Synthesis and Characterization of Cross-Bridged Cyclams and Pendant-Armed Derivatives and Structural Studies of Their Copper(II) Complexes

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Abstract: A series of 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane ligands, including the parent compound, *N*,*N*′-dialkyl variants, and the first *N*,*N*′-di-pendant-arm derivatives have been synthesized by a short, efficient, and conceptually novel approach. Their copper(II) complexes have been prepared, and four of these were structurally characterized by X-ray diffraction. In all four complexes, the cross-bridged tetraamine ligand was found to be *cis*-folded, coordinating the metal cation within its molecular cleft using all four nitrogen lone pairs. Geometries intermediate between idealized square pyramidal and trigonal bipyramidal coordination were found for three of the complexes, whereas a distorted octahedral copper coordination was found for the complex of a di-pendant-arm cross-bridged cyclam.

Introduction

The design, synthesis, and coordination chemistry of new polyamine ligands and pendant-arm derivatives continues to stimulate intense research effort due to realized and potential applications in radiopharmaceutical, catalysis, and biomimetic chemistry.[1−3] Wainwright and Hancock have investigated "structurally-reinforced" macrocyclic tetraamines whereby adjacent nitrogens (i.e., those without intervening nitrogens) are linked by ethylene bridges to favor *trans* coordination of metal cations.[4,5] We have communicated the syntheses of several members of a novel class of ligands having nonadjacent nitrogens bridged by $(CH_2)_2$, the "cross-bridged" tetraamines.[6,7] We designed these bicyclo[6.6.2], [6.5.2], and [5.5.2] tetraamines to be capable of adopting conformations[8,9] having all four nitrogen lone pairs convergent upon a cleft (*in*,*in* at the bridgehead nitrogens[10]) for complexation of small metal ions and encap-

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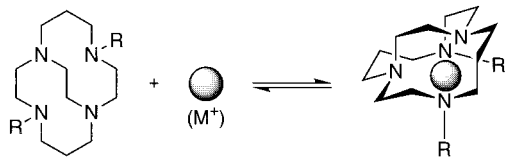

Figure 1. Metal complexation by cross-bridged cyclams.

sulation of protons. Such ligands may be thought of as "clamshells" of facially coordinating triazacycloalkanes.[11] The constitutional design precludes *trans* coordination and ensures that these flexible ligands may adopt low-strain medium-ring conformations ideal for *cis*-folded coordination. The viability of this concept was verified with the demonstration[6] that dialkyl cross-bridged tetraamines are proton sponges[12] and Li^+-selective alkali metal ion complexers. Our communication on Cu(II) and Ni(II) complexes appeared in 1996.[7] The structural results showed that the [6.6.2] cross-bridged cyclams indeed form *cis*-folded complexes, the tetraamines adopting C_2 conformations with each of the 10-membered rings in the distorted diamond-lattice [2323] conformation[13] that was anticipated on the basis of our ligand design (Figure 1).[14] More recently, we reported related Zn(II) complexes of cross-bridged cyclam.[15] Since 1998, Busch, Alcock and co-workers have also reported their work on 3d-transition metal complexations[16,17] using our cross-bridged ligands and a *C*-hexamethyl analogue.[17] Busch et al. have described the cross-bridged ligands as "ultra-rigid".[16a,d] However, because bridgehead bicyclic tetraamines having two medium rings are conformationally flexible and inhomogeneous (EFF Monte Carlo searches of conformational space find scores of energetically accessible conformations[18]), we prefer not to use that term. Micheloni and Ciampolini, Springborg, and others have also reported a number of interesting cross-bridged tetraamines having longer bridging groups[19] and their Cu(II) and Ni(II) complexes.[20]

Herein we present detailed procedures for the efficient synthesis of cross-bridged cyclam ligands, including the first pendant-armed derivatives. The rationale of the synthetic strategy is described and structures of two alkylated tetracyclic bisaminal synthetic intermediates are presented. Preparation and structural characterizations of four Cu(II) complexes of the ligands are detailed.

Results and Discussion

Ligand Synthesis and Rationale. Our short, efficient route to the cross-bridged cyclams and selected pendant-arm derivatives is shown in Scheme 1. In summary, the approach involves (a) condensation of glyoxal and cyclam (**1**) to give tetracyclic bisaminal **2**,[21] (b) highly regioselective dialkylation of **2** to give bis-quaternary ammonium halides **3**, and (c) reduction to give double-ring-expanded cross-bridged cyclams **4.** *N*,*N*′-Dibenzyl cross-bridged cyclam **4a** is cleanly debenzylated by atmospheric hydrogenolysis to give the parent cross-bridged ligand **5**, which can be subsequently elaborated to pendant-arm derivatives. This synthetic strategy avoids the problems inherent in synthesis of 10-membered rings by cyclization methodologies.[2e,22]

Bisaminal Alkylation. Our synthetic design and the ultimate success of the implemented synthesis of the cross-bridged cyclams was predicated upon the concept that the regioselectivity of the dialkylation should be a consequence of the conformation of tetracyclic bisaminal **2**. As shown in Figure 2, the global minimum of *cis*-fused **2** is an all-chair C_2 conformation possessing a cleft.[21,23] Two homotopic *exo* nitrogens have lone pairs which protrude from the convex face of the molecule, whereas two homotopic *endo* nitrogens have lone pairs which are more sterically concealed on the concave face. Enantiomerization of **2**, which exchanges the *exo* and *endo* nitrogens, is fast on the laboratory time scale. The barrier of this enantiomerization, a multistep conformational process which involves net inversion of all four nitrogens and both piperazine rings, is approximately 15 kcal/mol.[21,24] Initial alkylation takes place on a more sterically accessible *exo* nitrogen of **2** (alkylation of only one of the enantiomers of **2** is shown in Figure 2 for simplicity). The *endo*-alkylation is sterically less favorable than *exo*-alkylation because the transition state of the former involves two incipient g^+g^- interactions (R−N^+−C−N−C and R−N^+−

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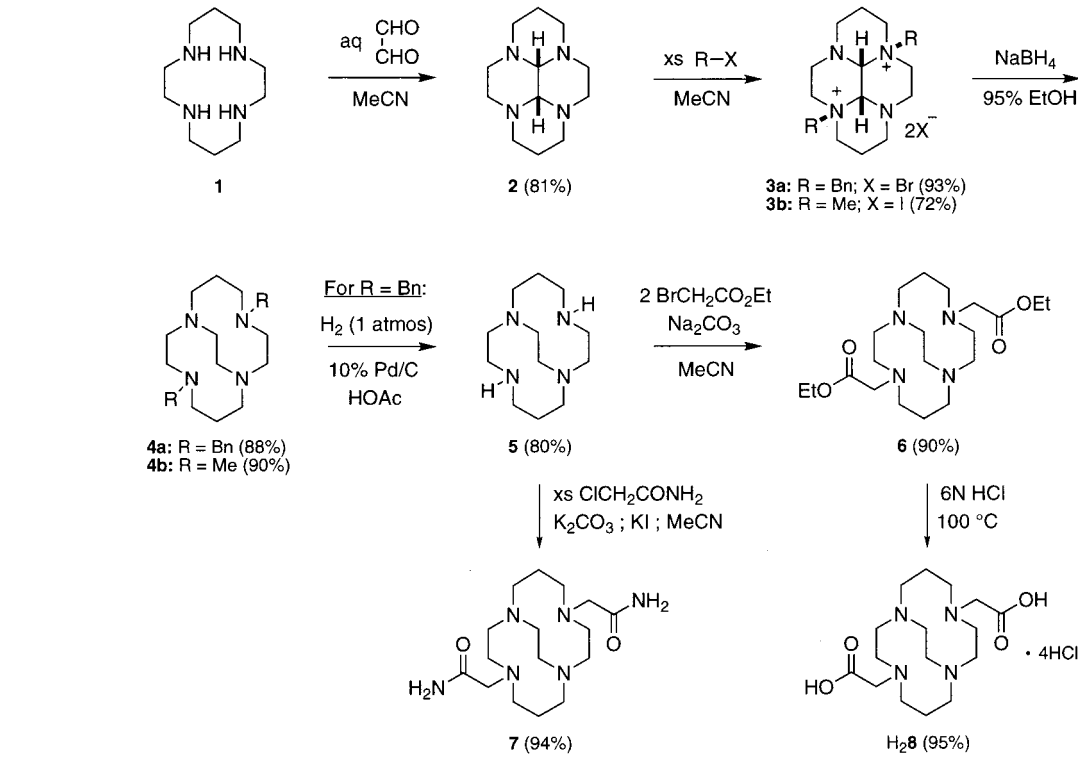
Scheme 1



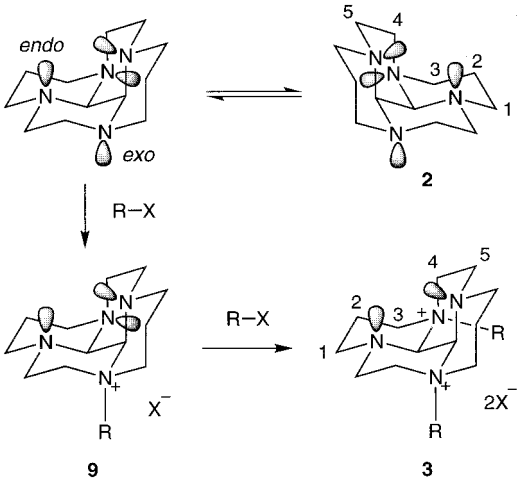


Figure 2. Alkylation of tetracyclic bisaminal **2**.

C−C−N). The *exo*-alkylated product (**9**) is conformationally locked by the quaternary nitrogen, which precludes any conformational changes other than to high-energy twist-boat conformations. The highly regioselective second alkylation, which is qualitatively slower than the first, occurs on the remaining *exo* nitrogen, which is less sterically hindered than the two remaining *endo* nitrogens. *exo*-Alkylation also minimizes Coulombic repulsion relative to alkylation at either of the *endo* nitrogens of **9**. The relative importance of these factors in determining the regioselectivity is unknown. The high stereoselectivity of the first step suggests that the steric factor alone could account for the results of the second alkylation, but it is also known that dialkylation of monocyclic aminals (e.g. dimethylhexahydropyrimidine) requires extreme conditions,[25,26] so clearly, both factors favor the desired product **3**.

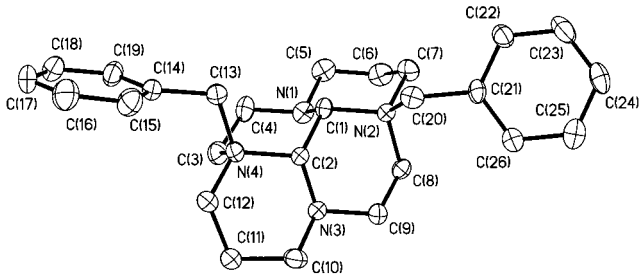


Figure 3. X-ray structure of **3a**.

