

Preparation of the New Macropolycycle Containing N-CH₂-N Linkages and Its Reaction with Methanol in the Presence of Cu²⁺ Ion: Formation of a Copper(II) Complex Bearing Two N-Methoxymethyl Groups

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The synthesis of new types of *N*-functionalized polyaza macrocyclic compounds has received much attention because of the effects of the functional groups on their chemical properties and coordination geometry.¹⁻⁸ Formaldehyde has been utilized for the preparation of polyaza macrocyclic and macropolycyclic compounds containing N-CH₂-N linkages.⁹⁻²⁰ For example, the macrocycles L⁵ and L⁶ readily react with formaldehyde to yield L⁷ and L⁸, respectively, containing two 1,3-diazacyclohexane rings.¹²⁻¹⁸ It has been also reported that the reaction of L⁵ with formaldehyde at -20 °C produces a mixture of L⁷ (70%) and L⁹ (30%); however, L⁹ containing two 1,3-diazacyclopentane rings has not been isolated.¹³

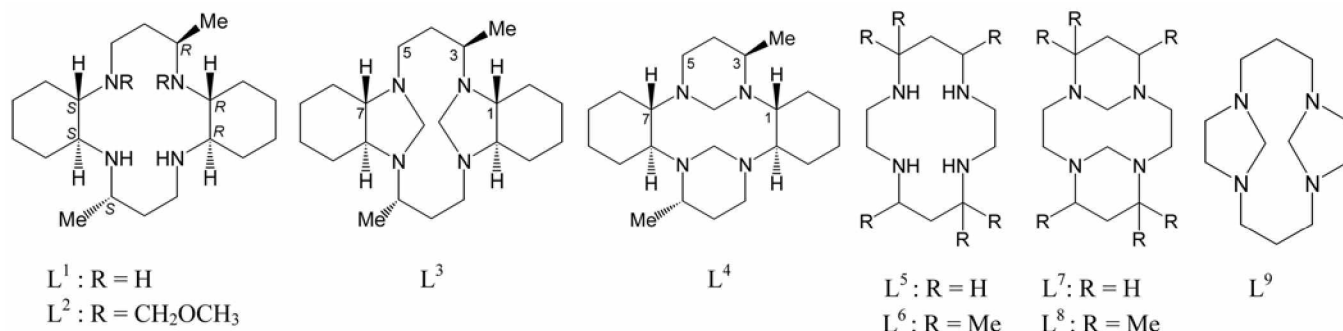
In this work, we have examined the reaction of formaldehyde with L¹ containing two *trans*-1,2-diaminocyclohexane subunits. Interestingly, the major product prepared from the reaction is 3,14-dimethyl-2,6,13,17-tetraazapentacyclo[16.4.1^{2,17}.1^{6,13}.0.0^{7,12}]tetracosane (L³) containing two 1,3-diazacyclopentane rings. Furthermore, L³ reacts with methanol in the presence of Cu²⁺ ion to yield [CuL²](ClO₄)₂·CH₃CN (**1**) (L² = 2,6-bis(methoxymethyl)-3,14-dimethyl-2,6,13,17-tetraazatricyclo[16.4.0.0^{7,12}]docosane), in which one of the two N-CH₂OCH₃ groups is coordinated to the metal ion. This note reports the synthesis and chemical properties of L³ and **1**. There are few reports on the formation of polyaza macrocyclic complexes bearing N-CH₂OCH₃ group(s).^{19,20} However, as far as we know, coordination behaviors of such pendant arm in 14-membered tetraaza macrocyclic complexes are not reported to date.

Experimental

Measurements. Electronic absorption spectra were obtained using an Analytic Jena Specord 200 UV/vis spectrophotometer and IR spectra with a Shimadzu IR-440 spectrophotometer, and NMR spectra with a Varian Mercury 300 FT NMR spectrometer. GC-mass spectra were measured with a Shimadzu GCMSD-QP5050 spectrometer. Conductance measurements were taken with a Metrohm Herisau Conductometer E518. FAB-mass spectra and elemental analyzes were performed at the Korea Basic Science Institute, Daegu, Korea.

