Basicity of organic bases and superbases in acetonitrile by the polarized continuum model and DFT calculations†

Zoran Glasovac,*[a] Mirjana Eckert-Maksić[a] and Zvonimir B. Maksić[ab]

Received (in Montpellier, France) 26th August 2008, Accepted 17th October 2008
First published as an Advance Article on the web 11th December 2008
DOI: 10.1039/b814812k

The basicities of a large number of organic bases and superbases, including nitrogen basic centers in various chemical environments occurring in phosphazenes, amidines, amines, anilines and pyridines, have been studied in acetonitrile by the isodensity polarized continuum model employing two DFT computational schemes differing in the basis sets for final single-point calculations. It turned out that the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) method serves the purpose giving good agreement for basicities with experiment for both gas phase and acetonitrile solutions treating widely different bonding situations of basic nitrogen atoms on an equal footing. An attempt is made to correlate the experimental pK_a(MeCN) values with the proton affinities (*PA*) in MeCN. The results are less accurate than those achieved by using basicities in acetonitrile. In particular, the *PA*(MeCN)s frequently failed in reproducing the pK_a(MeCN) values in systems possessing multiple intramolecular hydrogen (IMH) bonds formed *via* corona effects. In such cases the use of basicities is mandatory instead. A useful corollary of these calculations on systems with multiple IMH bonds is that comparison of the theoretical and experimental pK_a values can provide an insight into the structure of the most stable conformations in solutions.

Introduction

Neutral organic bases and superbases are useful auxiliary ingredients in organic syntheses, because they require mild reaction conditions and exhibit better solubility at higher temperatures than their inorganic counterparts.[1–3] They provide very efficient catalysts, if immobilized on appropriate surfaces, thus being a suitable approach in green chemistry.[4,5] Recent advances in computational chemistry enabled a wide use of modern many-electron quantum chemical methods in tackling chemical problems, making them reliable partners of experimental research in general. In particular, they are indispensable tools in acid–base chemistry.[6,7] For instance, the gas phase calculations of intrinsic proton affinities and basicities is straightforward and inexpensive by using density functional theory (DFT) methods nowadays.[8–14] The latter represent a very useful alternative to more accurate, but at the same time more intricate and expensive, *ab initio* methods,[15–18] which are sometimes not feasible in large systems of great interest. However, a transition from the isolated molecule in the gas phase to liquid solutions is not trivial, if the solvents are highly polar molecules. It is, therefore, gratifying that in aprotic solvents of low or medium polarity a simple model of the dielectric polarized continuum[19,20] works very well for families of closely related bases. The continuum solvation models have been authoritatively discussed *in extenso* by Tomasi *et al.*[21,22] and by Orozco and Luque.[23] Further, it was convincingly demonstrated by Wiberg and others[24,25] that the isodensity polarized continuum model (IPCM) gives computed pK_a(MeCN) values in very good accordance with the available measured data for guanidines, polyguanides and related polycyclic compounds.[26] Theoretical estimates of the pK_a(MeCN) values were obtained by correlating proton affinities (PAs) computed in acetonitrile with the experimental pK_a(MeCN), which has subsequently led to their linear dependence with the regression coefficient R = 0.997 and the mean absolute error (MAE) of only 0.4 units. In the present work we address the question whether the IPCM model is applicable in very large numbers of nitrogen bases exhibiting a wide variety of structural and bonding motifs and different hybridization states of the nitrogen atom to be protonated. Moreover, we shall examine whether it is sufficient to consider PA(MeCN)s alone in obtaining estimates of the pK_a values, or should the computational model involve basicity in acetonitrile expressed by the Gibbs free energy, as might be intuitively expected. These questions are relevant, since acetonitrile is one of the important and frequently used solvents in organic synthesis due to its moderate polarity, low basicity and chemical inertness.

---

[a] *Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, P.O.B. 180, HR-10 002 Zagreb, Croatia. E-mail: glasovac@emma.irb.hr. E-mail: mmaksic@emma.irb.hr; Fax: +385-1-4680-195; Tel: +385-1-4561-008*
[b] *Faculty of Science, University of Zagreb, Horvatovac 102a, HR-10000 Zagreb, Croatia. E-mail: zmaksic@spider.irb.hr; Fax: +385-1-4561-117; Tel: +385-1-4680-235*

† Electronic supplementary information (ESI) available: Correlation between experimental pK_a values and $\Delta G_{a,sol}$ or $\Delta H_{a,sol}$ for the reference set of nitrogen bases (excluding pyridines in the case of $\Delta G_{a,sol}$). Solvation energies using different grid parameters w(ϕ) and w(θ) calculated for the reference bases are also given. See DOI: 10.1039/b814812k

Methodology

The standard free energy change of the reaction in the gas phase (g), which describes deprotonation of the conjugate acid, is given by:

$$(B_\alpha H^+)_{(g)} \rightarrow B_{(g)} + H_{(g)}^+ \qquad (1)$$

The change in Gibbs free energy $\Delta G_{gas}(BH)^+$ is the intrinsic basicity of the base B. The standard enthalpy change $\Delta H_{gas}(BH)^+$ of this reaction is the proton affinity $PA_{(g)}$. It is given at room temperature by formula (2):

$$\Delta H_{gas}(B_\alpha H)^+ = PA_g(B_\alpha) = (\Delta E_{el})_\alpha + (\Delta E_{vib})_\alpha + \tfrac{5}{2}RT \qquad (2)$$

where

$$(\Delta E_{el})_\alpha = E_{el}(B) - E_{el}(B_\alpha H)^+ \qquad (3)$$

and

$$(\Delta E_{vib})_\alpha = E_{vib}(B) - E_{vib}(B_\alpha H)^+ \qquad (4)$$

Here α denotes the site of protonation, *i.e.* the most basic nitrogen atom. Further, $(\Delta E_{el})_\alpha$ is the electronic contribution to proton affinity, whereas E_{vib} includes the zero point vibrational energy (ZPVE) and enthalpy corrections including temperature change to 298.2 K. The change in $\Delta G(BH)^+$ is given by $\Delta H_{gas}(BH)^+ - T\Delta S(BH^+)$, where $\Delta S(BH^+)$ stands for the change in entropy.

It is useful to make a connection between the protonation processes in solution with those in the gas phase. This is achieved by a standard thermodynamical cycle[27] depicted in Scheme 1, where "*" refers to the Gibbs energy of deprotonation of the conjugate acid $(B_\alpha H)^+$ taken at standard conditions of 1 mol dm^{-3} and subscript "a" signifies deprotonation of the conjugate acid.[28,29] It follows that $\Delta G^*_{a,sol}(B_\alpha H)^+$ can be expressed as:

$$\begin{aligned}\Delta G^*_{a,sol}(B_\alpha H)^+ = {} & G^\circ_{gas}(B) + \Delta G^*_{sol}(B) - G^\circ_{gas}(B_\alpha H)^+ \\ & - \Delta G^*_{sol}(B_\alpha H)^+ + G^\circ_{gas}(H^+) \\ & + \Delta G^*_{sol}(H^+) + RT\ln(24.46) \qquad (5)\end{aligned}$$