In practice, the dialkylations to give **3** were very clean reactions under our experimental conditions (MeCN, room temperature); there was no evidence for the presence of other constitutional isomers in the crude reaction product. (However, it should be noted that increasing the temperature resulted in impure products and lower yields; vide infra.) NMR results for **3a** and **3b** are completely consistent with the C_2 *exo,exo* structure. The X-ray crystal structure of **3a** (Figure 3) confirms this.[27] An X-ray structure of **3b** has also been reported recently.[17]

Implicit in the above discussion is the assumption that the initial stereoselective alkylation of **2** is kinetically controlled rather than thermodynamically controlled. However, the question of kinetic vs thermodynamic control must be considered if alkyl halides (rather than tosylates, triflates, etc.) are employed for the alkylation of tertiary amines; halides are good nucleophiles, making such S_N2 alkylations reversible under certain conditions. Although we expected that the reactions reported herein would be kinetically controlled under the conditions of our experiments, it remained to be demonstrated. Monobenzyl salt **9a** was cleanly generated by alkylation of **2** with benzyl bromide in toluene, dibenzylation being prevented by precipitation of **9a** from

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(27) During the preparation of this paper and after the completion of our work, a structure of the dihydrate of **3a** appeared.[28]

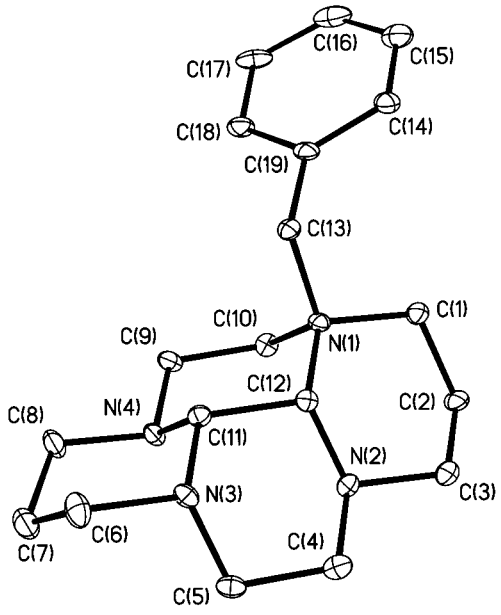
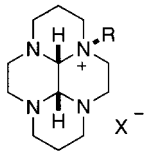
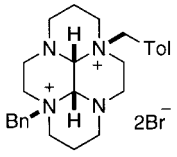


Figure 4. X-ray structure of **9a**.

solution (kinetic control).[29,30] The *exo*-benzylated structure of **9a** was verified by X-ray crystallography (Figure 4). When a solution of **9a** in MeCN was treated with excess *p*-methylbenzyl bromide under our standard conditions for conversion of **2** to **3a** (MeCN, room temperature, typical concentrations) but for a period of only 1 h, ^{1}H and ^{13}C NMR analysis (after the removal of the excess alkylating agent by washing) showed the crude product to be a mixture of two compounds: the starting **9a** and unsymmetrical dialkylated salt **10**. The fact that no mono- or di-*p*-methylbenzylated products were observed demonstrates that the second alkylation of **9a** is much faster than debenzylation, proving that the first benzylation is, indeed, under strict kinetic control.



9a (R=Bn; X=Br)
9b (R=Me; X=I)



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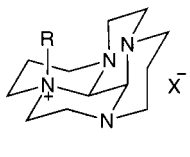
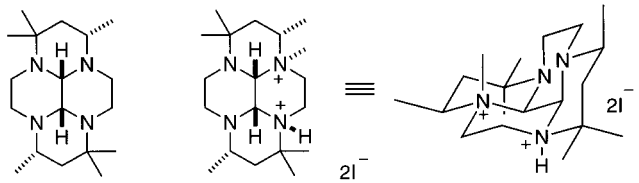


11a (R=Bn; X=Br)
11b (R=Me; X=I)

Although neither we[6,7] nor others[17,28,30] have observed any *endo*-alkylation products of **2** (indeed, we had hoped *not* to!), the question of the relative thermodynamic stabilities of *exo* salts **9** and their *endo* analogues **11** is certainly very interesting. Although the former alkylated aminals are favored on steric grounds, the latter are favored stereoelectronically. In **11**, the remaining nitrogen lone pair of the alkylated aminal unit is antiperiplanar (*ap*) to the aminal C−N$^+$ bond, the arrangement that maximizes the stabilizing hyperconjugative $n_N \rightarrow \sigma^*$ interaction. The corresponding lp−N−C−N$^+$ torsion angle in **9** is synclinal (*sc*), a less stabilizing geometry. Alder and one of us have documented studies of such stereoelectronic effects in aminals, protonated aminals, and alkylated aminals.[31,32] This type of stabilization (a generalized anomeric effect) is no doubt responsible for the fact that the *endo* nitrogens of **2** and the *endo* nitrogen of the unalkylated aminal functionality of **9b** are more basic than the respective *exo* nitrogens, as reported by Busch and Alcock.[17] (It should be noted that *endo*-protonation is not sterically demanding and is under thermodynamic control.) The bond lengths of di-*endo*-protonated **2**[17] exhibit the expected structural anomeric effects (C−N shortened and C−N$^+$ lengthened).[31] An attempt to equilibrate **9a** with **11a** (∼60 °C, 16 h) led only to decomposition of **9a**, which is consistent with our observations that the dialkylations of **2** are cleaner at room temperature than at higher temperatures. We believe this decomposition likely involves proton-transfer disproportionation through an iminium ion (vide infra) to give **9a**·HBr and a triaminoethylene, but we cannot rule out the possibility that the initial step of the decomposition is equilibration to **11a**. We expect **11a** to be more labile than **9a**, because it is stereoelectronically set up for opening to an iminium ion (*ap* lp−N−C−N$^+$).

Interestingly, Busch and Alcock have reported that reaction of methyl iodide with hindered hexamethyl-bisaminal **12** under our conditions (rt) gave *endo*-methylated product; use of forcing conditions (100 °C, 24 h) gave *endo*-methylated, *exo*-protonated diiodide **13** (major) and dimethylated diiodide (minor). This may be a consequence of steric inhibition of *exo*-methylation by flanking *C*-methyls, that is, a kinetic effect. It must be noted, however, that the sample used for the X-ray structure of **13** was derived from the high-temperature methylation, where thermodynamic control is a possibility. The fact that hydroiodide **13** was obtained provides further support for the hypothesis that monoalkylated **2** decomposes via proton-transfer disproportionation.



12 **13**

To shed some additional light on the question of the relative thermodynamic stabilities of *exo*- and *endo*-alkylated **2** (**9** and **11** respectively), as well as **14** and **15**, we have carried out a series of molecular mechanics and density functional theory (DFT) calculations. As might be expected, a variety of popular force fields place **9a/b** well below **11a/b**, because the force fields are generally well-parametrized for steric interactions but are not properly parametrized for the α-amino ammonium ion (alkylated aminal) functionality. Of the force fields that we investigated, the Merck Molecular Force Field (MMFF)[33] gave the smallest **11**−**9** (*endo*−*exo)* energetic differences, placing the **9a** cation (*exo*) 2.9 kcal/mol below the **11a** cation (*endo*) and the **9b** cation (*exo*) 2.0 kcal/mol below the **11b** cation (*endo*). It also places *exo*-methyl cation **15** 6.1 kcal/mol *above* *endo*-methyl analogue **14**. MMFF also gave geometries that were in reasonable accord with the available crystallographic results. Density functional calculations were carried out by the

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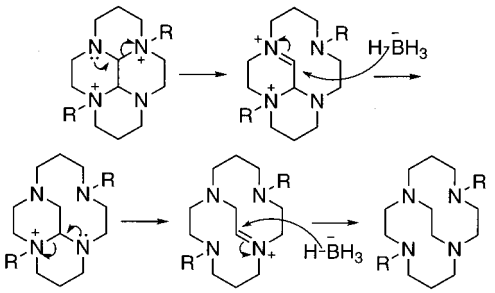
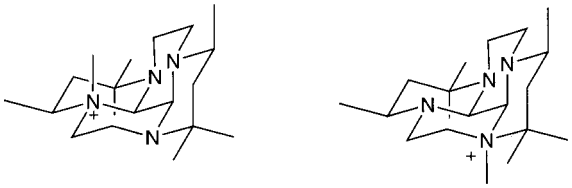


Figure 5. Mechanism for double-reductive ring expansion of **3**.

perturbative Becke-Perdew[34] method implemented in Spartan V5.1.3,[35] using the DN** numerical basis set, which is similar to 6-31G**. pBP/DN**//MMFF calculations place the **9a** cation (*exo*) 1.3 kcal/mol below the **11a** cation (*endo*), but the **9b** cation (*exo*) 0.2 kcal/mol above the **11b** cation (*endo*). pBP/DN**// MMFF on cations **14** and **15** gave the same result as the MMFF calculations: *endo* **14** is 6.1 kcal/mol more stable than **15**. Geometry optimizations of the **9b** cation (*exo*) and the **11b** cation (*endo*) at the DFT level (pBP/DN**//pBP/DN**) were also carried out, yielding the result that the latter (*endo*) is more stable by 2.1 kcal/mol. However, the C(aminal)−N^+ bond length in the geometry-optimized **11** cation was unusually long (1.66 Å), and it has been pointed out that DFT calculations tend to overestimate anomeric effects,[36] so these computational results must be interpreted with appropriate caution. Nevertheless, the calculations are in qualitative accord with the *endo*-methylation of **12** observed by Busch and Alcock (whether it is a kinetic or a thermodynamic process). The calculations also suggest to us that *endo*-benzylation of **2** is unlikely under any conditions but that thermodynamic *endo*-methylation of **2** cannot be excluded as a possibility.



14 **15**

Reductive Ring Expansion. The purpose of the regioselective dialkylation that was discussed in the previous section is to set the system up for double reductive ring expansion via iminium ions to the bicyclo[6.6.2] ring system (Figure 5). Ring expansion approaches to medium rings and polycyclic systems have been reviewed.[37] Prior to our work, Alder and co-workers had ingeniously used reductive cleavage of tricyclic α-amino ammonium salts (alkylated aminals) to prepare a series of medium-ring bridgehead bicyclic diamines.[38] They generally used $LiAlH_4$ in ether solvents for their reductions, but we found $NaBH_4$ in 95% EtOH at room temperature to be the system of choice for preparation of the cross-bridged cyclams. Although the reductions of **3** are slow under these conditions, they are remarkably clean. The use of higher temperatures or larger proportions of water generally led to impure product, presumably as a result of iminium hydrolysis. Salts **3** are not reduced at an appreciable rate by $LiAlH_4/Et_2O$, which suggests that the more polar medium is necessary for intermediate iminium ion formation. It should be noted that unalkylated **2** is resistant to $NaBH_4$ or $LiAlH_4$ reduction and is reduced to 1,5,8,12-tetraazabicyclo[10.2.2]hexadecane by DIBALH.[39] The reduction mechanism proposed in Figure 5 is supported by the fact that $NaBD_4$ reduction is stereoselective but not stereospecific.[40] We suggest that the rate-determining step of the reaction is the first step, in which tetracyclic **3** is converted to a tricyclic iminium ion via a twist-boat conformation of **3** in order to achieve the *ap* lp−N−C−N^+ torsion angle that is stereoelectronically ideal for cleavage.

