Syntheses and Structures of Novel Optically Active Dinuclear Copper(II) Complexes of Structurally Reinforced Macrocyclic Polyamines

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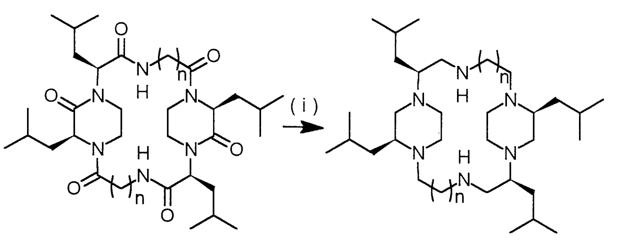
Optically active μ-chloro and μ-hydroxo dinuclear copper(II) complexes of structurally reinforced chiral 18-membered azamacrocycle (2*S*,8*S*,11*S*,17*S*)-2,8,11,17-tetraisobutyl-1, 4, 7, 10, 13, 16-hexaazatricyclo[14. 2. 2. $2^{7,10}$]docosane and 20-membered one (2*S*,9*S*,12*S*,19*S*)-2,9,12, 19- tetraisobutyl-1, 4, 8, 11, 14, 18 -hexaazatricyclo [16. 2. 2. $2^{8,11}$] tetracosane obtained by BH_3 reduction from structurally constrained macrocyclic pseudopeptides were newly synthesized and characterized.

Syntheses of structurally reinforced macrocycles, especially large membered rings, and their metal complexes are currently very important topics in host-guest and bioinorganic chemistry.[1] Generally, ligands with large cavity such as 18-aneN_6 tend to collapse in on themselves, and the cavity is lost.[2] The first attempt to reinforce the structure of cyclic polyamine was carried out by Ramasubbu and Wainwright.[3] It was shown that the double bridging of nitrogen atoms can achieve very strong size-selectivity.[4] While many reports detailing the synthesis of nitrogen substituted polyazamacrocycles have appeared, carbon backbone functionalized versions are less common.[2] There is difficulty in creating chiral ligands with large cavities that are highly preorganized.[2] Recently, Aston and his colleagues presented a general method for the asymmetric synthesis of carbon backbone functionalized pentaazacyclopentadecane system by complete hydride reduction of the corresponding macrocyclic peptide precursors.[5] This is a useful means of obtaining asymmetric polyazamacrocycles which have possibilities of chiral catalysis.

We report here the syntheses of novel carbon backbone functionalized and structurally reinforced chiral 18-membered cyclic polyamine (2*S*,8*S*,11*S*,17*S*)-2,8,11,17-tetraisobutyl-1,4,7, 10, 13, 16-hexaaza-tricyclo[14. 2. 2. $2^{7,10}$]docosane **3** and 20-membered one (2*S*,9*S*,12*S*,19*S*)-2,9, 12,19-tetraisobutyl-1,4,8,11, 14, 18-hexaazatricyclo[16. 2. 2. $2^{8,11}$]tetracosane **4**, and their dinuclear copper(II) complexes.[6]

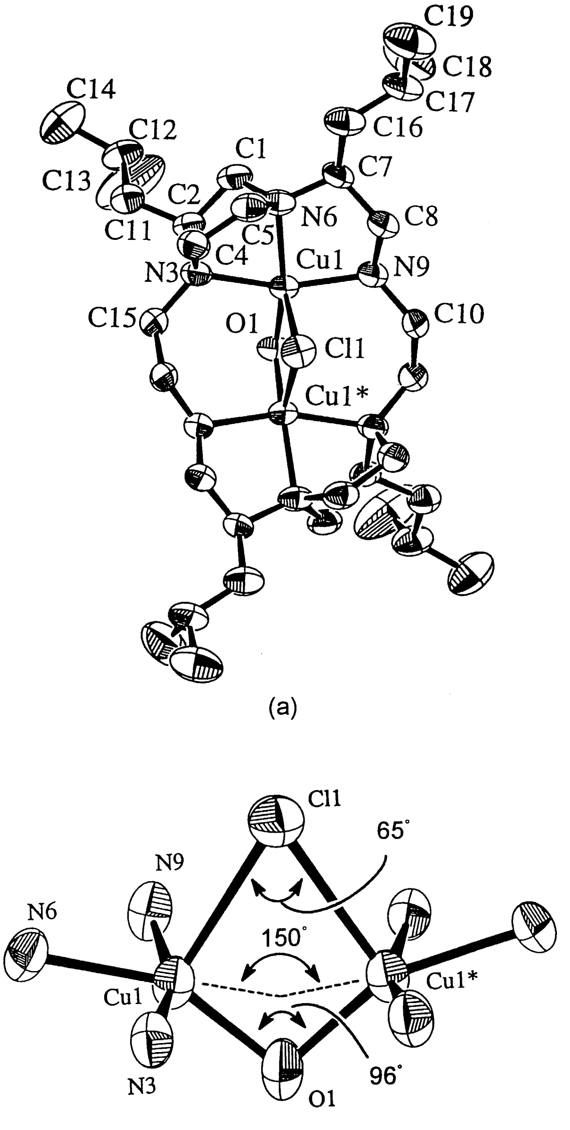
The macrocyclic ligands **3** and **4** were prepared in quite high yield (68, 66%)[7,8] by the BH_3 reduction of the structurally constrained macrocyclic pseudopeptide precursors cyclo[(2*S*, 3'*S*)-2-(3'-isobutyl-2'-oxo-piperazin-1'-yl)-4 -methyl -pentanoyl-glycyl and -β-alanyl]$_2$ **1** and **2**, respectively,[9] which have been studied as hydrophobic host molecules.[6]