The pK_a is defined by:

$$pK_a = \frac{\Delta G^*_{a,sol}(B_\alpha H)^+}{2.303 \times RT} \qquad (6)$$

Since the Gibbs energy of the proton in a solvent $[G^o_{gas}(H^+) + \Delta G^*_{sol}(H^+)]$ and $RT\ln(24.46)$ at the particular temperature T are constants, their sum will be signified as $C' = [G^o_{gas}(H^+) + \Delta G^*_{sol}(H^+) + RT\ln(24.46)]$, where $\Delta G^*_{sol}(H^+) = \Delta G_{sol}(H^+) + RT\ln(24.46)$ represents the Gibbs free energy of solvation of the proton in acetonitrile assuming the standard state of 1 mol dm^{-3}, while $G_{gas}(H^+)$ is Gibbs free energy of the proton in the gas phase, which is −6.28 kcal mol^{-1}.[30] Thus, the pK_a value can be given in the form:

$$pK_a = \frac{1}{2.303RT} \times [\Delta G'_{a,sol}(B_\alpha H^+) + C'] \qquad (7)$$

where $\Delta G'_{a,sol}(B_\alpha H)^+ = G^o_{gas}(B) + \Delta G^*_{sol}(B) - G^o_{gas}(B_\alpha H)^+ - \Delta G^*_{sol}(B_\alpha H)^+$ is reduced basicity, which gives pK_a values up to a common additive constant. It is useful in determining and discussing basicities relative to a selected standard base. It turns out that pK_a is a linear function of the $\Delta G'_{a,sol}$ (7). In the ideal case, the slope of the linear function (7) is 0.733. However, Klamt and coworkers pointed out that all polarized continuum solvent models inherently contain systematic errors, which result in lower proportionality constants in pK_a calculations and the actual slope varies with respect to the applied computational method and the studied family of compounds.[31] This is also the case in the present calculations (*vide infra*).

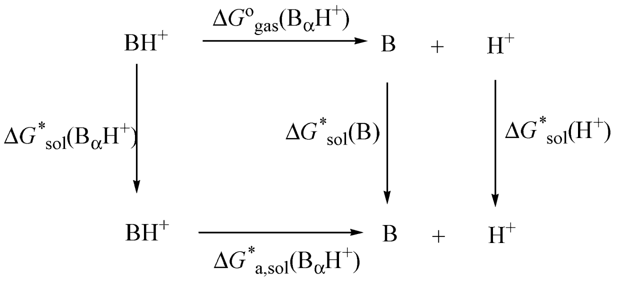
If it is tacitly assumed that the change in entropy is constant or very close to zero ($\Delta S_a(BH^+) = [\Delta S(B) + \Delta S(H^+) - \Delta S(BH^+)] \cong 0$) sp that its variations could be neglected in a series of examined acids or bases and that it could be neglected, then a similar equation holds for the proton affinities:

$$pK_a = \frac{1}{2.303RT} \times \Delta H'_{a,sol}(B_\alpha H)^+ + C'' \qquad (8)$$

where $\Delta H'_{a,sol}(B_\alpha H^+) = \Delta H^o_{a,gas}(B_\alpha H^+) + \Delta G^*_{sol}(B) - \Delta G^*_{sol}(B_\alpha H^+)$ and C'' includes additionally an entropy term: $C'' = [H_{gas}(H^+) + \Delta H_{sol}(H^+) + RT\ln(24.46) - \Delta S_a(BH^+)]$.

We shall employ the B3LYP method despite some criticism of its use in treating hydrogen bonds. The reason is that we found the B3LYP methodology quite satisfactory in describing ionic intramolecular hydrogen bonds formed upon protonation of nitrogen bases. All structures are optimized in the gas phase at the B3LYP/6-31G(d) level and the equilibrium geometries are tested by the vibrational criterion (NImag = 0). The single point calculations were performed by using 6-311+G(d,p) and 6-311+G(2df,p) basis sets for isolated molecules. The corresponding computational procedures are denoted B3LYP(S) and B3LYP(L), where S and L correspond to smaller and larger basis sets, respectively. The temperature corrections to the total energies are obtained according to standard formulae employed in the Gaussian03 suite of programs.[32] The ZPVE values are computed by using the B3LYP/6-31G(d) scheme without any scaling. The solvation energies were computed at the IPCM/B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) model, where the surface of a cavity is determined by the prescribed constant electron density on the solute–solvent interface of each molecule. It is implicitly assumed in the PCM models that the equilibrium geometries are taken from the gas phase. The isodensity parameter of the molecular cavities in solution embracing solute molecule was 0.0004 e a_0^{-3}.

Convergence problems were overcome by parametrical variation of w(φ) and w(θ) parameters, which represent angular integration weights over the corresponding polar coordinates.[25] The full convergence was achieved by using



Scheme 1

100 and 20 points for w(φ) and w(θ), respectively. The dielectric constant of acetonitrile used was 36.64. The calculations were carried out by Gaussian03.

Results and discussion

Basicity in the gas phase

The explored compounds, which encompass a large variety of organic nitrogen bases differing in their structures and bonding features, are depicted in Fig. 1. Let us denote for the sake of brevity $\Delta G^{o}_{gas}(B_{\alpha}H)^{+}$ and $\Delta H_{gas}(B_{\alpha}H)^{+}$ as GB_g and PA_g, respectively. A subscript "sol" will be analogously used in solutions. The calculated PA_g values are compared with available measured data[33] in Fig. 2.

Inspection of Fig. 2(a) and (b) reveals a good accordance with experiment as evidenced by the mean average error (MAEs) being 1.2 and 1.4 kcal mol^{-1} for B3LYP(S) and B3LYP(L) methods, respectively. It should be pointed out that the experimental accuracy is on average about the same magnitude. Interestingly, the smaller basis set S (S ≡ 6-311+G(d,p)) performs slightly better than L (L ≡ 6-311+G(2df,p)), which is also reflected in the larger proportionality constant, being closer to 1, and the smaller free additive constant. The latter should be zero in the ideal case, whereas the exact slope should be 1.0. This is at first sight surprising. However, all DFT methods employ *ad hoc* functionals and because of that they do not belong to *ab initio* theoretical approaches. A great deal of their success is a result of cancellation of errors. Consequently, it is sometimes possible that smaller basis sets are better suited for retaining a fine balance between different terms than the more intricate basis sets. A thorough study of the correlation energy within the B3LYP method[34] is particularly relevant in this respect and the interested reader is encouraged to study this important point, which is pivotal for all DFT methods. A similar outcome is found for the basicities GB_g presented in Fig. 3. Accordance with experiment is even more satisfactory than for the proton affinities as evidenced by higher proportionality constants and lower free additive terms of 1.6 and 4.0 kcal mol^{-1} for the B3LYP(S) and B3LYP(L) methods, correspondingly. The performance of the efficient B3LYP(S) scheme is remarkable indeed, which is gratifying, because it is applicable in large systems in an economical way. One can safely conclude that both methods withstood a critical test of good accuracy and reliability *in vacuo*.

