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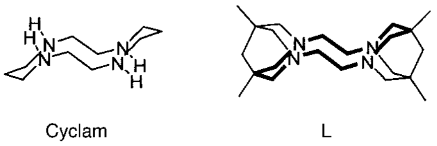
A Very Rigid Bis-bispidine Tetraazamacrocycle and Its Unusual Copper(II) Complex[**]

Peter Comba,* Hans Pritzkow, and Wolfgang Schiek

Dedicated to Professor Dieter Sellmann
on the occasion of his 60th birthday

Macrocyclic ligands have been used extensively to stabilize metal ions in specific oxidation and electronic states, and to tune the metal ion selectivity.[1–5] The 14-membered tetraazamacrocycle cyclam (1,4,8,11-tetraazacyclotetradecane; Scheme 1) is known to provide an ideal donor set and geometry for tetragonal coordination of copper(II) centers.



Scheme 1. The ligands cyclam and L (=**3**).

The conformational flexibility of the five- and six-membered chelate rings and the configurational flexibility of the coordinated secondary amino groups of cyclam and other tetraazamacrocyclic ligands may be reduced and, therefore, the selectivity increased by substituents at the amines or the carbon backbone or by reinforcing the backbone with rings or multiple bonds.[6–8] Several attempts have been made to decrease the flexibility of the cyclam backbone, for example, with derivatives containing one or two piperazine rings.[9, 10] The bispidine backbone (bispidine = 3,7-diazabicyclo[3.3.1]-nonane) is known to be an extremely rigid fragment, and a range of *N*,*N*′-substituted tetradentate,[11, 12] as well as C^{α},$C^{\alpha'}$-substituted tetra-,[13–18] penta-, and hexadentate ligands,[18] and their transition metal compounds have been prepared and studied. Macrocyclic cyclam derivatives with two bispidine caps are expected to be highly preorganized and extremely rigid. These ligands have no configurational flexibility; with respect to the conformation there are only two possible arrangements of the five-membered chelate rings: λ,λ and λ,δ.

Derivatives of L have been proposed and reported but neither a full characterization, including an experimental structure, nor any spectroscopically or structurally characterized metal complexes have been published.[19, 20]

Molecular models of the free ligand L and the corresponding copper(II) compound (two conformations each) are shown in Figure 1.[21–25] These indicate that, indeed, L is highly preorganized for coordination of copper(II). The only distortions are a zigzag orientation for the λ,δ conformer and a twist of the two planes defined by the two N donors and the central carbon atom of the methylene bridge of each bispidine cap for the λ,λ conformer. These distortions arise due to the

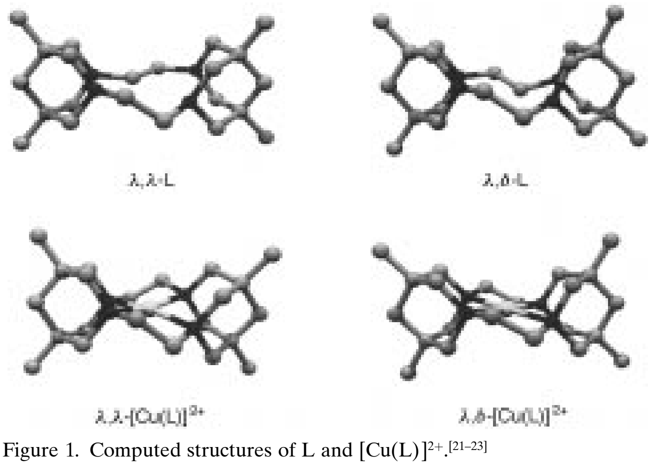


Figure 1. Computed structures of L and $[Cu(L)]^{2+}$.[21–23]