4a and **4b** are remarkably basic (proton sponges).[6,7] Although this aspect of the behavior of the cross-bridged tetraamines will be detailed in the future,[18] it is worth pointing out here that dissolution of *N*,*N*′-dialkyl cross-bridged cyclams in chloroform for other than brief periods (even for NMR spectroscopy) should be avoided, because they react.

Debenzylation and *N*,*N*′-Pendant-Arming. Debenzylation of **4a** was achieved by catalytic hydrogenolysis (1 atm) using 10% Pd/C in glacial acetic acid. The crude product after workup (benzene extraction) was >99% pure by NMR in some reactions but may be recrystallized from Et_2O at low temperature (−78 °C) if necessary. Compound **5** is a crystalline, sublimable solid that is soluble not only in water and polar aprotic solvents (DMSO, CH_3CN) but also in nonpolar solvents, including pentane and CCl_4. This suggests that the N−H hydrogens form N−H···N transannular hydrogen bonds to the bridgehead tertiary amino nitrogens, thus allowing the molecule to present a lipophilic exterior to solvent. The ^{1}H NMR spectra of **5** in C_6D_6, $CDCl_3$, and CD_3CN (δ_{N-H} = 3.5−3.7) and IR spectra (N−H stretch of 3260 cm^{-1} invariant over concentration range of 0.016−0.13 M **5** in $CHCl_3$) are consistent with intramolecular H-bonding. Compound **5** is also considerably less basic than either **4a** or **4b**.[18]

Parent cross-bridged cyclam **5** has been converted to a number of *N*,*N*′-difunctionalized pendant-arm derivatives by standard secondary amine functionalization routes. The derivatives that were used as ligands in this study are included in Scheme 1. One unanticipated result was encountered: an attempt to convert diester **6** to diamide **7** by reaction with aqueous ammonia under standard conditions gave diacid **8** (after pH adjustment) instead. We surmise that the basicity of the cross-bridged moiety is the cause of the unexpected reaction, generating sufficient hydroxide to compete nucleophilically with the ammonia.

Preparation and Spectral Characterization of Copper(II) Complexes. Copper(II) complexes of these cross-bridged ligands were readily prepared in methanol or ethanol solvents. These include $Cu(ClO_4)_2$·**5**, $CuCl_2$·**5**, $Cu(ClO_4)_2$·**4b**, $CuCl_2$·**4a**, Cu·**8, and Cu(ClO$_4$)$_2$·7**. Elemental analyses were consistent with the formation of 1:1 complexes in each case. In addition, the following spectral data were obtained.

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Table 1. Summary of Electronic Spectral Data for the Copper Complexes

complex	electronic absorption maxima, λ_{max} (ϵ, M^{-1} cm^{-1})
$Cu(ClO_4)_2$·**5**	
in MeCN	567 nm (120)
solid state	582 nm
$CuCl_2$·**5**	
in MeCN	596 nm (196)
solid state	579 nm
$Cu(ClO_4)_2$·**4b**	
in MeCN	618 nm (76)
solid state	625 nm
$CuCl_2$·**4a**	
in MeCN	680 nm (75)
solid state	675 nm
Cu·**8**	
in MeOH	642 nm (20)
solid state	629 nm
$Cu(ClO_4)_2$·**7**	
in MeCN	630 nm (24)
solid state	625 nm

Infrared Spectra. In the spectrum of $Cu(ClO_4)_2$·**5**, a slightly broadened N−H stretching band at 3269 cm^{-1} of medium intensity was observed (parent ligand ν_{NH} is at 3260 cm^{-1}). The very strong and broad perchlorate band that was centered at approximately 1090 cm^{-1} was not sufficiently resolved to be of diagnostic value for the perchlorate coordination modes found to be present in the X-ray structure of this complex (vide infra).[41] The IR spectrum of $CuCl_2$·**5** revealed the presence of lattice H_2O by a broad, medium-intensity band at 3438 cm^{-1}. A broadened N−H stretch was also found at 3212 cm^{-1}. A broad water of hydration band of medium intensity was observed between 3400 and 3470 cm^{-1} in the IR spectrum of $CuCl_2$·**4a**. For the pendant-armed ligand complex Cu·**8**·$NaClO_4$, no IR absorptions attributable to COOH groups (usually between 1720 and 1740 cm^{-1} for the protonated ligand) were observed. Instead, carboxylate bands at 1590, 1616 cm^{-1} were noted, which is consistent with metal coordination. Known carboxymethyl pendant-armed macrocyclic tetraamine complexes of copper(II) have these bands between 1570 and 1640 cm^{-1}.[42] Typical copper glycinate ν_{CO} bands range from 1593 to 1607 cm^{-1}.[43] Broad OH bands from the waters of hydration were also found at 3580 and 3365 cm^{-1}. An intense, broad perchlorate absorption at 1098 cm^{-1} was of little diagnostic value for the anion's coordination mode. In the IR spectrum of the amide-armed ligand complex $Cu(ClO_4)_2$·**7**, a coordinated amide carbonyl band at 1665 cm^{-1} was observed which was red-shifted from the free-ligand value of 1685 cm^{-1}. Kaden has previously reported ν_{CO}'s of 1580−1660 cm^{-1} for coordinated amide-pendant arms of tetraamine macrocyclic complexes.[44]

Electronic Spectra. Solid-state and solution electronic spectra of the described copper complexes are summarized in Table 1. In the solid phase, broad ligand-field bands were observed with maxima ranging from 579 to 675 nm, which is consistent with the blue−blue-green colors of these complexes. Their acetonitrile or methanol solution $d-d$ transitions were found between 567 and 680 nm, with each spectrum reasonably similar to the corresponding solid-state data, which suggests similar coordination environments. For comparison, Springborg and co-workers have prepared related trimethylene cross-bridged cyclen copper(II) complexes that are five-coordinate in the solid-state as well as in solution.[20a,b] Their aqueous solution electronic spectra have $d-d$ bands ranging from 595 to 633 nm, depending on the lone ancillary ligand. The strongest ligand field for our copper complexes was found with the parent ligand **5** (567 nm), whereas the *N*,*N*′-dibenzyl ligand **4a** has the weakest (680 nm) ligand field, with the *N*,*N*′-dimethyl ligand **4b** between (618 nm) them. A similar trend has been observed for copper(II) complexes of cyclen and its tetra-N-substituted derivatives where the ligand field strengths are ranked in the order Bn_4−cyclen (614 nm) < Me_4−cyclen (602 nm) < cyclen (590 nm).[45]

EPR Data. In the room-temperature solid-state EPR spectrum of $Cu(ClO_4)_2$·**5**, a single broad signal with $g = 2.104$ was observed. In a frozen methanol matrix, however, an axial spectrum with $g_{\|} = 2.271$, and $g_{\perp} = 2.146$ was obtained. For the complex $CuCl_2$·**5**, its solid-state EPR spectrum at room temperature is rhombic with $g_1 = 2.171$, $g_2 = 2.087$, and $g_3 = 2.050$. By contrast, its frozen methanol solution spectrum is quite complex, with the presence of $\Delta M = 2$ transitions indicative of the possible existence of a dimeric species.[46] At room temperature in the solid state, an approximately axial EPR spectrum was observed for the complex $CuCl_2$·**4a,** with $g_{\|} = 2.234$ and $g_{\perp} = 2.094$. In a frozen methanol matrix at 77 K, the signals are at $g_{\|} = 2.284$ and $g_{\perp} = 2.098$. Only a single broad EPR signal was observed for Cu·**8** at room temperature in a solid sample, with $g \sim 2.06$. In frozen methanol, the EPR spectrum is near axial, with $g_{\|} = 2.289$ and $g_{\perp} = 2.096$. Detailed simulation and assignment of these spectra have not been completed. However, all have $g_{\|} > g_{\perp} > 2.0$, which is consistent with Jahn−Teller distorted square-pyramidal or octahedral geometries.[47]

X-ray Structural Studies of the Copper(II) Complexes $Cu(ClO_4)_2$·5, $CuCl_2$·5, $CuCl_2$·4a·H_2O, and $[Cu$·8·$Na(H_2O)ClO_4]_2$·H_2O. As predicted on the basis of molecular mechanics calculations,[48] each Cu(II) complex structure has four convergent ligand nitrogen donors coordinating the Cu(II) that is inside the molecular cleft in a *cis*-V-folded coordination configuration,[49] with the ligand in a slightly distorted [2323]/[2323] diamond-lattice conformation. The crystal structures of $Cu(ClO_4)_2$ ·**5** (Figure 6), $CuCl_2$·**5** (Figure 7), and $CuCl_2$·**4a**·H_2O (Figure 8) all exhibit five-coordinate copper. As shown in Figure 6, only one of the perchlorates in $Cu(ClO_4)_2$ ·**5** is directly coordinated [Cu(1)−O(1) at 2.166(6) Å], although the second is H-bonded to a secondary amine hydrogen, N(2)−H(2N). In addition, a weak Cu(1)···O(2A) interaction [2.749(6) Å] to the coordinated perchlorate of another cationic unit blocks the sixth potential coordination site (see Supporting Information). The axial secondary amine N(2)−Cu(1) bond lengths of 1.961(7) Å and N(4)−Cu(1) of 1.970(7) Å are, as expected,[50] significantly

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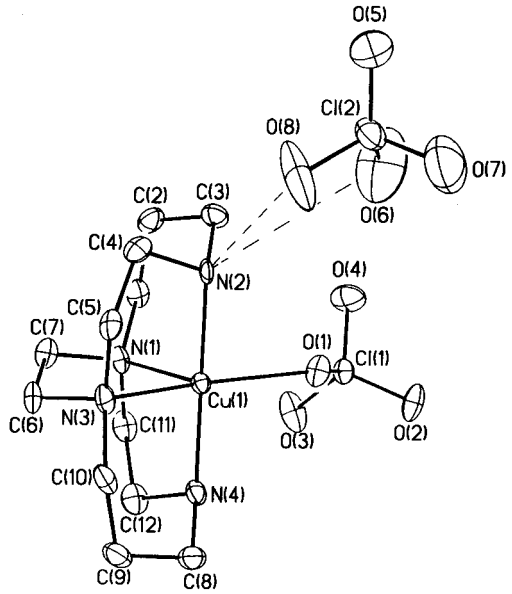

Figure 6. X-ray structure of the $Cu(ClO_4)_2$·**5** complex.