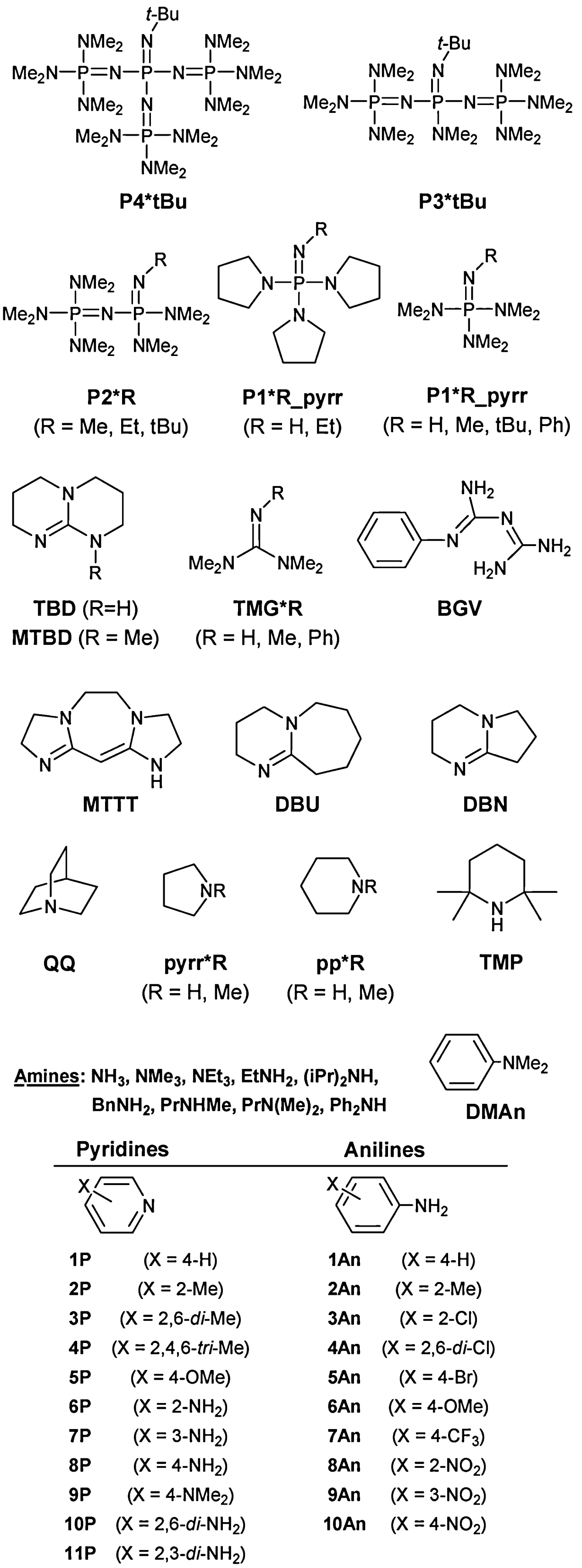


Fig. 1 Schematic representation of the structures of the investigated nitrogen bases.

Basicities in acetonitrile

We shall focus next on the basicity in MeCN. It should be reiterated that the solvation energies were computed by the IPCM/B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) model, whereas the gas phase energies were obtained either by the B3LYP(S) or B3LYP(L) methods. The former procedure treats the gas phase and solutions on an equal footing. The solvation energies were calculated by a grid of points on the cavity surface. Several combinations of the w(ϕ) and w(θ) parameters were examined, which define a grid (Table S1 in ESI†). Satisfactory results considering the convergence and quality of results were obtained by employing grid points defined by parameters w(ϕ) = 100 and w(θ) = 20, which

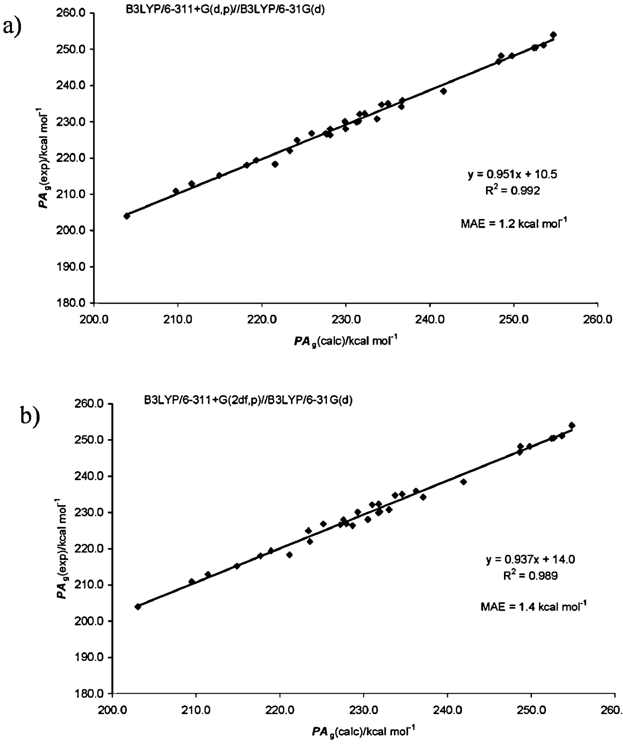


Fig. 2 Comparison between theoretical (PA_g(calc)) and experimental proton affinities (PA_g(exp)) for the tested set of nitrogen bases.

ensure consistency and convergence of the calculations. Correlation between the experimental pK_a(MeCN) and $\Delta G'_{a,sol}(B_\alpha H)^+$ according to formula (7) are shown in Fig. 4.

It turns out that the B3LYP(S) scheme offers a slightly better correlation than the B3LYP(L) according to the correlativity parameters. The results of the former approach (*viz*. Fig. 4a) exhibit deviations from the experiment about 1 pK_a unit on average. This is a very good accordance in view of inherent errors in measurements and calculations. The factor of proportionality is by 25% lower than the ideal 0.733 in formula (7).

It is interesting to examine errors of the regression equations (Table 1). Inspection shows that the calculated pK_as are systematically too high in pyridines by roughly 2 pK_a units, which could be taken as the offset value. For pyridines alone, the B3LYP(S) model resulted in the correlation given in eqn (9) with $R^2 = 0.929$, MAE = 1.9. The largest discrepancy is found in 2,6-diaminopyridine, which is 2.6 units.

$$pK_a(\text{exp})_{\text{pyr}} = 0.588 \times \Delta G'_{a,sol}(B_\alpha H)^+ - 147.3 \qquad (9)$$

Obviously, the family of substituted pyridines is distinctly different from all other molecules due to the fact that the proton attacks the nitrogen atom, which is a member of the aromatic ring. However, by diminishing all pK_a values by 2 kcal mol^{-1}, realistic estimates are obtained in pyridines too. In substituted anilines, on the other hand, the protonation occurs exclusively at the amino group and the calculated pK_as are lower by 1 kcal mol^{-1} than the measured data, which is probably a consequence of the regression analysis, since pyridines have a significant influence on the slope of the straight line. Again, this value could be used as an offset correction. This conjecture is tested by excluding the family of pyridines from the least squares procedure (Fig. S1, ESI†).

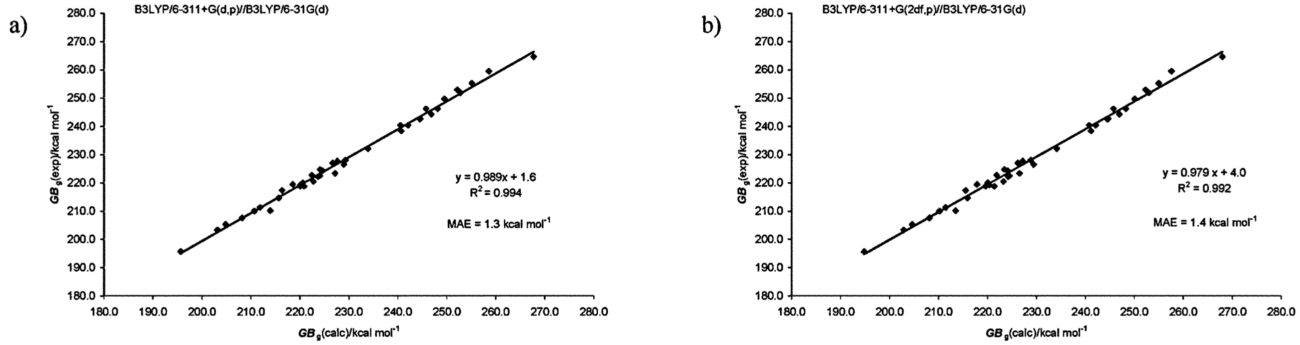


Fig. 3 Comparison between theoretical (GB_g(calc)) and experimental gas-phase basicities (GB_g(exp)) for the examined nitrogen bases.

