Strongly Basic Medium-ring Diamines which Mimic Gas Phase Behaviour in Solution: 1,6-Dimethyl-1,6-diazacyclodecane

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Monocyclic medium-ring diamines whose monoprotonated ions can form transannular hydrogen bonds have enhanced basicities in solution; structural data for 1,6-dimethyl-1,6-diazacyclodecane suggest that the enhanced basicity may reflect steric inhibition of solvation, leading to gas-phase-like behaviour.

Simple acyclic diamines have strongly enhanced gas-phase basicities when compared to appropriate monoamines.[1] The effect reaches a maximum in the homologous series with 1,4-diaminobutane, which can form a monoprotonated ion with an almost linear hydrogen bond in a seven-membered ring. Solution pK_a values for these diamines are essentially normal; specific solvation (*e.g.* hydrogen bonding) destroys the energetic advantage of the intramolecular hydrogen bond.[2] More rigid derivatives, such as the aromatic 'proton sponges,' have enhanced solution basicity due to a complex combination of steric inhibition of resonance in the free base, relief of strain on protonation, restricted solvation of the diamine, and enforced hydrogen bonding in the protonated ion.[3,4] We report that some simple medium-ring diamines are strong bases in solution.

Medium-ring monocyclic diamines (**1**)—(**5**)† have aqueous pK_{a1} $\geqslant$12 making accurate measurement difficult,[5] so their relative basicities were measured by equilibration with one of the strongest 'proton sponges' 2,7-dimethoxy-1,8-bis-(dimethylamino)naphthalene (**6**), in [$^2H_6$]dimethyl sulphoxide (DMSO) (Table 1). Compound (**6**) has a pK_{a1} of 16.1 in 35% aqueous DMSO,[6] so the *apparent* pK_{a1} of (**5**) is 16.5, but

Table 1. pK_a Values.

Compound	pK_{a1} in H_2O[a]	pK_{a2} in H_2O[a]	ΔpK_a with respect to (**6**) in [$^2H_6$]DMSO[c]
(**1**)	11.9 ± 0.1	5.54 ± 0.1	-1.64 ± 0.06
(**2**)	>12	3.12 ± 0.2	-1.11 ± 0.03
(**3**)	>12	1.5 ± 0.2	-0.89 ± 0.04
(**4**)	>12	1.5 ± 0.2	
(**5**)	>12	0.4 ± 0.3[b]	$+0.48 \pm 0.04$

[a] Measured by potentiometric titration,[5] except as stated. [b] Measured by integration of a slow-exchange ^1H n.m.r. spectrum of the mixture of mono- and di-cations in dilute hydrochloric acid. [c] Measured by integration of slow-exchange ^1H n.m.r. spectra of solutions of the alicyclic diamine with an equivalent of a protonated salt of (**6**). Reported values are averages of triplicate determinations on separate solutions, each averaged over at least three integrations.

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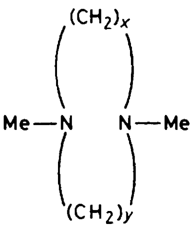
† Compound (**5**) was prepared by condensation of 4-chlorobutanal and 1,4-diaminobutane to give 1,6-diazabicyclo[5.3.0]decane, followed by reductive cleavage to 1,6-diacacyclodecane, using 1 equivalent of Bu^{n}Li and excess of Bu$^i_2$AlH.[19] Condensation of the product with methanal, quaternisation with MeI, and reductive cleavage with $LiAlH_4$ gave (**5**). Compounds (**1**)—(**4**) were prepared from the parent diazacycloalkanes.[20] All compounds gave satisfactory analytical and spectroscopic data.



(1) $x = y = 3$
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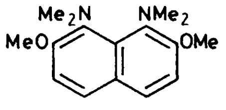
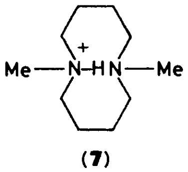
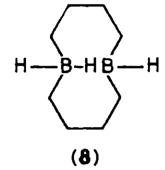
(4) $x = 5$; $y = 4$
(5) $x = y = 4$



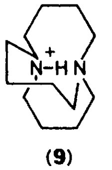
(6)



(7)



(8)



