PERKIN 2 COMMUNICATION

Synthesis and properties of a chiral bis-tetrahydroisoquinoline proton sponge†

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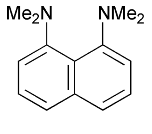
A new chiral proton sponge has been prepared, and the reasons for its unusually high basicity elucidated by a quantum chemical study.

Since Alder's landmark synthesis of 1,8-bis(dimethylamino)naphthalene **1**,[1] the synthesis of novel organic superbases continues to generate considerable interest[2,3] with recent work focusing on chiral targets.[4] Despite its potential in this area, and more generally in asymmetric catalysis, the bis-tetrahydroisoquinoline ring system has seldom been reported. Herein we report preliminary results in the preparation of derivatives of compound **2**, including the important observation that **3** is a C_2-symmetric chiral proton sponge, and compare the basicity of compound **3** with that of compound **1** and of TMEDA (**4**).



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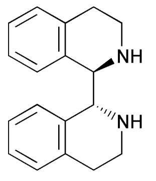

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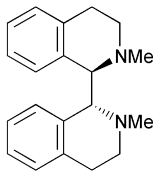

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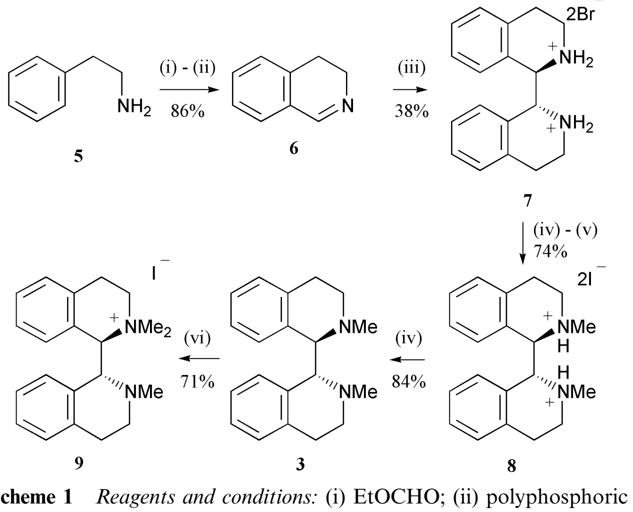
The syntheses of both diastereoisomers of **2** have been previously reported.[5] However, while this route provided the desired compound, it features a hydrogenation step which we found to be capricious, and so an alternative synthesis was developed as shown in Scheme 1. Reaction of phenylethylamine **5** with ethyl formate, followed by cyclisation with polyphosphoric acid gave dihydroisoquinoline **6** cleanly. Dimerisation of **6** using zinc with 1,2-dibromoethane and chlorotrimethylsilane gave a 1 : 1 mixture of diastereoisomers of **2**, from which the *dl* isomer was easily separated and characterized as the double hydrobromide salt **7**. Liberation of the free base from **7** and treatment with excess methyl iodide led to the formation of the double hydroiodide salt **8**, from which the free base **3** was readily liberated and purified by recrystallisation from ethanol–diethyl ether, and characterised by single crystal X-ray diffraction (Fig. 1).[6] ‡



Scheme 1 *Reagents and conditions:* (i) EtOCHO; (ii) polyphosphoric acid; (iii) Zn, Me_3SiCl, $BrCH_2CH_2Br$ then HBr, H_2O; (iv) NaOH, H_2O, CH_2Cl_2; (v) CH_3I; (vi) CH_3I, THF.

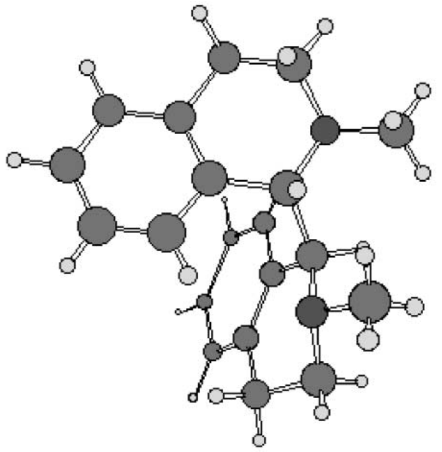
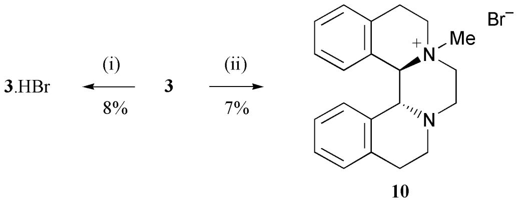


Fig. 1 Structure of **3** from single crystal X-ray diffraction data.