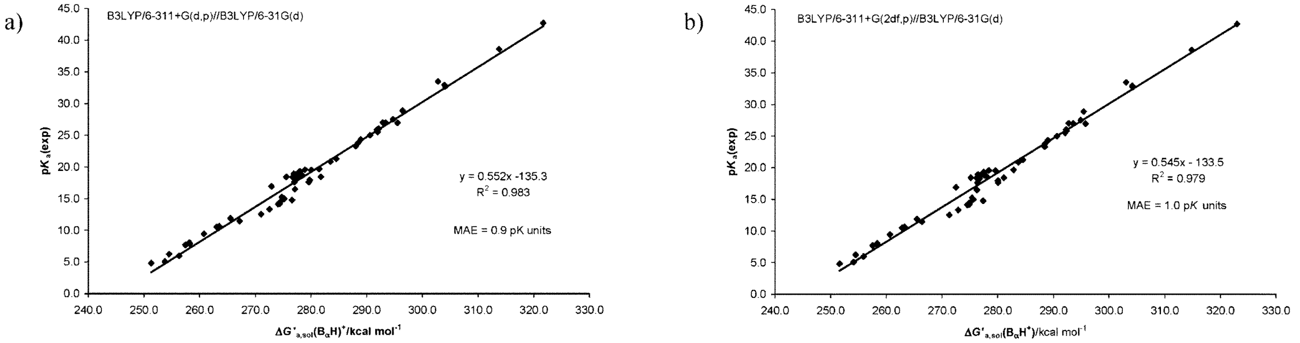


Fig. 4 Correlation between pK_a(exp) and $\Delta G'_{a,sol}(B_\alpha H^+)$ estimated by (a) B3LYP(S) and (b) B3LYP(L) methods.

Table 1 Calculated data for the pK_a estimation for the given set of the bases[a]

Base	$\Delta G^{o}_{gas}(B_{\alpha}H^{+})$/ kcal mol^{-1}	$\Delta(\Delta G^{*}_{sol}(B_{\alpha}H^{+}))$/ kcal mol^{-1}	$\Delta G'_{a,sol}(B_{\alpha}H^{+})$/ kcal mol^{-1}	pK_a(exp)	pK_a(calc)	Δ (pK_a)
P4*tBu	291.1	−24.3	321.7	42.7	42.2	−0.5
P4*tBu	[292.4]	−24.3	[323.0]	42.7	[42.6]	[−0.1]
P3*tBu	281.5	−26.0	313.8	38.6	37.9	−0.7
P3*tBu	[282.6]	−26.0	[314.9]	38.6	[38.2]	[−0.4]
P2*tBu	266.7	−29.8	302.8	33.5	31.8	−1.7
P2*tBu	[267.0]	−29.8	[303.1]	33.5	[31.8]	[−1.7]
P2*Et	267.7	−30.0	304.0	32.9	32.4	−0.5
P2*Et	[268.0]	−30.0	[304.2]	32.9	[32.4]	[−0.6]
P2*Me	268.2	−29.7	304.1	32.7	32.5	−0.2
P2*Me	[268.3]	−29.7	[304.3]	32.7	[32.4]	[−0.3]
P1*Ph	245.8	−32.5	284.5	21.3	21.7	0.5
P1*Ph	[245.8]	−32.5	[284.5]	21.3	[21.7]	[0.4]
P1*tBu	252.2	−35.0	293.4	27.0	26.6	−0.4
P1*tBu	[252.3]	−35.0	[293.5]	27.0	[26.6]	[−0.4]
P1*Et_pyr	258.6	−31.6	296.5	28.9	28.3	−0.6
P1*Et_pyr	[257.6]	−31.6	[295.5]	28.9	[27.6]	[−1.3]
P1*H_pyr	255.1	−31.5	292.9	27.0	26.3	−0.7
P1*H_pyr	[255.0]	−31.5	[292.7]	27.0	[26.1]	[−0.9]
P1*Me	252.8	−35.6	294.7	27.5	27.3	−0.2
P1*Me	[253.0]	−35.6	[294.9]	27.5	[27.3]	[−0.2]
P1*H	249.5	−36.0	291.8	25.9	25.7	−0.1
P1*H	[250.1]	−36.0	[292.4]	25.9	[25.9]	[0.1]
MTTT	258.2	−31.1	295.6	27.0	27.8	0.9
MTTT	[258.4]	−31.1	[295.8]	27.0	[27.8]	[0.9]
MTBD	248.1	−37.6	292.0	25.5	25.8	0.3
MTBD	[248.3]	−37.6	[292.1]	25.5	[25.8]	[0.3]
TBD	246.8	−39.1	292.2	26.0	25.9	−0.1
TBD	[246.9]	−39.1	[292.3]	26.0	[25.9]	[−0.1]
DBU	244.6	−38.1	288.9	24.3	24.1	−0.2
DBU	[244.6]	−38.1	[289.0]	24.3	[24.1]	[−0.2]
DBN	242.1	−40.1	288.5	23.8	23.9	0.1
DBN	[242.1]	−40.1	[288.5]	23.8	[23.8]	[0.0]
TMG	240.7	−41.0	288.0	23.3	23.6	0.3
TMG	[241.1]	−41.0	[288.4]	23.3	[23.8]	[0.5]
TMG*Me	244.5	−39.8	290.6	25.0	25.1	0.1
TMG*Me	[244.6]	−39.8	[290.7]	25.0	[25.0]	[0.0]
TMG*Ph	240.6	−36.7	283.5	20.8	21.1	0.3
TMG*Ph	[240.8]	−36.7	[283.7]	20.8	[21.2]	[0.4]
BGV	237.2	−38.0	281.5	19.7	20.0	0.4
BGV	[238.6]	−38.0	[282.9]	19.7	[20.8]	[1.1]
QQ	227.6	−46.1	280.0	19.5	19.2	−0.3
QQ	[227.2]	−46.1	[279.6]	19.5	[19.0]	[−0.5]
TMP	229.3	−42.9	278.5	18.6	18.4	−0.3
TMP	[228.8]	−42.9	[278.0]	18.6	[18.1]	[−0.5]
DMAn	216.3	−44.6	267.2	11.4	12.1	0.7
DMAn	[215.6]	−44.6	[266.4]	11.4	[11.8]	[0.4]
pp*H	220.1	−52.5	278.9	19.6	18.6	−1.0
pp*H	[219.6]	−52.5	[278.4]	19.6	[18.3]	[−1.2]
pp*Me	224.1	−47.0	277.4	18.3	17.8	−0.5
pp*Me	[223.5]	−47.0	[276.7]	18.3	[17.4]	[−0.8]
pyrr*H	220.1	−52.5	278.9	19.6	18.6	−1.0
pyrr*H	[219.6]	−52.5	[278.4]	19.6	[18.3]	[−1.2]
pyrr*Me	227.2	−48.3	281.8	18.4	20.2	1.8
pyrr*Me	[226.5]	−48.3	[281.1]	18.4	[19.8]	[1.4]
Me_3N	218.5	−52.2	277.0	17.6	17.6	0.0
Me_3N	[217.8]	−52.2	[276.3]	17.6	[17.2]	[−0.4]
Et_3N	226.7	−45.1	278.0	18.8	18.1	−0.7
Et_3N	[226.2]	−45.1	[277.5]	18.8	[17.8]	[−1.0]
NH_3	195.7	−75.1	277.1	16.5	17.6	1.1
NH_3	[194.9]	−75.1	[276.3]	16.5	[17.2]	[0.7]
$EtNH_2$	210.7	−59.7	276.7	18.4	17.4	−1.0
$EtNH_2$	[210.2]	−59.7	[276.2]	18.4	[17.1]	[−1.3]
$PrNH_2$	211.9	−57.4	275.6	18.4	16.8	−1.7
$PrNH_2$	[211.5]	−57.4	[275.2]	18.4	[16.6]	[−1.9]
$BnNH_2$	213.9	−52.7	272.9	16.9	15.3	−1.6
$BnNH_2$	[213.5]	−52.7	[272.5]	16.9	[15.1]	[−1.8]
PrNHMe	218.4	−52.2	276.9	18.9	17.5	−1.4
PrNHMe	[218.0]	−52.2	[276.4]	18.9	[17.3]	[−1.7]
$PrNMe_2$	222.5	−48.1	276.9	18.3	17.5	−0.8
$PrNMe_2$	[221.9]	−48.1	[276.3]	18.3	[17.2]	[−1.1]

