Ab Initio Quantum Mechanical Study on the Origin of the pK_a Differences of the Proton Sponges 1,8-Bis(dimethylamino)naphthalene, 1,8-Bis(dimethylamino)-2,7-dimethoxynaphthalene, 1,6-Dimethyl-1,6-diazacyclodecane, and 1,6-Diazabicyclo[4.4.4]tetradecane

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Ab initio quantum mechanical calculations were used in studying the origin of the exceptionally high basicities of four diamines (**13**−**16**) with pK_{a1} values ranging from 12.1 to 25. The computational approach involved the calculation of the gas-phase proton affinities of the molecules studied at the MP2/6-31G*//HF/6-31G* level and the solvation energies with the polarizable continuum model at the HF/6-31G* level. The calculated gas-phase and aqueous-phase proton affinities of a structurally diverse series of amines were compared with the corresponding experimental gas-phase proton affinities and pK_{a1} values. The calculated values were found to be in reasonable agreement with the experimental ones. The high basicities of the studied diamines were found to originate from the nitrogen lone-pair repulsion, solvation effects, and strong intramolecular hydrogen bonds. Each of these factors were found to be able to increase the pK_{a1} values of the high-basicity diamines by 2−6 pK_a units. The relative contributions of the factors varied between the compounds. The nitrogen lone-pair repulsion was estimated to be the most important factor in increasing the pK_{a1} values. In addition, barriers for proton transfers between the nitrogens of selected diamines were calculated, and comparison was made between the barrier heights and the geometries of the diamines.

Introduction

Aromatic and cyclic diamines which have exceptionally enhanced basicity are called the “proton sponges”.[1,2] These compounds have two basic amine sites closely positioned and can accept a proton between the nitrogens. A large number of such compounds have been synthesized and their properties extensively studied by crystallographic and spectroscopic methods. Several reviews have been published on the “proton sponges”.[1−4] The enhanced basicity of the “proton sponges” has been attributed to a complex combination of several factors such as repulsion of the nitrogen lone-pairs of the neutral molecule, relief of repulsion and strain on protonation, solvation effects, and enforced hydrogen bonding in the protonated ion.[1,2,5] Although these factors are known to be important in determining the basicities, quantitative information on the relative magnitudes of the factors is lacking. The monoprotonated diamines with high basicity characteristically have a strong hydrogen bond between the amine nitrogens. This strong hydrogen bond can be of a single or double potential minimum type.[4] The strength of the very strong hydrogen bond (or low-barrier hydrogen bond) in condensed phases has recently been of significant interest.[6−9] In this context the high basicities of the “proton sponges” (Figure 1, **13** and **14**) have been used in support of the high strength of the low-barrier hydrogen bonds in solution.[10]

In the present work we have used *ab initio* quantum mechanical computations to analyze the factors that are responsible for the pK_{a1} values of 1,8-diaminonaphthalene (**12**, pK_{a1} = 4.6),[11] 1,8-bis(dimethylamino)naphthalene (**13**, pK_{a1} = 12.1),[12] 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene (**14**, pK_{a1} = 16.1),[13] 1,6-dimethyl-1,6-diazacyclodecane (**15**, pK_{a1} = 16.5), and 1,6-diazabicyclo[4.4.4]tetradecane (**16**, pK_{a1} ≈25).[14] Here we will first show that the computational approach chosen reproduces the relative experimental proton affinities (PA) and pK_{a1} data of a structurally diverse set of amine compounds (**1**−**16**, Tables 1 and 2, Figures 1 and 2) at a level of accuracy that allows us to use computed results in explaining the pK_{a1} values of the diamines. The computational approach involves (1) calculating the geometries of the neutral and monoprotonated forms of the amines using *ab initio* quantum mechanical methods, (2) calculating the gas-phase PAs, and (3) calculating electrostatic solvation energies (ΔE_{solv}) using the polarizable continuum model of Tomasi.[25−27] The gas-phase PAs

