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Brønsted Basicities of Diamines in the Gas Phase, Acetonitrile, and Tetrahydrofuran

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Abstract: A comprehensive basicity study of α,ω-alkanediamines and related bases has been carried out. Basicities in acetonitrile (AN, pK_a values), tetrahydrofuran (THF, pK_α values), and gas phase (GP, *GB* values), were measured for 16, 14, and 9 diamine bases and for several related monoamines. In addition the gas-phase basicities and equilibrium geometries were computed for 19 diamino bases and several related monoamines at the DFT B3LYP 6-311+G** level. The effects of the different factors (intrinsic basicity of the amino groups, formation of intramolecular hydrogen bonds, and molecular strain) determining the diamine basicities were estimated by using the method of isodesmic reactions. The results are discussed in terms of molecular structure and solvation effects. The GP basicity is determined by the molecular size and polarizability, the extent of alkylation, and the energy effect of intramolecular hydrogen bond formation in the protonated base. The basicity trends in the solvents differ very much from those in GP: 1) The solvents severely compress the basicity range of the bases studied (3.5 times for the 1,3-propanediamine family in AN, and 7 times in THF), and 2) while stepwise alkylation of the basicity center leads to a steady basicity increase in the gas phase, the picture is complex in the solvents. Significant differences are also evident between THF and AN. The high hydrogen bond acceptor strength of THF leads to this solvent favoring the bases with "naked" protonation centers. In particular, the basicity order of N-methylated 1,3-propanediamines is practically inverse to that in the gas phase. The picture in AN is intermediate between that of GP and THF.

Keywords: basicity · diamines · hydrogen bonds · isodesmic reactions · solvent effects

Introduction

Owing to the high importance and wide usage of diamines, their design and basicity both in the gas phase[1–9] and liquid phase[6–11] has been the topic of a number of reports and a review.[12] It is well known that the enhanced basicity of diamines in the gas phase with respect to similar monoamines is caused by the intramolecular hydrogen bond[1,2] and that in the condensed phase this effect can be, depending on the solvent and on the accessibility of the protonated amine for solvent molecules, lower or absent.[12,13] The energetic effect of hydrogen bond formation on basicity has been the subject of studies on several types of diamines such as α,ω-alkanediamines,[1,2] bicyclic amines and diamines,[4] proton sponges,[5] and bispidines.[8] The situation is, however, more complicated and the formation of intramolecular hydrogen bonds cannot be regarded as a standalone process. It is instead coupled with strain effects,[12] and it is desirable to estimate the effect of different contributing factors separately. Howard[5] has summarized the factors that are responsible for determining the eventual basicity of a diamine: 1) The

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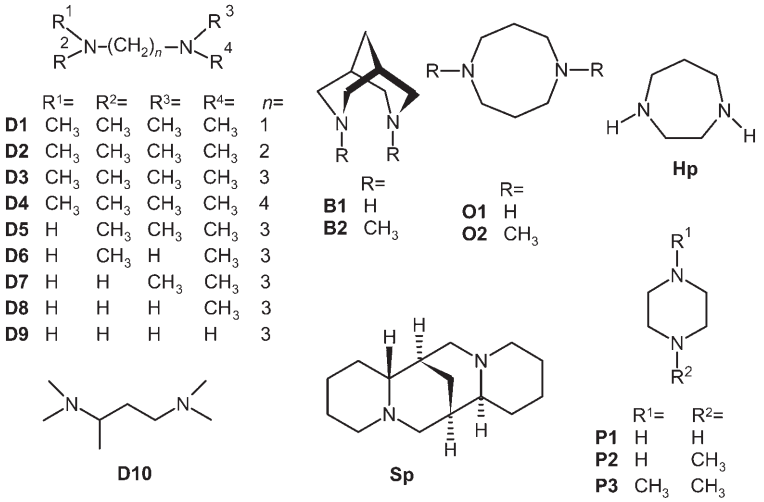
Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author. This material contains structures and sources of reference compounds, measurements in the gas phase, acetonitrile, and tetrahydrofuran, information about the isodesmic reaction treatment, and involved gas-phase calculations of amines, hydrocarbons, and hydrogen bond complexes.

effective proton affinity of one of the amino groups; 2) the stabilization effect caused by formation of the intramolecular hydrogen bond in the cation; 3) the relief of steric strain on protonation by loss of repulsion between lone pairs of electrons in the neutral molecule; 4) introduction of steric strain by "folding" of the diamine molecule during the formation of intramolecular hydrogen bonds; 5) the difference in solvation energies of the neutral and the protonated forms.

Energetic contributions of these effects to diamine basicity have been estimated in several works. Aue et al have studied a series of α,ω-alkanediamines in the gas phase.[1] Their results indicate that the protonated forms are cyclic due to intramolecular hydrogen bonding. The formation enthalpies of the hydrogen bonds were estimated by using the proton affinity (*PA*) values of monoamines of similar size and polarizability, and were found to be in the range of 20 kcal mol^{-1}.[1] Yamdagni et al have investigated several different reactions of amines in the gas phase, including the proton transfer reactions between monoamines and α,ω-alkanediamines.[2] The conclusions were similar to those given in reference [12]. In addition, strain energy effects of hydrogen bond formation were investigated. Rigorous computational gas-phase thermochemical investigation of the protonation of 1,2-ethanediamine and 1,4-butanediamine has been carried out by Bouchoux et al.[3] However, the contributions of different factors to the basicity were not discussed. An insightful quantitative estimation of these factors (using a computational approach) has been performed by Howard, who studied the basicity of a series of proton sponge diamines (simple α,ω-alkanediamines were not included in that study) quantum-chemically using the approach of isodesmic reactions.[5] An interesting finding of that work was that the loss of destabilizing strain energy on protonation is usually not the dominating contribution to the enhanced basicity in proton sponges; rather it is the efficient intramolecular hydrogen bond formation. This finding has been disputed for several bases by Alder[6] and the debate continues.



Scheme 1. Diamines studied in this work.

The basicities of the simplest class of diamines—α,ω-alkanediamines—and their alkyl-substituted derivatives has been the topic of numerous reports.[1–3,13–15] However, to the best of our knowledge no systematic studies aiming at insight into the origin of their basicity (similar to ref. [5]) and involving a wide structural variety of compounds, have been reported.

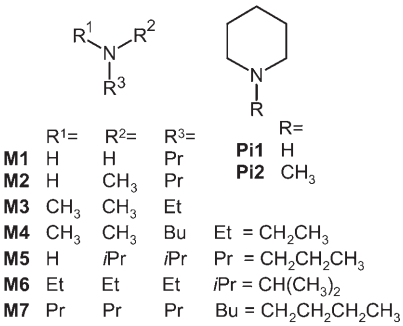
Amines and diamines are bases with rather localized charge in their protonated forms. Their basicity in solution is thus strongly influenced by solvation.[1,10,12] Nevertheless we are not aware of any systematic studies available discussing the basicities of simple diamines in different solvents. This is due, at least in part, to the scarcity of data on diamine basicities in different condensed media. For example, most of the diamine pK_a data in acetonitrile (AN) date back to 1965[11] and there have to date been no reports on the basicity of α,ω-alkanediamines in tetrahydrofuran (THF).

In this work we attempted to fill the aforementioned gaps by carrying out a comprehensive basicity study of α,ω-alkanediamines (Scheme 1), their alkylated derivatives, and some related bases (Scheme 2) both experimentally and computationally. As a result, basicities (pK_a values [Eq. (4)] in AN, pK_α values [Eq. (9)] in THF, and *GB* values [Eq. (11)] in the gas phase) were measured for 16, 14, and 9 diamine bases in AN, THF, and GP, respectively. In addition the gas-phase basicities and equilibrium geometries were computed for 19 diamino bases and 15 related monoamines at the DFT B3LYP 6-311+G** level. The effects of the different factors (intrinsic basicity of the amino groups, formation of intramolecular hydrogen bonds, and molecular strain, see above) determining diamine basicities were estimated for a number of α,ω-alkanediamines and related bases using the method of isodesmic reactions.

The basicity of a base B in solvent S is defined by using Equation (1) and is expressed as a dissociation constant K_a of the conjugate acid HB^+ of the base B, or more commonly its negative logarithm pK_a (Eq. (2)).

$$HB^+ + S \overset{K_a}{\rightleftharpoons} B + HS^+ \quad (1)$$

$$K_a = \frac{a(HS^+)\,a(B)}{a(HB^+)} \quad pK_a = -\log K_a \quad (2)$$



Scheme 2. Studied monoamines related to the diamines in this work.