Treatment of **3** with additional methyl iodide cleanly provided **9**, with no evidence for further methylation.

The basicity of **3** was determined by competitive NMR studies with **1** in deuterated acetonitrile. A 1 : 1 mixture of **3** and the perchlorate salt of **1** showed clearly that the salt of **1** was approximately 50% deprotonated under these conditions, leading to the conclusion that **3** and **1** have essentially identical pK_a values (18.2)[7] in acetonitrile. While the free base and salt of **1** exchange protons relatively slowly at room temperature, the corresponding exchange in **3** is rapid on the NMR timescale.

Two different products were isolated from the reaction of **3** with 1,2-dibromoethane. At room temperature little reaction occurred, but the desired bridged double salt underwent demethylation to give **10** as a single stereoisomer (unknown stereochemistry) at nitrogen. At higher temperatures the only product isolated was the single salt of **3** (Scheme 2). In both cases the balance of material was recovered **3**.



Scheme 2 *Reagents and conditions:* (i) $BrCH_2CH_2Br$, 60 °C; (ii) $BrCH_2CH_2Br$, 25 °C.

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† Dedicated to Professor Harry Heaney on the occasion of his 70th birthday.

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Table 1 Main structural features (HF/6-31G** and crystallographic)

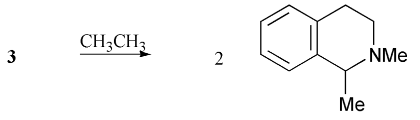
	Free base		Monoprotonated cation			
	*r*N··N/Å	NCCN/°	NCCN/°	*r*N··N/Å	*r*N··H/Å	N–H··N/°
1	2.791	–	–	2.684	1.706	155.1
3 *syn*	2.679	11.8	15.1	2.585	1.772	133.1
anti	3.781	179.6	–	–	–	–
X-ray	3.672	143.2				
4 *syn*	2.955	46.1	46.2	2.749	2.099	119.7
anti	3.760	175.5	174.9	3.776	3.945	73.0

Table 2 B3LYP/6-31+G**//HF/6-31G** proton affinities (PA)[a] and strain energies (SE) for the bases; plus hydrogen bond + strain energies (HB + SE)$^+$ and hydrogen bond energies (HB) and intramolecular proton transfer barriers (PT) for the monoprotonated cations, all in kJ mol^{-1}[a]

	PA	SE	PT	(HB + SE)$^+$	HB
1	1030.7 [1030 ± 2][b]	26.9	0	−66.8	−78.2
3	1037.0	42.3	2	−17.8	≈ −38
4	998.6	−2.4	15	–	≈ −37.6
11	975.9	–	–	–	–

[a] The PA's, SE's and (HB + SE)$^+$ values include scaled HF/3-21G thermal energy corections.[9] [b] Experimental gas phase PA measured by Lau *et al.*[10] Values for **1** taken from reference 8(*e*).

Quantum chemistry provides a powerful tool in proton sponge design.[8] Using the methodology described recently[8e] we have explored the *syn* and *anti* conformers of **3** and **4** and their mono-protonated cations, and have quantified the relative contributions of hydrogen bonding and strain release to their basicities. Structures were first optimised and frequency-tested at the HF/3-21G level, followed by HF/6-31G** optimisation and B3-LYP/6-31 + G** single points at these geometries. Strain energies (SE) for **1** and **3** have been calculated from isodesmic reactions (Schemes 3 and 4). Proton transfer energies (PT) were also estimated from calculations on C_2-symmetrised cations.



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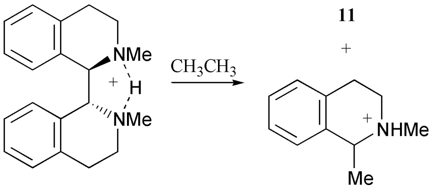
Scheme 3 Isodesmic reaction used to obtain proton sponge strain.



Scheme 4 Isodesmic reaction used to obtain cation H-bond energy.