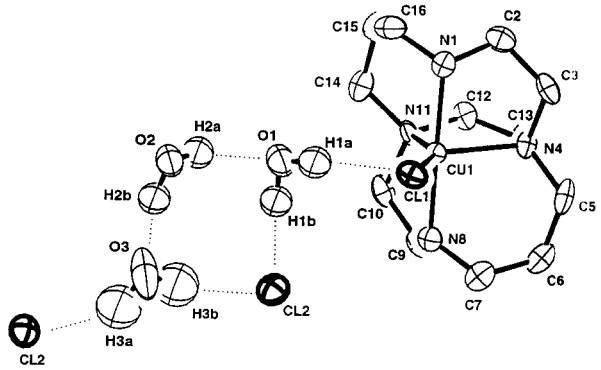

Figure 7. X-ray structure of the $CuCl_2$·**5**·$3H_2O$ complex.

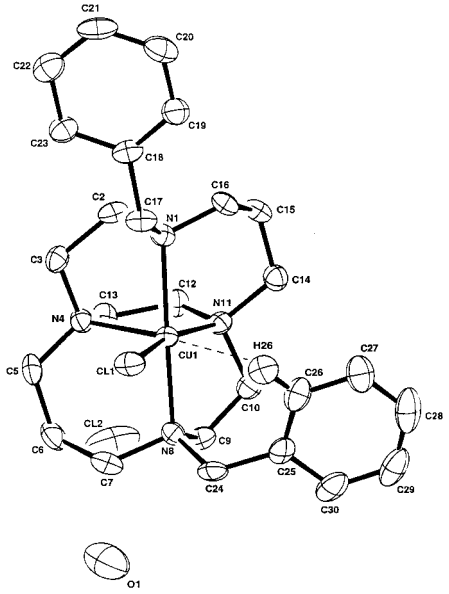

Figure 8. X-ray structure of the $CuCl_2$·**4a**·H_2O complex.

shorter than the equatorial tertiary N(1)−Cu(1) bond lengths of 2.138(6) Å and N(3)−Cu(1) of 2.081(7) Å.

Applying Addison and Reedjik's τ-parameter for describing five-coordinate geometries along the Berry rearrangement between a trigonal bipyramid and a square pyramid [for which $\tau = (\beta-\alpha)/60$, with $\tau = 1$ for trigonal bipyramidal (D_{3h}) and 0 for square pyramidal (C_{4v})], we obtained a value of 0.38 {τ = [N(2)−Cu(1)-N(4) angle minus O(1)−Cu(1)-N(3) angle]/60} here.[51] Alternatively, the dihedral δ angle criterion of Muetterties and Guggenberger can be used. In this approach, the angle between the normals to the N(2)−O(1)−N(3) and N(4)−O(1)−N(3) faces is used to gauge the distortion along the Berry intramolecular exchange process from idealized trigonal bipyramidal (*TBPY*, 53.1°) to idealized square pyramidal (*SP*, 0°).[52] The δ angle is found to be 25° for this structure, which therefore lies almost halfway between the two idealized five-coordinate geometries. The longer equatorial N(1)−Cu(1) bond length of 2.138(6) Å [as compared to N(3)−Cu(1) of 2.081(7) Å] then reflects the weaker apical bonding of N(1), which can be viewed as the apex of a distorted square pyramid, while N(2), N(3), N(4), and O(1) make up the four basal donor set. Other relevant bond distances and angles are listed in Table 2.

Table 2. Selected Bond Distances (Å) and Bond Angles (deg) for $Cu(ClO_4)_2$·**5**

Cu(1)−N(2)	1.961(7)	Cu(1)−N(4)	1.970(7)
Cu(1)−N(3)	2.081(7)	Cu(1)−N(1)	2.138(6)
Cu(1)−O(1)	2.166(6)		
N(2)−Cu(1)−N(4)	179.7(3)	N(2)−Cu(1)−N(3)	86.6(3)
N(4)−Cu(1)−N(3)	93.7(3)	N(2)−Cu(1)−N(1)	92.9(3)
N(4)−Cu(1)−N(1)	87.1(3)	N(3)−Cu(1)−N(1)	88.5(3)
N(2)−Cu(1)−O(1)	87.9(3)	N(4)−Cu(1)−O(1)	91.8(3)
N(3)−Cu(1)−O(1)	156.7(2)	N(1)−Cu(1)−O(1)	114.5(2)

The crystal structure of the $CuCl_2$·**5** complex is shown in Figure 7. One of the chlorides, Cl(1), is also directly coordinated, although the second, Cl(2), is not but is, instead, H-bonded to associated waters of hydration. A potential sixth copper coordination site is blocked by a water molecule, which in turn H-bonds to both chlorides. The secondary nitrogen−Cu bond lengths of 1.996(5) and 2.003(5) Å are quite similar, with a nearly linear N(1)−Cu−N(8) bond angle of 176.9(2)°. Again, both of the two tertiary N−Cu bond lengths are longer as well as significantly different from each other, with N(4)−Cu at 2.140(5) Å and N(11)−Cu at 2.081(6) Å.

Addison and Reedjik's τ-parameter here gives an intermediate value of 0.44, whereas the dihedral δ angle criterion of Muetterties and Guggenberger using the angle between the normals to the N(1)−Cl(1)−N(11) and N(8)−Cl(1)−N(11) faces gives a value of 29°,[51,52] again almost halfway between the two idealized geometries. The significantly longer N(4)−Cu(1) bond allows N(4) to be ascribed to the less strongly coordinating apex of a distorted square pyramid. Donor atoms N(1), N(8), N(11), and Cl(1) then represent the basal set. A recently reported structure of a $CuCl_2$ complex of the related cross-bridged ligand **4b** by Busch and co-workers has a very similar coordination geometry that was described as square pyramidal (actual τ = 0.32).[17] Comparison of our $CuCl_2$·**5** structure to a related trimethylene cross-bridged cyclen copper bromide complex shows that the latter's reported coordination geometry (δ = 31°) is also an intermediate one.[20a] A significant difference between our $(CH_2)_2$ cross-bridged complex and the $(CH_2)_3$ cross-bridged analogue is found in the substantially smaller equatorial N−Cu−N angle of 87.8(2)°, as compared to the latter's 99.0(3)°. Relevant bond distances and angles are presented in Table 3.

In the crystal structure of $CuCl_2$·**4a**·H_2O (Figure 8), the sixth potential coordination site is blocked by what may be described as an agostic interaction between Cu(1) and an *ortho*-hydrogen,

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Table 3. Selected Bond Distances (Å) and Bond Angles (deg) for $CuCl_2$·**5**

Cu(1)−Cl(1)	2.304(2)	Cu(1)−N(8)	1.996(5)
Cu(1)−N(1)	2.003(5)	Cu(1)−N(11)	2.081(6)
Cu(1)−N(4)	2.140(5)		
Cl(1)−Cu(1)−N(1)	90.3(2)	N(1)−Cu(1)−N(8)	176.9(2)
Cl(1)−Cu(1)−N(4)	122.0(1)	N(1)−Cu(1)−N(11)	92.3(2)
Cl(1)−Cu(1)−N(8)	92.8(2)	N(4)−Cu(1)−N(8)	93.0(2)
Cl(1)−Cu(1)−N(11)	150.2(2)	N(4)−Cu(1)−N(11)	87.8(2)
N(1)−Cu(1)−N(4)	85.0(2)	N(8)−Cu(1)−N(11)	85.2(2)

Table 4. Selected Bond Distances (Å) and Bond Angles (deg) for $CuCl_2$·**4a**

Cu(1)−Cl(1)	2.296(1)	Cu(1)−N(8)	2.101(3)
Cu(1)−N(1)	2.188(3)	Cu(1)−N(11)	2.082(3)
Cu(1)−N(4)	2.166(4)		
C1(1)−Cu(1)−N(1)	94.74(9)	N(1)−Cu(1)−N(8)	176.0(2)
C1(1)−Cu(1)−N(4)	107.2(1)	N(1)−Cu(1)−N(11)	90.7(1)
C1(1)−Cu(1)−N(8)	89.23(9)	N(4)−Cu(1)−N(8)	94.2(1)
C1(1)−Cu(1)−N(11)	166.0(1)	N(4)−Cu(1)−N(11)	86.1(1)
N(1)−Cu(1)−N(4)	84.7(1)	N(8)−Cu(1)−N(11)	85.4(1)

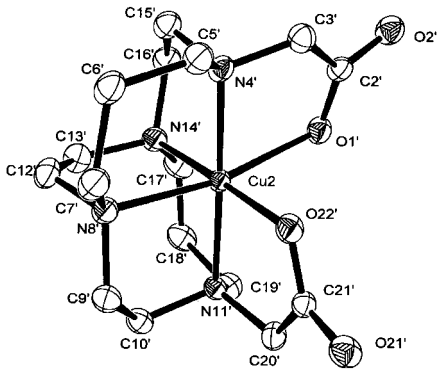

Figure 9. Coordination geometry at a copper center of the [Cu·**8**·Na$(H_2O)ClO_4]_2$·H_2O structure.

H(26), of a pendant benzyl phenyl group. This Cu(1)···H(26) distance is 2.74 Å. Treating this as a five-coordinate complex, both the τ-parameter of 0.17 and dihedral δ angle of 17° reveal a closer relationship to a square pyramidal geometry,[51,52] with N(4) as the apical site. Important bond angles and distances are tabulated in Table 4.

In contrast to the other complexes, the crystal structure of the pendant-armed ligand complex [Cu·**8**·Na$(H_2O)ClO_4]_2$·H_2O (Figure 9) shows that copper is fully enveloped by the bicyclic ligand and its two pendant arms in a distorted octahedral N_4O_2 donor set. The structure features two independent but similar copper macrobicyclic units which form a head-to-tail chain along the crystallographic *x*-axis, connected by two types of dimeric sodium units (see Supporting Information for a structural depiction showing these interactions). Around each independent copper core, only one of which is shown in Figure 9, the Jahn−Teller distortion is manifested in the copper bonding to one axial carboxylate oxygen, O(1) and O(1′), and one axial tertiary nitrogen, N(8) and N(8′), respectively. These axial bonds are significantly elongated, with an average $Cu-O_{ax}$ distance of 2.31 Å and $Cu-N_{ax}$ distance of 2.23 Å, as compared to the more strongly ligated equatorial copper-donor atom distances (average $Cu-O_{eq}$ distance is 2.00 Å; $Cu-N_{eq}$ distance is 2.05 Å). Each copper atom and its respective equatorial donor atoms are coplanar, with equatorial *cis* angles at both copper centers summing to exactly 360.0°. Important bond distances and angles are presented in Table 5. This coordination geometry differs from that of the Cu(II) complex of 1,8-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane,[53] which has *trans*-carboxylate oxygens at the axial sites and four equatorial cyclam nitrogens. It also differs substantially from the structure of the Cu(II) complex of 1,4,8,11-tetrakis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (TETA), which features two axial nitrogen donors and a N_2O_2 equatorial donor set.[54] Recently, a copper(II) complex of a dibenzo-cyclam derivative was reported which has a very similar *cis*-folded ligand conformation as well as axial bond elongations.[55] However, the Jahn−Teller distortions in this case amount to only 2−3% of the Cu−N and Cu−O bond lengths.

