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SYNTHESIS OF STRUCTURALLY REINFORCED CHIRAL MACROCYCLIC POLYAMINES AND THEIR METAL COMPLEXES

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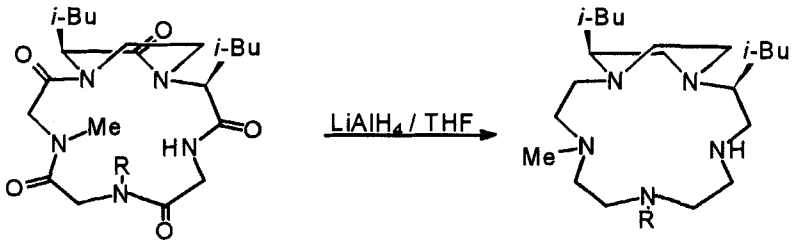
Abstract Two structurally reinforced chiral 15-membered azamacrocycles (2*S*, 14*S*)-2,14-diisobutyl-10-methyl-1,4,7,10,13 -pentaazabicyclo[11.2.2]heptadecane and (2*S*,14*S*)-2,14-diisobutyl-7,10-dimethyl-1,4,7,10,13-pentaazabicyclo[11.2.2] heptadecane as a new type of ligand were conveniently synthesized by $LiAlH_4$ reduction from their corresponding macrocyclic pseudopeptides cyclo[(2*S*,3'*S*)-2-(3'-isobutyl-2' -oxopiperazine-1'-yl)-4 -methyl -pentanoyl -glycyl -glycyl -sarcosyl] and cyclo[(2*S*, 3'*S*)-2-(3' -isobutyl-2' -oxopiperazine -1' -yl)-4-methyl-pentanoyl-glycyl-sarcosyl-sarcosyl], respectively. Their copper(II) complexes were also prepared and characterized.

INTRODUCTION

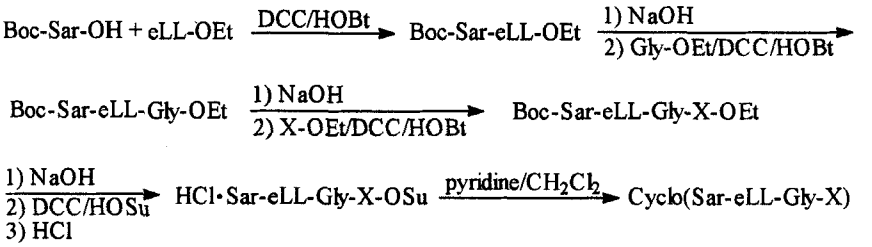
Structurally reinforced macrocyclic ligand provides a relatively rigid cavity, and produces enhanced complex stability when there is a match between size of the cavity and the metal ion being complexed.[1,2] Nonbridged 15-aneN_5 is able to coordinate too small octahedral metal ions such as high-spin Ni(II) or Zn(II) very satisfactorily, because the ligand can fold and coordinate with metal ion, i.e., the nonrigid cavity changes its form largely. However, the rigid cavity of a ligand such as B-15-aneN_5 cannot collapse and coordinate with small metal ions.[3] The increase in ligand field strength is due to increasing covalency in the M-N bond which accompanies the increase in nitrogen donor strength,[4] in the order of primary<secondary<tertiary. However, an increase in the basicity of the nitrogens by the addition of methyl groups into 14-aneN_4 is overcome by the resulting steric strain.[5]

We have interested in studying a series of novel structurally reinforced chiral B-15-aneN_5 derivatives accompanied by methyl groups to amine nitrogens and isobutyl groups to a carbon backbone as shown in Scheme 1, because of the possible high selection of metal ions. Ethyl (2*S*,3'*S*)-2-(3'-isobutyl-2'-oxo-piperazine-1'-yl)-4-methyl-pentanoate (eLL-OEt) was prepared from (*S*)-leucine according to our method reported previously.[6] The metal complexes with chiral ligands having additional steric strain are expected to be asymmetric catalysts.



1 (R = H), **2** (R = Me) **3** (R =H), **4** (R = Me)

SCHEME 1 Macrocyclic compounds synthesized in this paper.



1 (X = Gly), **2** (X = Sar)

SCHEME 2 The synthetic routes of **1** and **2**.