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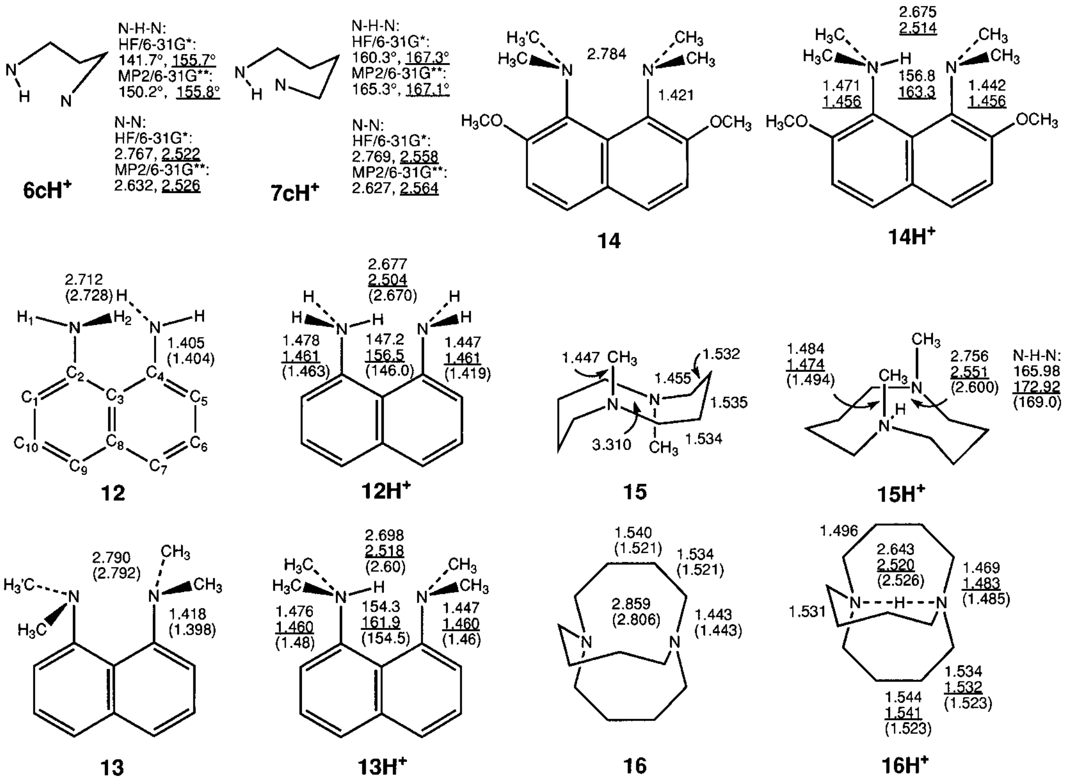

Figure 1. Selected geometric parameters of **6cH**$^+$ and **7cH**$^+$ calculated at the HF/6-31G* and MP2/6-31G** level and of neutral and monoprotonated **12**−**16** at the HF/6-31G* level. Parameters calculated for geometries with hydrogen central to two amine nitrogens are underlined. Parameters from X-ray crystal structures are in parentheses.[5,14−24]

and the electrostatic solvation energies are combined to get the calculated aqueous PAs (PA(aq)). In addition, proton-transfer barriers for several diamines are computed, and a comparison is made between the barrier heights and the geometries of the molecules.

Computational Details

Geometries of the compounds in the neutral and protonated forms were optimized at the HF/6-31G* and HF/3-21G level using Gaussian94 program.[31] HF/6-31G* geometries were used in the energy calculations at the MP2 level (MP2/6-31G*//HF/6-31G*) and in calculating solvation energies (HF/6-31G*) using the continuum solvation model of Tomasi[25,26] as implemented in Gaussian94 (IPCM option in Gaussian).[27] In the solvent calculations a dieletric constant (*e*) of 78.3 was given for solvent (water) and a value of 0.0004 *e* B^{-3} was used for the charge density in the determination of the cavity boundary. Due to the large size of some of the molecules of this work, vibrational frequencies were calculated at the 3-21G level. Zero point energies (ZPEs) were scaled by 0.89. In addition, computations at higher level were performed to investigate the effects of larger basis sets and correlation corrections on the geometries and energies of selected compounds. These are separately indicated in the text.

Results and Discussion

Geometries of the Compounds. Selected calculated geometric parameters of the diamines **6cH**$^+$ and **7cH**$^+$ (**c** denotes cyclic conformation) and calculated and experimental[5,14−24] parameters of the neutral and monoprotonated **12**−**16** are shown in Figure 1. For all these molecules geometries with hydrogen central to the two amine nitrogens were computed in addition to geometries with unsymmetrical hydrogen bonds. Experimental values of **13H**$^+$ shown in Figure 1 are means from eight different X-ray structures.[17−23]

The optimized N−N distances of **6cH**$^+$ and **7cH**$^+$ with unsymmetrical intramolecular hydrogen bonds can be