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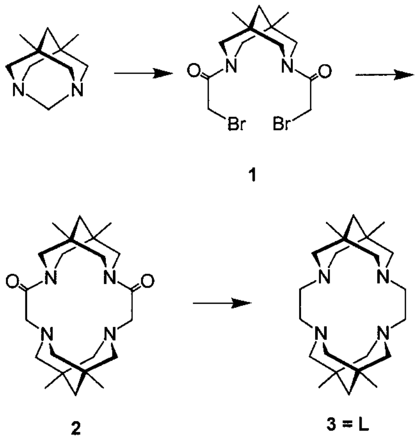
geometry of ethylene bridges between the two caps (en-type "chelate" rings) and the repulsion of the lone pairs of electrons at the N atoms. A similar but less pronounced distortion occurs in the calculated structures of the copper(II) complexes. Moreover, the calculations indicate that, owing to repulsion by the methylene groups of the bispidine caps, the bonds to the axial donors, Cu–OH$_2$, are much elongated (Cu six-coordinate: ca. 2.97 Å vs. ca. 2.48 Å in [Cu(cyclam)(OH$_2$)$_2$]$^{2+}$;[26] Cu five-coordinate: ca. 2.66 Å vs. ca. 2.3 Å[27]). The Cu–N distances of about 1.98 Å[23, 28] are significantly shorter than those in [Cu(cyclam)(OH$_2$)$_2$]$^{2+}$ (ca. 2.01 Å[26]). This and the fact that tertiary amines are stronger σ donors than secondary amines[27, 29] leads to the expectation that L might produce copper(II) complexes with a very strong ligand field, especially for the four-coordinate Cu^{II} compounds (high energy shift of the $d_{x^2-y^2}$ orbital due to Cu–N bond strengthening; low energy shift of the d_{z^2} orbital due to elimination of the interaction with axial donors). Furthermore, from molecular mechanics MM calculations it appears that the reduced complex with four-coordinate Cu^I has a similar structure but is less stable than the oxidized Cu^{II} form shown in Figure 1 (ca. +6 kJ mol^{-1}, Cu^I–N = 2.00 Å (av)).

The d–d transitions can be obtained starting from computed structures by MM-AOM calculations (AOM = angular overlap model).[27, 29–34] The predicted transition energies for the six- and four-coordinate copper(II) complexes with L[35] are compared with experimental data and data of [Cu(cyclam)(OH$_2$)$_2$]$^{2+}$ in Table 1. These computations support the expectation that L induces extremely high ligand fields for the copper(II) center, which is in sharp contrast to preliminary data of an analogous compound of L.[19]

Table 1. Computed (MM-AOM) and experimentally determined electronic transitions of [Cu(L)]$^{2+}$ and [Cu(L)(OH$_2$)$_2$]$^{2+}$ as well as [Cu(cyclam)]$^{2+}$.[a]

Compound	$E_1(xz)$[b,c]	$E_2(yz)$[b,c]	$E_3(xy)$[b,c]	$E_4(z^2)$[b,c]
[Cu(L)(OH$_2$)$_2$]$^{2+}$ in H$_2$O (exp.)	23250 (430)	–[d]	–[d]	ca. 19200 (520)
λ,λ-[Cu(L)(OH$_2$)$_2$]$^{2+}$ (calcd)	23000	23380	22120	19530
λ,δ-[Cu(L)(OH$_2$)$_2$]$^{2+}$ (calcd)	23560	23640	22650	19640
[Cu(L)]$^{2+}$ in MeNO$_2$ (exp.)	25640 (390)	–[d]	–[d]	–[d]
λ,λ-[Cu(L)]$^{2+}$ (calcd)	24660	25040	23400	23580
λ,δ-[Cu(L)]$^{2+}$ (calcd)	24660	25220	23770	23770
[Cu(cyclam)]$^{2+}$ (exp.)[42]	19900 (500)	–[d]	–[d]	–[e]
[Cu(cyclam)]$^{2+}$ (calcd)[42]	19200	20020	20400	13600

[a] Similar results are obtained for [Cu(L)(OH$_2$)]$^{2+}$.[25, 35] [b] In cm^{-1} (nm); arbitrary assignment. [c] See ref. [27] for AOM parameters. [d] Single unresolved band. [e] Not reported.



Scheme 2. Synthesis of the tetraazamacrocycle **3**.

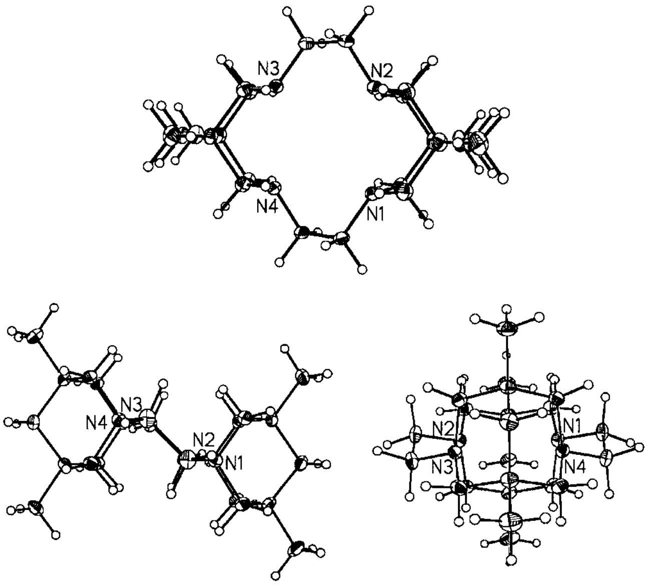


Figure 2. Structure of L (ORTEP plots[38]).