Table 1 **(*continued*)**

Base	$\Delta G^{\circ}_{gas}(B_{\alpha}H^{+})$/ kcal mol^{-1}	$\Delta(\Delta G^{*}_{sol}(B_{\alpha}H^{+}))$/ kcal mol^{-1}	$\Delta G'_{a,sol}(B_{\alpha}H^{+})$/ kcal mol^{-1}	pK_a(exp)	pK_a(calc)	Δ (pK_a)
(*i*-Pr)$_2$NH	224.6	−46.5	277.4	18.8	17.7	−1.1
(*i*-Pr)$_2$NH	[224.1]	−46.5	[276.9]	18.8	[17.5]	[−1.3]
Ph$_2$NH	207.8	−42.3	256.3	6.0	6.2	0.2
Ph$_2$NH	[207.3]	−42.3	[255.9]	6.0	[6.1]	[0.1]
1An	203.1	−54.1	263.5	10.6	10.1	−0.5
1An	[202.9]	−54.1	[263.3]	10.6	[10.1]	[−0.5]
2An	204.8	−52.0	263.1	10.5	9.9	−0.6
2An	[204.6]	−52.0	[262.8]	10.5	[9.8]	[−0.7]
3An	199.6	−52.3	258.2	7.9	7.2	−0.7
3An	[199.7]	−52.3	[258.3]	7.9	[7.4]	[−0.5]
4An	196.5	−50.9	253.7	5.1	4.7	−0.3
4An	[196.9]	−50.9	[254.1]	5.1	[5.1]	[0.0]
5An	199.5	−55.0	260.8	9.4	8.6	−0.8
5An	[199.3]	−55.0	[260.7]	9.4	[8.6]	[−0.8]
6An	208.2	−51.1	265.5	11.9	11.2	−0.6
6An	[208.1]	−51.1	[265.5]	11.9	[11.3]	[−0.6]
7An	193.9	−57.9	258.2	8.0	7.2	−0.9
7An	[194.1]	−57.9	[258.4]	8.0	[7.4]	[−0.6]
8An	193.6	−51.4	251.3	4.8	3.4	−1.4
8An	[193.9]	−51.4	[251.6]	4.8	[3.7]	[−1.1]
9An	191.2	−60.0	257.5	7.7	6.8	−0.9
9An	[191.3]	−60.0	[257.5]	7.7	[6.9]	[−0.7]
10An	188.6	−59.6	254.5	6.2	5.1	−1.1
10An	[188.6]	−59.6	[254.5]	6.2	[5.3]	[−0.9]
1P	215.7	−49.1	271.1	12.5	14.3	1.8
1P	[215.9]	−49.1	[271.3]	12.5	[14.5]	[1.9]
2P	220.1	−46.2	272.6	13.3	15.1	1.8
2P	[220.4]	−46.2	[272.9]	13.3	[15.3]	[2.0]
3P	224.1	−43.8	274.1	14.1	16.0	1.8
3P	[224.5]	−43.8	[274.5]	14.1	[16.2]	[2.1]
4P	227.5	−41.4	275.2	15.0	16.6	1.6
4P	[227.9]	−41.4	[275.6]	15.0	[16.8]	[1.8]
5P	223.7	−44.2	274.2	14.2	16.0	1.8
5P	[224.2]	−44.2	[274.7]	14.2	[16.3]	[2.1]
6P	220.9	−47.3	274.4	14.5	16.1	1.7
6P	[221.4]	−47.3	[275.0]	14.5	[16.4]	[2.0]
7P	222.8	−45.3	274.4	14.2	16.1	1.9
7P	[223.3]	−45.3	[274.9]	14.2	[16.4]	[2.2]
8P	229.0	−44.4	279.6	17.6	19.0	1.4
8P	[229.4]	−44.4	[280.1]	17.6	[19.2]	[1.6]
9P	233.9	−39.6	279.8	18.0	19.1	1.1
9P	[234.2]	−39.6	[280.0]	18.0	[19.2]	[1.3]
10P	224.6	−45.7	276.6	14.8	17.3	2.6
10P	[225.4]	−45.7	[277.4]	14.8	[17.8]	[3.0]
11P	223.2	−45.3	274.8	15.2	16.3	1.1
11P	[223.8]	−45.3	[275.4]	15.2	[16.7]	[1.5]

[a] pK_a(calc) values are obtained by linear relationships pK_a = 0.552 $\Delta G'_{a,sol}(B_{\alpha}H^{+})$ − 135.3 and pK_a = 0.545 $\Delta G'_{a,sol}(B_{\alpha}H^{+})$ − 133.5 (in the corresponding units) as obtained by B3LYP(S) and B3LYP(L) [within square brackets] methods, respectively, the latter values being given within the square brackets. Energies are given in kcal mol^{-1}; $\Delta(\Delta G_{sol}(B_{\alpha}H^{+})) = \Delta G_{sol}(B_{\alpha}H^{+}) - \Delta G_{sol}(B)$; Δ(p$K_a$) is defined as p$K_a$(calc) − p$K_a$(exp).

In that case anilines nicely fit the straight line indicating that one should be very careful in interpreting results of the statistical analyses. Thus, taking into account discussion of the results for pyridines and anilines one concludes that excellent agreement with accurate experimental data could be obtained by considering separately the families of related compounds. Let us illustrate this conjecture by phosphazenes (Fig. 5). The quality of correlation is excellent as evident by $R^2 = 0.994$ and MAE = 0.3 pK_a units. It turns out that the mean absolute error is by 75% smaller compared to correlation involving all compounds (Fig. 4).

At the end of this section let us briefly consider use of proton affinities in correlating experimental pK_a values. The correlations between pK_a(exp) and $\Delta H_{a,sol}(B_{\alpha}H^{+})$ are illustrated by Fig. S2 (ESI†). It appears that the quality of the regression is

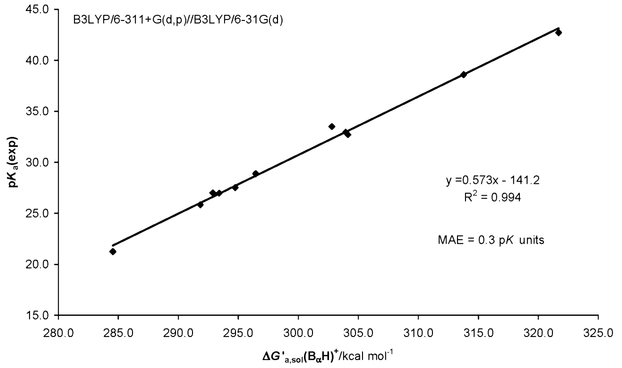


Fig. 5 Correlation between pK_a(exp) and $\Delta G'_{a,sol}(B_{\alpha}H)^{+}$ for the series of phosphazenes by the B3LYP(S) method.

slightly lower compared to that achieved by Gibbs free energies (*vide supra*). For example, the results obtained by the B3LYP(S) method yield:

$$\mathrm{p}K_\mathrm{a}(\mathrm{exp}) = 0.553 \times \Delta H_{\mathrm{a,sol}}(\mathrm{B}_\alpha\mathrm{H})^+ - 136.2 \qquad (10)$$

with $R^2 = 0.981$ and MAE = 0.9 pK_a units, whereas the B3LYP(L) method results offer a relationship:

$$\mathrm{p}K_\mathrm{a}(\mathrm{exp}) = 0.548 \times \Delta H_{\mathrm{a,sol}}(\mathrm{B}_\alpha\mathrm{H})^+ - 134.7 \qquad (11)$$

which possess regression coefficient $R^2 = 0.978$ and MAE = 1.0 pK_a units. It is fair to say that these results are reasonable. However, it should be stressed that proton affinity fails in reproducing the basicity of molecules with multiple intramolecular hydrogen bonds (IMHBs) in acetonitrile, which will be discussed in some detail in the next section.