Table 5. Selected Bond Distances (Å) and Bond Angles (deg) for [Cu·**8**·Na$(H_2O)ClO_4]_2$·H_2O

Cu(1)−O(1)	2.301(2)	Cu(1)−N(11)	2.027(2)
Cu(1)−O(22)	2.007(2)	Cu(1)−N(14)	2.073(2)
Cu(2)−O(1′)	2.327(2)	Cu(2)−N(4′)	2.050(2)
Cu(2)−O(22′)	1.998(2)	Cu(2)−N(8′)	2.245(2)
Cu(1)−N(4)	2.034(2)	Cu(2)−N(11′)	2.043(2)
Cu(1)−N(8)	2.224(2)	Cu(2)−N(14′)	2.068(3)
O(1)−Cu(1)−O(22)	93.50(8)	O(1′)−Cu(2)−N(4′)	80.28(9)
O(1′)−Cu(2)−O(22′)	91.70(8)	O(1′)−Cu(2)−N(8′)	169.43(9)
O(1)−Cu(1)−N(4)	81.33(9)	O(1′)−Cu(2)−N(11′)	102.78(9)
O(1)−Cu(1)−N(8)	171.09(8)	O(1′)−Cu(2)−N(14′)	88.86(9)
O(1)−Cu(1)−N(11)	99.02(9)	O(22′)−Cu(2)−N(4′)	93.5(1)
O(1)−Cu(1)−N(14)	88.13(9)	O(22′)−Cu(2)−N(8′)	95.1(1)
O(22)−Cu(1)−N(4)	91.80(9)	O(22′)−Cu(2)−N(11′)	84.69(8)
O(22)−Cu(1)−N(8)	93.5(1)	O(22′)−Cu(2)−N(14′)	178.5(2)
O(22)−Cu(1)−N(11)	85.69(9)	N(4)−Cu(l)−N(8)	93.0(1)
O(22)−Cu(1)−N(14)	178.4(2)	N(4)−Cu(1)−N(11)	177.5(1)

In summary, in stark contrast to the three *trans* as well as the two *cis* coordination configurations well-established for cyclam and its unbridged derivatives,[56] all of the copper(II) complexes reported here feature the respective cross-bridged ligand in a *cis*-V-folded complexing geometry. This is a direct consequence of the ligand design. Five-coordinate complexes $Cu(ClO_4)_2$ ·**5**, $CuCl_2$·**5**, and $CuCl_2$·**4a**·H_2O are all intermediate between idealized square pyramidal and trigonal bipyramidal coordination, while pendant-armed complex [Cu·**8**·Na(H_2O)-$ClO_4]_2$·H_2O is best described as distorted octahedral.

Conclusion

Short, efficient syntheses of 1,8-ethylene-cross-bridged cyclams and pendant-arm derivatives have been described in detail and the stereochemical basis for the success of the approach has been discussed. The synthetic strategy relies upon the highly regioselective kinetic alkylation of a conformationally well-defined tetracyclic bisaminal derivative of cyclam and a subsequent double reductive ring expansion to the tetraazabicyclo[6.6.2] system. The parent molecule **5** is readily synthesized from cyclam via *N*,*N*′-dibenzyl cross-bridged cyclam **3a** in four steps in an overall yield of 53%. The ability of the cross-bridged cyclams to complex copper(II) in their molecular clefts using four convergent nitrogen lone pairs has been confirmed by the syntheses and characterization of these copper(II) complexes. In each case, cross-bridging enforces a folded cis-V ligand geometry around the metal center, leading to a distorted square pyramidal coordination sphere. Further, the attachment of

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pendant arms to the parent ligand has been shown to result in full envelopment of the copper(II) cation in a six-coordinate octahedral embrace. We believe that these ligands and the related [6.5.2] and [5.5.2] systems will prove highly valuable in diagnostic and therapeutic biomedical applications and catalytic chemistry, as well as stereoselective synthesis. We and others are actively working toward these ends.[18,40,57]

Experimental Section

Caution! *Although we did not encounter any difficulties, metal perchlorate salts with organic ligands and solvents are potentially explosive and should be prepared and handled in only small quantities with great care.*

General Methods. Unless indicated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded at 360.13 and 90.56 MHz, respectively, and referenced against internal TMS. MeCN was used as the secondary internal standard for NMR spectra of D_2O solutions; the methyl resonance was set at δ 2.06 and δ 1.7 for ^{1}H and ^{13}C spectra, respectively. Resonance assignments are indicated only where they are firmly established, for example, by coupling and symmetry considerations or additional NMR experiments such as DEPT, COSY, HETCOR, or DNMR. IR spectra were recorded as KBr pellets on a Nicolet MX-1 FT spectrophotometer. Electronic spectra were obtained on a Cary 219 spectrophotometer. X-band EPR spectra were recorded on a laboratory-assembled spectrometer with a Bruker ER 041 XK−H microwave bridge. Low-resolution MS and elemental analyses were obtained from the University of New Hampshire University Instrumentation Center. HRMS were obtained from the Dupont Merck Pharmaceutical Company (Wilmington, DE) or the Midwest Center for Mass Spectrometry (Lincoln, NE). Melting points are uncorrected. Reactions were run under nitrogen atmosphere with magnetic stirring. Bulk solvent removal was by rotary evaporation under reduced pressure and trace solvent removal from solids was by vacuum pump. Unless specified otherwise, anhyd Na_2SO_4 was used to dehydrate organic solutions.

Materials. Solvents were either used as purchased or dried according to standard literature procedures.[58] Benzyl bromide, methyl iodide, ethyl bromoacetate, α-chloroacetamide, and glyoxal (40 wt % aq soln) were obtained from the Aldrich Chemical Co. 1,4,8,11-Tetraazacyclotetradecane (cyclam, **1**) was obtained from the Strem Chemical Co. Copper salts were obtained from Alfa Aesar.

***cis*-Decahydro-1*H*,6*H*-3a,5a,8a,10a-tetraazapyrene (2).** Modification and scale-up of the previously reported prepn:[21,59] A solution of **1** (8.47 g, 42.3 mmol) and 7.0 mL of 40 wt % aq glyoxal in 700 mL of MeCN were stirred at room temperature for 1 h, then at 50−60 °C for 2 h. After the reaction mixture was cooled to room temperature, the solvent was removed, the resulting orange solid was taken up in $CHCl_3$ (500 mL), the solution was dried and filtered, and $CHCl_3$ was removed from the filtrate to give a white solid product (Et_2O trituration aids solidification). Sublimation (80 °C, 0.02 mmHg) gave pure **2** (7.65 g, 81%): mp 82−84 °C (lit[21] 82.5−85 °C); ^{1}H NMR ($CDCl_3$) δ 1.22 (dp_{app}, 2H, J = 13.1, 2.6 Hz, H_{2eq}), 2.05−2.17 (tm_{app}, 2H, J = 11.4 Hz, H_{1ax}), 2.15−2.17 (m, 4H, H_{2ax} and H_{5ax}), 2.28−2.36 (dm, 2H, J = 10.9 Hz, H_{4eq}), 2.69−2.77 (dm, 2H, J = 11.0 Hz, H_{5eq}), 2.87−3.03 (m, 6H, H_{3eq} and H_{3ax} and H_{1eq}), 3.08 (s, 2H, N−C*H*−N), 3.44−3.60 (tm_{app}, 2H, J = 10.3 Hz, H_{4ax}); ^{13}C NMR ($CDCl_3$) δ 19.7 (C_2), 44.8 (br, C_4), 52.6 (br, C_3), 54.4 (br, C_5), 56.1 (br, C_1), 77.1 (N*C*N) [Note: ^{1}H COSY, ^{1}H−^{13}C HETCOR, NOESY experiments, as well as connectivities derived from ^{13}C DNMR, were used to make resonance assignments (see Figure 2 for compound numbering)]; IR (CCl_4) 2835, 2855, 2705, 2650 cm^{-1}. Anal. Calcd for $C_{12}H_{22}N_4$: C, 64.83; H, 9.97; N, 25.20. Found: C, 65.02; H, 10.31; N, 25.12.

(10bα,10cα)-Decahydro-3a,8a-bis(phenylmethyl)-1*H*,6*H*-3a,5a,-8a,10a-tetrazapyrenium Dibromide Monohydrate (3a·H$_2$O). Details of the previously communicated prepn:[7] Benzyl bromide (100 g, 0.585 mol) was added in one portion to a stirred solution of **2** (9.04 g, 40.6 mmol) in MeCN (200 mL), and the reaction mixture was stirred for 14 days. The precipitate was collected by suction filtration, washed with MeCN (2 × 20 mL) followed by CH_2Cl_2 (2 × 50 mL), and residual solvent was removed to give the product as a white powder (21.35 g, 93%): mp 147−151 °C (dec); ^{1}H NMR (D_2O) δ 1.86−1.96 (dm, 2H, J = 15.2 Hz, C−CH_{eq}−C), 2.20−2.39 (qm, 2H, J = 15.2 Hz, C−CH_{ax}−C), 2.81 (td, 2H, J = 12.3, 2.8 Hz), 3.17−3.30 (dm, 4H, J = 12.3), 3.39−3.65 (m, 6H), 3.74 (td, 2H, J = 13.2, 3.4 Hz), 4.43 (td, 2H, J = 13.1, 4.0 Hz), 4.75 and 5.27 (AB, 4H, J = 13.0 Hz, CH_2Ph), 5.08 (s, 2H, C*H*), 7.40−7.80 (m, 10H); ^{13}C NMR (D_2O) δ 18.8, 46.7, 47.5, 51.9, 61.1, 63.1, 77.5, 125.5, 130.2, 132.2, 134.0; IR (KBr) 3051, 3030, 3003, 2995, 2960, 2943, 2869, 2853, 2844, 2812, 1456, 1356, 1137, 1056, 871, 722, 706 cm^{-1}. Anal. Calcd for $C_{26}H_{36}N_4Br_2\cdot H_2O$: C, 54.36; H, 6.67; N, 9.75. Found: C, 54.71; H, 6.79; N, 9.40.