Computational Methods. Density functional and *ab initio* calculations for L³, L⁴, L⁷, and L⁹ were performed by Gaussian 03.²¹ Initial conformations were collected by stochastic conformational search method²² using GMMX software²³ with MM3²⁴ force field. Conformations within 5 kcal/mol from the global minima were selected as starting structures for the quantum mechanical calculations. The geometries and energies were then obtained from the optimization at B3LYP/6-31G(d) level,²⁵ after successive optimizations at RHF/3-21G* and RHF/6-31G(d) levels. Calculated carbon NMR chemical shifts were obtained by GIAO method at B3LYP/6-31G(d) level.²⁶

Preparation of L³. The macrocycle L¹ (*C-meso* isomer) was prepared according to the published procedure;²⁷ the reagent 1,2-diaminocyclohexane used for the preparation of the macrocycle is a mixture of isomers. A methanol (30 mL) solution of L¹ (3.0 g, 9.0 mmol) and 35% formaldehyde (6.0



mL, 76.5 mmol) was stirred at room temperature for 4 h. During which time, a white solid was produced. The crude product was collected by filtration and dissolved in a minimum volume of chloroform at room temperature. After the addition of methanol (20 mL), the resulting solution was evaporated at room temperature to produce a white solid. The product was filtered, washed with cold methanol, and dried in air (Yield: ~80%). Anal. Calc. for $C_{22}H_{40}N_4$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.08; H, 11.28; N, 15.40%. Mass (m/z): 360. 1H NMR ($CDCl_3$): δ 1.15 (*d*, Me). ^{13}C NMR ($CDCl_3$): 24.5, 25.5, 26.1, 28.9, 29.3, 34.2, 51.9, 61.9, 64.7, 71.5, and 77.9 (N- CH_2 -N) ppm.

After the filtration of the white solid (L^3) from the reaction solution, the addition of 1.0 M NaOH aqueous solution to the filtrate produced a white solid. Mass and IR spectra of the solid as well as the elemental analysis are identical with those of L^3 . However, ^{13}C -NMR spectra show that the solid is a mixture of L^3 (major) and L^4 (minor; 20.0, 21.8, 25.71, 25.79, 28.1, 31.7, 49.7, 52.2, 52.5, 61.3, 66.5 (N- CH_2 -N) ppm). All our efforts to isolate L^4 from the mixture were unsuccessful.

Preparation of $[CuL^2](ClO_4)_2 \cdot CH_3CN$ (1). To a warm methanol solution (30 mL) of $Cu(OAc)_2 \cdot H_2O$ (*ca.* 3.0 g) was added L^3 (2.0 g). The mixture was refluxed for > 5 h and then cooled to room temperature. After the addition of an excess amount of $HClO_4$ or $NaClO_4$, the mixture was stored in a refrigerator to precipitate a red-purple solid. The product was recrystallized from a hot acetonitrile-water (1:1) solution (Yield: ~80%). Anal. Calcd for $C_{26}H_{51}N_5CuCl_2O_{10}$: C, 42.89; H, 7.06; N, 9.62. Found: C, 42.41; H, 7.27; N, 9.33%. FAB mass (m/z): 487.4 $[Cu(L^2)-H]^+$, 586.5 $[Cu(L^2) + ClO_4]^-$. IR (cm^{-1}): 3200 (ν N-H), 3220 (ν N-H), 1100 (ν ClO₄). Electronic absorption spectra (λ_{max} , nm (ϵ , $M^{-1}cm^{-1}$): 520 (Nujol mull), 524 (102) (CH_3NO_2), 533 (100) (CH_3CN).

Crystal Structure Analysis. Single-crystals of 1 suitable for X-ray study were grown from water-acetonitrile. The data were collected using a STOE STADI4 diffractometer equipped with Mo-K α ($\lambda = 0.71069$ Å).²⁸ In the ω -2 θ scan mode at 298(2) K. The data were corrected for Lorentz and polarization effect (X-RED). The empirical absorption correction based on a series of ϕ scans was applied (X-SHAPE). The structure was solved by the direction method and refinement calculations were carried out by SHELXL97-2.²⁹

