Two amidine derivatives studied by ^{1}H, ^{13}C, ^{14}N, ^{15}N NMR and GIAO-CHF calculations

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^{1}H, ^{13}C, ^{14}N, and ^{15}N NMR data are presented for two amidine derivatives and their complexes with TFA in 1:1 and 1 : 2 molar ratios. The protonation site at the N5 atom was established based upon the observed coupling constants, NOE interactions, and chemical shift change. The GIAO-CHF calculations were also performed for the free bases and their N5 cations.

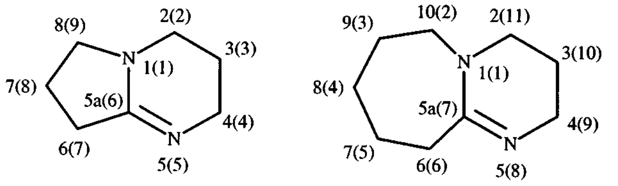
Introduction

1,5-Diazabicyclo[4.3.0]non-5-ene **1a** (DBN) and 1,7-diazabicyclo[5.4.0]undec-7-ene **2a** (DBU) (Fig. 1) are very strong bases with pK_a values in acetonitrile of 23.79 and 24.31 respectively.[1] Both of them have amino (N1) and imino (N5) type nitrogen atoms forming the amidine group. The nature of these compounds is not well known. In the literature it is possible to find some controversial data concerning deuteration of DBU.[2,3]

In the present work we report a multinuclear magnetic resonance investigation for the free bases (**1a** and **2a**) and their complexes with CF_3COOH (TFA) in 1 : 1 (**1b** and **2b**) and 1 : 2 (**1c** and **2c**, see Fig. 1) ratios in dry acetonitrile at room temperature. The results of *ab initio* molecular orbital calculations for the free molecule and the appropriately protonated form are also included.

Results and discussion

We have measured the ^{1}H, ^{13}C, ^{15}N, and ^{14}N NMR spectra in acetonitrile at room temperature (25 °C) of compounds **1a**, **2a** and their complexes with TFA **1b**,**c**, **2b**,**c** (Tables 1 and 2). We have also calculated, by means of the GIAO-CHF method, molecular properties such as: absolute nuclear shieldings, bond lengths, orders and angles, and atomic charges for compounds **1a**,**c** and **2a**,**c** (Tables 2 and 3).



1a DBN **2a** DBU
complexes with TFA (molar ratio of base and acid):
1b (1:1) **2b** (1:1)
1c (1:2) **2c** (1:2)

Fig. 1 Compounds studied **1a**, **2a** and their complexes **1b**,**c**, **2b**,**c** (IUPAC numeration is given in parentheses).

Table 1 ^{1}H NMR data for compounds **1a**, **2a** and their complexes **1b**,**c** and **2b**,**c**

	Free base	Complex with TFA			
		1:1		1:2	
	δ	δ	Δδ	δ	Δδ
DBN	**1a**	**1b**		**1c**	
H2	3.13	3.31	0.18	3.35	0.22
H3	1.68	1.95	0.27	1.96	0.28
H4	3.16	3.28	0.12	3.32[a]	0.16
H6	2.25	2.72	0.47	2.80	0.55
H7	1.85	2.03	0.18	2.08	0.23
H8	3.20	3.51	0.31	3.60	0.40
5NH	—	10.28	—	8.65	—
DBU	**2a**	**2b**		**2c**	
H2	3.19	3.39	0.20	3.45	0.26
H3	1.70	1.91	0.21	1.97	0.27
H4	3.12	3.24	0.12	3.28[b]	0.16
H6	2.29	2.61	0.32	2.67	0.38
H7	1.60	1.68	0.08	1.68	0.08
H8	1.62	1.73	0.11	1.72	0.10
H9	1.54	1.66	0.12	1.66	0.12
H10	3.17	3.44	0.27	3.51	0.34
5NH	—	8.19	—	8.03	—

Coupling constant ^{3}J(H4–5N*H*) is [a] 2.8 Hz, [b] 3.2 Hz. Δδ means the difference: δ(complex) − δ(base).

