3, the amide base residue is twisted relative to the central four membered ring. This twist is observed in all mixed aggregates and in the structure of THF-solvated LDA.[13] Since this is consistently observed in different molecular and solid-state environments, it is likely to be intrinsic to the coordination behavior of metalated secondary amides. To our knowledge, this observation has not been predicted by theoretical work on lithium amides[14] nor noted in previous structures of LHMDS[15] or NHMDS.[12]

Structures **1**, **3**, and **4** demonstrate the scope and generality of mixed aggregation. This phenomenon is now observed with three distinct types of enolates, with two different metal amide bases, and with two different metal cations. A complex between LDA and the monoanion of phenyl acetonitrile was also structurally characterized recently.[16] Coupled with this structural information is the chemical evidence suggesting that these mixed aggregates maintain their integrity in solution.[2,3] As these complexes are explored synthetically, they should prove extremely useful in controlling enolate reactivity and selectivity. Experiments designed to probe these points with chiral, ionic, non-covalent auxiliaries are in progress.

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Supplementary Material Available: Details of the diffraction analysis, plots of atom labels, and tables of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **3** and **4** (18 pages). Ordering information is given on any current masthead page.

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Cross-Bridged Cyclam. Protonation and Li^+ Complexation in a Diamond-Lattice Cleft

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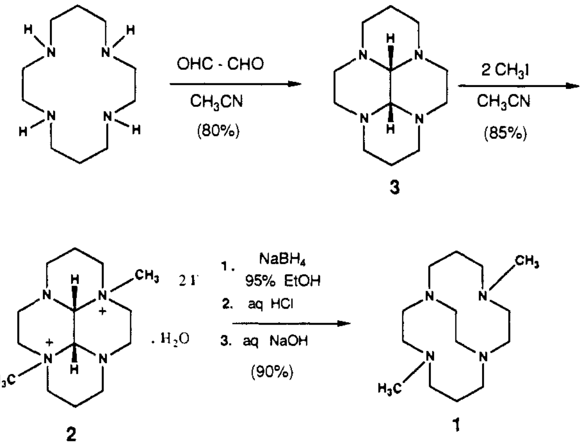
Polycyclic polyamines are of current interest because members of this class of compounds have been shown to exhibit unusual basicity,[3-5] redox behavior,[4] and coordination chemistry.[5,6] Polycyclic tertiary amines also hold promise for the synthesis of alkalides and electrides.[7] Structural modifications of the important macrocyclic ligand cyclam (1,4,8,11-tetraazacyclotetradecane) involving ethylene bridging of adjacent nitrogens have been reported.[8,9] "Cross bridging" of cyclam (i.e., bridging of nonadjacent nitrogens) with CH_2CH_2 would result in a flexible bicyclo[6.6.2] tetraamine that is capable of adopting conformations having all four nitrogen lone pairs convergent on a cleft or cavity for complexation of metal ions. Herein we report a rational and efficient synthesis of the first example of such a cross-bridged cyclam, **1** (4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane), and our preliminary investigations into its basicity and alkali ion complexation.[10]

Scheme I



The synthetic route to **1**[11] (Scheme I) is based upon reductive ring cleavage[12] of dimethylated bisaminal diiodide **2**,[11] prepared in good yield by exhaustive methylation of the readily available bisaminal **3**.[13] The high regioselectivity of the bis quaternization of **2** is a consequence of its conformation.[13] As shown in Figure

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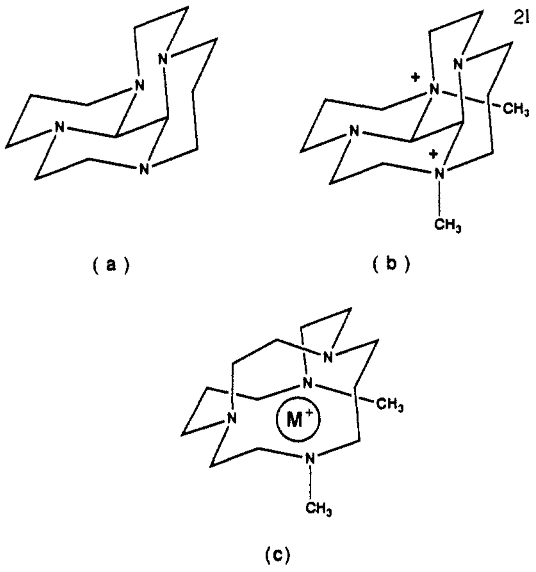

Figure 1. (a) Conformation of bisaminal **3**. (b) Configuration of **2**. (c) Proposed conformation of Li^+ complex of **1**.

1a, **2** has a convex face and a concave face, so that only the two N lone pairs on the convex face are sterically available for alkylation. 1D and 2D NMR results confirmed the expected configuration of product **2** (Figure 1b).