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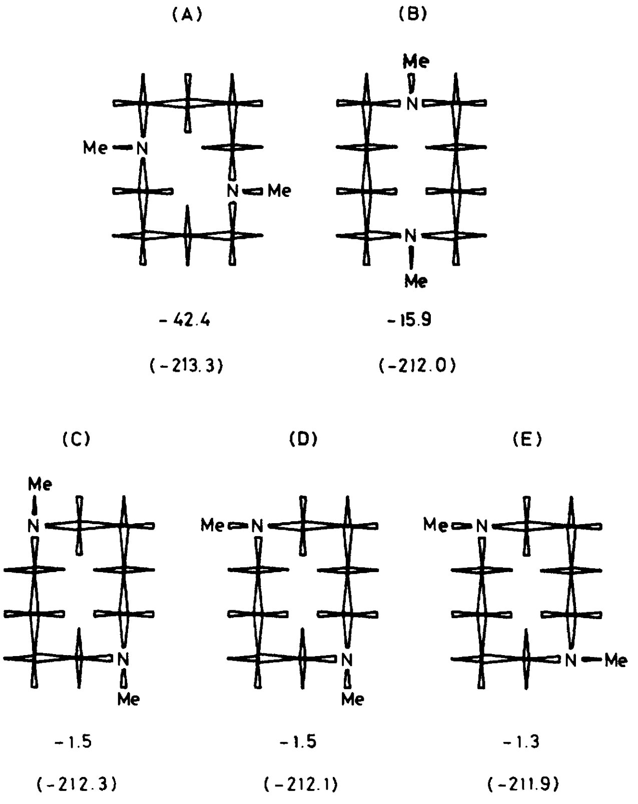

Figure 1. [2323] (Boat–chair–boat) conformations for 1,6-dimethyl-1,6-diazacyclodecane (**5**) which place methyl groups in unhindered external positions. Heats of formation are given in kJ/mol; those in parentheses are for the corresponding hydrocarbons with C–H replacing N.

it should be noted that the ΔpK_a for Et_3N with respect to (**6**) is -2.00 ± 0.05, so the increase in pK_a for (**5**) with respect to this simple amine is 2.5 log units.[7] Second pK_a values decrease as pK_{a1} increases, typical behaviour for diamines forming intramolecular hydrogen-bonded monocations. It seems that the greatest stabilisation of the monoprotonated ion is provided when the hydrogen bond is part of a seven-membered ring, as with the simple diamines in the gas phase, but further discussion is only possible at present for (**5**), where the conformation of the free base and its protonated ion are known precisely.

1,6-Dimethyl-1,6-diazacyclodecane (**5**) is an oil, but its preferred conformation can be defined from low temperature n.m.r. measurements and effective force field (MM2)[8] calculations. Five favourable [2323][9] conformations (A)—(E) are posible for (**5**) (Figure 1). In conformation (A), the transannular C–H · · · H–C interactions in cyclodecane are replaced by lone pair · · · H–C interactions (which may even be attractive),[10] so that most of the strain energy (54 kJ/mol)[11] in cyclodecane is absent. At −111 °C in 1:5 CD_2Cl_2/CS_2, the ^{13}C n.m.r. spectrum shows five lines and the proton spectrum shows nine types of hydrogen, with one possessing a much greater chemical shift (δ 3.63) than any other ($<\delta$ 2.42).‡ This downfield resonance is assigned to the hydrogen which is transannular to the lone pair in conformation (A); numerous examples of this 'steric compression' effect are known.[12] Observed vicinal coupling constants are also in good agreement with those calculated[13] from MM2 structure (A). In conformation (A) normal solvation of the lone pairs will be obstructed by the ring. To investigate whether the preference for conformation (A) might be altered by hydrogen-bonding solvation, we examined the ^1H n.m.r. spectrum in CD_2Cl_2 containing methanol (20 mol/mol of diamine). However the high basicity of (**5**) resulted in partial formation of the methoxide salt even in this relatively non-polar medium. Lowering the temperature increased the extent of ionisation and only protonated diamine was observed at −90 °C.