To exclude the necessity to measure the solvated hydrogen ion (HS^+) activity in AN, the equilibrium shown in Equation (3) between two bases B_1 and B_2 was studied.

$$B_2 + HB_1^+ \rightleftharpoons HB_2^+ + B_1 \tag{3}$$

The relative basicity of the two bases B_1 and B_2 (ΔpK_a) is defined in Equation (4).

$$\Delta pK_a = pK_a(HB_2^+) - pK_a(HB_1^+) = \log\frac{a(HB_2^+)\,a(B_1)}{a(HB_1^+)\,a(B_2)} \tag{4}$$

The simple acid dissociation equilibrium [Eq. (1)] used to describe the strength of an acid in polar solvents (water, acetonitrile, etc.) does not describe the actual situation in media of relatively low polarity ($D \leq 15\ldots20$)[16] such as THF, where an extensive ion-pairing takes place. The extent of ion-pairing of the protonated base cations with anions (A^-) depends on the solvent, the size of the ions, and the charge distribution in the ions. The general trend is that small ions tend to form solvent separated ion-pairs (SSIP) [Eq. (5)], while large ions with delocalized charge tend to form contact ion-pairs (CIP) [Eq. (6)].

$$HB^+ + A^- \rightleftharpoons HB^+_s \cdot A^-_s \tag{5}$$

$$HB^+ + A^- \rightleftharpoons [HB^+A^-]_s \tag{6}$$

In THF we consider the ions to be fully ion-paired, and thus the proton distribution equilibrium between two bases B_1 and B_2 [Eq. (3)] can be presented as in Equation (7).

$$\begin{aligned} &B_2 + HB_1^+A^- \overset{K_d^{HB_1^+A^-}}{\rightleftharpoons} B_2 + HB_1^+ + A^- \overset{K_\alpha}{\rightleftharpoons} HB_2^+ \\ &+B_1 + A^- \overset{1/K_d^{HB_2^+A^-}}{\rightleftharpoons} HB_2^+A^- + B_1 \end{aligned} \tag{7}$$

The constants K_d are the dissociation constants of the respective ion pairs. The directly measured quantity is the relative ion-pair basicity—ΔpK_{ip}—of bases B_1 and B_2. This is expressed by Equation (8).

$$\begin{aligned} \Delta pK_{ip} &= pK_{ip}(HB_2^+A^-) - pK_{ip} = pK_{ip}(HB_1^+A^-) \\ &= \log\frac{K_\alpha\,K_d^{HB_1^+A^-}}{K_d^{HB_2^+A^-}} = \log\frac{a(HB_2^+A^-)\,a(B_1)}{a(HB_1^+A^-)\,a(B_2)} \end{aligned} \tag{8}$$

If the K_d values can be measured or estimated then the ΔpK_α (an estimate of the ΔpK_a) can be found using Equation (9).

$$\Delta pK_\alpha = pK_\alpha(HB_2^+) - \Delta pK_\alpha(HB_1^+) = \Delta pK_{ip} - \log\frac{K_d^{HB_1^+A^-}}{K_d^{HB_2^+A^-}} \tag{9}$$

The term gas-phase basicity (GB) refers to the equilibrium shown in Equation (10).

$$B + H^+ \overset{\Delta G_b}{\rightleftharpoons} BH^+ \tag{10}$$

GB is defined as negative Gibbs' free energy of reaction (10) [Eq. (11)].

$$GB = -\Delta G_b \tag{11}$$

The directly measured quantity, similarly to the case of AN or THF, is the relative basicity of two bases $\Delta\Delta G_b$, given by Equations (12)–(14).

$$B_2 + B_1H^+ \overset{\Delta\Delta G_b}{\rightleftharpoons} B_2H^+ + B_1 \tag{12}$$

$$\Delta\Delta G_b = \Delta G_b(B_2) - \Delta G_b(B_1) = R\,T\ln K \tag{13}$$

$$K = \frac{p(B_1)\,I(B_2H^+)}{p(B_2)\,I(B_1H^+)} \tag{14}$$

The p values are the partial pressures, and the I values are the relative ion intensities of the respective species in the mass spectra.

Experimental Section

Chemicals and solvents: Compounds **B1** and **B2** were the same origin as in previous work.[17] Other diamines **D2**-**D10**, **Hp**, **Sp**, **P1**–**P3**, and monoamines **M1**–**M7**, **Pi1**, and **Pi2**, were of commercial origin. The reference compounds used in this work **R1**–**R18** (see Scheme S1 in Supporting Information) were of the same origin as in previous work.[18–24] Solutions of commercial trifluoromethanesulfonic acid (≥99%) or methanesulfonic acid (≥99%) were used as acidic titrant. Solutions of phosphazene bases **R19** (tBuP$_1$(pyrr), ≥98%) in AN and **R20** (EtP$_2$(dma), ≥98%) in THF were used as basic titrants (see Scheme S1 in Supporting Information for exact structures). Commercial THF (≥99.9%) and AN (≥99.9%) with water concentration stated by the producer as below 0.005% were used. The water content of AN determined in our lab by coulometric Karl Fischer titration was below 0.004%. THF was distilled from $LiAlH_4$ under argon before use.

Methods of pK determination in AN and THF: Most diamino bases used in the present work do not have favorable spectra in the UV range. Due to this, the "pure" spectrophotometric ΔpK calculation method that was used for constructing self-consistent basicity scales in these two media in previous works,[18,19,21,23] was not applicable. As an alternative, a more commonly known ΔpK calculation method, which is also described in

ref [18], was used. This method is based on titration of the mixture solution of known amounts (in moles) of "visible" (i.e. having absorption bands in the mid-UV range) indicator base and "invisible" (i.e. not having such absorption bands) amino base with a solution of acidic titrant of known concentration. After each addition of a known amount of acidic titrant, the spectrum was recorded. From this spectrum, the indicator ratio for the "visible" indicator [B]/[BH^+] is obtained. Knowing the amounts of bases (in moles) in the titration vessel, and the number of moles of added titrant, the indicator ratio for the "invisible" base is obtained. After that, the calculation of ΔpK_{ip} in THF and ΔpK_a in AN according to Equations (8) and (4) is straightforward. For some bases, **P2**, **P3**, **Sp**, **M7,** and **M3,** in THF the general ΔpK calculation method[18,22,25] was also used. A good consistency of ΔpK_{ip} values was observed for these two different calculation methods. Preparation of solutions of bases and titrants, and titration experiments, were carried out in a glovebox to ensure that the environment was free of humidity and oxygen. The absorbance measurements were carried out in an external cell compartment UV/vis spectrophotometer, situated in the glovebox. The cell compartment was connected to the UV/vis spectrophotometer by means of two quartz fiber optic cables.

For each investigated base the ΔpK was measured with at least two different reference bases, for which the basicities in AN and THF are known from earlier works.[18,19,21,23]

The correction for ion-pairing in THF was calculated by using the Fuoss equation as described in refs [18] and [26]. The ionic radii of the used compounds are given in Table S1 in the Supporting Information (SI). In acetonitrile the pK_a values for the reference indicator bases were taken from ref [23]. Detailed experimental results for both solvents are given in Tables S2 and S3 in the Supporting Information.

Measurements of gas-phase basicity (*GB*): The *GB* values were determined by using the Extrel FTMS 2001 FT-ICR mass spectrometer with a 3.0 T superconductive magnet. Each equilibrium measurement is a measurement of the relative basicity of bases B_1 and B_2 (that is "each arrow" in Table S4 in Supporting Information) according to Equations (12), (13), (14). The partial pressures of the neutrals were measured using the Bayard-Alpert gauge and were corrected for the differences in ionization cross-sections (see ref [27] for details). The nominal pressures of the single neutral bases varied between 9×10^{-8} and 1.1×10^{-6} Torr, and the sum of pressures of the bases varied between 3.7×10^{-7} and 1.2×10^{-6} Torr. The ratio of the ion intensities in the mass spectrum was used as the estimate of the ratio of the numbers of ions in the cell. The bases were introduced using leak valves from the conventional sample introduction system, the so-called "oven" that was maintained at 50–130 °C. For several compounds the equilibrium measurements were carried out at different partial pressures of the neutrals. Good agreement (difference mostly not more than 0.3 kcal mol^{-1}) was obtained between the $\Delta\Delta G_b$ values at different ratios of partial pressures. At given partial pressures of the neutrals the equilibrium measurements were carried out as a series of pulse sequences with different reaction times. Each sequence consisted of generating ions by an electron impact (20 eV) pulse of 30 ms, giving them time to react (reaction time) and exciting and detecting the ions (see ref [27] for more details). From the ion intensity ratios at different reaction times (and at constant partial pressures of the neutrals) time plots were constructed. From the time plots it was found that between 1 and 30 s of reaction time was necessary to reach equilibrium (depending on the reacting bases and their partial pressures). To ensure that equilibrium was reached, reaction times significantly longer (at least two times longer) than required to reach the plateau on the time plot were used in all cases. All experiments were carried out at cell temperatures of 373 K.