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Table 1. Total (au) and Electrostatic Solvation Energies (ΔE_{solv}, kJ mol^{-1}) of the Neutral and Monoprotonated 1−19 and Differences in Zero-Point Vibrational Energies (ΔZPE, kJ mol^{-1}) between the Neutral and Monoprotonated Molecules

	molecule	total energies[a] MP2/6-31G*//HF/6-31G*	total energies[b] MP2/6-31G*//HF/6-31G*	ΔE_{Solv}[a] HF/6-31G*	ΔE_{Solv}[b] HF/6-31G*	ΔZPE[c] 3-21G
1	NH_3	−56.35371	−56.69955	−16.7	−328.8	38.7
2	$MeNH_2$	−95.50178	−95.86730	−13.0	−287.9	40.3
3	Me_2NH	−134.66443	−135.03568	−9.4	−258.0	38.5
4	Me_3N	−173.82758	−174.20461	−7.4	−232.9	38.5
5	$N(CH_3)_2CH_2CH{=}CH_2$	−250.95353	−251.33639	−7.5	−214.3	38.7
6	$NH_2(CH_2)_3NH_2$ (linear)	−229.01899	−229.38802	−24.0	−274.0	36.8
6c	$NH_2(CH_2)_3NH_2$ (cyclic)		−229.41595		−230.5	39.9
7	$NH_2(CH_2)_4NH_2$ (linear)	−268.18471	−268.55438	−34.7	−287.6	37.3
7c	$NH_2(CH_2)_4NH_2$ (cyclic)		−268.58843		−221.9	39.7
8	$PhNH_2$	−286.64851	−287.00228	−20.3	−257.4	36.8
9	$PhNHCH_3$	−325.80618	−326.17217	−17.4	−224.2	36.8
10	$PhN(CH_3)_2$	−364.96388	−365.34055	−13.7	−212.3	35.8
11	naphthyl-1-amine	−439.80347	−440.16090	−20.0	−234.3	37.4
12	1,8-diaminonaphthalene	−494.99623	−495.37240	−25.8	−219.9	34.8
13	1,8-bis(dimethylamino)naphthalene	−651.61956	−652.02978	−18.2	−168.8	35.1
14	1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene	−879.98048	−880.41243	−15.0	−151.0	39.4
15	1,6-dimethyl-1,6-diazacyclodecane	−501.99370	−502.40710	−1.5	−171.3	33.9
16	1,6-diazabicyclo[4.4.4]-tetradecane	−579.14116	−579.57413	−0.8	−168.3	36.8
17	1-dimethylaminonaphthalene	−518.11990	−518.49617	−16.3	−202.9	37.0
18	1-dimethylamino-2-methoxynaphthalene	−632.30373	−632.69003	−16.4	−189.8	38.6
19	naphthalene[d]	−384.61186		−12.1		

[a] Energies of the neutral molecules. [b] Energies of the monoprotonated molecules. [c] Calculated zero-point vibrational energies were scaled by 0.89. [d] ZPE of **19** is 374.1 kJ mol^{-1}.

seen to be slightly longer and N−H−N angles smaller at the HF/6-31G* than at the MP2/6-31G** level. The geometries with symmetrical hydrogen bonds are in good agreement at the two levels. The N−N distances of all the studied diamines are within a rather narrow range. For unsymmetrical hydrogen bonds the distances are 2.64−2.77 Å and for symmetrical ones 2.50−2.55 Å. It should especially be noted that although the N−H- - -N angles of **12H**$^+$−**16H**$^+$ increase in this series (smallest for **12H**$^+$, largest for **16H**$^+$) from 147.2° to 180.0° for the unsymmetrical hydrogen bonds and from 156.5° to 180.0° for symmetrical bonds, no clear tendency can be seen in the N−N distances.

