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A novel hindered macrocyclic tetramine containing two bispidine units. A new type of proton sponge

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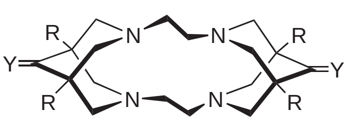
Abstract—A novel cyclam-like macrocyclic tetramine **1a** was synthesized via coupling of bispidine and its bis(α-chloroacetamide) followed by reduction. Strongly basic but encrypted nitrogens of **1a** were found to abstract a proton from chloroform to form dichlorocarbene. © 2001 Elsevier Science Ltd. All rights reserved.

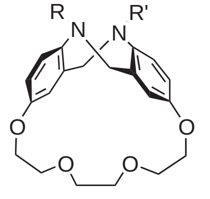
Hancock et al. mentioned in their review that macrocyclic tetramine **1a** had been their target molecule as an ultimate extension of their work on cyclam chemistry in anticipation that the four tertiary nitrogens in the very rigid framework would lead to in-plane ligand field with unprecedented strength.[1]

We became interested in this molecule in our studies on systems where nitrogen lone pairs are located in close proximity as in Tröger base-derived chiral diamine **2**.[2] In view of putative isolation of a copper complex of the tetraphenyl derivative **1c**,[3] and ready availability of 1,5-diphenylbispidine **3b**, however, we first synthesized its tetraphenyl derivative **1b**.[4] Unfortunately, the solubility of **1b** in organic solvents was unexpectedly low for detailed investigation of its properties. Here we report synthesis of the parent **1a** whose high solubility allowed us to examine its peculiar properties due to the rigid and encrypted tetramine system.

Since the existing methods for the synthesis of bispidine **3a** are impractical, because many cumbersome steps are



1a (R = H, Y = H_2)
1b (R = Ph, Y = H_2)
1c (R = Ph, Y = O)



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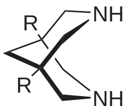
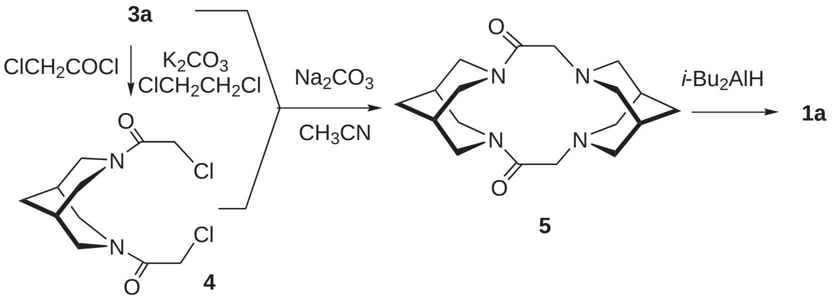


3a (R=H)
3b (R=Ph)



Scheme 1.

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involved[5] or long reaction times are required,[6] we developed a new convenient route starting from allyl amine.[7] With quantities of **3a** at hand, the rest of the synthetic route was the same as that for **1b**, as shown in Scheme 1. The coupling of **3a** and its bis(chloroacetamide) **4** was remarkably efficient, affording **5** in 83% yield, if care was taken to minimize exposure of the base-sensitive **4** to Na_2CO_3.[8] Reduction of **5** with i-Bu_2AlH readily provided the desired macrocyclic tetramine **1a** (bp 203–206°C/1.0 mmHg, mp 78–79.5°C) in 68% yield.[9]

As we hoped, **1a** is readily soluble in solvents ranging from nonpolar hexane to highly polar water, with the exception of dipolar aprotic solvents like CH_3CN, DMSO and DMF. This solubility profile resembles that of cyclam and appears to be reflecting the outer aliphatic surface of the molecule towards nonpolar solvents and the inner nitrogens which can interact with hydroxylic solvents.

To be avoided, however, are halogenated solvents. When **1a** was dissolved in $CDCl_3$, the initially colorless solution immediately turned yellow and the resultant solution gave complex signals in the ^1H NMR spectrum and, on standing, colorless crystals deposited.

Upon recrystallization of the crystals from $CHCl_3$ one of the crystals was suitable for X-ray crystallographic analysis.[10] As shown in Fig. 1, a deuteron resides in each bispidine unit with 50% probability in a stepped structure like those found in cyclam disalts.[11] Namely, DCl was eliminated from $CDCl_3$ to provide a mono DCl salt of **1a**. After the proton abstraction, the resultant CCl_3^- was broken down to dichlorocarbene, which could be trapped with cyclohexene to afford 7,7-dichloronorcarane.[12] Actually, mono HCl salt of **1a** was best prepared by allowing **1a** to react with $CHCl_3$ containing a large excess of cyclohexene for 20 h at room temperature (72% yield). On the other hand, **1b** did not show any sign of elimination of DCl from $CDCl_3$, probably because the large phenyl groups shield the nitrogen lone pairs and/or rigidify the ring system.[4]