NMR signal assignment

The signals of the proton nuclei appear in three different ranges of chemical shifts. Signals of hydrogen nuclei α to nitrogen atoms (H2, H4, H8 of DBN and H2, H4, H10 of DBU) are in the range 3.6–3.1 ppm, α to a double bond (the H6 nucleus) at about 2.8–2.2 ppm, and other ring hydrogen nuclei (H3, H7 of DBN and H3, H7, H8, H9 of DBU) at 2.1–1.5 ppm (Table 1). In the ^{1}H NMR spectra of complexes **1b** and **2b** we observe one acidic proton in the range 10.3–8.2 ppm, while in the case of the complexes **1c** and **2c** two such protons are present. One of the protons appears at about 8.6–8.0 ppm, and is attached to an amidine molecule. The other one is at about 16.3 ppm and is

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Table 2 Experimental and calculated data for the carbon and nitrogen nuclei of the compounds and complexes studied

	Free base	Complex with TFA				Calculated data					
		1:1		1:2							
	δ[a]	δ[a]	$\Delta\delta$[a]	δ[a]	$\Delta\delta$[a]	σ_{abs}[a]	δ_{rel}[a,b]	q[c]	σ_{abs}[a]	δ_{rel}[a,b]	q[c]
DBN	**1a**	**1b**		**1c**		base			cation		
N1	−288.8	−258.7	30.1	−255.5	33.3	178.1	−241.9	−0.10	131.6	−213.4	0.03
C2	43.8	43.3	−0.5	43.3	−0.5	153.7	42.5	−0.04	153.4	42.7	−0.05
C3	21.8	19.8	−2.0	19.5	−2.3	170.6	23.1	−0.12	174.5	18.6	−0.12
C4	44.6	39.7	−4.9	39.2	−5.4	152.0	44.3	0.00	155.9	39.9	−0.02
N5	−187.6	−263.8	−76.2	−277.7[c]	−90.1	49.3	−164.6	−0.41	162.7	−232.6	−0.09
C5a	160.5	164.8	4.3	165.8	5.3	26.7	158.7	0.33	11.4	174.0	0.40
C6	31.8	30.9	−0.9	31.1	−0.7	163.4	31.3	−0.13	162.7	32.2	−0.14
C7	20.4	19.6	−0.8	19.3	−1.1	172.4	21.0	−0.11	174.4	18.7	−0.10
C8	51.9	53.7	1.8	54.6	2.7	146.5	50.6	−0.03	141.7	56.2	−0.03
DBN	**2a**[d]	**2b**		**2c**		base			cation		
N1	−290.0	−263.4	26.6	−259.2	28.8	184.0	−293.5	−0.10	136.0	−255.7	0.01
C2	48.2	49.2	1.0	49.3	1.1	147.8	48.8	−0.03	147.7	48.9	−0.04
C3	22.3	20.8	−1.5	20.0	−2.3	169.8	23.8	−0.12	174.0	19.0	−0.11
C4	43.9	39.9	−4.0	39.0	−4.9	125.5	43.5	−0.01	156.4	39.0	−0.03
N5	−173.0	−260.6	−87.6	−265.1[f]	−92.1	34.9	−175.9	−0.40	152.5	−268.7	−0.08
C5a	161.5	166.2	4.7	167.1	5.6	26.5	158.9	0.30	10.2	175.2	0.38
C6	37.0	33.8	−3.2	33.3	−3.7	156.1	39.3	−0.13	158.6	36.5	−0.14
C7	25.8	25.1	−0.7	24.5	−1.1	168.1	25.7	−0.11	170.6	22.8	−0.10
C8	29.6	29.8	0.2	29.5	−0.1	164.1	30.2	−0.10	166.3	27.8	−0.10
C9	28.3	27.6	−0.7	27.1	−1.2	163.0	31.5	−0.11	167.5	26.4	−0.11
C10	52.7	54.6	1.9	55.1	2.4	146.1	50.7	−0.05	141.7	55.6	−0.05