This paper describes the preparations of two 15-membered ring peptides cyclo[(2*S*,3'*S*)-2-(3'-isobutyl-2'-oxopiperazine-1'-yl)-4-methyl -pentanoyl -glycyl -glycyl-sarcosyl], cyclo(Sar -eLL -Gly -Gly), **1** and cyclo[(2*S*, 3'*S*) -2-(3' -isobutyl -2' -oxo-piperazine-1'-yl)-4-methyl-pentanoyl-glycyl-sarcosyl-sarcosyl], cyclo(Sar-eLL-Gly-Sar),

2 (Scheme 2). Cyclic polyamines (2*S*, 14*S*) -2,14 -diisobutyl -10 -methyl -1,4,7,10,13-pentaazabicyclo[11.2.2]heptadecane **3** and (2*S*,14*S*)-2,14-diisobutyl-7,10-dimethyl-1,4,7, 10,13-pentaazabicyclo[11.2.2]heptadecane **4** and their copper(II) complexes were also prepared and characterized.

EXPERIMENTAL

Preparations

A procedure for the preparations of **1** and **2** is outlined in Scheme 1. The intermediates obtained in this route were proved to be sufficiently pure by IR, NMR, and TLC. The cyclizations were carried out in pyridine/CH_2Cl_2 (vol. ratio 1:5). **1** was obtained as a powder purified by silica gel (Fuji Silisia Chemical, LTD., BW-820MH) column chromatography and successive recrystallization from $CHCl_3$. **2** was obtained as a powder by silica gel and then sephadex LH-20 column chromatographies.

TABLE I Analytical and physical data of **1**, **2**, **3**, and **4**.

Compound	Analysis Found/Calcd. % C	H	N	FAB MS m/z $[M+1]^+$	m.p. °C	$[\alpha]_D$ deg dm^{-1} g^{-1} cm^3 in MeOH	yield %
1·H_2O	55.36	8.02	15.38	438	128-130	+68	36[a]
	55.37	8.19	15.37				
2·H_2O	56.33	8.22	14.91	452	151-153	+16	22[a]
	56.27	8.37	14.91				
3·3HCl·4H_2O	46.06	10.10	12.65	368	170-173	+30	30[b]
	45.94	10.28	12.76				
4·5HCl·4H_2O	42.97	9.44	10.99	382	195-200	+28	37[b]
	42.75	9.45	11.33				

[a] Cyclization yield. [b] Reduction yield.

Macrocyclic polyamines **3** and **4** were obtained by $LiAlH_4$ reduction of **1** and **2**, respectively, for 48 hours in THF under reflux, and then were purified as oily materials by basic silica gel (Fuji Silisia Chemical, LTD., Chromatrex NH-DM 1020) and successively alumina activated 200 (Nacalai Tesque) column chromatographies. The

hydrochloride salts of **3** and **4** were obtained by the addition of 4N HCl/AcOEt in MeOH. Their analytical and physical data are shown in Table 1.

The copper(II) complexes $[Cu(\mathbf{3})(ClO_4)](ClO_4)$ **5** and $[Cu(\mathbf{4})(ClO_4)](ClO_4)$ **6** were prepared by the reaction of **3** and **4** with copper(II) perchlorate in methanol for several hours at room temperature. Evaporation of methanol resulted in violet color residues. **5** and **6** were recrystallized from hot water. Characterization of **5**: yield; 67 %. m.p. 267-270 °C, $[\alpha]_D$ -374 deg dm^{-1} g^{-1} cm^3 (MeOH), and FAB MS m/z $[M+H]^+$ 431 and 530 for $[Cu(\mathbf{3})]^{2+}$ and $[Cu(\mathbf{3})(ClO_4)]^+$, respectively. Elemental analysis, Found: C; 40.04, H; 7.22, N; 11.07, Cl; 11.33%. Calcd. for $CuC_{21}H_{45}N_5 \cdot 2ClO_4$: C; 40.03, H; 7.20, N; 11.12, Cl; 11.25%. Characterization of **6**: yield; 72 %. m.p. 236-240°C, $[\alpha]_D$ -323 deg dm^{-1} g^{-1} cm^3 (MeOH), and FAB MS m/z $[M+H]^+$ 445 and 544 for $[Cu(\mathbf{4})]^{2+}$ and $[Cu(\mathbf{4})(ClO_4)]^+$, respectively . Elemental analysis,. Found: C; 40.34, H; 7.43, N; 10.63, Cl; 10.71%. Calcd. for $CuC_{22}H_{47}N_5 \cdot 2ClO_4 \cdot 1/2H_2O$: C; 40.46, H; 7.41, N; 10.72, Cl; 10.86%.