The ligand L (= **3**) was prepared by reaction of 5,7-dimethyl-1,3-diazaadamantane and the bis(α-bromoacetamide) (**1**) of 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane, following a general method,[36] and reduction of the resulting cyclic bis-amide **2** with diisbutylaluminum hydride (DIBAL-H; Scheme 2). Analytically pure samples of L and crystals suitable for the determination of the structure by X-ray crystallography were obtained by sublimation (see Experimental Section).[37] The structure of L is shown in Figure 2.[38] The ligand is, as predicted by the force-field calculations, highly preorganized, and the crystallized λ,δ conformer shows the expected zigzag geometry. The ligand backbone efficiently shields the cavity, and the rigidity of the structure prevents a dynamic process which could make the amine lone pairs more accessible for coordination. Therefore, the expectations are that coordination of metal ions and metal ion exchange might be processes with high activation barriers (see ref. [39, 40] for mechanistic studies of macrocycle complexation and dissociation). Furthermore, coordination of donors in the axial positions should be sterically hindered.

Copper(II) complexes were obtained by refluxing an equimolar mixture of L and Cu(CF$_3$SO$_3$)$_2$ in CH$_3$CN/THF. The orange perchlorate salt precipitated from a purple solution, which was obtained by ion-exchange chromatographic purification of an aqueous solution of the crude product (see Experimental Section). Because of the assumed high basicity of L,[19] water was omitted during the complexation process. Complexation experiments at room temperature in CH$_3$CN afforded only insoluble greenish powders with the stoichiometry Cu^{2+}:L:CF$_3$SO$_3^-$ = 1:1:2 (elemental analysis). This underlines the role of the high activation barrier.

The electronic spectra are in good agreement with the expectations (see Table 1 and Figure 3). The four-coordinate, orange, Cu^{II} compound has the strongest ligand field for a Cu^{II}–tetramine donor set observed so far.[29] In comparison with the parent [Cu(cyclam)]$^{2+}$ compound there is a shift of the maximum by 110 nm (5740 cm^{-1}, 68 kJ mol^{-1}) to lower wavelengths. This is the result of the increased nucleophilicity of the amines, a significant shortening of the Cu–N bonds, and the shielding of the axial coordination sites.[27, 29, 41, 45]

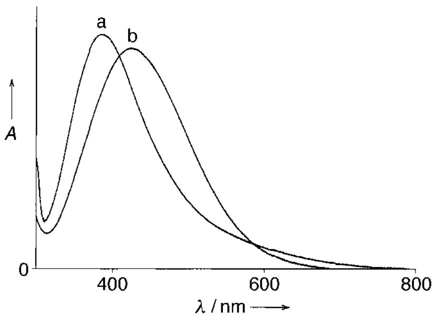


Figure 3. Electronic spectra of [Cu(L)](ClO$_4$)$_2$ in CH$_3$NO$_2$ (a) and in H$_2$O (b).

Experimental Section

A solution of bromoacetyl chloride (7.1 g, 45.1 mmol) in THF (50 mL) was added dropwise to a solution of 5,7-dimethyl-1,3-diazaadamantane (2.26 g, 14.8 mmol)[43] and NaHCO$_3$(4.2 g, 50 mmol) in THF/H$_2$O (120 mL; 2/1). The mixture was stirred at 0 °C for 2 h. Evaporation of THF at room temperature led to a white precipitate, which was filtered and washed with H$_2$O. Recrystallization from ethylacetate yielded 3,7-bis(2-bromoacetyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (**1**) in the form of white needles (4.9 g; 83 %). Elemental analysis (%) calcd for C$_{13}$H$_{20}$Br$_2$N$_2$O$_2$ (396.12): C 39.42, H 5.09, Br 40.34, N 7.07, O 8.08; found: C 39.51, H 5.09, Br 40.38, N 7.07; ^{1}H NMR (200 MHz, CDCl$_3$, 20 °C): $\delta = 0.98$ (s, 6H; CH$_3$), 1.48 (s, 2H; H9), 2.45 (dd, $J = 13.9$, 2.5 Hz, 2H; H2a, H6a), 3.00 (dd, $J = 13.7$, 2.5 Hz, 2H; H4a, H8a), 3.66 (d, $J = 13.9$ Hz, 2H; H2e, H6e), 3.68 (d, $J = 11.3$ Hz, 2H; CH$_2$Br), 4.04 (d, $J = 11.3$ Hz, 2H; CH$_2$Br), 4.54 (d, $J = 13.7$ Hz, 2H; H4e, H8e); ^{13}C NMR (75 MHz, CDCl$_3$, 20 °C): $\delta = 24.1$ (CH3), 26.4 (CH$_2$Br), 31.1 (C1, C5), 46.7 (C9), 51.1 (C2, C8), 56.3 (C4, C6), 165.8 (CO).