[a] In ppm. Chemical shifts are relative to TMS (carbon nuclei) or external neat nitromethane (nitrogen nuclei). [b] Recalculated to chemical shift scale according to equations given in Fig. 5. [c] In atomic units. [d] Coupling constants $^1J(^{13}C–^{13}C)$ are [in Hz]: 33.7 (C2–C3); 31.5 (C3–C4); 54.4 (C5a–C6); 32.3 (C6–C7); 35.8 (C7–C8); 37.8 (C8–C9) and 35.0 (C9–C10). Coupling constant ^1J(N5–5N*H*) is [e] 97.9 Hz, [f] 96.5 Hz. $\Delta\delta$ means the difference: δ(complex) − δ(base).

Table 3 Calculated *ab initio* bond data for the free bases and their cations

	length[a]		order		angle[b]		
Bond	base	cation	base	cation		base	cation
DBN							
N1–C2	1.439	1.462	1.30	1.25	C2–N1–C5a	119.7	123.0
N1–C5a	1.374	1.301	1.42	1.71	C5a–N1–C8	112.5	112.9
N1–C8	1.443	1.469	1.30	1.23	N1–C2–C3	107.8	109.1
C2–C3	1.522	1.522	1.38	1.38	C2–C3–C4	110.5	111.2
C3–C4	1.528	1.521	1.38	1.39	C3–C4–N5	114.3	109.1
C4–N5	1.450	1.466	1.33	1.23	C4–N5–C5a	117.9	122.4
N5–C5a	1.254	1.306	2.03	1.68	N1–C5a–N5	127.6	123.1
C5a–C6	1.510	1.499	1.40	1.39	N1–C5a–C6	107.7	111.3
C6–C7	1.531	1.534	1.40	1.38	C5a–C6–C7	103.9	102.4
C7–C8	1.530	1.531	1.38	1.37	C6–C7–C8	103.3	104.1
					N1–C8–C7	102.4	102.8
DBU							
N1–C2	1.452	1.473	1.28	1.23	C2–N1–C5a	119.4	121.4
N1–C5a	1.378	1.307	1.44	1.71	C5a–N1–C10	122.5	122.1
N1–C10	1.452	1.478	1.28	1.22	N1–C2–C3	110.3	111.4
C2–C3	1.516	1.512	1.39	1.38	C2–C3–C4	109.2	109.9
C3–C4	1.519	1.514	1.38	1.39	C3–C4–N5	112.6	108.2
C4–N5	1.444	1.461	1.34	1.25	C4–N5–C5a	119.7	124.8
N5–C5a	1.262	1.314	2.02	1.67	N1–C5a–N5	125.7	121.4
C5a–C6	1.511	1.505	1.39	1.39	N1–C5a–C6	117.3	121.2
C6–C7	1.534	1.538	1.38	1.36	C5a–C6–C7	115.0	113.6
C7–C8	1.526	1.525	1.39	1.39	C6–C7–C8	114.9	114.5
C8–C9	1.525	1.525	1.39	1.39	C7–C8–C9	115.2	115.2
C9–C10	1.526	1.524	1.37	1.37	C8–C9–C10	114.4	114.2
					N1–C10–C9	114.4	114.0

[a] In Å. [b] In degrees.

