The Azatriquinenamine Trimer—A Novel Proton Chelate**

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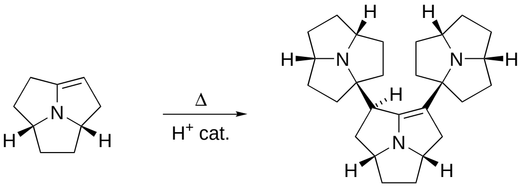
Proton sponges and neutral organic superbases are molecules of both theoretical and practical interest.[1, 2] Their extraordinary basicity is attributed in the former to the relief of lone pair repulsion between basic sites in enforced proximity and the establishment of a high quality H-bond on protonation, and in the latter to extensive resonance stabilization of the HB^+ ion.

In the course of our synthetic studies in the azatriquinane series, we prepared *cis*-10-azatricyclo[5.2.1.$0^{1,10}$]dec-1-ene (azatriquinenamine **1**),[3] as a pivotal intermediate in the syntheses of azatriquinane, azatriquinadiene, and azatriquinacene.[4] This compound is a distillable liquid which is stable under ambient conditions. However, heating **1** at >100 °C in the presence of a proton source leads to solidification of the reaction mixture, the principle component of which was assigned the trimeric structure **2** (Scheme 1) on the basis of spectroscopic data.



1

2

Scheme 1. Formation of **2**.

We believe this type of enamine trimerization to be unique. Although the $\Delta^{1,8}$-dehydropyrrolizidine enamine dimerizes in an analogous manner, it does not proceed to give a trimer.[5] The *N*-methyl-Δ^2-pyrroline enamine has also been observed to both dimerize and trimerize,[6] but in the latter case the central ring functions first as an enamine nucleophile and then as an imine electrophile, unlike in **2** where the central azatriquinenamine reacts as a nucleophile, tautomerizes, and then reacts a second time as a nucleophile.

It was not, however, until an X-ray crystal structure of the hydrochloride salt of **2** was carried out that a remarkable feature of this unusual nonacyle was recognized, that is that the two terminal azatriquinane rings were situated face-to-face, chelating the H^+ with an N ⋯ N distance of 2.75 Å and an N–H ⋯ N angle of 177° (Figure 1a).[7] The bis-trialkylamino environment around the acidic proton is reminiscent of the 1,6-diazabicyclo[4.4.4]tetradecane H^+ cryptate of Alder, et al.,[8] except that in **2**H^+ the conformation down the $R_3N–H\cdots NR_3$ axis is nearly perfectly staggered (Figure 1b). Interestingly, we had previously noted the enhanced basicity of the azatriquinane molecule relative to other trialkylamines due to the acute and enforced pyramidalization of the apical nitrogen atom in this rigid tricycle,[3] and so the high intrinsic basicity of the subunits of **2** in combination with its overall tweezerlike structure led us to consider whether this might render the molecule particularly basic.