As a final comment we would like to stress that acetonitrile is a "well behaved" solvent due to its low polarity. In spite of that MeCN does form hydrogen bonds with solute molecules. Hence, a physically more satisfactorily model should include clusters formed by the solute compound and solvent molecules *via* hydrogen bonds, which is subsequently immersed in the bulk solvent treated as a polarized continuum. This picture is under consideration for MeCN and some other more polar solvents.

The influence of the intramolecular hydrogen bonds on the solvent effect

The formation of intramolecular hydrogen bonds upon protonation is one of the most important motifs in tailoring strong organic bases and proton sponges since Alder's

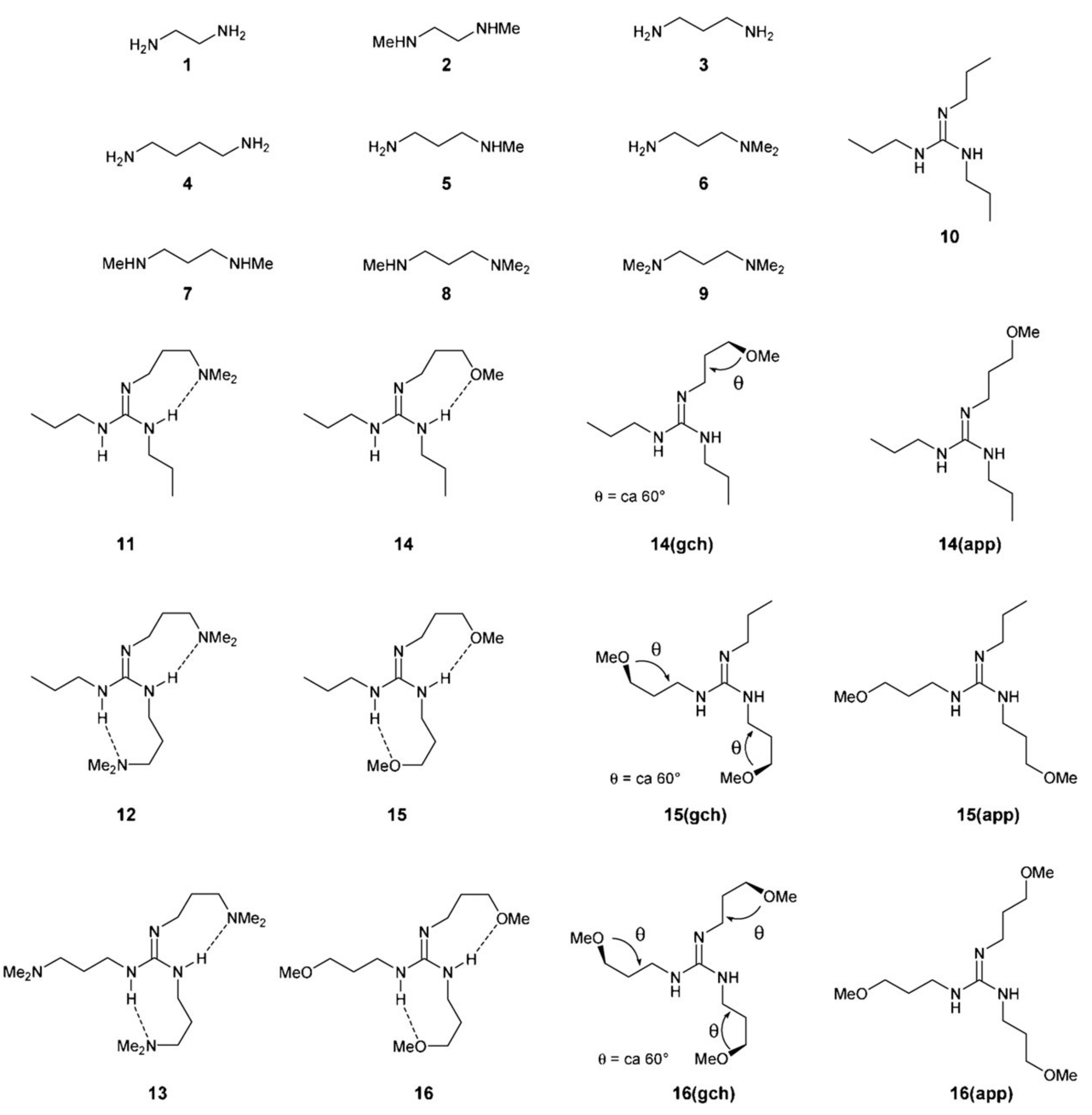


Fig. 6 Structural representation of bases possessing intramolecular hydrogen bond(s) (IMHB(s)).

DMAN[35,36] and related superbases.[11,37,38] This concept is generalized by introducing the so-called corona effect[39–43] formed by pseudo-six- or pseudo-eight-membered rings, the latter being formed by the aminopropyl side chains in initial bases and/or conjugate acids. The formation of pseudo-rings through IMHB upon protonation of amines is illustrated by Fig. 6 and 7 starting with **9**H$^+$. The calculated pK_a values are presented in Table 2. They are obtained *via* $\Delta G'_{a,sol}(B_\alpha H^+)$ (eqns given in Fig. 4 and Table 1) and $\Delta H'_{a,sol}(B_\alpha H^+)$ (eqn (10)), respectively. Gibbs energies and enthalpies are compared with the measured values[44] in Table 2. Inspection of the results shows that proton affinities fail in reproducing the experimental data. In contrast, $\Delta G'_{a,sol}$ basicity computations offer good agreement with experiment. The underlying reason is that basicity includes the change in entropy taking place upon formation of IMH bond(s).

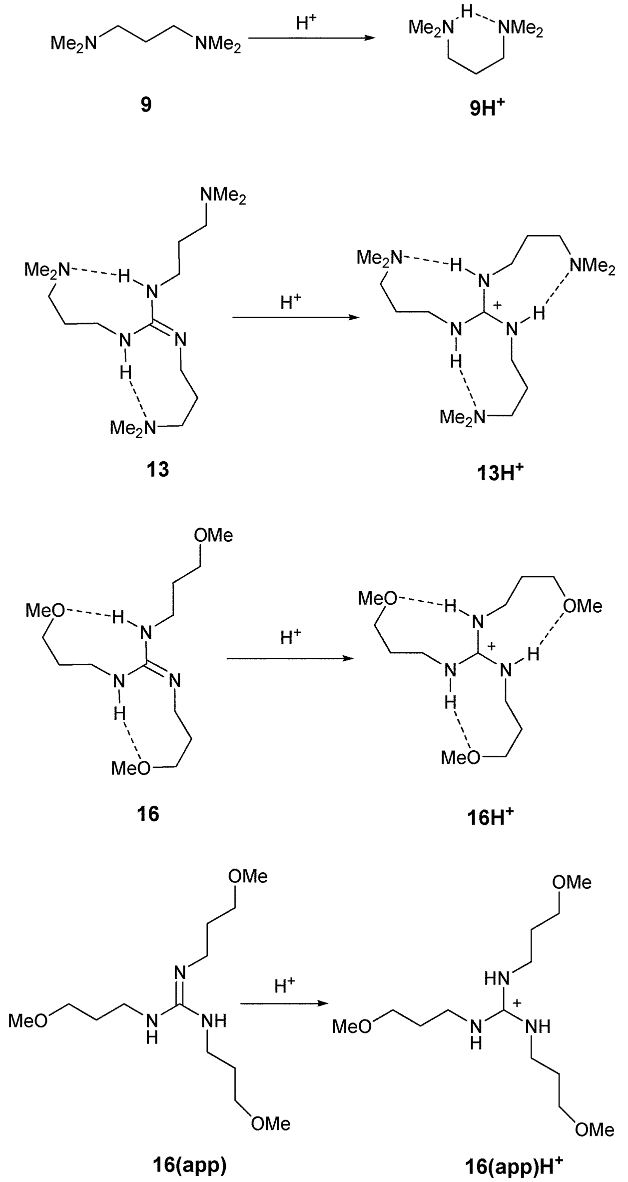


Fig. 7 Examples of the hydrogen bond formation processes upon protonation in bases **9**, **13** and **16**. In the case of base **16(app)** and other (**gch**) and (**app**) bases, no formation of intramolecular hydrogen bonds is assumed.