probably exchanging between two trifluoroacetic anions. ^1H NMR data show a fast configuration inversion for both of the aliphatic DBN and DBU rings. We observe signals of pseudo-axial and pseudo-equatorial protons with vicinal $^1H–^1H$ interactions of less than 1 Hz. We used NOE, COSY and INEPTLR (see also below) experiments for the assignment of the proton signals given in Table 1. All of the ^1H nuclei are deshielded after protonation. The biggest observed changes are for the H2, H3, H6, and H8 (DBN) or H10 (DBU) nuclei (more than 0.2 ppm). ^{1}H NMR data for complexes **1c**, **2c** are sufficient for the determination of the place of protonation. This occurs at the N5 position. This proposal is confirmed by the ^{1}H–^{1}H coupling constant between the 5N*H* and H4 nuclei, and also by the NOE effect observed between the 5N*H*–H4 and 5N*H*–H6 nuclei.

The carbon spectra show similar behaviour to that found for the proton spectra (Table 2). The carbon nuclei α to nitrogen atoms are more deshielded (signals appear in the range 55–39 ppm), then the C6 nucleus (α to double bond)—at about 38–31 ppm—and finally the other aliphatic carbon nuclei are more shielded (signals appear in the range 30–19 ppm). We also observe one quaternary carbon atom at about 160 ppm, which is attributable to C5a. All of the carbon signals are distinguished by the ^{13}C–^{1}H INEPTLR (selective polarization transfer from a proton to carbon nuclei, for an example see Fig. 2) and ^{13}C–^{1}H 2D XHCORRD experiments. The first experiment was also helpful in the assignment of the proton signals. After protonation the biggest changes of chemical shifts are observed for the C4, C6, C3 nuclei (increase in shielding), and the C5a, C8 (DBN), C10 (DBU) nuclei (decrease in shielding).

In the ^{15}N NMR spectra of the free bases **1a**, **2a** we observe two signals at about −290 ppm and −180 ppm. From the literature[4] it is known that the amino nitrogen nucleus should be more shielded than the imino one by about 100 ppm. So we assign these two signals to the N1 and N5 nuclei, respectively (Table 2). After protonation the N5 nucleus is more shielded, while N1 is deshielded. In the 1 : 1 complexes both of the nitrogen signals are close together. The ^{1}H–^{15}N GHMQC measurements (Fig. 3) provide unambiguous evidence for the assignment of these two ^{15}N signals given in Table 2. In the case of 1 : 2 complexes **1c**, **2c**, the signal appearing at high field is a doublet of about 90 Hz. This splitting is due to a one bond interaction between the N5 nucleus and the 5N*H* proton. As a consequence of this the other signal, appearing at low field, is assigned to N1.

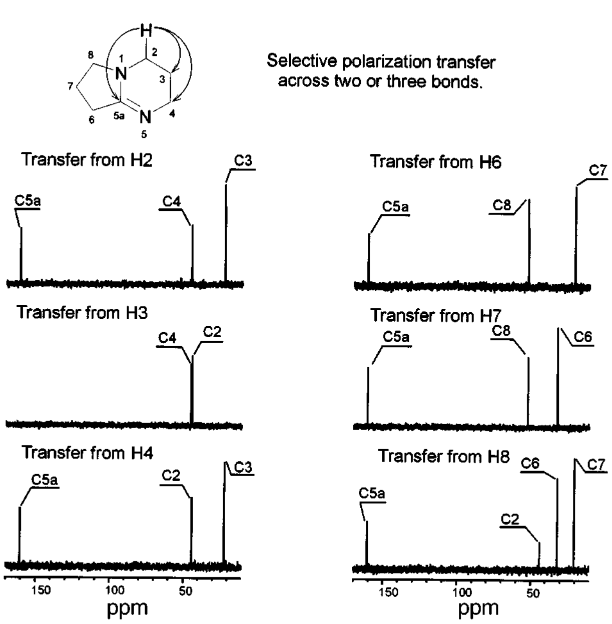


Fig. 2 ^{13}C INEPTLR spectra for compound **1a**.