Calculations: The quantum-chemical calculations reported in this work were carried out using the Gaussian 2003 series of programs.[28] Density functional theory (DFT) calculations were performed by using the B3LYP hybrid functional. Full geometry optimizations and vibrational analyses were performed using the 6-311+G** basis set. This approach has been demonstrated by some of us to describe with reasonable accuracy the gas-phase basicities[29,30] of a wide variety of relatively simple molecules. All stationary points were found to be true minima ($N_{imag}=0$). Unscaled B3LYP 6-311+G** frequencies were used to calculate the gas-phase basicities (*GB*) and proton affinities (*PA*) of the neutral bases taking into account the zero point frequencies, finite temperature 0–298 K correction, the pressure-volume work term, and the entropy term as appropriate. The terms gas-phase basicity (*GB*) and proton affinity (*PA*) refer to the equilibrium given in Equation (15)

$$B + H^+ \overset{\Delta G_b,\ \Delta H_b}{\rightleftharpoons} BH^+ \tag{15}$$

GB and *PA* are defined by Equation (16).

$$GB = -\Delta G_b \quad PA = -\Delta H_b \tag{16}$$

For protonated diamines (DAH^+) with the possibility of intramolecular hydrogen bond (HB) formation two conformers were calculated: one with hydrogen bond DAH^+_{HB} and the other without hydrogen bond DAH^+_{NHB}, where HB formation was not allowed by using the straight chain or *trans-trans* conformation of DAH^+. In cases where non-bonded conformer was more stable the most stable hydrogen-bonded conformer was also calculated. Detailed information of gas phase basicity and proton affinity calculations can be found in Table S5 in Supporting Information.

Calculations of basicity contributions using the isodesmic reactions method: The basicity contributions were outlined in the introduction. The method of isodesmic reactions described in ref [5] was used to estimate the energetic contributions of the above mentioned factors on the basicity of the studied diamines. The reactions used are presented in equations ID1–ID16. For each type of diamine two isodesmic reactions are used: one for estimating the strain energy *SE*(DA) in the neutral diamine DA and the other for estimating the joint contribution of strain energy and hydrogen bond energy [*HB*(DAH^+) + *SE*(DAH^+)] (below termed also as $(HB+SE)^+$) in the protonated diamine DAH^+. These contributions were found as given in Equations (17) and (18).

$$SE(DA) = H(DA) + x\,H(HC) - H(MA_1) - H(MA_2) \tag{17}$$

$$[HB(DAH^+) + SE(DAH^+)] = H(DAH^+) + x\,H(HC) - H(MA_1H^+) - H(MA_2H) \tag{18}$$

The number of hydrocarbons (HC) participating in the reaction is denoted by *x*. MA_1, MA_2 are the respective monoamines. The monoamine that is a stronger base is denoted by MA_1. The enthalpies of diamines (*H*(DA)), their protonated forms (*H*(DAH^+)), hydrocarbons (*H*(HC)), monoamines (*H*(MA)), and protonated monoamines (*H*(MAH^+)) were found computationally as described above. The treatment can, in principle, be carried out either in terms of enthalpy or free energy. We have chosen enthalpy to avoid the complications arising from the large entropy effects that are present if the number of molecules changes in the course of the reaction or if a cycle opens or closes, and also in order to facilitate comparison with earlier works.

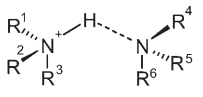
For splitting the joint contribution [*HB*(DAH^+) + *SE*(DAH^+)] into components, the intramolecular hydrogen bond energy *HB*(DAH^+) is found as described in ref [5] from the model systems presented in Scheme 3 according to the Equation (19).

$$HB(DAH^+) = H(R^1R^2R^3NH^+\cdots NR^4R^5R^6) - H(R^1R^2R^3NH^+) - H(NR^4R^5R^6) \tag{19}$$

In Equation (19) $R^1R^2R^3NH^+\cdots NR^4R^5R^6$ is a model hydrogen-bonded complex obtained from the respective protonated diamine by freezing the geometry of the hydrogen bond and reducing the alkyl fragments to small size in order to avoid their steric interaction. The species $R^1R^2R^3NH^+$ and $NR^4R^5R^6$ are the partners in the model HB complex with geometries frozen to match those in the complex. The strain energy in the protonated diamine can be obtained as given in Equation (20).

$$SE(DAH^+)] = [HB(DAH^+) + SE(DAH^+)] - HB(DAH^+) \tag{20}$$

Detailed information about isodesmic reactions and intramolecular hy-



	>N⁺-				>N-	
	R¹	**R²**	**R³**	**R⁴**	**R⁵**	**R⁶**
a	-CH_3	-CH_3	-H	-CH_3	-CH_3	-H
b	-CH_3	-CH_3	-H	-CH_3	-CH_3	-CH_3
c	-CH_3	-CH_3	-CH_3	-CH_3	-CH_3	-H
d	-CH_3	-CH_3	-CH_3	-CH_3	-CH_3	-CH_3
e	-CH_3	-H	-H	-CH_3	-H	-H
f	-CH_3	-H	-H	-H	-H	-H
g	-CH_3	-CH_3	-H	-CH_3	-H	-H
h	-CH_3	-CH_3	-H	-H	-H	-H
i	-H	-H	-H	-H	-H	-H
j	Pr	-H	-H	Pr	-H	-H

Scheme 3. Model systems for estimating hydrogen bond energies.

drogen bond energy calculations can be found from Tables S6 and S7, and Scheme S2 in the Supporting Information.

Results

The results of basicity measurements and calculations are presented in Table 1. Full results of basicity measurements in THF, AN, and both measurements and calculations in the gas phase are available in Tables S2–S5 of the Supporting Information (SI).

Basicity measurements in AN: The absolute pK_a values were calculated as in the previous papers[23,40] by minimizing the sum of squares of differences between directly measured ΔpK_a values and assigned pK_a values, while keeping the pK_a values of reference bases (taken from ref [23]) constant. It should be stressed that the absolute pK_a values of the bases given in Table 1 are not as accurate as the relative pK_a values. The consistency of the results can be assessed using a consistency criterion s as defined by Equation (8) of reference [40]. For our results the s value for compounds measured in this work is 0.04 pK_a units ($nm=58$, $n_c=23$) (see Supporting Information for more details).

Basicity measurements in THF: The basicity values of the bases were obtained using the same approach as described above for AN. The consistency of the ΔpK_{ip} and ΔpK_α values in THF (only the measurements of this work involved) is similar to previous results,[21] that is, $s=0.08$ ($nm=47$, $n_c=22$). The pK_α values of compounds **D9** and **B1** could not be measured in THF. For **D9** the reason was the low solubility of the acid–base complex. For **B1** the p$K_{\alpha1}$ and p$K_{\alpha2}$ values were too close together to be determined by our method. Recently absolute pK_a values for a large number of bases in THF have been obtained by using a combined method of potentiometry and conductometry.[41] However, since the following discussion is concerned first of all with basicity differences, we use here the directly obtained pK_α values rather than the pK_a values obtained from a correlation with pK_α values.

Basicity measurements in the gas phase: There are several compounds on the basicity ladder (see Table S4 in Supporting Information) with published *GB* values.[31] Tripropylamine **M7** was chosen as the anchoring point for the results of this work for the following reasons. 1) There is an excellent agreement between the *GB* value 243.9 kcal mol^{-1} of **R13** ($PhP_1(dma)_2Me$) measured with **M7** as the anchor point (see the Supporting Information) and the *GB* value 243.7 kcal mol^{-1} of the same compound measured with MTBD (7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) as the anchor compound in reference [35]. This means that the present *GB* values are consistent with *GB* values of many other bases over the range 229.5 to at least 264 kcal mol^{-1}. 2) Doing so provided the best agreement observed between measured and calculated *GB* values for the compounds of the present work.

Gas-phase basicity calculations: The average difference between the calculated and experimental results is 0.1 kcal mol^{-1}, indicating that there is no systematic under- or overestimation of basicity. It is important to note that all qualitative conclusions drawn in the discussion below remain valid, irrespective of whether computational or experimental data are used. See the Supporting Information for more details.

Factors determining the basicity of diamines: We attempted to quantify the abovementioned factors (1) to (4) using the approach based on isodesmic reactions similarly to that described in reference [5]. The isodesmic reactions ID1 to ID16 were used. Below each of these reactions, the bases or their protonated forms for which the corresponding reaction is relevant are listed. The substituents $-R^x$ not described here are given in Scheme 1. The model systems used for estimating intramolecular hydrogen bond energies are given in Scheme 3. The results of the treatment are presented in Table 2. Full details are given in Tables S6 and S7 in the Supporting Information.

Discussion

Basicities of 1,3-propanediamines D3–D9: The basicity changes in the row of substituted 1,3-propanediamines (and some other bases) in different media are illustrated in Figure 1.