Particularly interesting is a group of trisubstituted guanidines (**11–16**) involving 1, 2 or 3 dimethylamino or methoxy substituents at the tails of the propyl chains. The parent compound **10** has no IMHB since propyl groups assume zig-zag conformations. Its calculated pK_a(calc)$_G$ and pK_a(calc)$_H$ values obtained *via* basicity and proton affinity, respectively, are in excellent agreement with the experiment. Compounds **11** and **12** have one or two IMHBs, respectively, whereas system

Table 2 Comparison of experimental and calculated pK_as as obtained from the linear regressions based on $\Delta G'_{a,sol}$ (B3LYP(S) and B3LYP(L))[a] or $\Delta H'_{a,sol}$

		B3LYP(S) [B3LYP(L)]		Based on $\Delta H'_{a,sol}$	
Base	pK_a(exp)[b]	pK_a(calc)$_G$	Δ(pK_a)	pK_a(calc)$_H$	Δ(pK_a)
1	18.46	18.16 [17.72]	0.30 [0.74]	14.83	−3.63
2	19.63	18.28 [17.71]	1.35 [1.92]	14.83	−4.80
3	19.70	20.36 [19.90]	−0.66 [−0.20]	17.19	−2.51
4	20.12	22.27 [21.81]	−2.15 [−1.69]	19.16	−0.96
5	20.04	21.10 [20.54]	−1.06 [−0.50]	17.77	−2.27
6	19.57	21.43 [20.88]	−1.86 [−1.31]	18.02	−1.55
7	20.39	20.55 [19.96]	−0.16 [0.43]	17.26	−3.13
8	20.01	20.88 [20.30]	−0.87 [−0.29]	17.48	−2.53
9	19.27	19.75 [18.99]	−0.48 [0.28]	17.23	−2.04
MAE			**0.99** **[0.82]**		**3.0**
10	24.92	24.94 [25.15]	0.02 [0.23]	24.89	−0.03
11	25.80	26.25 [26.15]	0.45 [0.35]	26.35	0.55
12	26.63	26.79 [26.68]	0.16 [0.05]	28.03	1.40
13	27.15	27.68 [27.56]	0.53 [0.41]	29.50	2.35
14	24.81	25.57 [25.44]	0.76 [0.63]	25.56	0.75
15	24.84	26.02 [25.73]	1.18 [0.89]	26.23	1.39
16	24.72	26.46 [25.87]	1.74 [1.15]	27.20	2.48
14(gch)	24.81	24.55 [24.67]	−0.26 [−0.14]	24.24	−0.57
15(gch)	24.84	24.80 [24.82]	−0.04 [−0.02]	24.85	0.01
16(gch)	24.72	23.92 [23.89]	−0.80 [−0.83]	23.73	−0.99
14(app)	24.81	24.28 [24.46]	−0.53 [−0.35]	24.13	−0.68
15(app)	24.84	24.02 [24.20]	−0.82 [−0.64]	23.97	−0.87
16(app)	24.72	23.40 [23.61]	−1.32 [−1.11]	23.50	−1.22
MAE[c]			**0.32** **[0.29]**		**0.84**

[a] B3LYP(L) values are given in square brackets. [b] Experimental pK_as for compounds **1–9** are taken from ref. 45, while the pK_as for **10–16** are taken from ref. 44. [c] Calculated for the bases **10–13** and **14(gch)–16(gch)**.

13 possesses two IMHBs in the initial state, but gains an additional one in the protonated form (Fig. 7). The pK_a(calc)$_H$ values exhibit large errors in systems **11–13**, while the corresponding pK_a(calc)$_G$ values remain reasonably accurate.

The same conclusion holds for methoxy derivatives **14–16**, but the absolute errors are significantly larger than for the dimethylaminopropyl series. The reason behind the failure of the proton affinities in reproducing the experimental results is the lack of the entropy term. In contrast, Gibbs free energy establishes a good accordance with measured data. It is obvious that the entropy effect is important here.

Finally, it is very interesting to mention that methoxy derivatives can also exist in the open forms without IMHB cyclization(s) yielding structures **14(gch)–16(gch)** and **14(app)–16(app)**. Here "**gch**" and "**app**" denote *gauche*-antiperiplanar and fully zig-zag antiperiplanar conformations, respectively (*viz*. Fig. 6). It is difficult to predict which conformations are more stable in MeCN solution. A comparison with the measured pK_a values might be helpful in this respect. Perusal of the results presented in Table 2 reveals that the pK_a(calc)$_G$ are in much better agreement with the experiment for **14(gch)**, **15(gch)** and **16(gch)** conformations compared to the both "cyclic" and fully zig-zag ones. This example provides evidence that combined experimental and theoretical efforts in estimating pK_a values could be useful in providing valuable information on conformations in solutions. It follows also that the gas phase geometries cannot be transferred and used in solutions without due care, particularly if intramolecular (ionic) hydrogen bonds are present.

Conclusions

The basicities of a large number of nitrogen organic bases and superbases were studied by using the isodensity polarized continuum model and DFT computational schemes. The investigated bases encompass nitrogen basic centers in widely different chemical environments such as in phosphazenes, amines, amidines, guanidines, anilines and pyridines. The gas-phase basicities were treated by the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) and B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) methods. The effect of MeCN solvent was considered at the B3LYP/6-311+G(d,p) level single point calculations employing the gas-phase equilibrium geometries in solutions and the isodensity polarized continuum model (IPCM) in estimating the solvent effect. It turns out that the smaller basis set (6-311+G(d,p)) is sufficient in both the gas phase and solution implying that basicity can be treated at the same level of theory in both phases. The results for pK_a(MeCN) are in good agreement with the available experimental data meaning that if basicities in MeCN are calculated, then the pK_a values of different families of nitrogen compounds are put on the same straight line. An attempt is made to correlate the experimental pK_a(MeCN) values with proton affinities in MeCN. Results are satisfactory, but less accurate than those achieved by Gibbs free energies in acetonitrile. However, proton affinities frequently fail in describing the pK_a(MeCN) values of molecules possessing multiple intramolecular hydrogen bonds occurring via corona effects. In these cases, the use of basicities is a must. A useful corollary of the pK_a(MeCN) calculations based on Gibbs free energies is that comparison of experimental and theoretical results provides a useful insight into the structures of the most stable conformations in solutions for systems possessing IMH bond(s).

Acknowledgements

Financial support of this work by the Ministry of Science, Education and Sport of Croatia (Z. G. and M.E.M. through the project no. 098-0982933-2920 and Z. B. M. through the project no. 098-0982933-2932) is acknowledged. Our thanks go also to the Computing Centre of the University of Zagreb (SRCE) for granting computation time on the ISABELLA cluster.