The *X*-ray structure of the monoprotonated ion (**7**) as its iodide salt is shown in Figure 2.§ The structure resembles *cis*-decalin, with the central C–C bond replaced by an apparently symmetrical hydrogen bond having an N · · · N distance of 2.600(3) Å, and an N–H–N angle of 169(2)°; the N–H distance is 1.30(5) Å. Because of the long N · · · N distance relative to *cis*-decalin, this is by no means an unstrained structure; C–C–C bond angles average 115.6° and torsion angles are larger than in a typical *cis*-decalin. The *cis*-decalin structure is probably preferred to *trans* because, as the distance between the bridgehead atoms in decalin is increased, it is much easier to maintain an almost co-linear orientation of the bridgehead orbitals (and thus an almost linear hydrogen bond) in the case of the *cis*-isomer. *Ab initio* calculations on $H_3NH^+ \cdots NH_3$ show that the *cis* bending mode maintains more of the hydrogen bond strength than the *trans* mode.[14] The structure of (**7**) is very similar to borane anion (**8**), which has a symmetrical $B \cdots H{-}B^-$ hydride bridge.[15] The transannular hydrogen bonding in (**7**) can be compared with the intrabridgehead bonding in (**9**), which is linear by symmetry.[16] The pK_a for formation of (**9**), which

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‡ The dynamic n.m.r. behaviour of (**5**) will be discussed in our full paper.

§ *Crystal data* for the iodide salt of (**7**) as its dichloromethane solvate: $C_{10}H_{23}N_2{}^+I^- \cdot 0.67CH_2Cl_2$, M = 354.83, rhombohedral, $R\bar{3}c$, a = 14.508(1), c = 34.060(7) Å, U = 6209 (1.8) Å^3, Z = 18, D_c = 1.71 g cm^{-3}, $\bar{\lambda}$ = 0.71069 Å, μ(Mo-K_α) = 25.32 cm^{-1}, $F(000)$ = 3180. Data were collected on a Nicolet P3m diffractometer at 196 K for $4 < 2\theta < 55°$. The structure was solved by heavy atom methods and refined by least squares to R = 0.0262 for 1445 unique, observed [$I > 1.5\sigma(I)$] absorption corrected data. The cation lies at a site of crystallographic two-fold (C_2) symmetry; the solvent molecule is disordered about a D_3 site. All hydrogen atoms were directly located and included in the refinement model [C–H distances fixed at 0.96 Å, H(1) on the two-fold axis]. Atomic co-ordinates, bond lengths and angles, and thermal parameters for $(7)\cdot I \cdot 0.67CH_2Cl_2$ have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

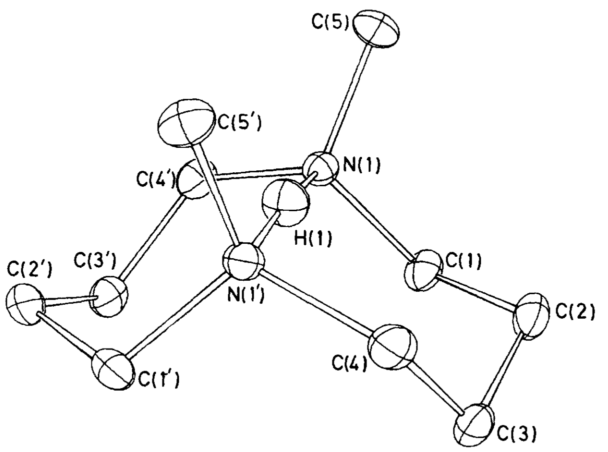

Figure 2. Molecular structure for cation (**7**) with methylene and methyl hydrogen atoms omitted for clarity; important bond distances (Å) include: N(1)–C(1) 1.483(3), N(1)–C(5) 1.494(4), N(1)–C(4') 1.494(4), C(1)–C(2) 1.527(4), C(2)–C(3) 1.555(5), C(3)–C(4) 1.505(4).

cannot be measured directly since the proton cannot be inserted or removed by normal proton transfers, has been estimated as 25.[17] Specific solvation of (**7**) by hydrogen-bond accepting solvent molecules will be restricted by the ring and the methyl groups, as in (**9**) and other inside-protonated bicyclic diamines.[18]

In conclusion, we have shown that enhanced basicity can be achieved in quite simple medium-ring diamines. The strongest base, (**5**), does not seem much more strained than its protonated ion, (**7**), but both (**5**) and (**7**) suffer steric inhibition of specific solvation, so that diamine (**5**) can be said to mimic gas-phase behaviour in solution. Compound (**5**) and similar diamines are unlikely to be useful reagents for *E*2 and similar reactions which involve rate-limiting proton transfer; (**5**) may only be able to react as a base *via* conformations like (C)—(E).

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