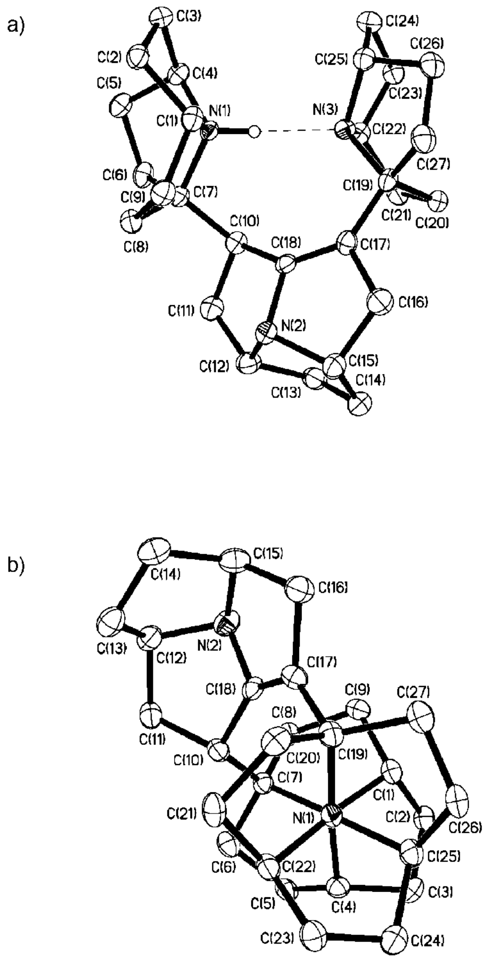


Figure 1. a) View of the X-ray crystal structure of the **2**H^+ ion normal to the N–H ⋯ N axis. b) View of the X-ray crystal structure of the **2**H^+ ion down the N–H ⋯ N axis.

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We thus undertook an investigation of the basicity of **2** using both chemical and computational approaches. A standard experimental protocol for deriving the pK_a values of strong, neutral bases is potentiometric titration in acetonitrile solution.[9] By this method, the dissociation constants of several well known amines have been measured and are available for comparison. Substantial work has also been published on the computational determination of gas-phase proton affinities and their correlation to solution basicity.[10] The overall results for **2** are presented in Table 1, and show that the molecule is in fact highly basic; about seven orders of magnitude more so than 1,8-bis(dimethylamino)naphthalene ("proton sponge") and 4-dimethylaminopyridine (DMAP). Indeed, it was our experience in the isolation of **2** that its handling in dichloromethane led directly to the hydrochloride salt, presumably by α-dehydrohalogenation of the solvent. The free base could not be liberated by shaking with aqueous NaOH solution, but was obtained by treatment of **2**$\cdot$HCl with potassium hexamethyldisilazide, and was observed to quickly reprotonate on exposure to atmospheric moisture.

Table 1. Calculated protonation energies (ΔE_{prot}, kcal mol^{-1}) and conjugate acid dissociation constants (pK_a) of known organic superbases and **2**.

Amine	$\Delta E_{\text{(prot)}}$	p$K_{\text{a(theory)}}$	p$K_{\text{a(MeCN)}}$
DMAP[a]	243.4	18.2	18.2[16]
"proton sponge"[b]	243.8[2d]	18.3	18.5[17]
PhTMG[c]	252.6	21.5	20.6[18]
DBU[d]	256.9	23.0	23.9[18]
2	265.3	26.0	25.1
$(Me_2N)_3P{=}N\textit{t}Bu$	265.8	26.2	26.9[2a]

[a] 4-Dimethylaminopyridine. [b] "Proton sponge", 1,8-bis(dimethylamino)naphthalene, is a registered trademark of Sigma-Aldrich, Milwaukee, WI, USA. [c] *N*-Phenyltetramethyl guanidine. [d] 1,8-Diazabicyclo-[5.4.0]undec-7-ene.

A computational study of the proton affinity of **2** supports the experimental determination of its high pK_a. Monte Carlo molecular mechanics simulations with the MM2* and MM3* force fields[11] suggested that the lowest energy conformer of the free base **2** was unexpectedly similar to that of the protonated form, that is the convex surfaces of the terminal azatriquinanes, although offset relative to **2**$\cdot$HCl, still faced each other, in spite of the fact that a number of alternative structures with completely divergent nitrogens are possible. The protonation energy (ΔE_{prot})[12] of **2** was calculated to be -265.3 kcal mol^{-1} using the HF/6-31G(d)//HF/6-31G(d) theoretical model. This could be correlated to a solution pK_a of about 26.0 by the linear relationship p$K_{\text{a(theory)}} = -0.357$ (ΔE_{prot}) $-$ 68.8, derived by plotting ΔE_{prot} against experimental pK_a values in acetonitrile for the bases in Table 1 (regression coefficient 0.98). The agreement with the measured pK_a value of $\mathbf{2}H^+$ (25.1) is remarkably good considering the modest level of theory applied and the different classes of bases to which it was compared.