Crystal and refinement data: $C_{26}H_{51}Cl_2CuN_5O_{10}$, $M =$

728.16, monoclinic, $P2_1/n$, $a = 14.314(1)$, $b = 15.998(1)$, $c = 14.756(2)$ Å, $\beta = 92.987(6)^\circ$, $V = 3374.5(6)$ Å³, $Z = 4$, $D_{calc} = 1.433$ g cm^{-3} , $\mu = 8.64$ cm^{-1} . Goodness-of-fit on $F^2 = 1.100$, Final $R_1 = 0.0500$, $wR_2 = 0.1248$ ($I > 2\sigma(I)$), $R_1 = 0.0704$, $wR_2 = 0.1436$ (all data), Largest diff. peak and hole = 1.003 and -0.604 $e\text{Å}^{-3}$.

Results and Discussion

Synthesis. The reaction of L^1 with excess formaldehyde in methanol at room temperature produced L^3 containing two 1,3-diazacyclopentane rings in high yield (> 80%). The formation of a small amount (< 5%) of L^4 containing two 1,3-diazacyclohexane rings was also observed (*see* Experimental section); however, we could not isolate the compound as its pure form.

The mass spectrum of L^3 gives m/z value of 360, which is in accord with the molecular weight of the compound. In the infrared spectrum of L^3 , no band around 3200 cm^{-1} corresponding to ν N-H was observed. The structure of L^3 was confirmed by the preparation of 1, which was prepared from the reaction of L^3 with methanol in the presence of Cu(II) ion (*see* below). To identify the formation of L^3 and L^4 , their ^{13}C -NMR chemical shifts were theoretically calculated by the GIAO method at B3LYP/6-31G(d) level.²⁶ The calculated results are summarized in Table 1, along with the experimental data. The standard deviation between the experimental chemical shifts and calculated values for L^3 and L^4 were found to be 1.49 and 0.82 ppm, respectively. Table 1 shows that the calculated chemical shifts for the selected carbon atoms of each isomer are in good agreement with the experimental ^{13}C -NMR spectral data. The carbon peak of the N-C-N linkage on the 1,3-diazacyclopentane ring in L^3 is downfield shifted than that on the 1,3-diazacyclohexane ring in L^4 , which is in accord with the reported chemical shift patterns for L^7 and L^9 .¹³ It is also seen that the C(3) and C(7) atoms are more deshielded in L^3 than in L^4 .

The preparation of L^3 as the major product is quite interesting because the present result is quite different from the reported trend that the major product prepared from the reaction of L^5 or L^6 with formaldehyde at room temperature is L^7 or L^8 containing two 1,3-diazacyclohexane rings.¹¹⁻¹⁸ To resolve this disagreement, global minima for L^3 , L^4 , L^7 , and L^9 were obtained from DFT calculation at B3LYP/6-

Table 1. Calculated (DPF) Energies and Calculated (GAIO) ^{13}C NMR Chemical Shifts for the Macropolycycles

Compound	E, au	E _{rel} , kcal/mol	δ , ppm ^a				
			N-C-N	C(1)	C(3)	C(5)	C(7)
L^3	-1081.401778	0	75.41 (77.87)	64.20 (64.66)	59.90 (61.94)	51.59 (51.88)	69.51 (71.49)
L^4	-1081.394191	4.76	65.23 (66.32)	62.06 (61.37)	52.33 (52.27)	49.15 (49.76)	53.42 (52.57)
L^7	-690.684147	0					
L^9	-690.672131	7.54					

^a Values in parentheses are the experimental data.

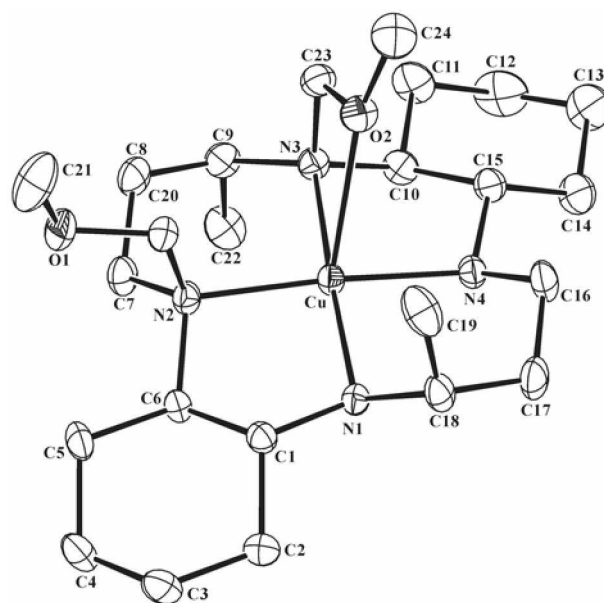
Table 2. Bond distances [Å] and angles [deg] for **1**