The optimized structures of **12H**$^+$−**16H**$^+$ have strong intramolecular hydrogen bonds, and the geometries of the diamine parts of the molecules are similar. In contrast, there are more structural differences in the geometries of the neutral diamines. This is due to the proximity of the nitrogen lone-pairs and consequent lone-pair repulsion which is minimized by rotation of amine groups and/or geometrical changes in the molecular structures. In the case of **12** the NH_2 groups are rotated in such a way that there are close contacts between the nitrogen lone-pairs and the amino hydrogens. In the case of **13** the $N(CH_3)_2$ groups are rotated by 35−40° (τC−N−C2−C1 = −29.6° and 104.4°) as compared to the protonated molecule (**13H**$^+$, τC−N−C2−C1 = ±64.1° and ±64.6°). Also, the aromatic ring of **13** is distorted (τC1−C2−C3−C4 = 174.9°) in order to relieve the lone-pair repulsion. In **14** the methoxy groups at positions 2 and 7 hinder the rotation of the $N(CH_3)_2$ groups considerably. Consequently, the rotation of the $N(CH_3)_2$ groups of **14** is only about 10°, and the naphthalene ring is considerably twisted (τC1−C2−C3−C4 = 173.1°). In the case of **15** the neutral form adopts a different conformation as compared to the protonated molecule (Figure 1).[14] In the calculated structure of the neutral form the N−N distance is 3.31 Å and there are two short N- - -H−C contacts of 2.58 and 2.70 Å. In this structure the nitrogen lone-pairs point inside the hydrophobic interior of the hydrocarbon ring. Alder et al.[14] have made molecular mechanical computations (MM2) on several conformations of neutral **15** and made similar observations. The bicyclic ring of **16** forces the lone pairs to be exactly faced which causes severe lone-pair repulsion. Here the N−N distance is 2.859 Å, which is 0.339 Å longer than in the protonated minimum energy structure with central hydrogen. In contrast to the unsymmetrical hydrogen bonds between the amine nitrogen of **12H**$^+$−**14H**$^+$, the X-ray structures of **15H**$^+$ and **16H**$^+$ have a symmetrical N- - -H- - -N bridge. The computed geometric parameters for the symmetrical structures of **15H**$^+$ and **16H**$^+$ agree well with the X-ray parameters. The available X-ray structures and the optimized HF/6-31G* geometries of the neutral and monoprotonated forms of **12H**$^+$−**16H**$^+$ are in good agreement. The comparison between the experimental and computed (at the HF/6-31G level) geometries of the neutral and protonated **13** have been reported recently.[32]

Intramolecular Proton Transfers. The monoprotonated "proton sponges" have strong hydrogen bonds between the nitrogens of the amine groups. These strong hydrogen bonds can have a double or single minimum potential well. The difference between ^{1}H and ^{2}H ($\Delta\delta(^1H,^2H)$) NMR chemical shifts has been used to determine whether the strong hydrogen bond has a single or double minimum potential well.[4] For the double minimum hydrogen bond $\Delta\delta(^1H,^2H)$ is positive, and for the single minimum (i.e. central) bond negative.[33] Excluding **16H**$^+$, the compounds of this work have $\Delta\delta(^1H,^2H)$ values of 0.5−0.7, indicating the existence of a strong double minimum hydrogen bond.[4] **16H**$^+$ has a $\Delta\delta(^1H,^2H)$ value of 0.06 which indicates that this compound had a very strong hydrogen bond with a single minimum potential well. Although **15H**$^+$ has a $\Delta\delta(^1H,^2H)$ value of 0.54[34] (in $CHCl_3$−$CDCl_3$), there is a central hydrogen bond in the X-ray structure of that compound.[14]

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Table 2. Calculated (PA(calc), kJ mol^{-1}) and Experimental Proton Affinities (PA(exp), kJ mol^{-1}), Calculated Aqueous Proton Affinities (PA(aq), kJ mol^{-1}), and Experimental[29,30] pK_{a1} Values for 1−16

molecule	PA(calc)	PA(exp)	PA(aq)	pK_{a1}
1	869.3	854	1181.4	9.2
2	919.4	896	1194.3	10.7
3	936.3	923	1184.9	10.8
4	951.4	942	1176.8	9.8
5	966.5		1173.3	8.8
6	932.1		1182.1	10.5
6c	1002.3	979		
7	933.3		1186.2	10.7
7c	1020.2	994		
8	892.0	877	1129.1	4.7
9	924.1	913	1130.9	4.9
10	953.2	935	1151.8	5.2
11	901.0	908[a]	1115.3	3.9
12	952.8	936	1146.9	4.6
13	1042.0	1012	1192.6	12.1
14	1094.7		1230.7	16.1
15	1051.5		1221.3	16.5
16	1100.0		1267.5	25

[a] PA for the ring-protonated molecule.