(10bα,10cα)-Decahydro-3a,8a-dimethyl-1*H*,6*H*-3a,5a,8a,10a-tetrazapyrenium Diiodide Monohydrate (3b·H$_2$O).[6] Excess MeI (10 mL, 161 mL) was added in one portion to a stirred solution of **2** (2.34 g, 10.5 mmol) in MeCN (75 mL). The reaction mixture was stirred at room temperature for 72 h in a tightly capped flask, during which time the product crystallized from the solution. Excess MeI was evaporated with a stream of N_2, and the reaction mixture was concentrated to approximately one-half volume (35 mL). The white crystalline product was collected by suction filtration and washed with MeCN (35 mL), and residual solvent was removed (100 °C, 0.5 mmHg) to yield 5.18 g of crude product. This was recrystallized from MeOH to give 3.99 g (72%) of pure product: mp ∼220 °C (dec); ^{1}H NMR (D_2O) δ 1.86−1.96 (dm, 2H, J = 15.3 Hz, H_{2eq}), 2.31−2.47 (m, 2H, H_{2ax}), 2.74 (td, 2H, J = 12.4, 3.3 Hz, H_{1ax}), 3.13−3.23 (m, 6H, H_{1eq} and H_{4eq} and H_{5ax}), 3.23−3.33 (dm, 2H, J = 12.5 Hz, H_{5eq}), 3.36 (s, 6H, CH_3), 3.68 (td, 2H, J = 13.2, 3.8 Hz, H_{3ax}), 3.74−3.83 (dm, 2H, J = 13.0 Hz, H_{3eq}), 4.47 (td, 2H, J = 13.7, 5.5 Hz, H_{4ax}), 4.69 (s, 2H, C*H*); ^{13}C NMR (D_2O) δ 19.0 (C_2), 46.8 (C_5), 48.9 (*C*H$_3$), 50.3 (C_4), 65.7 (C_3), 77.2 (*C*H) (Note: DEPT, ^{1}H COSY and ^{1}H−^{13}C HETCOR experiments were used to make resonance assignments. See Figure 2 for carbon numbering.); IR (KBr) 3010, 2990, 2945, 2905, 2840, 2790, 2740, 2665, 1460, 1450, 1380, 1375, 1270, 1105 cm^{-1}. Anal. Calcd for $C_{14}H_{28}N_4I_2\cdot H_2O$: C, 32.08; H, 5.77; N, 10.69. Found: C, 32.43; H, 5.66; N, 10.80. Note: A run employing 2.05 g of **2**, 12 mL of MeI, and 10 mL of MeCN stirred for 94 h at room temperature yielded 80% of **3b·H$_2$O** containing only trace impurities, making MeOH recrystallization unnecessary.

4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (4a). Details of the previously communicated prepn:[7] $NaBH_4$ (66.70 g, 1.76 mol) was added in small portions over 1 h to a stirred solution of **3a** monohydrate (20.25 g, 34.77 mmol) in 95% EtOH (900 mL). The reaction mixture was stirred at room temperature for 16 days. Excess $NaBH_4$ was then decomposed by slow addition (with cooling) of 3M HCl (700 mL), and the solvent was removed. The resulting white solid was dissolved in H_2O (400 mL), the pH was adjusted to 14 (KOH pellets with cooling), and the basic solution was extracted with benzene (6 × 250 mL). The combined extracts were dried and the solvent was removed to yield 12.44 g (88%) of **4a** (>99% purity by NMR): mp 89−91 °C; ^{1}H NMR ($CDCl_3$) δ 1.31−1.45 (m, 2H, C−C*H*−C), 1.50−1.65 (m, 2H, C−C*H*−C), 2.26−2.53 (m, 12H), 2.38−2.54 (XX′ of AA′XX′, 2H, NCH_2CH_2N cross-bridge), 2.85 (ddd, 2H, J = 13.0, 11.2, 4.0 Hz), 3.11−3.29 (AA′ of AA′XX′, 2H, NCH_2CH_2N cross-bridge), 3.17 and 3.78 (AX, 4H, J = 13.5 Hz, CH_2Ph), 3.96 (ddd, 2H, J = 12.1, 10.8, 4.3 Hz), 7.15−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.06 ($CH_2CH_2CH_2$), 52.0, 54.3, 56.6, 57.2, 57.6, 60.0, 126.5, 128.0, 128.9, 141.0; MS, *m*/*z* 406 (M^+); IR (KBr) 3050, 3025, 3000, 2960, 2945, 2915, 2900, 2860, 2800, 2770, 2720, 2860, 2655, 1445, 1435, 1345, 1093, 710, 660 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_4$: C, 76.80; H, 9.42; N, 13.78. Found: C, 76.72; H, 9.82; N, 13.82.

4,11-Dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (4b). Scale-up and optimization of the previously reported prepn:[6] $NaBH_4$ (4.00 g, 105 mmol) was slowly added in small portions to a stirred solution of **3b** monohydrate (5.71 g, 10.9 mmol) in 95% EtOH (200 mL). The reaction mixture was stirred at room temperature for 72 h. Excess $NaBH_4$ was then decomposed by slow addition of 10% aq HCl (50 mL) (final pH ∼ 1). Absolute EtOH (400 mL) was added and the

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mixture was reduced to dryness by rotary evaporation. The white residue was dissolved in H_2O (60 mL), the solution was made strongly basic (pH = 14) by slow addition of NaOH pellets with cooling, and the basic solution was extracted with benzene (4 × 100 mL). The combined extracts were dried and the solvent was removed to give the crude product, which was kugelrohr-distilled from KOH pellets (0.02 mmHg, air bath temp 70−75 °C) to yield 2.49 g (9.80 mmol; 90%) of pure **4b** as a viscous, colorless liquid: ^{1}H NMR (C_6D_6) δ 1.29−1.50 (m, 4H, C−CH_2−C), 2.12 (s, 6H, CH_3), 2.20 (dt, 2H, J = 11.9, 3.7 Hz), 2.20−2.31 (m, 4H), 2.36 (ddd, 2H, J = 13.0, 4.7, 3.0 Hz), 2.45−2.55 (XX′ of AA′XX′, 2H, NCH_2CH_2N cross-bridge), 2.46−2.54 (m, 2H), 2.71−2.80 (m, 4H), 3.15−3.25 (AA′ of AA′XX′, 2H, NCH_2CH_2N cross-bridge), 3.74 (td, 2H, J = 11.6, 4.3 Hz); ^{13}C NMR (C_6D_6) δ 28.5 ($CH_2CH_2CH_2$), 42.6 (CH_3), 51.6, 56.3, 56.4, 57.4, 61.6 (^{1}H COSY and ^{1}H−^{13}C HETCOR 2D experiments are also consistent with the structure); MS, *m*/*z* 254 (M^+); IR (KBr) 2945, 2920, 2900, 2820, 2800, 2775, 1445, 1355 cm^{-1}. Anal. Calcd for $C_{14}H_{30}N_4$: C, 66.09; H, 11.89; N, 22.02. Found: C, 66.15; H, 12.09; N, 22.13.

1,4,8,11-Tetraazabicyclo[6.6.2]hexadecane (5). Details of the previously communicated prepn:[7] Hydrogenolysis of **4a** was carried out in a glass apparatus designed for exclusion of O_2 and for measurement of H_2 uptake with maintenance of constant pressure. 10% Pd/C (0.80 g) and glacial HOAc (125 mL) were added to a 500 mL hydrogenation flask which was connected to the apparatus. The system was evacuated (by means of a water aspirator) and flushed with nitrogen four times. The system was then evacuated, filled with H_2 (759 mmHg), and catalyst was equilibrated for 1 h until H_2 uptake ceased. A solution of **4a** (4.54 g, 11.17 mmol) in glacial HOAc (5 mL) was then added, and the mixture was stirred under H_2 (759 mmHg). After 21 h the reaction was stopped (H_2 uptake was 525 mL, 97% of the theoretical value). The apparatus was evacuated and flushed with nitrogen four times, the reaction flask was removed from the apparatus, the contents were filtered through diatomaceous earth, and the catalyst and diatomaceous earth were washed with glacial acetic acid (3 × 10 mL). The solvent was removed from the filtrate and washings to give a light yellow oil which was dissolved in H_2O (20 mL). The solution was made strongly basic (pH 14, KOH pellets with cooling) and was extracted with benzene (6 × 25 mL). The combined extracts were dried and the solvent was removed under reduced pressure to give an oil (2.35 g, 93% crude yield). This oil was dissolved in Et_2O (17 mL) and then crystallized at −78 °C (acetone/dry ice bath) in a fritted Schlenk tube to yield 2.02 g (80%) of pure white **5** (hygroscopic): mp 48−49 °C; ^{1}H NMR (C_6D_6) δ 1.16 (dtt, 2H, J = 15.1, 6.8, 2.7 Hz, $H_{6,13eq}$), 1.53 (dtt, 2H, J = 15.0, 9.0, 2.7 Hz, $H_{6,13ax}$), 2.07−2.26 (overlapping AA′BB′, 4H and m, 2H, NCH_2CH_2N bridge and $H_{2,9}$ or $H_{3,10}$), 2.31 (ddd, 2H, J = 12.9, 6.7, 2.6 Hz, $H_{5,12}$ or $H_{7,13}$), 2.42−2.64 (m, 6H, $H_{5,12}$ and $H_{7,13}$ and $H_{2,9}$ or $H_{3,10}$), 2.74−2.86 (m, 4H, $H_{2,9}$ and/or $H_{3,10}$), 3.21 (ddd, 2H, J = 12.8, 8.8, 2.7 Hz, $H_{5,12}$ or $H_{7,13}$), 3.59 (br s, 2H, N*H*) (Note: ^{1}H COSY was used to make resonance assignments.); ^{13}C NMR (C_6D_6) δ 24.9 ($CH_2CH_2CH_2$), 47.4, 50.7, 52.4, 56.1, 59.0; IR ($CHCl_3$) 3260, 2955, 2925, 2890, 2870, 2825, 1490, 1352, 1248, 1135, 1090, 652 cm^{-1}; HRMS exact mass calcd for $C_{12}H_{26}N_4$, 226.2157; found, 226.2151.

