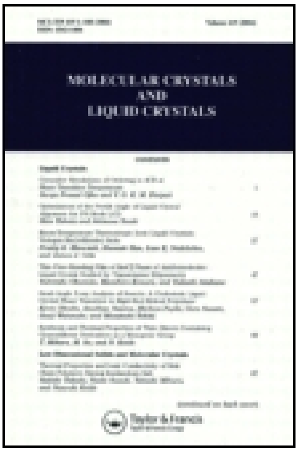

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Synthesis and Structure of Chiral Dinuclear Copper(II) Complex of Novel Structurally Reinforced Hexaazamacrocyclic Ligand

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SYNTHESIS AND STRUCTURE OF CHIRAL DINUCLEAR COPPER(II) COMPLEX OF NOVEL STRUCTURALLY REINFORCED HEXAAZA-MACROCYCLIC LIGAND

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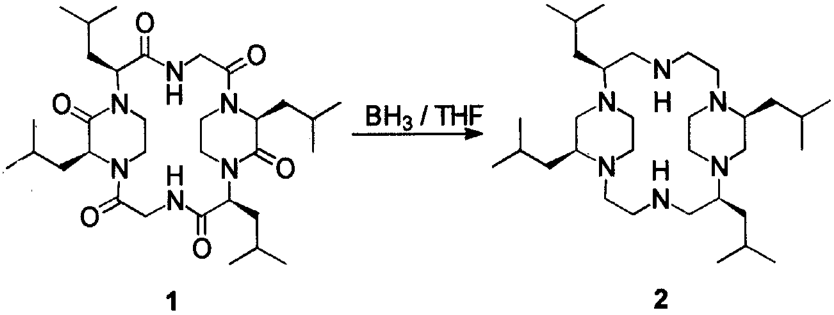
Abstract A structurally reinforced chiral 18-membered azamacrocycle (2*S*,8*S*,11*S*,17*S*)-2,8,11,17-tetraisobutyl-1,4,7,10,13,16 -hexaazatricyclo[14.2.2.$2^{7,10}$]docosane as a new type of ligand was conveniently synthesized by BH_3 reduction from the corresponding constrained macrocyclic pseudopeptide cyclo[(2*S*,3'*S*)-2-(3'-isobutyl-2'-oxo-piperazine-1'-yl)-4-methyl-pentanoyl-glycyl]$_2$. Its dicopper(II) complexes were prepared and characterized.

INTRODUCTION

Syntheses of structurally reinforced macrocycles, especially large membered rings, and their metal complexes are currently very important topics in such chemistry as host-guest and bioinorganic chemistry.[1] Small ligands tend to show higher levels of preorganization, but larger ligands 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] The macrocycles have a double bridge between at least one pair of adjacent nitrogen donors to give a piperazine ring. Such double bridging has been shown to achieve the very strong size-selectivity.[4] While numerous reports have appeared detailing the synthesis of nitrogen substituted polyazamacrocycles, carbon backbone functionalized versions are less common.[5]

As a new type of ligand, we report here the synthesis of the carbon backbone functionalized and structurally constrained 18-membered polyazamacrocycles (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, cyclo(eLL-Gly)$_2$, **2** from a macrocyclic pseudopeptide cyclo[(2*S*,3'*S*)-2-(3'-isobutyl-2'-oxo-piperazine-1'-yl)-4-methyl-pentanoyl-glycyl]$_2$ **1** (Scheme 1). Ethyl (2*S*,3'*S*)-2-(3'-isobutyl-2'-oxopiperazine-1'-yl)-4-methyl-pentanoate (eLL-OEt) was prepared from (*S*)-leucine.[6] Two copper(II) complexes of **2** were also prepared and characterized.



SCHEME 1 A reduction scheme from cyclo(eLL-Gly)$_2$ **1** to polyazamacrocycle **2**.

EXPERIMENTAL

Preparations

A macrocyclic pseudopeptide **1** was prepared by conventional liquid-phase methods from Boc-eLL-OH and Gly-OEt, and purified as a powder by silica gel (Fuji Silisia Chemical, LTD., BW-820MH) column chromatography and successive recrystallization from EtOH. The intermediates obtained by this route proved to be sufficiently pure by IR, NMR, and TLC. Characterization of **1**: Cyclization yield: 66%. Anal. Found: C; 61.86, H; 8.84, N; 13.45%. Calcd. for $C_{32}H_{54}N_6O_6$: C; 62.11, H; 8.80, N; 13.58%. FAB MS m/z $[M+H]^+$ 619. m.p. 264-268 °C. $[\alpha]_D$ +28.9 deg dm^{-1} g^{-1} cm^3 (MeOH). IR(nujol): 1650 cm^{-1}(amide C=O).