Table 3. Energies (kJ mol^{-1}) of the Proton-Transfer Barriers in the Gas-Phase (ΔE (gas)) and in Aqueous Solution (ΔE (aq)) at the MP2/6-31G*//HF/6-31G* Level

	ΔE (gas)	ΔE (aq)
6cH$^+$	5.2	11.6
7cH$^+$	0.5	5.8
12H$^+$	2.5	2.9
13H$^+$	−1.3	1.3
14H$^+$	−2.7	−2.1
15H$^+$	−4.0	−0.5
16H$^+$	−6.7	−1.2

Table 4. Energies (ΔE, kJ mol^{-1}) of the Proton-Transfer Barriers of 6cH$^+$ and 7cH$^+$ in the Gas-Phase[a]

	ΔE			
	MP2/ 6-31G**	MP2/ 6-311G**	MP3 /6-311G**	MP4(SDQ)/ 6-311G**
6cH$^+$	4.9	5.2	8.6	8.9
7cH$^+$	1.0	2.1	4.1	4.3

[a] MP2/6-31G** geometries were used.

Proton-transfer barriers were calculated for the protonated **6cH**$^+$, **7cH**$^+$, and **12H**$^+$−**16H**$^+$. The energies of the proton-transfer barriers in the gas-phase (MP2/6-31G*//HF/6-31G*) and with electrostatic solvation energies (HF/6-31G*) included are listed in Table 3. The effects of the basis set and the inclusion of electron correlation were studied by optimizing the geometries of **6cH**$^+$ and **7cH**$^+$ at the MP2/6-31G** level and calculating the energies at the MP4(SDQ)//6-311G**//MP2/6-31** level. These values are listed in Table 4. At the MP2/6-31G*//HF/6-31G* level **6cH**$^+$ and **7cH**$^+$ have proton-transfer barriers of 5.2 and 0.5 kJ mol^{-1}, respectively. This computational level slightly underestimates the barrier heights as compared to MP3 and MP4(SDQ) calculations. At the MP4(SDQ)/6-311G**//MP2/6-31G** level the proton-transfer barrier is 8.9 kJ mol^{-1} for **6cH**$^+$ and 4.3 kJ mol^{-1} for **7cH**$^+$. The higher barrier for **6cH**$^+$ is due to the smaller N−H−N angle (Figure 1) in the transition-state of the proton transfer. Duan and Scheiner[35] have studied proton transfer between the nitrogens of protonated methane-, ethane-, and propanediamine and showed that a larger N−H−N angle leads to smaller proton-transfer barrier. Among the diamines **12H**$^+$−**16H**$^+$ the gas phase proton-transfer barrier (MP2/6-31G*//HF/6-31G*) is the largest for **12H**$^+$ and it decreases in the series **12H**$^+$ > **13H**$^+$ > **14H**$^+$ > **15H**$^+$ > **16H**$^+$. Although the energetic values of the proton-transfer barriers cannot be taken as quantitative due to the inadequate level of the calculations for that purpose, the relative energies are thought to be reliable. Since the MP2/6-31G*//HF/6-31G* energies underestimate the barrier by 4 kJ mol^{-1} as compared to the computations at the higher level (Table 4), **16H**$^+$ can be estimated to be the only compound in the studied series which has a central hydrogen bond in the gas phase. In this series of diamines the barrier heights can be seen to correlate with the linearity of the hydrogen bonds (Figure 1, Table 3), and it seems that in the gas phase a single minimum potential well exists only in the case of a linear hydrogen bond.

Solvation has the largest effect on the barriers of **15H**$^+$ (3.5 kJ mol^{-1}) and **16H**$^+$ (5.5 kJ mol^{-1}). The calculated electrostatic solvation energies are small which probably is due to the fact that only small changes are needed in the geometries of the molecules when the proton is moved from the position of the unsymmetrical hydrogen bond to the position in symmetrical bond. Furthermore, it must be remembered that no geometry optimizations were done in the solvent calculations. When solvation energies are added to the energies of the proton-transfer barriers, the geometries with unsymmetrical hydrogen bond are the energetically favored structures for all the studied molecules. These computations indicate that it is unlikely that in aqueous phase the hydrogen bonds between sp^3-hybridized nitrogens can have a single minimum potential well.

Gas-Phase Proton Affinities and pK_a Values of the Compounds. The total energies calculated at the MP2/6-31G*//HF/6-31G* level and the electrostatic solvation energies (ΔE_{solv}) at the HF/6-31G* level of the neutral and protonated forms of **1**−**19** are listed in Table 1. The calculated and available experimental gas-phase proton affinities (PA) of **1**−**16** are listed in Table 2. The correlation between the calculated PAs in aqueous solution (PA + ΔΔE_{solv}) and the pK_{a1} values is shown in Figure 2.