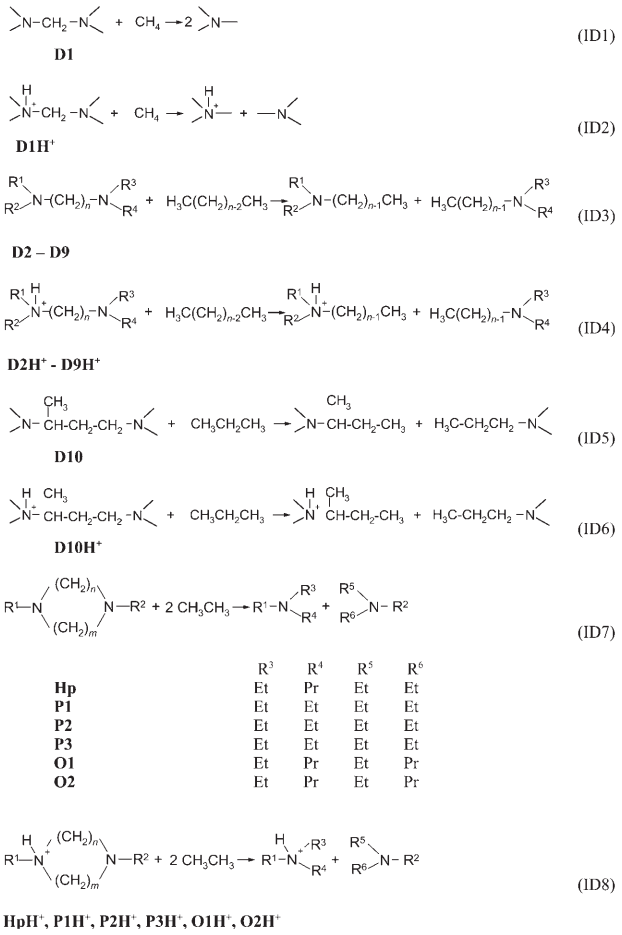
The basicity of the 1,3-propanediamines in the gas phase increases rather monotonously with an increasing level of methylation. This is easily rationalized based on the increase of molecular size and polarizability, as well as the electron-donating nature of the methyl substituents.[10] Computational results indicate that in all the studied 1,3-propanediamines protonation occurs at the most methylated nitrogen, and that the protonated forms of all 1,3-propanediamines are cyclic, due to intramolecular hydrogen bonds (HB). The diamines are clearly stronger than monoamines of similar size and substitution pattern by approximately 9–15 kcal mol^{-1}. Computations using the isodesmic reactions (see Table 2) indicate that, as expected, for open-chain di-

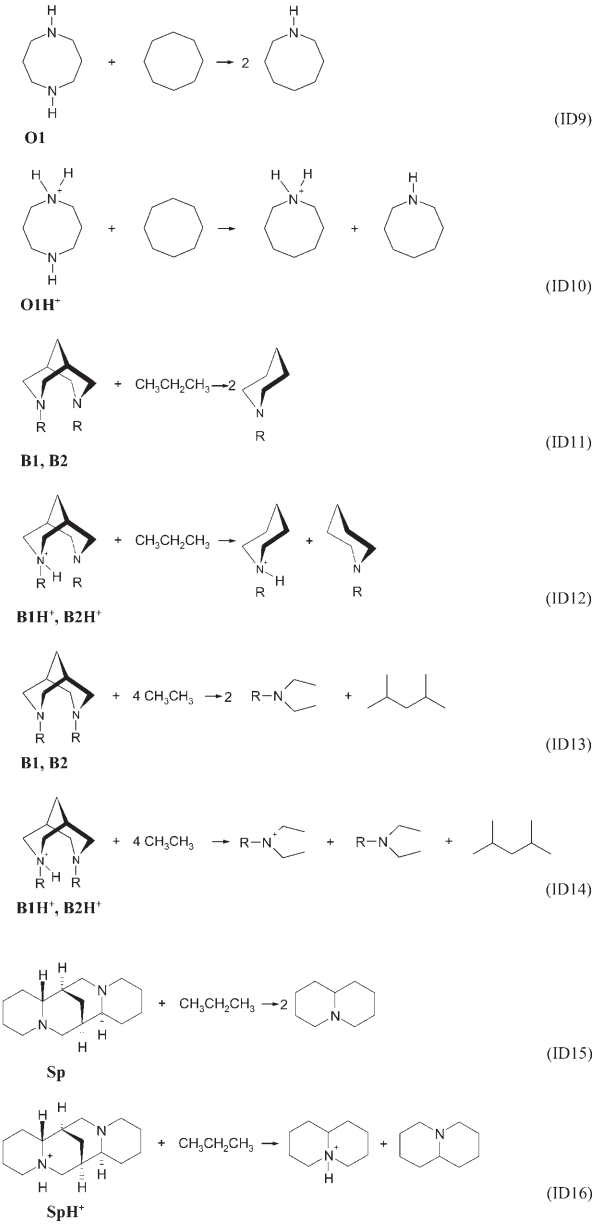
Table 1. Results of experimental basicity determinations in the gas phase, AN, and THF, and calculations in the gas phase.[a]

Base	pK_a(AN)	pK_{ip}(THF)	pK_α(THF)	pK_a(H_2O)	GB_{exp}[b]	GB_{calcd}
			diamines			
D1	–	–	–	7.67[c]	–	226.3
D2	18.68	13.4	12.8	9.15[c]	230.5, 232.0[d]	231.2
D3	19.27	13.6	13.0	10.6[c]	235.2, 235.5[d]	234.8
D4	19.93	13.4	13.1	10.80[c]	237.3[d]	236.4
D5	20.01	14.9	14.3	–	233.3	234.7
N,N′-dimethyl-ethanediamine	19.63[c]	–	–	10.1[c]	226.3[d]	–
D6	20.39	15.5	14.9	–	–	231.2
D7	19.57	15.3	14.7	9.75[c]	231.9, 233.1[d]	234.2
D8	20.04	15.8	15.2	–	227.3	231.4
1,2-ethanediamine	18.46[e]	–	–	10.1[c]	218.1[d]	–
D9	19.70, 19.70[e]	–	–	10.6[c]	224.7[d]	226.9
1,4-butanediamine	20.12[e]	–	–	10.72[c]	228.1[d]	–
D10	20.09	14.1	13.4	–	237.9	236.7
B1	21.55	–	–	–	–	232.7
B2	22.74	15.5	15.4	9.38[f]	240.8	238.5
Sp	21.66[g]	14.2	14.3	11.96[f],12.11[c]	243.4	240.8
Hp	19.10	15.1	14.4	10.41[f]	223.6	225.0
P1	18.69	14.9	14.2	9.7[c]	218.6[d]	218.8
P2	18.07	14.1	13.4	9.32[c]	–	223.0
P3	17.36	13.1	12.4	8.54[c]	–	227.2
			monoamines			
M1	18.43, 18.22[e]	14.7	13.8	10.7[c]	211.3[d]	211.8
M2	18.92	14.6	13.7	–	–	218.2
N,N-dimethyl-propylamine	18.3[h]	13.5[h]	12.7[h]	10.16[f]	222.7[d]	221.2
M3	18.33	13.6	12.6	10.16[f]	222.1[d]	221.4
M4	18.24	13.4	12.8	10.19[f], 10.65[c]	224.2[d]	222.8
M5	18.81	14.6	13.6	11.2[c]	222.9, 224.3[d]	222.1
M6	18.82[i]	14.0[j]	12.5[j]	10.7[c]	226.1, 227.0[d]	228.2
M7	18.25, 18.10[e]	13.1	13.0	10.7[c]	229.5[b]	229.0
Pi1	19.29, 18.92[e]	15.0	14.3	11.1[c]	220.0[d]	220.4
Pi2	18.25, 18.01[k]	13.6	12.9	10.1[c]	224.7[d]	224.0
			various other bases			
aniline	10.62[i]	7.0[j]	5.2[j]	4.6[f]	203.3[d]	204.4[j]
N,N-dimethylaniline	11.43[i]	6.5[j]	4.9[j]	5.1[f]	217.3[d]	216.2[j]
pyridine	12.53[i]	7.4[j]	5.5[j]	5.3[f]	214.7[d]	215.2[j]
guanidine	–	–	–	13.6[c]	226.9[d]	230.6[j]
TMG	23.3[j]	17.0[j]	15.5[j]	13.6[f]	238.4[d]	240.7[j]
PhTMG	20.84[i]	15.0[j]	14.0[j]	11.77[l]	240.4[d]	240.5[j]
DBU	24.34[i]	18.1[j]	16.9[j]	–	242.7[d]	241.3[j]
TBD	26.03[i]	21.7[j]	21.0[j]	–	244.3[d]	246.5[j]
MTBD	25.44[i]	18.6[j]	18.6[j]	–	246.2[d]	248.0[j]
HP_1(pyrr)	27.01[i]	20.8[j]	20.8[j]	13.9 [m]	255.2[j]	255.0[j]
tBuP_1(pyrr)	28.42[i]	20.2[j]	20.2[j]	–	258.7[j]	258.2[j]
PhP_1(pyrr)	22.34[i]	16.0[j]	16.0[j]	11.52[l]	251.7[j]	250.9[j]
HP_1(dma)	25.85[i]	19.7[j]	19.7[j]	13.3[m]	249.6[j]	249.9[j]
tBuP_1(dma)	26.98[i]	18.9[j]	18.9[j]	-	252.9[j]	252.1[j]
PhP_1(dma)	21.25[i]	15.3[j]	15.3[j]	10.64[l]	246.1[j]	245.3[j]
HP_1(tmg)	–	27.9[j]	28.6[j]	–	–	276.1[j]
PhP_1(tmg)	31.4[j]	23.7[j]	24.3[j]	–	–	274.0[j]
PhP_2(pyrr)	27.55[i]	20.2[j]	20.9[j]	–	–	–
EtP_2(dma)	32.94[n]	24.9[j]	25.3[j]	–	264.6[j]	265.9[j]
PhP_2(dma)	26.46[i]	19.4[j]	19.9[j]	–	261.7[j]	259.2[j]
Verkade's base	32.9[o]	–	–	–	259.1[j]	255.0[j]