It is noteworthy that a base such as **2** benefiting neither from conjugation nor the proton sponge effect competes nonetheless in terms of proton affinity with the likes of DBU and the P1-polyaminophosphazine base,[2a] although it is considerably less basic than Schwesinger's remarkable higher generation phosphazene[2a] and vinamidine[13] superbases. We also note that **2** is an unusual example of a chiral neutral superbase. Further investigations of the properties of **2**, as well as its resolution into enantiomers, will be reported elsewhere.

Experimental Section

2: Dichloromethane (1 mL) was added to the freshly distilled enamine **1** (0.781 g, 5.78 mmol) and the mixture was heated at 140 °C with stirring for 12 h. The reaction was then cooled to room temperature and the resulting brown solid dissolved in dichloromethane and applied to the top of a silica gel column. Elution with dichloromethane/methanol 10:1 gave the monohydrochloride salt of **2** (0.254 g, 30 %) as a hygroscopic, pink crystalline solid, m.p. 127–130 °C, ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.05$ (m, 1 H), 3.98 (m, 1 H), 3.72 (m, 1 H), 3.61–3.53 (m, 2 H), 3.45–3.40 (m, 1 H), 2.98 (dd, $J = 15.0$, 7.6 Hz, 1 H), 2.85 (dd, $J = 7.9$, 3.9 Hz, 1 H), 2.39 (d, $J = 15.1$ Hz, 1 H), 2.34–1.63 (m, 25 H), 1.60–1.47 (m, 3 H), 1.32–1.22 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 147.5$, 112.8, 81.7, 76.0, 67.6, 67.1, 66.7, 66.6, 62.2, 60.3, 43.0, 42.5, 36.8, 36.7, 36.3, 32.7, 32.1, 31.7, 31.0, 30.3, 30.1, 29.9, 29.7, (2 C), 29.6 (2 C), 28.6; MS (FAB): *m/z* (%): 406 ([$M+H$], 53), 307 (26), 155 (32), 154 (100), 138 (36), 137 (67), 136 (86), 107 (26), 91 (29), 73 (68), 57 (32), 55 (29); HRMS (FAB): *m/z* calcd for $C_{27}H_{40}N_3$ [M+H]: 406.3222; found: 406.3223.

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[7] Crystal data for **2**: $C_{27}H_{40}N_3^+Cl^- \cdot 4H_2O$, $M_r = 514.13$, monoclinic, space group $P2_1/c$, $a = 19.840(2)$, $b = 7.2998(4)$, $c = 20.452(2)$ Å, $\beta = 112.444(3)°$, $V = 2737.7(4)$ Å^3, $T = 150(2)$ K, $Z = 4$, $\rho_{\text{calcd}} = 1.247$ g cm^{-3}, $F(000) = 1120$, $\mu(\text{Mo}_{K\alpha}) = 0.176$ mm^{-1}. Crystal dimensions: 0.20 × 0.10 × 0.01 mm. A total of 46891 reflections was collected, 4769 unique ($R_{\text{int}} = 0.33$), $\theta_{\max} = 25.0°$, no absorption correction. The structure was solved by direct methods[14] and developed through subsequent cycles of least squares refinement and difference Fourier synthesis,[15] final $R1$ (2011; $F > 4\sigma(F)$) = 0.062, $wR2$ (all $F2$) = 0.149. Hydrogen atoms on N and O atoms were located while others were placed geometrically; the former were then refined with restraints to bond lengths and the latter as part of a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-166024. Copies of the data can be obtained free of charge on application to CCDC, 12 Union

Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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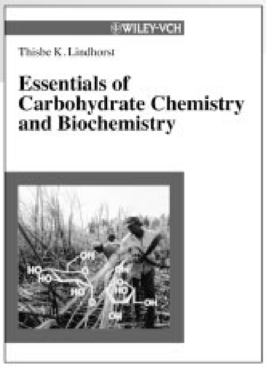

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