The calculated and experimental gas-phase proton affinities (Table 2) show good linear correlation (correlation equation: PA(exp) = 0.91 × PA(calc) + 64.0, r^2 = 0.99, s = 4.9). It must be noted that the theoretical PAs reported in Table 2 are calculated from the energies of the protonated and neutral amines at 0 K and corrected only by the corresponding ZPEs. No other thermodynamic corrections were done.[36] Partly from this reason the calculated values are uniformly 10−20 kJ mol^{-1} too high. Another reason for the overestimated PAs is the fact that more accurate computations of the absolute values of the gas-phase PAs would have required the use of larger basis sets.[37,38] This, however, was not possible in the present work because of the large size of the diamines. Good correlation between the calculated and experimental values of this work is in line with the recent report of Platts et al.[32] who also found a good correlation between the calculated (HF/6-31G*//HF/6-31G*) and experimental PAs for a small set of nitrogen bases.

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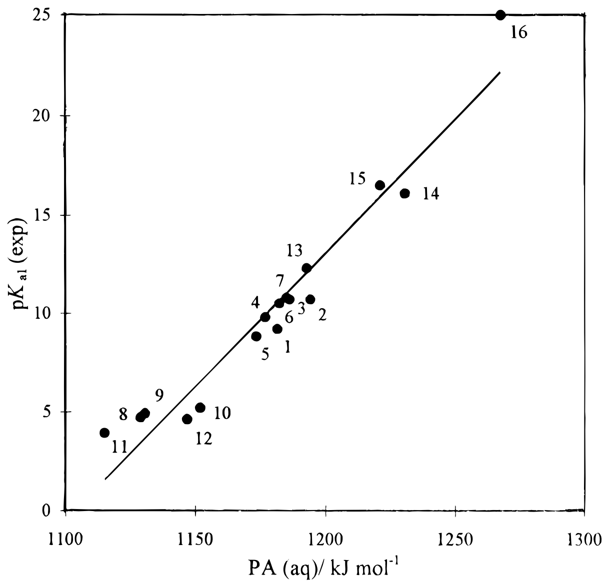

Figure 2. Correlation between the calculated aqueous proton affinities (PA(aq) = PA(gas) + $\Delta\Delta E_{solv}$) and experimental pK_{a1} values of **1**−**16**. Correlation equation: pK_{a1} = 0.12 × PA(aq) − 128.8, r^2 = 0.94, s = 1.0.

Detailed analyses on the basicities of diamines in the gas-phase and in aqueous solution based on experimental data can be found from refs. 39 and 40. Further, the effects of substituents and solvation on PA and pK_a values of amines have been investigated earlier.[41−43] The correlation coefficient between the calculated PAs in aqueous solution and the experimental pK_{a1} values for **1**−**16** (Figure 2) is 0.94. Although there is good correlation between the calculated and experimental results the correspondence is not quantitative: 1 pK_a unit corresponds to 7.0 kJ mol^{-1} in the calculated aqueous PAs in Figure 2, while the equation $\Delta\Delta$G=2.3RTδpK_a gives 5.7 kJ mol^{-1} for 1 pK_a unit.

The most of the calculated PA(aq) and experimental pK_{a1} values fall within 10 kJ mol^{-1} corresponding to about 1.5 pK_{a1} units. The pK_{a1} of **16** is predicted to be 22.2 which is 2.8 units lower than the literature value 25. However, pK_{a1} 25 of **16** is an estimate, because the inside proton of **16** cannot be inserted or removed by normal proton transfer.[14] Since the analyses on the individual components determining the pK_{a1} values are based on the calculated PAs and the electrostatic solvation energies, the differences between the calculated and experimental values of Table 2 and Figure 2 can be taken as indicators of errors in the analyses. The level of accuracy of the computed energies is thought to be adequate especially because we are comparing compouds (**12**−**16**) with pK_{a1} differences of 4−7 pK_a units.

Table 5. Energies (kJ mol^{-1}) of the Isodesmic Reactions at the MP2/6-31G*//HF/6-31G* + ΔZPE Level in the Gas-Phase (Δ*E*(gas)) and in Aqueous Solution (Δ*E*(aq)) for Neutral (1−3) and Protonated (4−6) 12, 13, and 14

	isodesmic reaction[a]	Δ*E*(gas)	Δ*E*(aq)
1	**12** + **19** → 2 **11**	−0.5	−2.7
2	**13** + **19** → 2 **17**	−22.8	−25.2
3	**14** + **19** → 2 **18**	−37.2	−42.9
4	**12H**$^+$ + **19** → **11** + **11H**$^+$	51.2	28.9
5	**13H**$^+$ + **19** → **17** + **17H**$^+$	68.3	29.9
6	**14H**$^+$ + **19** → **18** + **18H**$^+$	81.8	38.6

[a] See text for the details of the reactions.