[a] Values from this work if not indicated otherwise. The data for various other bases have been added for reference. For structures of bases see Scheme S1 and S3 in the Supporting Information. [b] The new measured gas-phase *GB* values (in kcal mol^{-1}) are anchored to the Tripropylamine (**M7**) *GB* value taken from reference [31]. [c] Taken from reference [32]. [d] Taken from reference [31]. [e] Taken from reference [11]. [f] Taken from reference [33]. [g] Taken from reference [34]. [h] Estimated as the average of measured basicities of **M3** and **M4**. [i] Taken from reference [23] [j] Most recent value from taken from references [18,19,21,35]. [k] Taken from reference [36]. [l] Taken from reference [37]. [m] Estimated values taken from reference [37]. [n] Taken from reference [38] [o] Taken from reference [39].

amines the strain energy in the neutral diamine has a negligible effect on the basicity enhancement, being below 1 kcal mol^{-1} in all 1,3-propanediamines. The $(HB+SE)^+$ effects (see above) computed using the isodesmic reactions vary





from −13.4 to −16.1 kcal mol^{-1}. The effect is largest in the unsubstituted 1,3-propanediamine **D9**. The obvious factors are that **D9** is the only base in the row where protonation occurs on the primary nitrogen, resulting in the strongest HB donor group in the row and the best mutual accessibility of the ammonium and amino groups for HB formation. These two factors outweigh the relative weakness of the primary amino group as an HB acceptor. The lowest HB stabilizing effect is observed in mono- and N,N-disubstituted bases: the primary amino group is a weak HB acceptor and neither of the abovementioned factors are operational. It is possible, although somewhat arbitrarily,[5] to separate the $(HB+SE)^+$ contribution into its components by computing the hydrogen bond dissociation energies of the model systems presented in Scheme 3. The HB energies found are rather coherent with $(HB+SE)^+$, and are in the range of −18.7 to −24.7 kcal mol^{-1}. The value of −24.7 for **D9** compares well with the estimate −23 kcal mol^{-1} for **D9** from ref [2] and −24 kcal mol^{-1} for 1,4-butanediamine from reference [1]. HB energies in the same range have been estimated for a number of proton sponges.[5] The HB energies are roughly coherent with the HB lengths, but as found previously for different systems containing intramolecular HBs, there is no quantitative relationship between the energetic and geometrical parameters of the HB.[7,42]

It is important to mention that the quantity $(HB+SE)^+$ described above is, by its meaning and quantitative value, similar to another quantity $[H(DAH^+_{HB})-H(DAH^+_{NHB})]$ (see footnotes to Table 2). Indeed, as shown in Table 2 these two quantities, although of different computational origin, are in good agreement, which indirectly validates the used isodesmic reactions approach.

Table 2. Results of the analysis of diamine basicity using the isodesmic reactions approach.[a]

Compound	*PA*(DA)[b] [kcal mol^{-1}]	*PA*(MA)[b] [kcal mol^{-1}]	*PA*(DA)–*PA*(MA) [kcal mol^{-1}]	*SE*(DA)[c] [kcal mol^{-1}]	[*HB*(DAH$^+$)+*SE*(DAH$^+$)][d] [kcal mol^{-1}]	[*H*(DAH$^+_{HB}$)–*H*(DAH$^+_{NHB}$)][e] [kcal mol^{-1}]	*HB*(DAH$^+$)[f] [kcal mol^{-1}]	*SE*(DAH$^+$)[g] [kcal mol^{-1}]	length of *HB*-(DAH$^+$)[h] [Å]	α(N$^+$H···N)[i] [°]
D1[j]	234.0	225.8	8.2	−2.3	−10.5		49.9	−60.4	2.57	72.1
D2	240.1	228.8	11.3	2.6	−8.7	−8.9	−10.9	2.2	1.93	125.8
D3	244.0	229.8	14.2	0.4	−13.8	−13.5	−21.0	7.2	1.73	153.6
D4	246.5	230.4	16.1	−0.1	−16.1	−17.2	−25.2	9.1	1.64	170.5
D5	243.8	229.8 225.9	14.0	0.4	−13.6	−13.7	−20.3	6.7	1.79	150.1
D6	240.4	225.9	14.6	0.2	−14.4	−14.5	−23.1	8.8	1.71	150.9
D7	243.4	219.5 229.8	13.6	0.2	−13.4	−13.3	−18.7	5.3	1.79	150.1
D8	240.6	225.9 219.5	14.7	0.4	−14.2	−14.2	−20.7	6.4	1.76	148.2
D9	236.1	219.5	16.6	0.4	−16.2	−16.1	−24.7	8.6	1.68	149.4
D10	246.0	229.8 230.5	15.5	−2.0	−17.5	−14.2	−21.1	3.6	1.72	155.6
B1[k]	240.7	228.0	12.7	2.3	−10.4		−17.2	6.8	1.84	130.1
B1[l]	240.7	227.5	13.2	2.3	−10.9		−17.2	6.4	1.84	130.1
B2[k]	246.7	231.5	15.2	5.3	−10.0		−17.2	7.2	1.83	134.4
B2[l]	246.7	231.4	15.3	−1.7	−17.1		−17.2	0.1	1.83	134.4
Sp	249.2	236.1	13.1	7.5	−5.6		−16.5	10.8	1.88	132.7
Hp	233.2	227.5 228.6	4.6	6.5	1.9	−4.5	−7.1	9.0	1.96	110.7
P1[m]	226.0	227.5	−1.5	2.3	3.8	2.1	0	3.8	2.34	85.9
P1[n]	223.9	227.5	−3.6	2.3	5.9	2.1	0	5.9	2.34	85.9
P2[m]	230.5	231.4 227.5	−0.9	−2.7	−1.8	4.5	0	−1.8	2.29	90.2
P2[n]	226.0	231.4 227.5	−5.3	−2.7	2.6	4.5	0	2.6	2.29	90.2
P3[m]	234.8	231.4	3.4	2.1	−1.3	0.4	−0.2	−1.1	2.32	90.4
P3[n]	234.4	231.4	3.0	2.1	−0.9	0.4	−0.2	−0.7	2.32	90.4
O1[o]	239.3	228.6	10.8	8.7	−2.1		−18.1	16.1	1.74	134.2
O1[p]	239.3	229.1	10.3	1.0	−9.3		−18.1	8.8	1.74	134.2
O2	245.6	232.5	13.1	7.2	−6.0	−11.2	−18.1	12.1	1.73	138.6

[a] The structures of the compounds are given in Scheme 1. The values in the Table are the values from: [b] [Eq. (16)], [c] [Eq. (17)], [d] [Eq. (18)], [f] [Eq. (19)], [g] [Eq. (20)]. The full Table with exact reactions for each compound, computational values of compounds and complexes shown in Scheme 3 is given in the Supporting Information, Table S6. [e] The enthalpy difference between the non-hydrogen-bonded *H*(DAH$^+_{NHB}$) and hydrogen-bonded *H*(DAH$^+_{HB}$) conformers of the protonated diamine (which at the same time is the *PA* difference involving these conformers) is denoted as [*H*(DAH$^+_{HB}$)–*H*(DAH$^+_{NHB}$)]. [h] The length of the intramolecular HB in protonated diamine. [i] The angle between nitrogen atoms and hydrogen of hydrogen bond. [j] The isodesmic reaction data of **D1** are in part meaningless and are given here to be used only in the discussion of the isodesmic reaction approach. [k] Isodesmic reactions ID11 and ID12. These are considered more justified than reactions ID13 and ID14 and are used in the discussion. [l] Isodesmic reactions ID13 and ID14. [m] Chair conformation. [n] Boat conformation. [o] Isodesmic reactions ID7 and ID8. These reactions are considered more justified than reactions ID9 and ID10 and are used in the discussion. [p] Isodesmic reactions ID9 and ID10.