Ab initio calculations

We calculated molecular properties for free bases and their cations with a proton attached to the N5 atom. Electron correlation effects are not taken into account. The most stable conformers generated by the *ab initio* calculations are presented in Fig. 4. We compared the calculated absolute nuclear shielding constants with the experimental chemical shifts of the carbon and nitrogen nuclei obtained for compounds **1a**,**c** and **2a**,**c**. We note that this relation is linear (Fig. 5). Due to the absence of electron correlation, it is well known[5–7] that the CHF shielding calculations may not give satisfactory results for nuclei with lone pair electrons and multiple bonds.[5–7] Consequently, we use the least squares method to calculate the relative chemical shifts given in Table 2. The relevant equation is $\delta_{\mathrm{exp}} = -0.789\sigma_{\mathrm{abs}} - 148.44$ with a correlation coefficient of 0.9978 for the nitrogen nuclei (Fig. 5a) and $\delta_{\mathrm{exp}} = -1.135\sigma_{\mathrm{abs}} + 216.54$ with a correlation coefficient of 0.9932 for the carbon nuclei (Fig. 5b). The C5a atom was not included in the calculation of this line, due to its unsaturated character[5–7] (carbon with double bond) and quite different chemical shift in comparison with all of the other carbon nuclei (saturated character). Good agreement between experimental and calculated data provide confirmation of the assignment of the NMR signals for the compounds studied.

Site of protonation

Analysis of the changes in chemical shifts of DBN and DBU, after adding acid, gives us the following conclusions. In the 1 : 2 complexes only one nitrogen atom is protonated, that in position 5. As a consequence, the shielding of the N5 nucleus increases by about 90 ppm. The arguments to explain this are given above: the observed coupling constants and NOE inter-

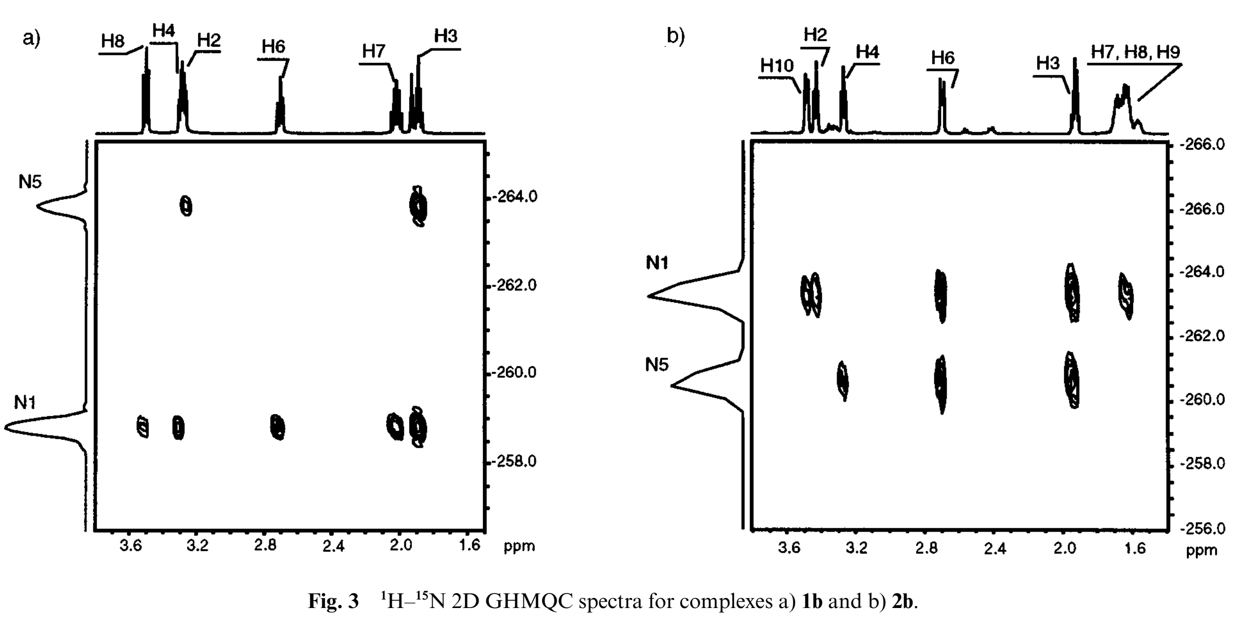


Fig. 3 ^{1}H–^{15}N 2D GHMQC spectra for complexes a) **1b** and b) **2b**.