1(n=1), **2**(n=2) **3**(n=1), **4**(n=2)

Scheme 1. (i) BH_3, THF

The copper(II) complexes of **3** and **4** were obtained.[10,11] Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of an aqueous solution containing the copper(II) complex of **3**.[12] The structure of $[Cu_2(\mathbf{3})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2$ (Figure 1) shows that this copper(II) complex is a dinuclear complex cation with a C_2 symmetric axis running through bridging atoms Cl1 and O1 and joint square bipyramidal with a single common ridgeline Cl1-O1. The copper(II) lies in



(a)

(b)

Figure 1. ORTEP drawing of (a) $[Cu_2(\mathbf{3})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2\cdot 4H_2O$ and (b) coordination geometry around copper(II).

almost both square plane (N3, N6, N9, O1), where Cl1 is a single axial ligand. The macrocyclic cavity is rugby-ball-shaped formed by two walls of piperazine rings. The symmetry-related metal ions (Cu1 and Cu1*) are separated by 2.832(3)Å; They are not remote, and yet are also not close enough to form a metal-metal bonding. Each copper(II) ion is coordinated by two nitrogen atoms of a piperazinic ring and a secondary nitrogen atom, with Cu-N bond distances in the range 1.999(6)-2.050(5) Å. The distance between Cu1(or Cu1*) and Cl1 is 2.647(2)Å, showing that they are more remote than Cu-N bond distances. The distance of Cu1(or Cu1*)-O1 is 1.908(7)Å. Dihedral angle between two symmetry-related planes (Cu1, N3, N6, N9) and (Cu1*, N3*, N6*, N9*) is about 150° and the angle of Cu1-O1-Cu1* is 95.8(5)°. The bridging oxygen O1 interacts *via* hydrogen bonding with water molecule O7 (O1---O7 2.90(2)Å). A hydrogen bound to a secondary nitrogen atom N9 is hydrogen bonded to O5 of a perchlorate anion (N9H---O5 2.46Å). Other hydrogen bondings involving water oxygens (O6, O7) and some oxygens of perchlorate anions (O2, O3, O4, O5) are also present.

The coordination structure of Cu(II) with 1,4,7,10,13,16-hexaazacyclooctadecane (Hex) in solution was shown as octahedral.[1] Thus, Hex which has no piperazine ring forms a mononuclear Cu(II) complex.

We easily created highly preorganized ligand with a large cavity which is rugby-ball-shaped and suitable for dinuclear metal complex. We are attempting to create piperazine contained ligands with larger cavities than 18- and 20-membered polyazamacrocycle **3** and **4** to develop a new multi-metal complex system.

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References and Notes

1 For example, M. Mitewa, and P. R. Bontchev, *Coord. Chem. Rev.*, **135**, 129(1994); M. Yamashita, H. Ito, and T. Ito, *Inorg. Chem.*, **22**, 2101(1983); R. W. Hay and M. P. Pujari, *Inorg. Chim. Acta*, **99**, 75(1985).

2 R. D. Hancock and A. E. Martell, *Chem. Rev.*, **89**, 1875(1989).

3 A. Ramasubbu and K. P. Wainwright, *J. Chem. Soc., Chem. Commun.*, **1982**, 277.

4 R. D. Hancock, A. Evans, M. P. Ngwenya, and P. W. Wade, *J. Chem. Soc., Chem. Commun.*, **1987**, 1129.

5 K. W. Aston, S. L. Henke, A. S. Modak, D. P. Riley, K. R. Sample, R. H. Weiss, and W. L. Neumann, *Tetrahedron Lett.*, **35**, 3687(1994).