In this series of compounds the stronger repulsion between the amine nitrogens' lone-pairs and larger (less negative) solvation energies of the neutral forms, and stronger intramolecular hydrogen bonds and smaller (more negative) solvation energies of the protonated forms, are properties of the molecules leading to higher basicities. Compound **16**, which has the highest pK_{a1} (≈25) of the molecules studied, has a linear short hydrogen bond when protonated and strong lone-pair repulsion in the neutral form. Both these factors increase the basicity of **16**. Compound **14**, which also has a strong intramolecular hydrogen bond when protonated and strong lone-pair repulsion in the neutral form, has 36.8 kJ mol^{-1} smaller aqueous PA than **16**. However, the calculated gas-phase PAs of **14** (1094.7 kJ mol^{-1}) and **16** (1100.0 kJ mol^{-1}) are similar as would be expected from the comparison of the PAs of the analogous pair of compounds *N*,*N*-dimethylaniline (**10**, 953.2 kJ mol^{-1}) and trimethylamine (**4**, 951.4 kJ mol^{-1}). This tells that the major part of the difference in the aqueous PAs between **14** and **16** is due to solvation. Namely, the solvation energy of the neutral form of **16** is 14.2 kJ mol^{-1} larger, and that of the protonated form 17.3 kJ mol^{-1} smaller than the corresponding values of **14**. Both these energies operate to the same direction and decrease the basicity of **14** relative to **16** contributing 31.5 kJ mol^{-1} to the difference in the PAs in aqueous solution. Thus, since the total calculated aqueous PA difference between the two compounds is 36.8 kJ mol^{-1}, the other factors but solvation have together only a small total effect on the relative basicities of the two compounds.

Compound **15** is an interesting one because due to its flexible 10-membered ring the lone-pair repulsion between the amine nitrogens is avoided by comformational change of the ring (Figure 1). As earlier pointed out by Alder et al.,[14] the lone-pairs point toward the hydrophobic cavity of the molecule which prevents normal solvation of the lone pairs. Since neutral **15** and **16** have similar solvation energies and in the protonated forms both compounds have intramolecular hydrogen bonds, the 46.2 kJ mol^{-1} difference in the aqueous PAs (ΔpK_{a1} = 7−9) probably originates mainly from the interactions present in the neutral forms. Thus, it is the severe lone-pair repulsion in neutral **16** that accounts for the major part of the difference in aqueous PAs between **15** and **16**. When compounds **12**−**14** are compared the differences in the solvation energies of the neutral and protonated forms operate in such a way that, if only these energies were considered, the order of the pK_{a1} values of the compounds would be the opposite to the experimental. This indicates that other factors, the most important of which are the lone-pair repulsion and the intramolecular hydrogen bond, are important for these molecules. The factors contributing to the differencies in the pK_{a1} values of **12**−**14** has been investigated with isodesmic reactions.

Isodesmic Reactions of 1,8-Diaminonaphthalene (12), 1,8-Bis(dimethylamino)naphthalene (13), and 1,8-Bis(dimethylamino)-2,7-dimethoxynaphthalene (14). Isodesmic reactions[36] (Table 5), which are

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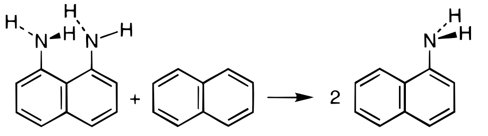
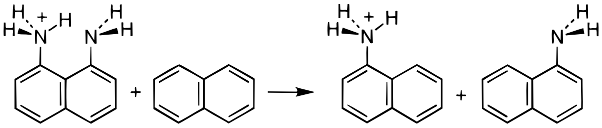
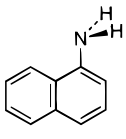
[39] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 2699.
[40] Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 1795.
[41] Meot-Ner (Mautner), M.; Hamlet, P.; Hunter, E. P.; Field, F. H. *J. Am. Chem. Soc.* **1980**, *102*, 6393.
[42] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 318.
[43] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.

constructed separately for the neutral (reactions 1−3) and protonated molecules (**3**−**6**), were used to quantitate the interactions between the two amine groups of **12**−**14**.