A macrocyclic polyamine **2** was obtained by BH_3 reduction of **1** for 48 hours in THF under reflux (Scheme 1) and purified by silica gel and successively by alumina activated 200 (Nacalai Tesque) chromatographies. The hydrochloride salt of **2** was obtained by the addition of 4HCl/AcOEt. Characterization of **2**: Reduction yield: 68%. Anal. Found: C; 51.26, H; 10.94, N; 10.33%. Calcd. for $C_{32}H_{66}N_6 \cdot 4HCl \cdot 4H_2O$: C;

51.05, H; 11.16, N; 10.44%. FAB MS m/z $[M+H]^+$ 535. m.p. 228-233 °C (dec.). $[\alpha]_D$ +43.8 deg dm^{-1} g^{-1} cm^3 (MeOH).

$[Cu_2(\mathbf{2})(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2$ **3** was prepared by the reaction of hydrochloride salt of **2** in the presence of equimolar lithium hydroxide with copper(II) perchlorate in methanol for several hours at room temperature. Evaporation of methanol resulted in a blue color residue. **3** was recrystallized from hot water. Characterization of **3**: Yield; 54%. m.p. 185-195 °C (dec.). $[\alpha]_D$ +1151 deg dm^{-1} g^{-1} cm^3 (MeOH). Anal. Found: C; 39.12, H; 7.53, N; 8.52, Cl; 10.91%. Calcd. for $[Cu_2(C_{32}H_{66}N_6)(\mu\text{-}Cl)(\mu\text{-}OH)](ClO_4)_2{\cdot}4H_2O$: C; 39.00, H; 7.67, N; 8.53, Cl; 10.79%.

$[Cu_2(\mathbf{2})(\mu\text{-}OH)](ClO_4)_3$ **4** was prepared by the reaction of **3** with silver(I) perchlorate in methanol for several hours at room temperature. Evaporation of methanol resulted in a bluish violet color residue. **4** was recrystallized from ethanol. Characterization of **4**: Yield; 53%. m.p. 223-228 °C (dec.). $[\alpha]_D$ +444 deg dm^{-1} g^{-1} cm^{-1} (MeOH). Anal. Found: C; 39.27, H; 6.93, N; 8.27, Cl; 10.16%. Calcd. for $[Cu_2(C_{32}H_{66}N_6)(\mu\text{-}OH)](ClO_4)_3{\cdot}C_2H_5OH{\cdot}3/4H_2O$: C; 39.38, H; 7.24, N; 8.10, Cl; 10.25%.

Instruments

A Jasco IRA-1, a Jeol GX-400, a Jasco DIP-4, a Jeol-JMS-100, Jasco J-720 and -730, and Hitachi U-3500T were used for IR, NMR, polarimeter, mass, CD, and visible spectra, respectively.

RESULTS AND DISCUSSION

There is difficulty in creating ligands with larger cavities that are highly preorganized.[2] Recently, Aston et al. presented a general method for the asymmetric synthesis of carbon-functionalized pentaazacyclopentadecane systems by complete hydride reduction of the corresponding cyclic pentapeptide precursors.[7] From various chiral macrocyclic pseudopeptides having *N, N'*-bridged ethylene to reinforce their macrocyclic skeleton,[6,8,9] we easily created such ligands with larger cavities that are highly preorganized. We also obtained stable dinuclear copper(II) complexes with this macrocyclic ligand **2**.

The structure of **3** has been confirmed by X-ray analysis of its single crystal as shown in Figure 1.[10] The complex ion has C_2 symmetry as an axis to the line of the bridged Cl^- and OH^- ions, and two copper(II) ions in **3** are the same distorted square pyramidals. The bond lengths between coordinated atoms (N_3, N_6, N_9, and O) and a copper(II) ion in a basal plane are in the range 1.91-2.05 Å, while the bond length between an apical Cl^- and Cu(or Cu*) is 2.65 Å, showing that it is remote, compared with the other coordinated atoms.