Both Table 1 and Figure 1 reveal that the basic behavior and basicity order of 1,3-propanediamines in solution is very different from in the gas phase. Amines are bases with rather localized charge in their protonated forms, and therefore the efficiency of solvation of the protonated forms strongly influences their basicity.[10,43] A similar situation has been demonstrated for substituted oxonium ions.[44] The factors responsible for the differences between the solution and the gas phase are: 1) the possible change of the protonation center compared to the gas phase; 2) the different degree of solvation of the protonated diamine, which is dependent on the level of methylation; and 3) the very low effect of molecular polarizability on the basicity in solution.[10,45]

An immediate conclusion from Figure 1 is the extreme compression of the basicity range in AN and THF. In the gas phase the basicity range of the 1,3-propanediamine family is 7.8 pK_a units (about 10.5 kcal mol^{-1}), while in THF this range is 2.2 pK_a units (there are no data for **D9**, but based on analogy with propylamine and methylpropylamine **D9** is not expected to be much more basic than **D8**), and in AN only 1.1 pK_a units (compression around 3.5 and 7 times, respectively). In very broad terms this is caused by the mutual cancellation of basicity increase due to the increased level of substitution, and the basicity decrease due to the decrease in accessibility of the protonated base (in particular, hydrogens attached to the protonated amino center) for solvent molecules.

In THF the basicity order of 1,3-propanediamines is almost opposite to that in the gas phase (Figure 1). Also, the basicity order of the monoamines is different: *N*-methylpropylamine is distinctly stronger than propylamine or *N*,*N*-dimethylpropylamine. This implies that the preferred center of protonation in diamines in THF is the methylamino group. Its basicity is enhanced by the one methyl substituent, and the one non-hydrogen-bonded hydrogen of the protonated form is still available for HB interaction with a solvent molecule. It is therefore expected that diamines with a methylamino group are protonated on that group. The least attractive protonation center in THF is the dimethylamino group.

Whether a protonated diamine forms intramolecular HBs in THF depends on which of the two possible stabilizing ef-

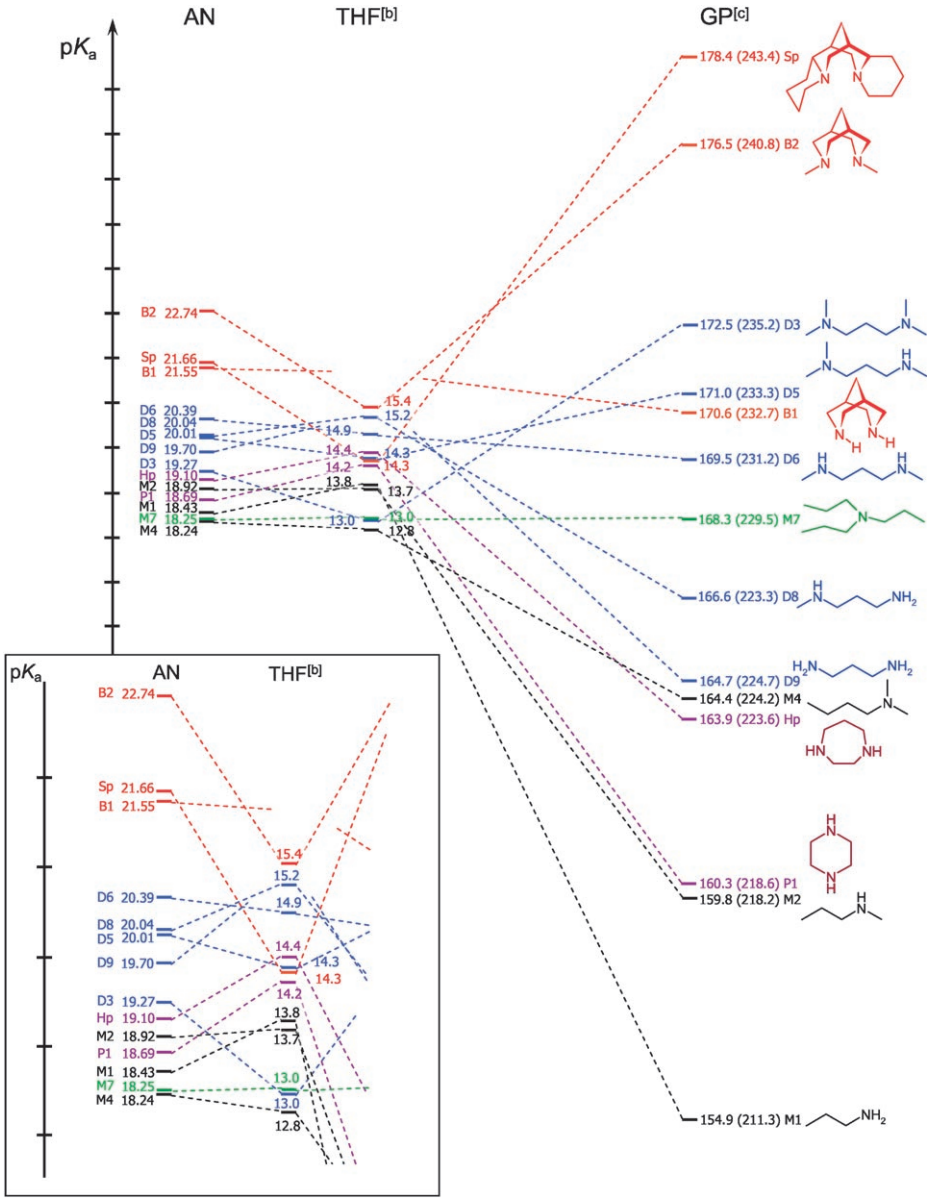


Figure 1. Interrelations between the basicities of some of the studied bases in different media. a) The absolute pK_a values in different media are not directly comparable, so tripropylamine has been used as an arbitrary reference compound for placement of the scales on the figure. The pK_a axis is divided into pK_a units but for the same reason absolute numbers cannot be added. The insert at the bottom left shows an expanded view of the AN and THF basicities. b) pK_α values. c) The pK_a values for the gas phase (GP) are found according to the following equation: $pK_a(GP) = GB \cdot 2.30/RT = GB/1.364$. The GB values (in kcal mol^{-1}) are given in brackets. Experimental values are used except for compounds **B1**, **D6**, and **M2**.

fects—1) intramolecular HBs with low efficiency of solvation, or 2) higher efficiency of solvation in the absence of intramolecular HB—prevails (given the low solvation energy of the neutral molecule). THF is a rather strong HB acceptor ($B' = 287$, $\beta = 0.55$, $DN = 20.5$)[16,46,47] and strongly solvates protonated amino groups. Qualitative conclusions can be drawn from pair-wise basicity comparisons of diamine basicities with basicities of similar monoamines. All our attempts to measure the basicity of **D9** in THF failed. Out of the substituted 1,3-propanediamines that were measured **D8** is the strongest ($pK_\alpha = 15.8$). All 1,3-propanediamines except **D3** are stronger, by at least one pK_a unit, than the respective monoamines, indicating stabilization of the protonated form by intramolecular HBs. The fully methylated diamine **D3** is only stronger than *N*,*N*-dimethylpropylamine by 0.3 pK_a units, indicating almost complete mutual cancellation of the effects of intramolecular HB formation and more efficient solvation of the non-hydrogen-bonding cation. If the intramolecular HB is formed in the protonated form of this base then there will be no proton left with which the solvent can form a hydrogen bond.

In AN the basicity order of the monoamines is the same as in THF. Thus the same protonation site preferences are to be expected. The basicity order of 1,3-propanediamines is, however, different from both THF and the gas phase, and the basicity range of the substituted 1,3-propanediamines is around two times narrower than in THF. The strongest of them is **D6** while **D3** is the weakest. The hydrogen bond acceptor strength of AN ($B' = 160$, $\beta = 0.31$, $DN = 14$)[16,46,47] is significantly lower than that of THF, but at the same time it has a smaller molecule size with a negatively charged cyano nitrogen readily accessible for solvation. Thus it is expected that **D8**, the high basicity of which, in THF, relies heavily on solvation, would be relatively weaker in AN than in THF, and the bases that have crowded protonation centers—**D3**, **D5**, and **D6**—are relatively stronger in AN compared to THF. It is evident from Figure 1 that this is exactly the case. Comparing the basicities of the 1,3-propanediamines and the related monoamines indicates that all protonated 1,3-propanediamines form intramolecular hydrogen bonds in AN. The same conclusion about **D9** has been reached in reference [11].