actions with the proton attached to the base (5N*H*). Instead, in the 1 : 1 complexes only rapid proton exchange between acid and base exists. The DBN and DBU molecules are only partially protonated and the change of the chemical shift of the N5 nucleus can be used as a measure of this process.

Next we observe deshielding of the N1 nucleus by about 30 ppm. The N1 is an amine type atom and the change of shielding of its nucleus should be around ±10 ppm.[4] Strong deshielding of amine type nuclei (even 140 ppm) was found in conjugated double bond systems.[4,8] The lone electron pair of a nitrogen nucleus is delocalised in conjugated double bond systems after protonation of the atom adjacent to the amino group[8] (Fig. 6). A similar situation exists in the compounds studied. Protonation of the N5 atom causes delocalization of the lone electron pair of the N1 atom towards to the N5 atom and both the N5–C5a and N1–C5a bonds should be partially unsaturated. The ^{14}N NMR spectra of the complexes **1c** and **2c** show that the positive charge is almost equally distributed between both of the nitrogen atoms. In addition we observe deshielding of the C5a nucleus by about 5 ppm and shielding of the C4 nucleus by about 5 ppm. These nuclei are α to the protonation site and both of them should be shielded after protonation, similar to the behaviour found in the case of azaindolizines.[9] The structures of the amidine cations are presented on Fig. 7.

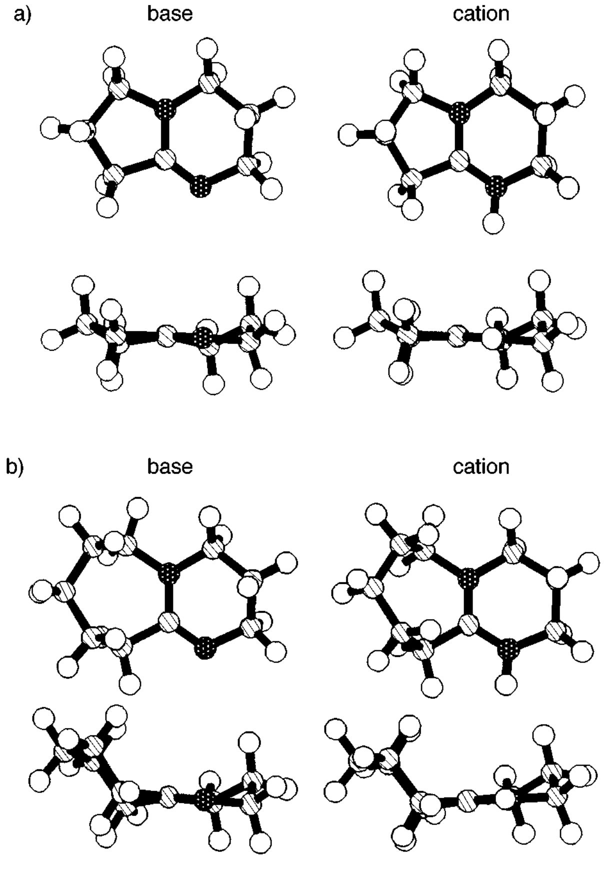


Fig. 4 Lowest energy conformers for a) DBN and b) DBU obtained by *ab initio* molecular orbital calculations.