6 All new compounds gave satisfactory elemental analyses.

7 Synthesis of **3**: $BH_3 \cdot THF$ solution (1.0 M, 41 ml) was added slowly to the powder of **1** (755 mg, 1.22 mmol) under Ar atmosphere and the mixture was refluxed for 24 hours. Additional borane solution (15 ml) was added, and the mixture was refluxed for an additional 24 h. To stop the reaction, water/tetrahydrofuran (20/10 ml) was added slowly and the mixture was allowed to stand for 12 hours. After evaporation of this solution, the crude macrocycle was purified by silica gel and activated alumina column chromatographies. This cyclic polyamine was changed to hydrochloride salt by 4N-HCl/1,4-dioxane. Reduction yield was 68% (623 mg). Characterization of **3**: mp. 228-233 °C (dec.). MS: m/z 535 $(M+1)^+$. $[\alpha]_D$=+43.8 deg dm^{-1} g^{-1} cm^3 (CH_3OH).

8 Synthesis of **4**: Cyclic polyamine **4** was synthesized by a method similar to **3**. Reduction yield: 66%. Characterization of **4**: mp. 225-230 °C (dec.). MS: m/z 563 $(M+1)^+$. $[\alpha]_D$= +55.5 deg dm^{-1} g^{-1} cm^3 (CH_3OH).

9 Synthesis of **1** and **2**: Two macrocyclic pseudopeptides **1** and **2** were prepared by conventional liquid-phase methods from Boc-(2*S*, 3'*S*) -2 -(3' -isobutyl -2' -oxo -piperazin -1' -yl) -4-methyl-pentanoic acid,[6] and Gly-OEt and β-Ala-OMe, and the cyclizations of the active esters of linear hexa-pseudopeptides by high dilution method, and purified by silica gel column chromatography and recrystallization from C_2H_5OH and CH_3OH (66 and 60% cyclic yields), respectively. Characterization of **1**. mp. 264-268 °C. MS: m/z 619$(M+1)^+$. $[\alpha]_D$=+28.9 deg dm^{-1} g^{-1} cm^3 (CH_3OH). IR ($CHCl_3$): 1650 cm^{-1}. Characterization of **2**. mp. 128-132 °C. MS: m/z 647 $(M+1)^+$. $[\alpha]_D$=+27.9 deg dm^{-1} g^{-1} cm^3 (CH_3OH). IR ($CHCl_3$): 1640 cm^{-1}.

10 Synthesis of $[Cu_2(\mathbf{3})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2 \cdot 4H_2O$: A methanol solution (2 ml) of $Cu(ClO_4)_2 \cdot 6H_2O$ (269.8 mg) was added to a methanol solution (5 ml) of **3**·4HCl (273.6 mg) and $LiOH \cdot H_2O$ (61.2 mg); the solution was stirred for 24 hours and then concentrated. $CHCl_3$ solution of resulting material was washed with water and concentrated, then recrystallized from hot water, 54% (191 mg) yield. mp. 185-195 °C (dec.). $[\alpha]_D$=+1151 deg dm^{-1} g^{-1} cm^3 (CH_3OH). The visible (ε: dm^3 mol^{-1} cm^{-1}) and CD (Δε: dm^3 mol^{-1} cm^{-1}) absorption maxima: 15.2 (616) kcm^{-1}, and 15.4 (-5.75) and 12.1 (+1.36) kcm^{-1}, in methanol at room temperature.

11 Synthesis of $[Cu_2(\mathbf{4})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2 \cdot 3/2H_2O$: The copper(II) complex of **4** was synthesized by the similar method of $[Cu_2(\mathbf{3})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2$ and recrystallized from water-methanol (5 : 1 v/v). Yield; 58%. mp. 171-175 °C (dec.). $[\alpha]_D$=-132 deg dm^{-1} g^{-1} cm^3(CH_3OH). The visible (ε: dm^3 mol^{-1} cm^{-1}) and CD (Δε: dm^3 mol^{-1} cm^{-1}) absorption maxima: 15.6 (287) kcm^{-1}, and 19.7 (-0.26), 14.9 (+0.18) and 12.6 (-0.61) kcm^{-1}, in methanol at room temperature.

12 Crystal data for $[Cu_2(\mathbf{3})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2 \cdot 4H_2O$: Blue crystal from water: $C_{32}H_{75}O_{13}N_6Cu_2Cl_3$, M = 985.43, monoclinic, space group C_2 (#5), a=28.60(3), b=8.576(2), c =9.937(5) Å, β=108.39(6)°, V=2313(2) Å^3, F(000)=1044, Z =2, D_c=1.415 g cm^{-3}, μ(CuKα)=32.50 cm^{-1}, $2\theta_{max}$=120.1°. Intensity data (1896 total (1854 independent) reflections) were collected on a Rigaku AFC 7R diffractometer. The final cycle of full-matrix least squares refinement was based on 1725 observed reflections (I>3.00σ(I)) and 253 variable parameters, and converged to R=0.056 and Rw=0.074. Maximum peak in final diff. map is 0.65 eÅ^{-3}. Programs used to solve structure: SIR88 and DIRDIF. All calculations including data reduction: TEXSAN crystallographic software package (Molecular Science Corporation).

13 H. Miyake and Y. Kojima, *Coord. Chem. Rev.*, in press.