The basicity range in water is also strongly compressed compared to the gas phase, and the basicity change on suc-

cessive methylation seems to proceed through a minimum. The data is, however, too scarce to draw far-reaching conclusions.

Basicity changes in the row of α,ω-bis(dimethylamino)alkanes: In the row of α,ω-bis(dimethylamino)alkanes **D1**–**D4**, the basicity in the gas phase increases monotonously. At the same time the length of the intramolecular HB in the protonated bases decreases: in protonated **D1** there is actually no HB and the HB length 1.64 Å in **D4** is the shortest of all the diamines studied in this work. The lack of intramolecular HBs in protonated **D1** is the consequence of the dimethylamino groups being bound to the same carbon atom (another consequence of this was that it was not possible to obtain meaningful data from the isodesmic reactions approach, see below). The calculated basicity difference between the diamine and its parent monoamine is the smallest in **D1**: 8.0 kcal mol^{-1}. The same difference in **D3** and in **D4** is equal: 13.6 kcal mol^{-1} (experimental: 12.5 and 13.1 kcal mol^{-1}, respectively). The steric strain in the neutrals due to the repulsion of free electron pairs is again low, as can be expected for open-chain compounds, being over 1 kcal mol^{-1} only for **D2**. The $(HB+SE)^+$ contribution is −8.7 kcal mol^{-1} for **D2** and, rather similarly, −15.1 and −16.1 kcal mol^{-1} for **D3** and **D4**, respectively. Separating $(HB+SE)^+$ into the constituent contributions reveals that the stabilization by HB is around two times lower in **D2** than in **D3** or **D4**. Also the strain energy in the protonated **D2** is dramatically lower. Out of the diamines studied in this work the strongest HB in the protonated form is observed in **D4**, in accordance with the generalizations presented in reference [12]. Comparison of the protonation entropies of diamines and monoamines (See Table S6 in the Supporting Informationfor computational values) is also very illustrative here. The protonation entropy values of the monoamines are in the narrow range of −24.5 to −25.6 cal K^{-1} mol^{-1}. The protonation entropy of **D1** is in the same range: −25.8 cal K^{-1} mol^{-1}. The same values for **D2**–**D4** are significantly more negative −29.6 (for **D2**) to −33.8 (for **D4**) indicating cyclization via intramolecular HBs. The same values for 1,3-propanediamines are mostly in the range of −30 to −31 cal K^{-1} mol^{-1}.

1,2-Ethanediamine, 1,3-propanediamine, and 1,4-butanediamine are less basic than **D2**–**D4** by 12.4, 10.5, and 9.2 kcal mol^{-1}, respectively (experimental data). The difference is smaller for the more stabilizing intramolecular HBs in the cation.

In the THF medium the span of basicity of **D2**–**D4** is only 0.3 pK_α units (compared to the 4 pK_α units in the gas phase, see Figure 1). All three diamines are of approximately the same strength as the corresponding monoamines. The differences 0.2, 0.3, and 0.3 pK_α units (for **D2**, **D3,** and **D4**, respectively) indicate that in all these bases, intramolecular HBs fail to compete efficiently with THF molecules in stabilizing the protonated bases.

In AN, **D2**–**D4** are stronger bases than the parent monoamines by 0.35, 0.99, and 1.69 pK_a units, respectively, meaning that the efficiency of intramolecular HB in stabilizing the protonated base increases from **D2** to **D4**, paralleling the situation in the gas phase. Comparison of **D2**–**D4** with their non-methylated parent compounds reveals that **D2** is more basic than 1,2-ethanediamine by 0.22 pK_a units, while **D3** and **D4** are weaker than their parent compounds by 0.43 and 0.19 pK_a units, respectively. The trends in water are roughly the same as in AN and THF.

A singular example of a diamine is the smallest diamine hydrazine, H_2NNH_2. The gas-phase basicity of hydrazine (GB = 196.6 kcal mol^{-1}) is only 0.9 kcal mol^{-1} higher than that of the respective monoamine, ammonia (GB = 195.7 kcal mol^{-1}). The basicity of hydrazine is determined by the competing influence of the destabilizing repulsion of lone electron pairs on adjacent nitrogen atoms of the neutral hydrazine molecule (base-strengthening effect) and the counteracting inductive effect of the weakly electronegative NH_2 groups (base-weakening effect). No base-strengthening intramolecular HB is possible in the protonated form $H_2NNH_3^+$ of hydrazine. A similar situation is observed in AN: the basicity of hydrazine (pK_a = 16.61,[11] 16.48[48]) is practically equal to that of ammonia (pK_a = 16.46[11]) in AN.

Basicities of bispidines: The basicities of a number of substituted bispidines in solution have been published recently[34] but the parent compound **B1** and the dimethyl derivative **B2** were not included in the study, and only AN as medium was considered. We have studied the basicity of three bispidine bases **B1**, **B2**, and **Sp** in this work. Several conformers of **B1** and **B2** can exist. It has been shown[8] that for **B1** the most stable conformation is the chair–chair conformation with the N-hydrogens in the *endo* and *exo* positions, respectively (see Figure 1) and for **B2** the stability of the chair–chair and chair–boat conformations (both methyl groups in *exo* positions in both cases) are of approximately the same stability. In our calculations the chair–chair conformer of **B2** (see Figure 1) was more stable, and so this conformer was used in the study.

The rather high basicity of bispidines can be attributed to the destabilization of the neutral base by repulsion between the lone pairs of the facing nitrogen atoms, and to the efficient intramolecular bond formation in the protonated bases. Analysis of their gas-phase basicity using the isodesmic reactions approach reveals that compared to the other diamine bases, the strain energies are indeed rather high in the substituted bispidines, being 5.3 kcal mol^{-1} for **B2** and 7.5 kcal mol^{-1} for **Sp**. The high strain energy in **Sp** is the consequence of additional rigidity introduced by the two cyclohexane rings. The strain energy in **B1** is only 2.3 kcal mol^{-1}. This is the consequence of the *exo–endo* geometry of this molecule, which eliminates the repulsion of the two lone electron pairs. However, no intramolecular HB is formed in the neutral **B1**: the N···H distance is 2.368 Å. The stabilizing joint contribution $(HB+SE)^+$ is similar in **B1** and **B2** (−10.4 and −10.0 kcal mol^{-1}, respectively), but is smaller in **Sp**: −5.6 kcal mol^{-1}. Disassembling this contribution into components reveals that the strength (as well as the bond angle and bond length) of the intramolecular HB are very similar in all three compounds, varying from −16.5 to −17.2 kcal mol^{-1}. At the same time the strain energy in the

cation is very different for **B1** and **B2** on one hand and **Sp** on the other hand (see Table 2). Similarly to earlier findings on different proton sponges[5] our results indicate that release of the steric strain in the neutral base on protonation is not a dominating basicity-increasing factor in bispidines: the steric strain energy in the protonated bispidines is higher than in the neutrals. The factor responsible for the enhanced basicity is the intramolecular hydrogen bond. The same is observed in reference [5] for Schwesinger's vinamidine.

For comparison, bases **O1** and **O2**, related to **B1** and **B2,** were included in the study. The **O1** molecule lacks the rigidity of **B1**, and has a proton affinity lower by 1.4 kcal mol^{-1}. The HB energy in protonated **O1** is only around 1 kcal mol^{-1} more negative. However, the strain energies (calculated with isodesmic reactions ID7 and ID8) both in the neutral and in the protonated form of **O1** are around 7–9 kcal mol^{-1} more positive than in **B1**. This is caused by the intrinsic strain of the cyclooctane cycle compared to the cyclohexane cycles, and the strain in the neutral and protonated form largely compensate each other. The comparison of **O2** with **B2** leads to similar results.

In the AN medium the bispidines are stronger bases than any other of the diamine bases studied in this work, thus roughly paralleling the gas-phase situation. The only significant change is the relative weakening of sparteine in AN. In THF, substituted bispidines **B2** and **Sp**, which cannot obtain basicity enhancement from stabilization by solvation, are relatively weak bases compared to the gas phase, and **Sp** is again weaker than **B2**. This basicity order reversal is caused first of all by the large molecule size and polarizability of **Sp** compared to **B2**. The polarizability is a powerful basicity-enhancing factor in the gas phase, but has a low effect in solution.[10]

All our attempts to obtain a reliable THF basicity value for the unsubstituted bispidine **B1** failed, and thus no comparison is possible. The expected pK_α value based on the trends seen in Figure 1 seems to be around 16.