A solution of **1** (5.3 g, 13.4 mmol), 5,7-dimethyl-1,3-diazaadamantane (2.2 g, 13.4 mmol), and Et$_3$N (5.5 mL, 40 mmol) in EtOH (650 mL) was refluxed for two days. The solvent was evaporated and the white residue washed with ice-cold water (20 mL). Filtration and drying yielded the crude macrocyclic bisamide **2** as a white powder (2.8 g, 53 %), which was used for the next step without further purification.

DIBAL-H (40 mL, 1 M solution in THF) was added to a solution of **2** (2.8 g, 7.2 mmol) in THF at −5 °C under argon. The mixture was slowly heated to 30 °C and stirred for 36 h. After addition of more DIBAL-H (20 mL) in THF, the mixture was heated to 50 °C for 2 h. Usual workup led to a yellow residue, from which pure **3** (1.3 g, 50 %) was obtained by sublimation at 100 °C and 0.1 Torr. Elemental analysis (%) calcd for C$_{22}$H$_{40}$N$_4$ (360.58): C 73.28, H 11.18, N 15.54; found: C 73.18, H 11.13, N 15.21; ^{1}H NMR (500 MHz, CDCl$_3$, 20 °C): $\delta = 0.80$ (s, 12H; CH$_3$), 1.24 (s, 4H; H9, H9′), 2.19 (d, $J = 10.3$ Hz, 8H; H2a, H4a, H6a, H8a, H2a′, H4a′, H6a′, H8a′), 2.56 (s, 8H; CH$_2$-CH$_2$), 2.74 (d, $J = 10.3$ Hz, 8H; H2e, H4e, H6e, H8e, H2e′, H4e′, H6e′, H8e′); ^{13}C NMR (125 MHz, CDCl$_3$, 20 °C): $\delta = 24.8$ (CH$_3$), 32.0 (C1, C5, C1′, C5′), 45.7 (C9, C9′), 52.4 (CH$_2$CH$_2$), 62.9 (C2, C4, C6, C8, C2′, C4′, C6′, C8′).

In an argon atmosphere, a solution of Cu(CF$_3$SO$_3$)$_2$ (2 g, 5.5 mmol) in THF/CH$_3$CN (50 mL; 4/1) was added dropwise to a refluxing solution of L (1.26 g, 3.5 mmol) in THF/CH$_3$CN (100 mL; 4/1) and the resulting solution was refluxed for 24 h. After evaporation of the solvent, the residue was dissolved in hot H$_2$O (500 mL), filtered and, after cooling, adsorbed onto a Sephadex SP C-25 cation exchange resin (Na$^+$ form). The macrocyclic complex was eluted with 0.15 M NaClO$_4$ as the first band. The orange product (0.15 g, 0.25 mmol; 7 %) precipitated upon concentration of the purple eluate to 20 mL. Elemental analysis (%) calcd for C$_{22}$H$_{40}$N$_4$ · Cu(ClO$_4$)$_2$ (623.03): C 42.41, H 6.47, N 8.99; found: C 42.55, H 6.60, N 9.10.

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Novel Amide-Based Molecular Knots: Complete Enantiomeric Separation, Chiroptical Properties, and Absolute Configuration**

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Recently we described the first knot-shaped molecule[1] containing amide bonds.[2] We now report the syntheses of new "knotanes",[3] the first complete separation of a racemic knotane mixture, and the experimental and theoretical characterization of the compounds; we also give hints about a possible formation mechanism.

The baseline separation of the racemic trefoil knot **3aα**[2] (see Scheme 1) was achieved by high-pressure liquid chromatography (HPLC)[4] on a Chiralpak-AD-type column that is not commercially available, in which the silica gel and the chiral stationary phase are covalently bound so that the material does not "bleed out", even if lipophilic eluents are used. While, previously, eluents like hexane/ethanol (85/15) without trichloromethane resulted only in incomplete resolution (peaks with "shoulders"),[2] we were now able to

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