References

1 A. H. Oediger, F. Möller and K. Eiter, *Synthesis*, 1972, 591–598.
2 J. Tang, J. Dopke and J. G. Verkade, *J. Am. Chem. Soc.*, 1993, **115**, 5015–5020, and references therein.
3 F. Hibbert and K. P. P. Hunte, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1895–1899.
4 U. Schuchardt, R. M. Vargas and G. J. Gelbard, *J. Mol. Catal. A: Chem.*, 1996, **109**, 37–44.
5 T. Ishikawa and T. Isobe, *Chem.–Eur. J.*, 2002, **8**, 552–557.
6 A. Alcami, O. Mó and M. Yañez, *Mass Spectrom. Rev.*, 2001, **20**, 195–245.
7 M. Alcami, O. Mó and M. Yañez, *J. Phys. Org. Chem.*, 2002, **15**, 174–186.
8 A. I. González, O. Mó, M. Yáñez, E. Léon, J. Tortajada, J. P. Morizur, I. Leito, P.-C. Maria and J. F. Gal, *J. Phys. Chem.*, 1996, **100**, 10490–10496.
9 (*a*) B. Kovačević and Z. B. Maksić, *Chem. Commun.*, 2006, 1524–1526; (*b*) I. Despotović, B. Kovačević and Z. B. Maksić, *Org. Lett.*, 2007, **9**, 4709–4712.
10 B. Kovačević and Z. B. Maksić, *Tetrahedron Lett.*, 2006, **47**, 2553–2555.
11 V. Raab, E. Gauchenova, A. Markoulov, K. Harms, J. Sundermayer, B. Kovačević and Z. B. Maksić, *J. Am. Chem. Soc.*, 2005, **127**, 15738–15743.
12 P. Burk, I. A. Koppel, I. Koppel, I. Leito and O. Travnikova, *Chem. Phys. Lett.*, 2000, **323**, 482–489.
13 G. Bouchoux, D. Leblanc, W. Bertrand, T. B. McMahon, J. E. Szulejko, F. Berruyer-Penaud, O. Mó and M. Yañez, *J. Phys. Chem. A*, 2005, **109**, 11851–11859.
14 Z. Glasovac, V. Štrukil, M. Eckert-Maksić, D. Schröder, M. Kaczorowska and H. Schwarz, *Int. J. Mass Spectrom.*, 2008, **270**, 39–46.
15 B. Smith and L. Radom, *Chem. Phys. Lett.*, 1994, **231**, 345–351.
16 W2 method: J. M. L. Martin and G. de Oliveira, *J. Chem. Phys.*, 1999, **111**, 1843–1856.
17 G2 and G3 methods: (*a*) L. A. Curtiss, P. C. Redfern, K. Raghavachari and J. A. Pople, *J. Chem. Phys.*, 1998, **109**, 42–55; (*b*) L. A. Curtiss, K. Raghavachari, P. C. Redfern, V. Rassolov and J. A. Pople, *J. Chem. Phys.*, 1998, **109**, 7764–7776.
18 CBS-Q method: J. A. Montgomery, Jr., M. J. Frisch, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1999, **110**, 2822–2827.
19 S. Miertuš, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117–129.
20 S. Miertuš and J. Tomasi, *Chem. Phys.*, 1982, **65**, 239–245.
21 J. Tomasi and M. Persico, *Chem. Rev.*, 1994, **94**, 2027–2094.
22 J. Tomasi, B. Mennuci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999–3093.
23 M. Orozco and F. Luque, *Chem. Rev.*, 2000, **100**, 4187–4226.
24 K. B. Wiberg, P. R. Rablen, D. J. Rush and T. A. Keith, *J. Am. Chem. Soc.*, 1995, **117**, 4261–4270.
25 J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian and M. J. Frisch, *J. Phys. Chem.*, 1996, **100**, 16098–16104.
26 B. Kovačević and Z. B. Maksić, *Org. Lett.*, 2001, **3**, 1523–1526.

27 For example see: G. Schüürmann, *Chem. Phys. Lett.*, 1999, **302**, 471–479; M. W. Palascak and G. C. Shields, *J. Phys. Chem. A*, 2004, **108**, 3692–3694; G. I. Almerindo, D. W. Tondo and J. R. Pliego, Jr, *J. Phys. Chem. A*, 2004, **108**, 166–171; Z.-K. Jia, D.-M. Du, Z.-Y. Zhou, A.-G. Zhang and R.-Y. Hou, *Chem. Phys. Lett.*, 2007, **439**, 374–380.

28 M. D. Liptak and G. C. Shields, *J. Am. Chem. Soc.*, 2001, **123**, 7314–7319; G. A. A. Saracino, R. Improta and V. Barone, *Chem. Phys. Lett.*, 2003, **373**, 411–415.

29 A. Ben-Naim, *J. Phys. Chem.*, 1978, **82**, 792–803.

30 I. A. Topol, G. J. Tawa, S. K. Burt and A. A. Rashin, *J. Chem. Phys.*, 1999, **111**, 10998–11104.

31 A. Klamt, F. Eckert, M. Diedenhofen and M. E. Beck, *J. Phys. Chem. A*, 2003, **107**, 9380–9386.

32 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision B.03)*, Gaussian, Inc., Pittsburgh, PA, 2003.

33 The experimental GB_g and PA_g for all compounds except for phosphazenes are taken from NIST compilation (http://webbook.nist.gov/chemistry). GB_g data for phosphazenes were taken from I. Kaljurand, I. A. Koppel, A. Kütt, Eva-Ingrid Rõõm, T. Rodima, I. Koppel, M. Mishima and I. Leito, *J. Phys. Chem. A*, 2007, **111**, 1245–1250.

34 D. Barić and Z. B. Maksić, *J. Phys. Chem. A*, 2003, **51**, 11577–11586.

35 R. W. Alder, P. S. Bowman, W. R. S. Steeele and D. R. Winterman, *Chem. Commun. (London)*, 1968, 723–724.

36 A. L. Llamas-Saiz, C. Foces-Foces and J. Elguero, *J. Mol. Struct.*, 1994, **328**, 297–323.

37 B. Kovačević and Z. B. Maksić, *Chem.–Eur. J.*, 2002, **8**, 1694–1702.

38 V. Raab, K. Harms, J. Sundermayer, B. Kovačević and Z. B. Maksić, *J. Org. Chem.*, 2003, **68**, 8790–8797.

39 A. Hernandez-Laguna, J. L. M. Aboud, H. Homan, C. Lopez-Mardomingo, R. Notario, Z. Cruz-Rodriguez, M. D. Haro-Ruiz and V. Bottella, *J. Phys. Chem.*, 1995, **99**, 9087–9094.

40 Z. B. Maksić and B. Kovačević, *J. Phys. Chem. A*, 1999, **103**, 6678–6684.

41 Z. B. Maksić, Z. Glasovac and I. Despotović, *J. Phys. Org. Chem.*, 2002, **15**, 499–503.

42 B. Kovačević, Z. Glasovac and Z. B. Maksić, *J. Phys. Org. Chem.*, 2002, **15**, 765–774.

43 Z. Glasovac, B. Kovačević, E. Meštrović and M. Eckert-Maksić, *Tetrahedron Lett.*, 2005, **46**, 8733–8736.

44 M. Eckert-Maksić, Z. Glasovac, P. Trošelj, A. Kütt, T. Rodima, I. Koppel and I. A. Koppel, *Eur. J. Org. Chem.*, 2008, 5176–5184.

45 E.-I. Rõõm, A. Kütt, I. Kaljurand, I. Koppel, I. Leito, I. A Koppel, M. Mishima, K. Goto and Y. Miyahara, *Chem.–Eur. J.*, 2007, **13**, 7631–7643.