Bonds and charges analysis

We note that the C–C and C–N bonds are almost single in the free molecules and their lengths are about 1.53 and 1.44 Å, respectively (Table 3). In the protonated DBN and DBU they become longer by less than 0.026 Å. The exceptions are the N1–C5a and N5–C5a bonds. In free bases these bonds are

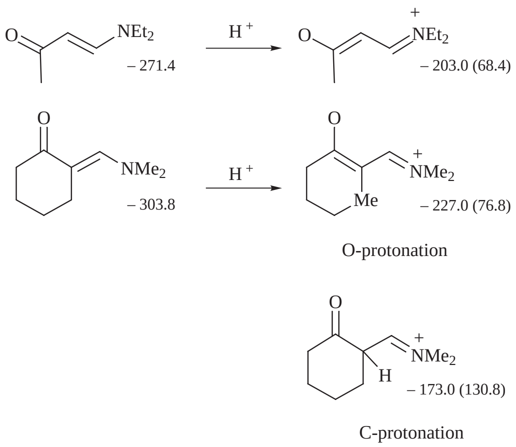
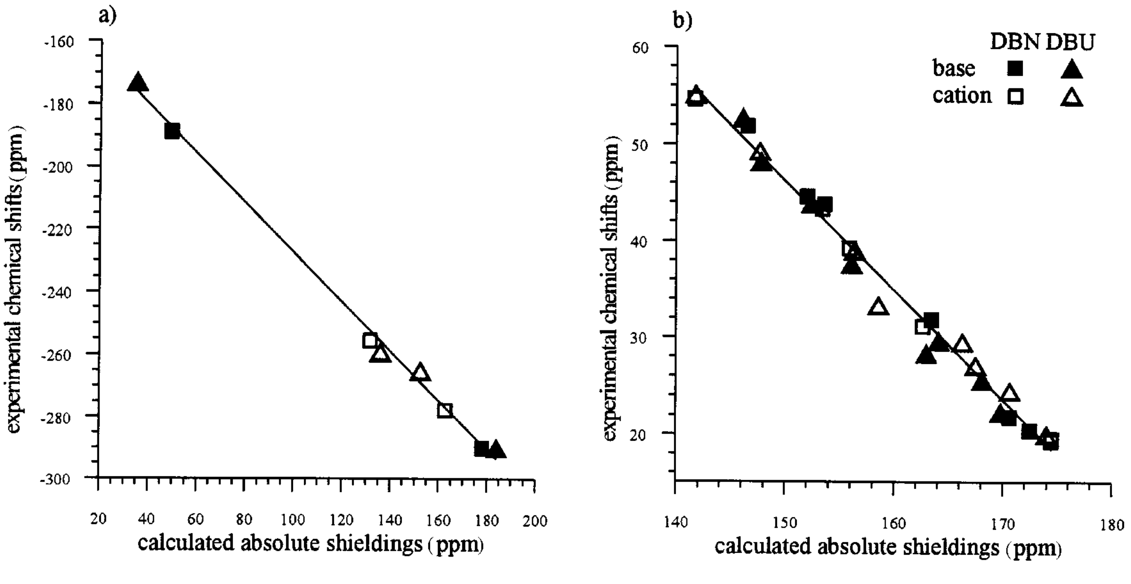


Fig. 6 Chemical shifts of the amine group in some enaminones with the change upon protonation of the atom adjacent to the amino group in parentheses.



Equation: $\delta_{\text{rel.}} = -0.789\ \sigma_{\text{abs.}} - 148.44$
number of points used = 8
correlation coefficient $r = 0.9978$

Equation: $\delta_{\text{rel.}} = -1.135\ \sigma_{\text{abs.}} + 216.54$
number of points used = 28
correlation coefficient $r = 0.9932$

Fig. 5 Plot of experimental chemical shifts *vs.* absolute shieldings for a) nitrogen and b) carbon nuclei for the compounds studied.

