paper, but it is plausible to conclude that the proton affinity in a solvent will be determined by the intrinsic basicity of the functional group and a difference in solvation energies $E(BH^+)_{\text{solv}}$ and $E(BH)_{\text{solv}}$ of conjugate acid and initial base, respectively, defined as positive entities in order to be compatible with a definition of the PA itself. Perusal of results (Table 1) shows that $E(B)_{\text{solv}}$ energies are rather small because bases are neutral. In contrast, conjugate acids are positively charged, exhibiting high solvation stabilizations. Interestingly, the smaller the conjugate acid, the higher the $E(BH^+)_{\text{solv}}$ values. This is in harmony with a picture of a distribution of the positive charge over the entire molecule due to the relaxation effect. Consequently, in larger cationic systems the peripheral atoms (hydrogens) have a

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smaller fraction of the positive charge, thus polarizing the solvent to a lesser extent. Illuminating examples are given by NH_3 and $EtNH_2$, where $E(BH^+)_{solv}$ assumes values 75.8 and 62.4 kcal/mol, respectively. It is noteworthy that the protonated NH_3 has the largest $E(BH^+)_{solv}$ energy of all systems examined here. Another point of interest is the solvation energy of bases, $E(BH)_{solv}$, which for NH_3 and $EtNH_2$ is 3.0 and 2.1 kcal/mol, respectively. Therefore, the large difference in the intrinsic (gas-phase) PA between $EtNH_2$ and NH_3, 14.5 kcal/mol, is diminished by 13.4 kcal/mol as a result of a difference in solvation energies of the corresponding conjugate acids. A small positive contribution is provided by a difference between $E(BH)_{solv}$ of these two molecules (0.9 kcal/mol), yielding as a final value PA-$(EtNH_2)_{solv} - PA(NH_3)_{solv} = 2$ kcal/mol. The corresponding increase in pK_a is 1.0. Previously, we provided conclusive evidence that the resonance effect in conjugate acids is of utmost importance in determining the basicity of extended π-systems.[11] This is evident in going from **3** to **4**, where in the latter molecule the protonation triggers aromatization of the five-membered ring (Scheme 1), whereby an aromatic

Scheme 1
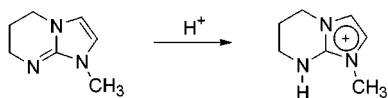
sextet is formed. The pK_a of **4** is higher by 0.6 kcal/mol. Comparison of pK_a values of **5** and **6** indicates that substitution of a CH_3 group on the nonionized nitrogen diminishes pK_a by 0.5.

Taking this into account, one concludes that the aromatization in **4** yields an increase of 1.1 in pK_a value. As the π-system is enlarged in **7**, **8**, and **9**, the PA(actn) assumes larger and larger values approaching finally a very high 305 kcal/mol. It is important to realize that inclusion of an additional double bond in the distal five-membered ring in **9** implies its aromatization upon the protonation as in **4** (Scheme 1).

Recently we suggested syntheses of a number of polyguanides that could serve as potent superbases.[11] Some of them are depicted in Figure 2. Interestingly, permethylation of biguanide **10** enhances the PA(actn) of **11** by a substantial 10.8 kcal/mol, yielding an increase in pK_a by 5.2 units. More important is perhaps the finding that heptaguanide **13** should be considerably more basic than Schwesinger superbases **8** and **9** exhibiting the PA(actn) of 309.5 kcal/mol with the corresponding pK_a value of 33.5. Both **12** and **13** support our earlier conjecture that bifurcation of guanide subunits close to the protonated center in polyguanides is of utmost importance in determining a strong basicity.[11] Consequently, preparation of polyguanides **12** and **13** is highly recommended indeed. We are confident that the relation in eq 1 will be useful in estimating pK_a values of other highly basic systems involving the imine functional group in acetonitrile.