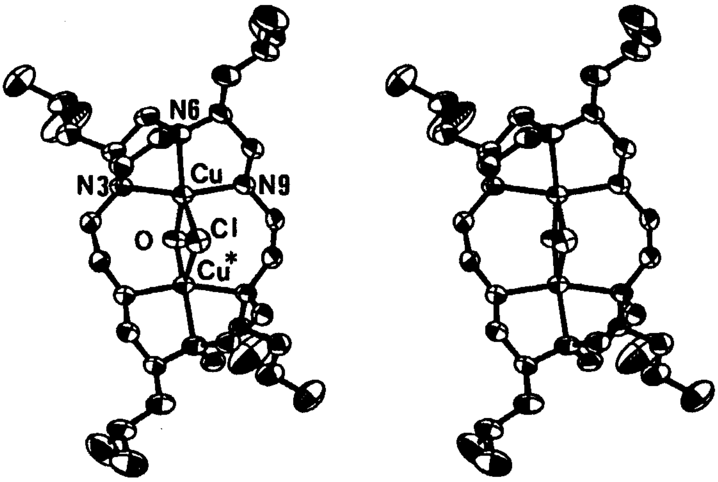


FIGURE 1 Stereoview of **3**.

Visible and CD spectra of **3** and **4** obtained in CH_2Cl_2 at room temperature are shown in Figure 2. The visible and CD absorption maxima of **3** and **4** in various solvents and solid state(powder) are shown in Table I.

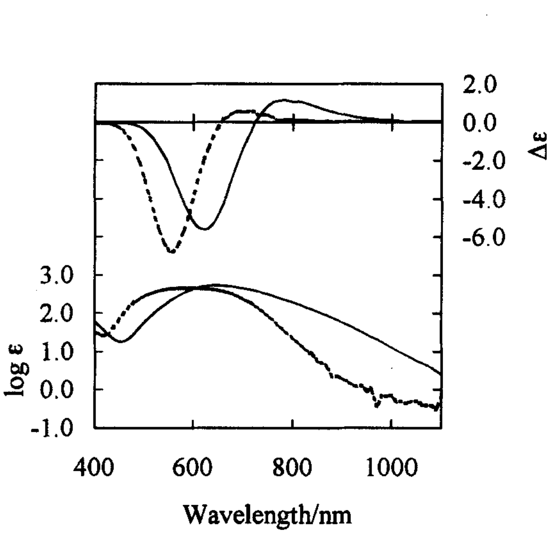


FIGURE 2 Visible and CD absorption spectra of **3**(—) and **4**(- - -) in CH_2Cl_2 at room temperature.

TABLE I Visible and CD absorption maxima of **3** and **4**.

Solvent	Visible Spectra, λ_{max} / kcm^{-1} (ε / dm^3 mol^{-1} cm^{-1})		CD Spectra, λ_{max} / kcm^{-1} ($\Delta\varepsilon$ / dm^3 mol^{-1} cm^{-1})			
	3	**4**	**3**		**4**	
Powder	15.1	16.8				
MeOH	15.2	17.3	15.4	12.1	17.8	13.4
	(616)	(508)	(-5.75)	(+1.36)	(-6.04)	(+0.48)
CH_3CN	15.4	16.5	16.0	12.6	17.9	13.9
	(516)	(498)	(-5.11)	(+0.93)	(-6.58)	(+0.28)
CH_2Cl_2	15.4	16.3	16.1	12.8	17.4	13.3
	(526)	(455)	(-5.65)	(+1.16)	(-6.77)	(+0.58)
DMSO	15.5	16.2	15.9	12.5	17.4	13.6
	(579)	(491)	(-5.47)	(+1.10)	(-3.93)	(+0.34)
H_2O/MeOH	15.8	17.2	16.4	13.1	18.0	14.3
(v./v. = 4/1)	(537)	(481)	(-5.57)	(+1.08)	(-5.28)	(+0.41)

The visible and CD absorption spectra of **3** and **4** are similar in various solvents, and their visible absorption maxima are also similar in powder. The CD absorption maxima of **3** at 15.4-16.4 and 12.1-13.1 kcm^{-1} are assigned to the transition of d_{xz}, $d_{yz} \rightarrow d_{x^2-y^2}$ and d_{xy}, $d_{z^2} \rightarrow d_{x^2-y^2}$, respectively, as distorted square pyramids. These results are supported by the apical long distance of the crystal structure of **3**. The CD absorption maxima of **3** shifted to blue field in missing apical Cl^- (12.1-13.1→13.4-14.3 kcm^{-1} and 15.4-16.4→17.4-18.0 kcm^{-1}), indicating the geometrical change of distorted square pyramid of **3** to square plane of **4**.

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