Aqueous solutions of **1** are strongly basic (0.1 M **1**, pH > 12.5). Addition of more than 2 equiv of NaOH to a 0.3 M D_2O solution of **1** resulted in phase separation of free amine, but addition of 8 equiv of solid $LiOH{\cdot}H_2O$ gave an approximately 1:2 equilibrium mixture of **1**-D^+ and **1**-Li^+ complex, the two species exhibiting separate, sharp, seven-line ^{13}C spectra in slow exchange.[14] The chemical shifts of **1**-D^+ are identical with those observed prior to base addition, indicating a high degree of monoprotonation of **1** in water. We estimate the acid dissociation constant of **1**-H^+ (pK_{a1}) to be greater than 13.5. Titration of aqueous **1** with DCl monitored by ^{13}C NMR (single seven-line spectrum; slight dynamic broadening) allowed estimation of pK_{a2} as 10.8 in D_2O. For comparison, pK_{a1} and pK_{a2} of tetramethylcyclam are 9.70 and 9.31, respectively.[15] When a CD_3CN solution of **1** was titrated with CF_3CO_2H, separate ^{13}C spectra were observed for **1**, **1**-H^+, and **1**-H_2^{2+}. Competition experiments (^{13}C NMR) involving the addition of 1 equiv of CF_3CO_2H to a 1:1 mixture of **1** and its monocyclic analogue, tetramethylcyclam, and to a 1:1 mixture of **1** and 1,8-bis(dimethylamino)naphthalene[16] showed **1** to be much more basic. In neither case was any free **1** detected. A similar experiment pitting **1** against 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) showed 34% protonated DBU (^{13}C chemical shift interpolation; fast exchange) and 66% protonated **1** (slow exchange). Based on this result and the reported pK_a of DBU-H^+ in CH_3CN (24.32[17]), the pK_{a1} of **1**-H^+ can be calculated to be 24.9.

The X-ray crystal structure of $[\mathbf{1}\text{-}H_2^{2+}][CF_3CO_2^-]_2$ (**4**) (from CD_3CN) has been determined (Figure 2).[18] Of the 10 reasonable diamond-lattice-type conformations of **1** having two [2323] 10-membered rings,[19] only one is disposed for two transannular $^+N-H{\cdots}N$ hydrogen bonds. The experimental (approximately C_2) dication geometry is a distortion of that conformation, having a *syn-periplanar* (12.5°) rather than a *syn-clinal* $N_1-C_{15}-C_{16}-N_8$ torsion angle.

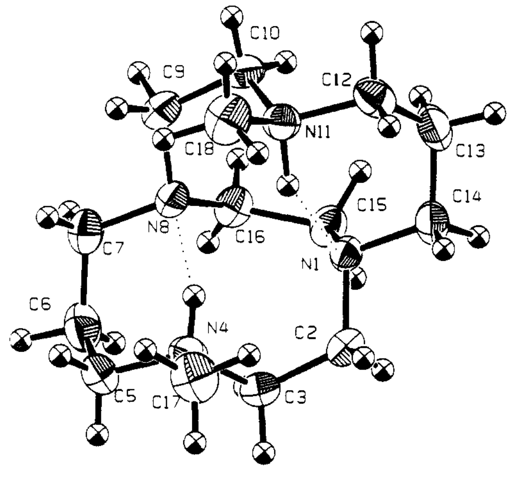

Figure 2. ORTEP drawing of **4** showing the 50% probability ellipsoids. Dotted lines indicate intramolecular H bonds.

The cleft of such a conformation is also appropriate for complexation of small metal ions. Indeed, **1** forms 1:1 complexes with $LiClO_4$ and $NaBPh_4$ in CD_3CN, each of which is in slow exchange with excess free ligand. A (1:1:1) $LiClO_4$-$NaBPh_4$-**1** competition experiment (CD_3CN) gave $K(Li^+)/K(Na^+) = 2 \times 10^2$, in agreement with our expectations based upon cavity size. The ^1H NMR spectra of these complexes (as well as that of **4**) are consistent with the diamond-lattice-type ligand conformation shown in Figure 1c. The adoption of such a conformation upon complexation[20] may account for the strong, selective Li^+ binding of **1** in CD_3CN and D_2O.

In summary, an efficient synthesis has yielded the first crossed-bridged cyclam, **1**, a new fast-equilibrating "proton sponge" tetraamine.[3] **1** complexes Li^+ selectively, adopting a novel, cleft-containing, diamond-lattice coordination geometry. Investigations of complexation of other main group and transition-metal ions by **1** and extension of the synthesis to additional members of this interesting new class of tetraamines are in progress.

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Supplementary Material Available: Synthetic details and characterization of compounds **1** and **2**, NMR spectra of protonated and complexed **1**, and tables of crystal data collection, atomic coordinates, bond distances, bond angles, torsion angles, and anisotropic thermal parameters for compound **4** (33 pages); tables of observed and calculated structure factors for **4** (27 pages). Ordering information is given on any current masthead page.

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(14) The identity of **1**-Li^+ was confirmed by its appearance as the minor component upon titration of a D_2O solution of **1** with LiBr.

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(18) Crystal Data: $C_{18}H_{32}N_4O_4F_6$, monoclinic $P2_1/c$, $a = 9.88$ (1) Å, $b = 14.00$ (6) Å, $c = 16.08$ (1) Å; $\beta = 91.4$ (1)°, $V = 2223$ Å^3, $Z = 4$, μ(Mo Kα) = 1.27 cm^{-1}, $D_{calcd} = 1.442$ g/cm^3, $T = 296$ K, $\lambda = 0.71069$ Å, colorless prisms, 0.60 × 0.45 × 1.0 mm, Rigaku AFC6S diffractometer, data collected in $\omega-2\theta$ scan mode. Of 4112 unique reflections measured, 2592 were considered observed ($I > 3.00\sigma(I)$) and were used in subsequent structure analyses. The final discrepancy index was $R = 0.047$, $R_w = 0.059$, GOF = 2.43, maximum peak in final difference map 0.19 e$^-$/Å^3.

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(20) The 360-MHz ^1H spectrum of free **1** is significantly different from those of protonated and complexed **1**, suggesting complexation-induced conformational biasing rather than a rigid preformed cleft. The spectrum of **1** is indicative of time-averaged 2-fold symmetry; the 1,8-ethylene bridge exhibits an AA'XX' subspectrum and mutual exchange between CH_2 geminal pairs is slow on the NMR time scale. Thus, ring inversion, which must result in tucking of the ethylene bridge through a 14-membered ring, is slow. Results of conformational analysis of free **1** by NMR and molecular mechanics will be further discussed in a full paper.