4,11-Bis-(carboethoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane (6). Anhydrous Na_2CO_3 (0.78 g, 7.3 mmol) and ethyl bromoacetate (1.23 g, 7.39 mmol) were added sequentially to a solution of **5** (0.831 g, 3.67 mmol) in MeCN (30 mL). The mixture was heated to 50 °C and stirred under N_2 for 22.5 h. The solvent was then removed and the residue was dissolved in 20% aq NaOH (30 mL) at ice bath temperature (0−5 °C). This solution was extracted with cold (0−5 °C) $CHCl_3$ (6 × 50 mL), the combined extracts were dried, and the solvent was removed to give 1.52 g of **6** (essentially quantitative): mp 57−59 °C; ^{1}H NMR (C_6D_6) δ 0.97 (t, X_3 of ABX_3, 6H, J = 7.1 Hz, CH_2CH_3), 1.19−1.41 (m, 4H, $CH_2CH_2CH_2$), 2.17 (ddd, 2H, J = 13.4, 3.7, 1.8 Hz), 2.29 (ddd, 2H, J = 13.0, 4.7, 2.5 Hz), 2.43−2.57 (XX′ of AA′XX′, 2H, NC*H*C*H*N), 2.55−2.90 (m, 10H), 3.08 and 3.20 (AB, 4H, J = 16.7 Hz, NCH_2COOEt), 3.21−3.35 (AA′ of AA′XX′, 2H, NC*H*C*H*N), 3.69 (td, 2H, J = 11.9, 4.4 Hz), 3.96 and 3.97 (AB of ABX_3, 4H, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 14.4 (CH_2CH_3), 28.2 ($CH_2CH_2CH_2$), 50.9, 53.3, 54.7, 56.4, 57.3, 59.8, 60.2, 171.6; IR (KBr) 2969, 2945, 2926, 2907, 2851, 2833, 2819, 2784, 1743 (CO), 1461, 1444, 1379, 1365, 1301, 1184, 1162, 1137, 1124 cm^{-1}; MS, *m*/*z* 398 (M^+); HRMS exact mass calcd for $C_{20}H_{39}N_4O_4$, 399.2971; found, 399.2963. When the reaction was scaled up to 2.14 g of **5**, 3.39 g (90%) of **6** were obtained. Stirring the crude product for 10 min in ice-cold 20% aq NaOH prior to extraction was necessary in order to avoid recovery of partially protonated product.

4,11-Bisacetamido-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane Hydrate (7·0.5H_2O). A solution of **5** (0.2425 g, 1.071 mmol) in MeCN (25 mL) was treated with anhyd K_2CO_3 (0.60 g, 4.3 mmol), KI (0.71, 4.3 mmol) and α-chloroacetamide (0.4233 g, 4.53 mmol), and the resulting mixture was heated at 60 °C under N_2 for 23 h. The solvent was then removed, the residue was dissolved in H_2O (15 mL), and the solution was made strongly basic (pH 14, slow addition of KOH pellets with cooling). The resultant solution was extracted with $CHCl_3$ (6 × 25 mL), the combined organic phases were dried, the solvent was removed, and the residue was dissolved in EtOH (25 mL). EtOH was subsequently removed (EtOH addition and removal is necessary in order to remove $CHCl_3$, which forms a solvate with the product) to afford 0.3501 g (94%) of waxy **7**: mp 164−165 °C dec; ^{1}H NMR (CD_3CN, ref CD_2HCN set at 1.94) δ 1.39−1.64 (m, 4H, $CH_2CH_2CH_2$), 2.33−2.58 (m, 12H), 2.66−2.75 (m, 4H), 2.79 and 3.07 (AB, 4H, J = 16.1 Hz, NCH_2CONH_2), 2.97−3.08 (AA′ of AA′XX′, 2H, NCH_2CH_2N bridge), 3.99 (ddd, 2H, J = 12.6, 9.0, 5.2 Hz), 5.76 (br s, 2H, amide N*H*), 6.78 (br s, 2H, amide N*H*); ^{13}C NMR (CD_3CN, ref CD_3CN set at 1.39) δ 28.3, 54.0, 54.2, 56.9, 58.0, 59.0, 61.0, 175.1; IR (KBr) 3444, 3325, 3248, 3184, 1685, 1651 cm^{-1}; MS (EI) *m*/*z* 340.3 (M^+); Anal. Calcd for C_{16} $H_{32}N_6O_2$·0.5 H_2O: C, 54.99; H, 9.52; N, 24.05. Found: C, 54.90; H, 9.18; N, 23.64.

4,11-Bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexa-decane Tetrahydrochloride Hydrate ($H_2$8·4HCl·1.5H_2O). Compound **6** (0.635 g, 1.593 mmol) was dissolved in 6 N HCl (30 mL), and heated to 100 °C with stirring under N_2 for 48 h. The solvent was removed under reduced pressure to give the product as an oil which crystallized after removal of residual solvent (0.777 g, 95%): mp 155−160 °C; ^{1}H NMR (D_2O) δ 1.63−1.89 (dm, 2H, J = 16.6 Hz), 2.23−2.53 (m, 2H), 2.93−3.05 (tm, 4H, J = 13.4 Hz), 3.04−3.10 (m, 4H), 3.24−3.43 (m, 4H), 3.45−3.73 (m, 8H), 3.50 and 3.90 (AB, 4H, J = 17.8 Hz, NCH_2-COOH); ^{13}C NMR (D_2O) δ 19.7 ($CH_2CH_2CH_2$), 47.4, 47.6, 53.3, 55.2, 57.7, 60.0, 172.9; IR (KBr) 3411, 3291, 3177, 2936, 2860, 2714, 2600, 2528, 1709 (CO), 1461, 1429, 1232, 989, 664 cm^{-1}. Anal. Calcd for $C_{16}H_{30}N_4O_4$·4HCl·1.5H_2O: C, 37.29; H, 7.24; N, 10.87. Found: C, 37.20; H, 7.41; N, 11.21.

Attempted Preparation of 4,11-bis-(acetamido)-1,4,8,11-tetra-azabicyclo[6.6.2]hexadecane (7). Actual Alternative Preparation of 4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexa-decane ($H_2$8). Compound **6** (69.8 mg, 0.175 mmol) was dissolved in concd aq NH_3 (2 mL). The mixture was heated to 100 °C for 3 days in a pressure tube. The mixture was cooled for 15 min (0−5 °C), and solvent was removed under reduced pressure to give an oil which crystallized after removal of residual solvent (37.2 mg, 62%): mp 270−275 °C (dec); ^{1}H NMR (D_2O) δ 1.70−1.77 (dm, 2H, J = 16.7 Hz), 2.20−2.45 (dtt, 2H, J = 16.0, 12.9, 3.2 Hz), 2.56 (dd, 2H, J = 13.6, 2.2 Hz), 2.80−3.79 (m, 17H), 3.31 (XX′ of AA′XX′, 2H, NC*H*C*H*N), 4.14 (AA′ of AA′XX′, 2H, NC*H*C*H*N), 3.69 (td, 2H, J = 14.5, 3.5 Hz); ^{13}C NMR (D_2O) δ 20.51 ($CH_2CH_2CH_2$), 49.1, 49.6, 52.6, 57.8, 58.8, 59.1, 171.5; MS (CI, NH_3), *m*/*z* 343 (M + 1); IR (KBr) 3409, 2999, 2991, 2957, 2898, 2838, 2810, 1629, 1485, 1404, 1392, 1101, 1062, 791, 740 cm^{-1}. HRMS exact mass calcd for $C_{16}H_{31}N_4O_4$, 343.2345; found, 343.2349.

(10bα,10cα)-Decahydro-3a-(phenylmethyl)-1*H*,6*H*-3a,5a,8a,10a-tetraazapyrenium Bromide Hydrate (9a·1.5H_2O).[29,30] Benzyl bromide (0.79 g, 4.62 mmol) was added in one portion to a stirred solution of **2** (0.75 g, 3.37 mmol) in toluene (25 mL) at room temperature. The reaction mixture was stirred for 11 days. Precipitated product was collected by suction filtration and was washed with toluene (3 × 15 mL). Residual solvent was removed under vacuum to give 0.82 g of white powder (62%) (additional pure product slowly crystallized from the filtrate): mp 137−140 °C (dec); ^{1}H NMR (D_2O) δ 1.40−1.51 (dm, 1H, J = 14.1 Hz, $H_{6\ or\ 13-eq}$), 1.70−1.83 (dm, 1H, J = 14.9 Hz, $H_{6\ or\ 13-eq}$), 2.09−2.34 (m, 3H), 2.41−2.53 (m, 2H), 2.65 (td, 1H, J = 12.2, 2.8 Hz), 2.92−3.18 (m, 7H), 3.20−3.27 (dm, 1H, J = 13.6 Hz), 3.28−3.36 (dm, 1H, J = 13.7 Hz), 3.43−3.61 (m, 2H), 3.68 (br s, 1H, C*H*,

Table 6. X-ray Crystal Data Collection and Refinement Details

	3a	9a	$Cu(ClO_4)_2$·**5**	$CuCl_2$·**5**·3H_2O	$CuCl_2$·**4a**·H_2O	[Cu·**8**·Na(H_2O)ClO_4]$_2$·H_2O
formula	$C_{26}H_{36}Br_2N_4$	$C_{19}H_{33}BrN_4O_2$	$C_{12}H_{26}Cl_2CuN_4O_8$	$C_{12}H_{32}Cl_2CuN_4O_3$	$C_{26}H_{40}Cl_2CuN_4O$	$C_{32}H_{62}Cl_2Cu_2N_8Na_2O_{19}$
fw	564.41	429.40	488.81	414.86	559.08	1106.85
space group	$P2_1/c$	$P2_1$	$P2_12_12_1$	$Pna2_1$	$P1$	$P2_1/c$
a (Å)	10.261(5)	9.1396(2)	9.295(2)	25.458(2)	10.079(1)	16.155(1)
b (Å)	16.513(4)	13.1846(3)	11.418(2)	7.659(1)	14.487(1)	9.377(1)
c (Å)	15.821(3)	9.1505(2)	17.598(3)	9.435(1)	9.869(1)	29.023(1)
α (deg)	90	90	90	90	97.751(6)	90
β (deg)	98.19(3)	114.7825(8)	90	90	111.072(4)	91.494(2)
γ (deg)	90	90	90	90	98.433(5)	90
V (Å^3)	2653.3(14)	1001.11(6)	1867.9(8)	1839.7	1302.4	4395.1
Z	4	2	4	4	2	4
ρ_{calc} (g·cm^{-3})	1.413	1.425	1.738	1.498	1.426	1.673
T (K)	250(2)	173(2)	256(2)	219	294	221
wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
R_1 indices [$I > 2\sigma(I)$]	0.0623	0.0474	0.0465	0.029 (R)	0.038 (R)	0.033 (R)
wR_2 indices (all data)	0.1798	0.1603	0.1265	0.027 (Rw)	0.035(Rw)	0.033 (Rw)

broadened by gauche coupling), 4.19 (td, 1H, J = 13.1, 3.5 Hz), 4.36 (br s, 1H, C*H*, broadened by gauche coupling), 4.77 and 5.05 (AB, 2H, J = 13.3 Hz, CH_2Ar), 7.45−7.68 (m, 5H); ^{13}C NMR (D_2O) δ 18.8 ($CH_2CH_2CH_2$), 19.1 ($CH_2CH_2CH_2$), 42.7, 47.4, 49.3, 52.1, 52.7, 54.0, 54.7, 60.6, 63.3, 70.3, 82.6, 126.4, 130.1, 131.8, 134.1; IR (KBr) 3063, 3034, 3025, 3006, 2947, 2931, 2901, 2861, 2838, 2793, 2772, 1651, 1457, 1357, 1142, 1110, 891, 707 cm^{-1}. Anal. Calcd for $C_{19}H_{29}N_4Br$·1.5H_2O: C, 54.28; H, 7.67; N, 13.32. Found: C, 53.95; H, 7.81; N, 13.13.