Basicities of cyclic diamines: The results in Table 2 reveal that the gas-phase basicity of unsubstituted cyclic diamines is determined by the possibility of intramolecular HB formation in the protonated base. This in turn is determined by the size of the cycle. As seen above, the eight-member cycle of **O1** allows easy formation of intramolecular HBs in the protonated form with the energy of -18.1 kcal mol^{-1}, which is well in the range observed for 1,3-propanediamines, as is the length of the HB: 1.737 Å. Very similar results are found for **O2**. The efficiency of HB in protonated **Hp** (seven-membered cycle) is dramatically lower than in **O1**. The stabilizing energy is only -7.1 kcal mol^{-1} and the bond angle is very low: 111°. In protonated **P1** there is no HB and the ion prefers the chair conformation to the boat conformation (the former is 2.1 kcal mol^{-1} more stable). The basicity order follows the same pattern: **O2** is among the most basic diamines studied in this work, while unsubstituted piperazine is the weakest. *N*-methylation of piperazine increases its gas-phase basicity as expected.

In solution, the basicity-increasing effect of intramolecular HBs in the protonated base is lower, due to the penalty of losing the solvation efficiency. In addition, the cyclic structure of the unsubstituted bases **P1** and **Hp** (no experimental value is available for **O1**) makes their protonated forms easily accessible for solvation. This leads to their rather high basicity in solvents compared to the gas phase. In THF both bases are stronger than tripropylamine, while in the gas phase both are weaker. The tremendous importance of solvation in THF is further demonstrated by the fact that **P1,** being in the gas phase the weakest diamine studied in this work, has in THF almost the same strength (pK_α = 14.2) as **Sp** (pK_α = 14.3), which in the gas phase is the strongest base studied in this work! In AN an intermediate situation holds: **P1** and **Hp** are stronger bases than tripropylamine but are distinctly weaker than bispidines or 1,3-propanediamines. Piperidine **Pi1** is, in both solvents, a stronger base than **P1**. N-methylation of **P1** reduces its basicity in both solvents dramatically. The effect of introducing the second methyl group has a stronger influence in both solvents indicating that protonation in **P2** occurs on the non-methylated nitrogen in both solvents, paralleling the situation with 1,3-propanediamines.

The isodesmic reactions approach: The approach used in reference [5] and in this work for estimating the contributions of different factors to the enhanced basicity of diamines is useful as it allows one to obtain estimates of energetic effects that are otherwise inaccessible. There are, however, two points in this approach that in our opinion need to be addressed.

1. The choice of isodesmic reaction (ID1–ID16) and the accuracy of the results: The choice of the isodesmic reaction is straightforward in the case of simple diamines. However, in the case of more complex molecules, for example, **B1**, **B2,** and **O1**, this is not so. With these compounds the treatment was carried out according to two different equations, one with opening the cycles (reactions ID13, ID14, ID9, and ID10) and the other with retaining cycles (reactions ID11, ID12, ID9, and ID10).

In the case of **B1** the two reactions ID11 and ID13 yielded almost identical SE contributions (2.3 kcal mol^{-1}, Table 2), which is to be expected since the intrinsic strain of a six-member aliphatic cycle is negligible.[49] For **B2** the SE contribution 5.3 kcal mol^{-1} obtained using reaction ID11 is well in line with those for **B1**, keeping in mind that the additional methyl groups force the molecule into an *exo-exo* conformation, creating repulsion between the lone pairs. However, using reaction ID13 for **B2** leads to a meaningless SE value of -1.7 kcal mol^{-1}. All our attempts to re-run calculations with different conformations for the reactants led to the same result. This finding can be rationalized based on an uncertainty analysis of the isodesmic reactions approach that has been presented in the Supporting Information. The analysis leads to three conclusions: 1) the isodesmic reactions should be designed with as small a number of participating molecules as possible; 2) small energetic effects

cannot be reliably estimated from this approach; 3) comparison of data for different molecules can be made if the used isodesmic reactions are similar (contain as many common molecules as possible, because then the experimental errors cancel out) or if the effects are large.

In the case of **O1** there is no reason to expect agreement (see above) and the obtained strain energy contributions are indeed different. In the case of the reaction proceeding with opening of the cycle, the strain inherent in a cyclooctane ring is also included in the strain component (altogether 8.7 kcal mol^{-1}), while in the case of the reaction proceeding with preservation of the cycle yields a strain energy of only 1.0 kcal mol^{-1}, which is the actual repulsion energy of the two amino groups.

2. Calculating intramolecular HB energy according to Equation (19): It is admitted in reference [5] that the approach to calculating the HB energy is approximate and is not entirely satisfactory. In some cases the strain energies in the protonated bases obtained from Equation (20) were negative, and thus without physical meaning.[5] In order to elucidate the actual meaning of *HB*(DAH^+) values from Equation (19) we computed (see above for methodology) the enthalpy of the reaction of formation of the hydrogen-bonded complex between trimethylamine and the trimethylammonium ion (below complex) from trimethylamine and the trimethylammonium cation [Eq. (21)]; geometries of all the species were optimized).

$$(H_3C)_3NH^+ + :N(CH_3)_3 \rightarrow (H_3C)_3NH^+ \cdots :N(CH_3)_3 \qquad (21)$$

The enthalpy change of this reaction $\Delta H = -19.1$ kcal mol^{-1} is what is normally perceived as the enthalpy of hydrogen bond formation in this system in the gas phase. The gas-phase enthalpy change of this reaction has also been determined experimentally by three independent groups, with results ranging from −22.0 to −22.6 kcal mol^{-1}.[50] At the same time, this enthalpy obviously includes some strain energy contribution due to the approaching of the methyl groups of the two species. The HB energy in the complex was also calculated by Equation (19) as described above. However, to mimic the situation encountered with diamines, whereby the amino groups in the model system may have some alkyl fragments replaced by hydrogen atoms, we used four different model systems: $(H_3C)_3NH^+\cdots:N(CH_3)_3$; $(H_3C)_2NH_2^+\cdots:NH(CH_3)_2$; $H_3CNH_3^+\cdots:NH_2CH_3$; $H_3NH^+\cdots:NH_3$. Complexes with di- and monomethylamines were created by replacing methyl groups with hydrogen atoms in such a way as to maximize the distance between the remaining methyl groups. The HB energies obtained were −23.1, −25.8, −28.0, and −29.3 kcal mol^{-1}, respectively. We see that the values obtained for the different model systems vary by 6 kcal mol^{-1}. The dependence of the HB energy on the chosen model system was also investigated with protonated **D4**. HB calculations were done in four different ways (trying both tri- and dimethylamine fragments in all combinations, see Table S7 in the Supporting Information for further information) and the resulting HB energies ranged over 4 kcal mol^{-1}, from −21.3 to −25.4 kcal mol^{-1} (the discussion presented above is based on dimethylamine fragments, in order to be coherent with the other molecules).

Two more conclusions follow: 4) The HB energies obtained with this approach are highly approximate, and no meaning should be ascribed to small differences in HB energies unless the parent molecules are very similar. 5) To be comparable, the HB energies of different molecules have to be derived using model systems as similar as possible.

In the case of the trimethylamine complex, all HB energies based on Equation (19) are significantly more negative than the above calculated reaction enthalpy −19.1 kcal mol^{-1}. The reason is of course that the latter value also contains the strain contribution. Depending on the experiment and the assumptions made, the strain component can be included or excluded from the experimental values. Therefore it needs some consideration whether to compare the experimental HB formation enthalpies to the HB energies based on Equation (19) or to the $(HB+SE)^+$ values.

It should also be noted that care must be taken in designing the model system for HB energy estimation. It is very important that no additional steric strain is introduced when replacing fragments of the original molecule by hydrogen atoms or methyl groups. An example of a molecule with which this is impossible is protonated **D1**. With this species this HB energy estimation method cannot be used because of strong repulsion between the hydrogens attached to the amino groups instead of the methylene fragment. The HB energy of 50.0 kcal mol^{-1} given in Table 2 is meaningless, and is given only as an illustration of the inapplicability of the approach.

Conclusion

A comprehensive basicity study of α,ω-alkanediamines and related bases has been carried out in AN, THF, and GP. As a result, basicity values for 16, 14, and 9 diamine bases are now available in these three media. In addition the gas-phase basicities and equilibrium geometries were computed for 19 diamino bases at the DFT B3LYP 6-311+G** level. The results indicate that the basicity in GP is determined by the molecular size and polarizability, the extent of alkylation, and the energy effect of intramolecular hydrogen bond formation in the protonated base. The basicity trends in AN and THF differ very much from those in GP: 1) The solvents severely compress the basicity range of the bases studied (3.5 times for the 1,3-propanediamine family in AN and 7 times in THF), and 2) while stepwise alkylation of the basicity center leads to a steady basicity increase in the gas phase, the picture is complex in the solvents. Significant differences are also evident between THF and AN. The high hydrogen bond acceptor strength of THF leads to a favoring by this solvent of bases with "naked" protonation centers. In particular, the basicity order of *n*-methylated 1,3-propanediamines is practically inverse to that in the gas phase. The

picture in AN is intermediate between that of GP and THF.

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