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

Polyazamacrocycles, which contain three or more nitrogen atoms within a cyclic carbon backbone, are highly preorganized ligand systems for metal coordination.[7] From the standpoint of designing and synthesizing biologically stable metalloenzyme mimetics, Aston and his colleagues prepared optically active macrocyclic polyamines by reducing cyclic peptides and found that polyazamacrocycles afford not only excellent ligand environments but also suitable platforms for building functionality capable of directing and/or enhancing programmed modes of catalysis.[8] While a large number of reports have appeared detailing the synthesis of nitrogen substituted polyazamacrocycles, carbon backbone functionalized versions are less common.[9] Also, it was illustrated that

the double bridging of nitrogen atoms can achieve very strong size-selectivity.[10]

Each azamcrocyclic cavity of **3** and **4** accommodates copper(II) ion, and their complexes **5** and **6** were prepared by the reaction of the ligands with copper(II) perchlorate.

Visible and CD absorption spectra of **5** and **6** are shown in Figure 1.

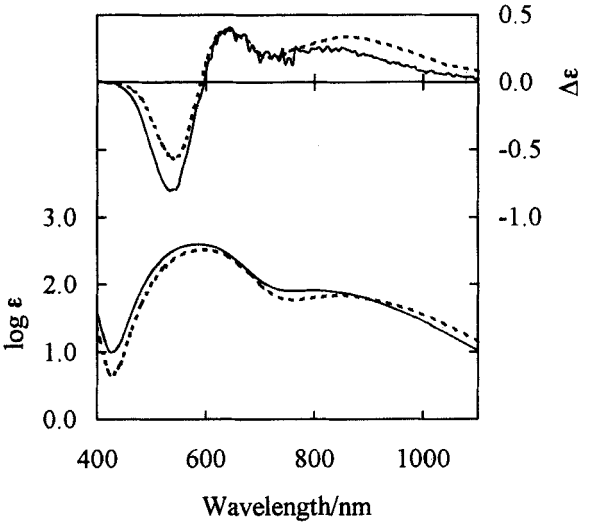


FIGURE 1 Visible and CD absorption spectra of **5**(---) and **6**(—) in MeOH at room temperature.

TABLE II Visible and CD absorption maxima of **5** and **6**.

Complex	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})		
	in MeOH		powder		in MeOH		
5	16.8	11.8	16.7	11.8	18.5	15.4	11.6
	(331)	(69)			(-0.58)	(+0.38)	(+0.34)
6	17.1	12.5	17.1	12.5	18.7	15.6	11.9
	(400)	(80)			(-0.81)	(+0.42)	(+0.26)

Table II shows the visible absorption maxima in MeOH and solid state (powder), and the CD absorption maxima in MeOH for the copper(II) complexes **5** and **6**. Their

visible absorption maxima and spectra in MeOH are identical with those of powder, suggesting that this solvent does not coordinate to a copper(II) ion. The CD absorption maxima of **5** at 18.5, 15.4, and 11.6 kcm^{-1} are assigned to the transition of d_{xz}, $d_{yz} \rightarrow d_{x^2-y^2}$, $d_{xy} \rightarrow d_{x^2-y^2}$, and $d_{z^2} \rightarrow d_{x^2-y^2}$, respectively as tetragonally distorted octahedral symmetry. Similarly the CD spectrum of **6** is interpreted.

The above results and Corey-Pauling-Koltun modeling propose a similar strained macrocyclic linkage mode for **5** and **6** as shown in Figure 2.

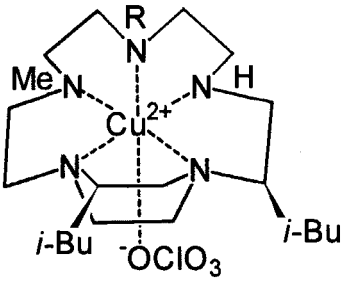


FIGURE 2 Proposed structure of **5** (R = H) or **6** (R = Me).

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