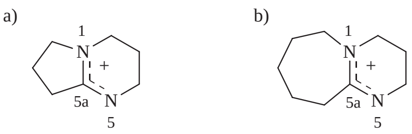


Fig. 7 Structures of a) DBN and b) DBU cations.

single and double, respectively (lengths of about 1.37 and 1.25 Å, respectively). For the protonated forms the calculated lengths of both of these bonds have almost the same value, of about 1.30 Å, thus they have partial double character (Table 3). This constitutes one more suggestion of delocalization of the lone electron pair on the N1 atom. The electron density around the N5, C5a, and N1 nuclei is lowest in the cation by comparison with the free bases. The biggest negative charge of about −0.4 au is localised at the N5 atom, whereas −0.1 au is found at the N1 atom. In the DBN and DBU cations, the charge density on both of the nitrogen nuclei is near zero. For the other carbon and nitrogen nuclei, not mentioned above, the charge distribution is very similar to that of the free bases and their cations (Table 2).

Conclusions

Multinuclear magnetic resonance studies of two bases DBN, DBU and their complexes with TFA give as follows: the proton accepting centre for this kind of molecule is the N5 atom. In 1 : 1 complexes rapid proton exchange between base and acid exists, while in 1 : 2 complexes the amidine cation was found. The high basicity of the compounds studied arises not only from the proton accepting character of the N5 atom, but also due to the possibility of delocalization of the lone electron pair of the N1 atom.

The results of the *ab initio* calculations performed for the free bases and their cations are in good agreement with the experimental data. Based on the good correlation between the chemical shifts and the calculated absolute shieldings the correctness of signal assignment is demonstrated. This dependence is also helpful in the prediction of protonation sites. All structural information which was obtained from the NMR spectra was also provided by the GIAO-CHF molecular orbital calculations. We conclude that the results of the *ab initio* calculations support the NMR data for the compounds studied.

Experimental

Preparation

Compounds **1a** and **2a** are commercially available. The complexes **1b**,**c** and **2b**,**c** were prepared by adding the molar ratio of acid to a solution of base in dry acetonitrile-d_6. The solvent was distilled and dried by 4 Å molecular sieves.

NMR measurements

^{1}H, ^{13}C, ^{14}N, and ^{15}N NMR spectra were taken on a Bruker AM 500 spectrometer, operating at 500.18, 125.76, 36.6, and 50.68 MHz, respectively, equipped with a standard variable temperature unit. The temperature employed was 25 °C and solutions were of concentration 0.1–0.3 M. Standard Bruker library programs were used for the measurements. Typical NMR conditions were used as follows: a relaxation delay of 10 s, a mixing time of 6 s for the NOEMULT, a data matrix of 2048 × 512, a relaxation delay of 2 s, a coupling constant of 140 Hz for the XHCORRD, a relaxation delay of 2 s, a coupling constant of 2.5 Hz or 100 Hz for the INEPT and INEPTRD, a pulse selectivity of 12.5 Hz, a coupling constant of 8 Hz for the INEPTLR. The ^{1}H–^{15}N 2D GHMQC spectra of *compounds* **1b** and **2b** were taken on a Varian 500 Inova spectrometer operating at 499.81 MHz for hydrogen nuclei. A data matrix of 2048 × 512, a relaxation delay of 2 s and a mixing time of 0.08 s were used.

Computational methodology

The *ab initio* GIAO-CHF molecular orbital calculations were performed on a Silicon Graphics Onyx Workstation using the Turbomole program of MSI.[10] The double-ζ basis set with a polarization function (dz + p)[11] was used for the geometry optimization, while the triple-ζ basis set with two polarization functions (tz + 2p)[11] was used for the molecular property calculations such as the SCF electronic energy, absolute nuclear shielding constants, molecular geometry, charge distribution and bond orders by the Roby–Davidson procedure.[10] The calculations have been carried out on isolated molecules in the gas phase with no solvent effects included. Electron correlation effects were not taken into account and C_1 symmetry was used in each case.

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