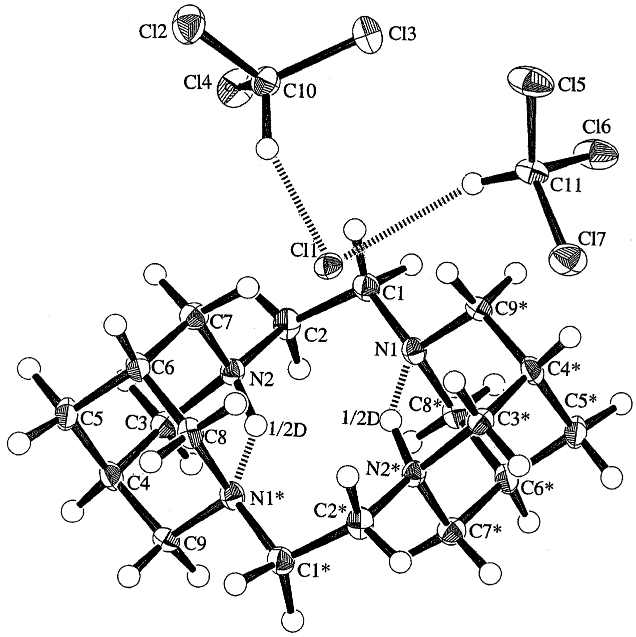
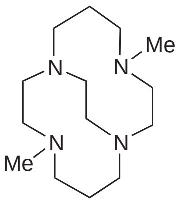
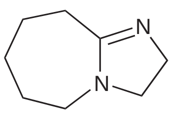


Figure 1. The ORTEP drawing of D^+@**1a**·Cl^-·$2CHCl_3$ (thermal ellipsoids are drawn at the 50% probability level).

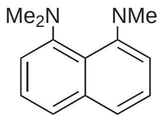
Since similar rapid decomposition also took place in CH_2Cl_2, the basicity of **1a** appeared to be very high.[13] We estimated the basicity from competition experiments using the well-known strong base DBU (pK_a 24.32).[14] A solution containing **1a**, DBU and CF_3CO_2H in a molar ratio of 1:1:1 in CD_3CN exhibited ^{13}C signals as exchange-averaged peaks for both DBU–DBU·H^+ and **1a**–**1a**·H^+ systems. Because free **1a** is insoluble in CD_3CN, the pK_a value of **1a** was estimated from the downfield shifts observed for the DBU carbons. By comparison with predetermined linear plots obtained by titrations of DBU with CF_3CO_2H, the population of DBU·H^+ in this equilibrium mixture was determined as 33.2%, which corresponds to a pK_a value of 24.9 for **1a**. Therefore, the basicity of **1a** is slightly higher than that of DBU and the same as Weisman's transannular ethylene bridged cyclam **6** (pK_a 24.9).[15]



6



DBU



Proton Sponge

It is interesting to note that, while free **1a** has little propensity to pick up a proton(s) even in rather wet C_6D_6 or DMSO-d_6, once converted to H^+@**1a**·Cl^-, a proton of residual water in the solvent becomes entrained in the cavity exhibiting a peak at δ 9.18 ppm for two protons, instead of one, in DMSO-d_6. This entraining effect may be interpreted as a result of shortening of the N–N distances of the bispidine units on protonation at one of the bispidine units, as well as polarization of the molecule. A similar entrainment effect was observed for **1b**, where its mono Li^+ complex always took a proton from the NMR solvent, whereas free **1b** did not show any protonation.[4] In this respect, it should be mentioned that the crystal of D^+@**1a**·Cl^- contained two molecules of $CHCl_3$ hydrogen bonded to the chloride ion ($Cl^-\cdots H\text{-}C_{10} = 3.382$ Å, $Cl^-\cdots H\text{-}C_{11} = 3.586$ Å), as shown in Fig. 1. Once the $CHCl_3$ molecules were lost on standing in the air, the resultant powder was very hygroscopic.

The included proton in **1a** rapidly shifts its position between the two bispidine units at room temperature in solution because the ^1H NMR spectrum (600 MHz, toluene-d_8) of H^+@**1a**·$(CH_3)_3CCO_2^-$ consists of simple averaged peaks for the bispidine units and ethylene bridges. This rate process became slowed down on cooling and the peaks were extremely broad at ca. −30°C. Although at −70°C the spectrum was comprised of complex but well-resolved peaks, suggesting fixation of the included proton to one of the two sites, we could not fully analyze the proton-transfer process because the peaks started to broaden again on further cooling, indicating the presence of another rate process.