Non-bonded distances *r*N··N and N–C–C–N torsion angles in both the free base and the cation are reported in Table 1, along with hydrogen bond geometries (cation only). Gas phase absolute PAs and other relevant electronic properties are reported in Table 2.

The calculations reveal that both **3** and **4** have stable *syn* (C_2 symmetric) and *anti* (C_1 or C_2) conformers. In agreement with the crystal structure of **3**, the *anti* conformer is predicted to be the most stable form, being some 17 kJ mol^{-1} more stable than *syn* in the gas phase. This is also consistent with the ^{1}H NMR data which suggest substantial conformational change (presumably *anti* ⟶ *syn*) on protonation. Isodesmic reactions reveal that **3** is quite strained (some 15 kJ mol^{-1} more strained than **1**) presumably due to steric interactions between the benzene rings. Calculation of the corresponding isodesmic reaction shows that compound **4** on the other hand is essentially strainless (the small negative SE is within the expected error for a thermoneutral isodesmic reaction). Additionally the energies of the *syn* and *anti* forms are within 1 kJ mol^{-1}.

Considering now the *syn* protonated species, **1**H$^+$ and **3**H$^+$ exhibit similar N–H ··· N hydrogen bonds. Compound **3**H$^+$ also has the very low barrier to intramolecular proton transfer typical of diamine proton sponges, and appears to have no stable *anti* protonated form. Serendipitously **4**H$^+$ *does* have a stable *anti* conformer, so the ≈ 38 kJ mol^{-1} *syn*/*anti* energy difference provides a good estimate of hydrogen bond strength. The gas phase PA of **3** is slightly higher than that of **1**. An additive scheme[8e] describing its PA is

$$PA(\mathbf{3}) = PA(\mathbf{11}) + [SE(\mathbf{3}H^+) - SE(\mathbf{3})] - HB(\mathbf{3}H^+)$$

Thus, the PA of **3** can be measured relative to a suitable, structurally-related monoamine **11** and is the sum of strain release on protonation and intramolecular hydrogen bond stabilization of **3**H$^+$. These latter two contributions we will refer to as the 'excess PA'. Taking HB(**3**H$^+$) ≈ HB(**4**H$^+$) this gives 1037 = 976 + 23 + 38 kJ mol^{-1}, so the 61 kJ mol^{-1} excess PA comes mostly from hydrogen bonding. This is in line with other sponges so far analysed in this way: for example, in the case of **3**, when the reference monoamine is chosen as 1-(dimethylamino)naphthalene[8e] we have 1031 = 937 + 16 + 78 (H-bond provides more than 80% of the 94 kJ mol^{-1} excess PA).

The main difference between **1**H$^+$ and **3**H$^+$ is clearly in the absolute magnitude of the hydrogen bond, that in **3**H$^+$ being only half the strength of **1**H$^+$ due to less favourable geometric constraints. However, the fact that the (gas-phase) basicity of **3** is marginally higher than that of **1** appears to be due to the higher intrinsic basicity of the aliphatic amine.

We believe that derivatives of compound **2** will have a range of useful applications in asymmetric synthesis. These studies are underway, and will be reported in due course.

Acknowledgements

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‡ CCDC reference number 167915. See http://www.rsc.org/suppdata/p2/b1/b110499n/ for crystallographic files in .cif or other electronic format.

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6 Selected crystallographic data for **3** are as follows: $C_{20}H_{24}N_2$ (M_r 292.41), monoclinic, $P2_1/c$, $a = 11.039(2)$, $b = 7.791(2)$, $c = 19.001$ Å.

$\beta = 104.31(3)°$, $Z = 4$, $V = 1583.5(6)$ Å^3, $D_c = 1.227$ g cm^{-3}, Mo-K$_\alpha$ radiation, $\lambda = 0.71073$ Å, $2.21 < \theta < 25.29°$. 11232 reflections were collected of which 2881 were unique. 1641 reflections having $I > 2.0\sigma(I)$ were used for refinement (272 parameters). Final R indices ($I > 2.0\sigma(I)$) $R_1 = 0.0461$ and $wR_2 = 0.0929$. Crystallographic data for **3** have been deposited at the CCDC, 12 Union Road, Cambridge, UK CB2 1EZ and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 167915.

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