Cu(ClO_4)$_2$·5. An amount of $Cu(ClO_4)_2$·6H_2O (160 mg, 0.43 mmol) and ligand **5** (100 mg, 0.44 mmol) in 10 mL of absolute methanol was refluxed for 2 h. The indigo solution was cooled to room temperature and filtered through diatomaceous earth. The filtrate was evaporated to dryness and recrystallized from 95% aq. ethanol/ether to give 135 mg (63% yield) of dark-blue crystals. Anal. Calcd for $C_{12}H_{26}Cl_2CuN_4O_8$·0.5H_2O: C, 28.95; H, 5.47; N, 11.25. Found: C, 29.13; H, 5.99; N, 11.19. UV−vis: (KBr) λ_{max}, 582 nm; (MeCN): λ_{max}, 567 nm (ϵ = 120 M^{-1} cm^{-1}). Dark-blue X-ray-quality single crystals were obtained by slow evaporation from a 95% ethanol/ether solution.

$CuCl_2$·5. A solution of 200 mg (0.88 mmol) of ligand **5** and 150 mg (0.88 mmol) of $CuCl_2$·2H_2O was refluxed in 10 mL of 95% aq ethanol for 2 h. The resulting dark-blue solution was filtered through diatomaceous earth and the filtrate was subjected to ether diffusion, whereupon dark-blue blocklike crystals were formed (238 mg, 71%). Anal. Calcd for $C_{12}H_{26}Cl_2CuN_4$·H_2O: C, 38.05; H, 7.45; N, 14.79. Found: C, 38.39; H, 7.68; N, 14.94. UV−vis: (KBr) λ_{max}, 579 nm; (MeCN) λ_{max}, 596 nm (ϵ = 196 M^{-1} cm^{-1}). X-ray-quality single crystals were obtained by slow ether diffusion into a 95% aq. ethanol solution.

Cu(ClO_4)$_2$·4b. A solution of $Cu(ClO_4)_2$·6H_2O (0.17 g, 0.46 mmol) and ligand **4b** (95 mg, 0.37 mmol) in methanol was refluxed for 2 h. The resulting dark-blue solution was cooled and subjected to slow ether diffusion. A 160 mg, 84% yield of the crystalline blue complex was obtained. An analytical sample was prepared by slow diffusion of a 1:1 benzene:hexane solution into a solution of the complex in methanol. This gave dark-blue crystals, which were finely ground and dried for elemental analysis. Anal. Calcd for $C_{14}H_{30}Cl_2CuN_4O_8$: C, 31.44; H, 6.03; N, 10.47. Found: C, 31.75; H, 6.22; N, 10.39. UV−vis: (KBr) λ_{max}, 625 nm; (MeCN) λ_{max}, 302 nm (ϵ = 5730 M^{-1} cm^{-1}), 618 nm (ϵ = 76 M^{-1} cm^{-1}).

$CuCl_2$·4a. A mixture of ligand **4a** (77 mg, 0.19 mmol) and $CuCl_2$·2H_2O (30 mg, 0.18 mmol) in 5 mL of methanol was refluxed for 2 h. The dark-green solution was cooled and filtered through diatomaceous earth. Ether diffusion into the filtrate yielded green crystals of the complex (68 mg, 68% yield). Anal. Calcd for $C_{26}H_{38}Cl_2CuN_4$·H_2O: C, 55.86; H, 7.21; N, 10.02. Found: C, 55.80; H, 7.19; N, 9.95. Electronic data: (KBr) λ_{max}, 675 nm; (MeCN) λ_{max}, 680 nm (ϵ 75). X-ray crystals were grown by slow evaporation of a MeCN solution.

Cu·8. A solution of H_2**8**·4HCl·1.5H_2O (171 mg, 0.33 mmol) and $Cu(ClO_4)_2$·6H_2O (123 mg, 0.33 mmol) in 5 mL of 95% ethanol was prepared. An aq solution (1.92 mL; 1.04 N) of sodium hydroxide (1.99 mmol) was added. The resulting clear blue solution was refluxed for 2 h, cooled, and evaporated to dryness. The blue residue was taken up in a minimal amount of methanol and filtered through diatomaceous earth. The filtrate was evaporated to dryness, and the residue was recrystallized from 95% ethanol/ether. The deposited blue crystals were collected and dried (111 mg, 61% yield). Anal. Calcd for $C_{16}H_{28}ClCuN_4NaO_8$·1.5H_2O: C, 34.72; H, 5.65; N, 10.12. Found: C, 34.45; H, 5.47; N, 9.90. Electronic data: (KBr) λ_{max}, 629 nm; (MeOH) λ_{max}, 642 nm (ϵ = 20 M^{-1} cm^{-1}).

Cu(ClO_4)$_2$·7. Compound **7** (39.9 mg, 0.117 mmol) was dissolved in EtOH (5 mL), $Cu(ClO_4)_2$ (46.2 mg, 0.125 mmol) was added to this solution, and the resulting mixture was heated at reflux for 4 h under N_2. Upon cooling to room temperature, two different materials precipitated. One was light blue in color and fluffy; the other was dark blue in color and granular. These two materials could be attributed to a complex (dark precipitate) and a polymer (light blue precipitate). EtOH (5 mL) was added and the heating was continued for 2.5 h. The reaction mixture was cooled to room temperature and the supernatant was removed by pipet and filtered through a glass wool plug in a pipet. The filtrate was placed in a closed chamber designed to allow slow diffusion of Et_2O into the solution. After 24 h, a granular solid had precipitated. This solid was dissolved in 95% EtOH (10 mL). Approximately 3 mL of this solution was diluted with 95% EtOH (9 mL) and this solution was put in the Et_2O diffusion chamber. After 5 days, crystals had formed, but these crystals were not suitable for X-ray crystallography: IR (KBr) 1665 cm^{-1} (C═O); UV−vis: (MeOH, 2.2 × 10^{-3} M) λ_{max}, 630 nm (ϵ = 24 M^{-1} cm^{-1}). Anal. Calcd for $C_{16}H_{32}N_6CuCl_2O_{10}$: C, 31.87; H, 5.35; N, 13.94. Found: C, 31.65; H, 5.19; N, 13.71. Other crystallization attempts with EtOH, 95% EtOH, and CH_3CN with Et_2O diffusion techniques were unsuccessful in affording X-ray quality crystals.

X-ray Diffraction Studies. Crystal, data collection, and refinement parameters of the six X-ray diffraction studies are given in Table 6. Additional details, including full atomic coordinates, complete bond lengths and angles, etc., are included in the Supporting Information. All software and sources of the scattering factors are contained in the SHELXTL (5.03) and (5.10) program library.[60] **3a**: Crystals suitable for crystallographic structural determination were obtained by allowing the MeCN filtrate from a benzylation of **2** to evaporate slowly over a period of 18 days to give colorless blocks of anhydrous **3a**. The systematic absences in the diffraction data are uniquely consistent with the space group P 2$_1$/c which was supported by the chemically reasonable and computationally stable results of refinement. The structure was solved by direct methods, completed by subsequent difference Fourier syntheses and refined by full-matrix least-squares procedures. All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were treated as idealized contributions. The two bromide counterions were disordered over two

(60) Sheldrick, G. Siemens XRD, Madison, WI.

positions, 90/10 and 85/15, respectively. **9a**: Crystals suitable for crystallographic structural determination were obtained by slow recrystallization of 0.03 g of **9a** from acetone (10 mL). Systematic absences were consistent with possible space groups $P2_1$ or $P2_1/m$. The *E*-statistics for the data suggested the chiral space group $P2_1$. The structure was solved using direct methods and atoms located by difference Fourier synthesis. Refinement was by full-matrix least-squares fitting. Non-hydrogen atoms were refined anisotropically while hydrogen atoms were added at calculated positions and treated as isotropic contributions with thermal parameters defined as 1.2 or 1.5 times that of the parent atom. $Cu(ClO_4)_2$·**5**: The systematic absences in the diffraction data were uniquely consistent for the orthorhombic space group $P2_12_12_1$, which yielded chemically reasonable and computationally stable results of refinement. The structure was solved by direct methods, completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares procedures. The absolute structure was confirmed [Flack parameter = −0.02(4)]. All non-hydrogen atoms were refined with anisotropic displacement coefficients. Amine hydrogens were located in the difference map, and the N−H bond distance was fixed to 0.9 Å. All other hydrogens were treated as idealized contributions. $CuCl_2$·**5**: The structure was solved by direct methods (SHELXS). Hydrogen atoms were idealized with C−H = 0.95 Å. Refinement was by full-matrix least-squares on F. All non-hydrogen atoms were refined anisotropically, while all H's were fixed. 198 parameters; data/parameter ratio = 5.44; final $R = 0.029$; $R_w = 0.027$; error of fit = 0.74; max $\Delta/\sigma = 0.04$; largest residual density = 0.42 e/Å^3 near the water molecules. $CuCl_2$·**4a**·H_2O: The structure was solved by automated Patterson analysis (PHASE), and hydrogen atoms were idealized with C−H = 0.95 Å. The water hydrogens were calculated in hydrogen-bonding positions with the chlorides. Refinement was by full-matrix least-squares on F. All non-hydrogen atoms were refined anisotropically, while all H's were fixed. 307 parameters; data/parameter ratio = 7.69; final $R = 0.038$; $R_w = 0.035$; error of fit = 0.86; max $\Delta/\sigma = 0.01$; largest residual density = 0.29e/Å^3, between N(8) and C(7). [Cu·**8**·$Na(H_2O)ClO_4]_2$·H_2O: Structure was solved by direct methods (MULTAN), hydrogen atoms were idealized with C−H = 0.95 Å. The water hydrogens were successfully located and refined. Refinement by full-matrix least-squares on F, scattering factors included anomalous terms for Cu, Cl, and Na. All non-hydrogen atoms were refined anisotropically, H's were either refined isotropically or fixed. 610 parameters; data/parameter ratio = 8.11; final $R = 0.033$; $R_w = 0.033$; error of fit = 1.02; max $\Delta/\sigma = 0.00$; largest residual density = 0.63e/Å^3, near Cl2, O11′, and O14′.

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Supporting Information Available: 360 MHz ^{1}H and 90 MHz ^{13}C NMR spectra of **5**, **6**, **7**, and H_2**8** (PDF). Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **3a**, **9a**, $Cu(ClO_4)_2$·**5**, $CuCl_2$·**5**, $CuCl_2$·**4a**, and [Cu·**8**·$Na(H_2O)ClO_4]_2$, as well as structural drawings for $Cu(ClO_4)_2$·**5** and [Cu·**8**·$Na(H_2O)ClO_4]_2$ showing H-bonding (PDF). This material is available free of charge via the Internet at *http://pubs.acs.org*.

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