It should be mentioned that, in contrast to the immediate reaction with CDCl$_3$ for **1a**, almost no change was observed in the cases of DBU and proton sponge,[16] except for gradual increase in the intensity of the CHCl$_3$ signal in the solvent due to base-catalyzed D–H exchange of CDCl$_3$ with residual water. Since the basicity of **1a** is only slightly higher than DBU, this remarkable difference may be ascribed to strike factors. Namely, while such bases as DBU and proton sponge having readily accessible nitrogen atoms are incapable of separating a proton completely from CHCl$_3$,[17] the sterically hindered nitrogens of **1a** can separate and withdraw the proton into the molecular cavity, allowing the resultant free CCl$_3^-$ to liberate Cl$^-$ to form dichlorocarbene. Therefore, **1a** behaves as a real proton sponge and will find applications as a non-nucleophilic base.

Probably for the same steric reasons, lithium was so far the only metal to form a stable complex with **1a**. However, interaction of **1a** with transition metal ions is evident from immediate color changes on mixing with the metal salts. Searches are underway to find suitable conditions for complexation.

Acknowledgements

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6. The double Mannich reaction of *N*-benzyl-4-pyperidone yielding *N*,*N*-dibenzylbispidinone requires 15 days at room temperature. See: Ruenitz, P. C.; Smissman, E. E. *J. Heterocycl. Chem.* **1976**, *13*, 1111–1113.
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8. Use of 6 equivalents of powdered Na$_2$CO$_3$ was optimal. In the case of **1b** the solubility of the corresponding bis-(chloroacetamide) in CH$_3$CN is so low that a Soxhlet extractor was required for its addition in the coupling reaction. Because of the low concentration in the reaction mixture, the yield appears to be less affected.
9. **1a**: ^{1}H NMR (400 MHz, C$_6$D$_6$): δ 2.87 (8H, d, $J=10.4$ Hz, NCH$_2$C), 2.32 (8H, s, N(CH$_2$)$_2$N), 2.22 (8H, dd, $J=2.5$, 10.4 Hz, NCH$_2$C), 1.67 (4H, s, bridgehead CH), 1.48 (4H, s, CCH$_2$C). ^{13}C NMR (100 MHz, C$_6$D$_6$): δ 57.67 (NCH$_2$C), 54.68 (N(CH$_2$)$_2$N), 33.38 (CCH$_2$C), 31.26 (bridgehead CH). IR (Nujol): δ 2945, 2853, 2785, 2754, 2730, 2715, 2684, 1462, 1357, 1308, 927, 903, 805, 728 cm^{-1}. FAB MS: m/z 305.18 ([M+H]$^+$).
10. X-Ray data of D$^+$@**1a**·Cl$^-$·2CHCl$_3$: a colorless prismatic crystal (0.3×0.3×0.2 mm^3) was measured at −150°C on a Rigaku RAXIS Rapid diffractometer (Weisenberg-type Imaging Plate area detector) with graphite monochromated Mo-Kα ($\lambda=0.71069$ Å). Orthorhombic, *Pbca* (#61), $a=12.9180(5)$, $b=13.0231(5)$, $c=21.5169(6)$, $V=3619.8(2)$ Å^3, $Z=8$, ρ_{calcd} 2.127 g/cm^3. After Lorentzian polarization correction 2544 reflections were assumed to be observed ($I>3.00\sigma(I)$). The structure was solved by direct methods (Sir92). All the hydrogen atoms were located and refined along with the heavy atoms by full-matrix least-squares method, but the positions of the hydrogen atoms were fixed in the final stages. Refinement of 182 parameters against $|F|$ converged to $R_1=0.030$ ($wR=0.031$). The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (e-mail: deposit@ccdc.cam.ac.uk) as CCDC 151044.
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12. Identified by comparison of its GC–MS spectrum with the database installed in a Hewlett–Packard HP5973 GC–MSD system.
13. Because of instability of the conjugate anion, the only reported carbon acidity of CHCl$_3$ (pK_a ca. 24) is the one estimated from the detritiation rate of CTCl$_3$ by OH$^-$ in water–DMSO: Margolin, Z.; Long, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 2757–2762. To our knowledge, no solution pK_a data is available for CH$_2$Cl$_2$, but the following gas-phase acidity order is reported: C$_5$H$_6$>CHCl$_3$, CH$_3$COCH$_3$>CH$_3$CN>CH$_2$Cl$_2$, CH$_3$SOCH$_3$. See: Bohme, D. K.; Lee-Ruff, E.; Young, L. B. *J. Am. Chem. Soc.* **1972**, *94*, 5153–5159.
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17. The CCl$_3^-$ may be associated with DBU·H$^+$. Therefore, the anion may enter into a reaction if an appropriate acceptor is present. Actually, it has been demonstrated in a recent paper that addition of chloroform to carbonyl compounds can be efficiently mediated by 1 equivalent of DBU without solvent at room temperature. See: Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211–7212.