(1)


(4)

Isodesmic reactions give a measure of the proximity effects of the substituents, in this case the second NH_2, $N(CH_3)_2$, and $N(CH_3)_2$ and OCH_3 groups, as compared to the corresponding compounds with only one substituent. The geometries of the reference molecules **11**, **17**, and **18** were optimized in the similar conformations as **12**, **13**, and **14**. The calculated aqueous proton affinities of **11**, **17**, and **18** are 1115.3, 1137.5, and 1149.1 kJ mol^{-1}, respectively.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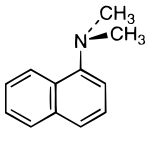
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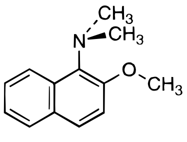
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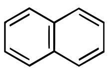
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These values show that part of the increased basicities of **13** and **14** originate from the methyl substituents on nitrogen and methoxy on the aromatic ring. The isodesmic reaction of neutral **12** (reaction 1) is thermoneutral in the gas-phase as well as in aqueous solution. This tells that in the gas-phase the possible lone-pair repulsion, which is present in **13** and **14**, is avoided by rotating the NH_2 groups. Since there was no difference in the energy of the isodesmic reaction of the neutral species, the reaction of **12H**$^+$ (reaction 4) should be responsible for the higher aqueous PA of **12** as compared to **11**. In the gas-phase the proximity of the amine groups and the possibility of an intramolecular hydrogen bond stabilize **12H**$^+$ by 51.2 kJ mol^{-1}. The solvation contribution decreases the energy of the isodesmic reaction to 28.9 kJ mol $^{-1}$. Solvation energies are only slightly unfavorable for neutral **13** and **14** while the gas-phase energies are unfavorable by 22.8 and 37.2 kJ mol^{-1}. This can be taken as a measure of the nitrogen lone-pair repulsion in these compounds. Due to larger steric crowding the repulsion is larger in **14** than **13**. The repulsion in **14** (42.9 kJ mol^{-1}, reaction 3) is of the same magnitude as the difference in the aqueous PAs between **15** and **16** (46.2 kJ mol $^{-1}$). The major part of this difference was attributed to lone-pair repulsion (see above). Energies of the gas-phase isodesmic reactions of **13H**$^+$ and **14H**$^+$ (reactions 5 and 6) are 68.3 and 81.8 kJ mol^{-1}. Inclusion of solvation lowers these energies to 29.9 and 38.6 kJ mol^{-1}. These values are estimates for the favorable intramolecular interactions between the amine groups in the monoprotonated diamines as compared to the corresponding molecules with only one amine group. The major part of these energies comes from the strong intramolecular hydrogen bonds.

In summary, the computations of the present work show that about half of the 11.5 units higher pK_{a1} value of **14** as compared to **12** originates from the lone-pair repulsion in neutral **14**. The strong intramolecular hydrogen bond increases the gas-phase PAs of **12**−**14** considerably, but this increase is attentuated by solvation effects. It can be estimated that the intramolecular hydrogen bond increases the pK_{a1} value of **14** by 3−4 units, and the methyl and methoxy substituents by 2−3 units.

Conclusions

In this work we used *ab initio* quantum mechanical gas-phase and continuum solvation calculations in studying the origin of the exceptionally enhanced basicities of diamines 1,8-bis(dimethylamino)naphthalene (**13**, pK_{a1} = 12.1), 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene (**14**, pK_{a1} = 16.1), 1,6-dimethyl-1,6-diazacyclodecane (**15**, pK_{a1} = 16.5), and 1,6-diazabicyclo[4.4.4]tetradecane (**16**, pK_{a1} ≈ 25). Also, barriers for proton transfers between the nitrogens of the compounds were investigated. The calculated gas-phase and aqueous-phase proton affinities and the corresponding experimental gas-phase proton affinities and pK_{a1} values of a structurally diverse series of amines were found to be in reasonable agreement.

The analyses of this work showed at least at the semiquantitative level how the relative basicities of the diamines studied originate from a combination of energy contributions arising from solvation of the neutral and protonated molecules, strong intramolecular hydrogen bond of the protonated molecules, and the lone-pair repulsion in neutral molecules. It was shown that in favorable cases the solvation energies and the intramolecular hydrogen bonding in the protonated forms can each increase the basicities of **13**−**16** by 2−4 pK_a units. The lone-pair repulsion was found to be able to increase the pK_{a1} values of the high-basicity diamines by up to 6 pK_a units. The relative contributions of the factors vary between the compounds, and only in the case of 1,6-diazabicyclo[4.4.4] tetradecane (**16**) all these factors are operating and together produce the exceptionally high basicity of this compound.

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