Cu-N(1)	2.023(2)	Cu-N(2)	2.061(3)
Cu-N(3)	2.093(3)	Cu-N(4)	2.025(3)
Cu-O(1)	4.178(2)	Cu-O(2)	2.471(2)
O(1)-C(20)	1.404(4)	O(1)-C(21)	1.414(5)
O(2)-C(23)	1.407(4)	O(2)-C(24)	1.428(5)
N(1)-Cu-N(2)	85.5(2)	N(1)-Cu-N(3)	175.8(2)
N(1)-Cu-N(4)	91.3(2)	N(2)-Cu-N(3)	97.7(2)
N(2)-Cu-N(4)	175.9(2)	N(3)-Cu-N(4)	85.4(2)
C(20)-O(1)-C(21)	111.3(3)	C(23)-O(2)-C(24)	112.8(3)

31G(d) level.²⁵ Structures of the global minima for L^3 and L^9 containing 1,3-diazacyclopentane rings are practically the same except the fused cyclohexane rings in L^3 and match the reported crystal structure for a derivative of L^9 .¹³ Likewise, L^4 and L^7 containing 1,3-diazacyclohexane rings have the structural similarity to a derivative of L^7 .¹³ As expected from the reported trend,¹³ L^7 containing two 1,3-diazacyclohexane rings is 7.54 kcal/mol more stable than L^9 (Table 2). In the case of the present system, however, the reverse energetic situation is found: L^3 containing two 1,3-diazacyclopentane rings is 4.76 kcal/mol more stable than L^4 . It can be suggested that the formation of L^3 as the major product is closely related to the thermodynamic stability of the compound. The compound L^4 contains a 10-membered inner ring and all atoms of the ring are also involved in the relatively rigid chair-like 6-membered cyclohexane or 1,3-diazacyclohexane rings. The structural rigidity prevents L^4 from relaxing the transannular strain between the facing atoms of the 10-membered ring fragment, such as a proton at N-CH₂-N and a nitrogen atom on the opposite side. On the other hand, L^3 has a 12-membered inside ring which is relatively free from transannular strain. Furthermore, the carbon atoms involved in the N-C-C-C-N linkages of L^3 are expected to be relatively flexible because they do not comprise additional fused rings. Therefore, one of the reasons for the enhanced thermodynamic stability of L^3 , comparing with L^4 , may be the relatively weak transannular strain caused by the larger inner ring size and the flexible ring fragments.

The macropolycycle L^3 readily dissolves in chloroform but poorly in methanol at room temperature. It is extremely stable in the solid state and in chloroform at room temperature. Interestingly, L^3 reacts with methanol in the presence of Cu²⁺ ion to produce [CuL³]²⁺ bearing two N-CH₂OCH₃ pendant arms. We were unable to prepare L^2 in the absence of the metal ion. It is obvious that the metal ion promotes the reaction of L^3 with methanol and/or stabilizes the product.

Crystal Structure and Properties of 1. The ORTEP drawing (Fig. 1) of [CuL³]²⁺ in **1** shows that two methoxymethyl groups are attached to the nitrogen atoms (N(2) and N(3)) involved in the same six-membered chelate ring. The macrocyclic ligand adopts the *trans*-III type *N*-conformation, and the two methoxymethyl groups are on the same side of the Cu-N₄ plane. Therefore, only one methoxymethyl

**Figure 1.** An ORTEP³⁰ drawing of [CuL³]²⁺ cation in **1**. Thermal ellipsoids are shown at the 30% probability level. Hydrogen atoms and lattice solvent have been omitted for clarity.

pendant arm is coordinated to the metal ion, and the complex has a distorted square-pyramidal coordination geometry with the apical Cu-O(2) bond. The Cu···O(1) distance (4.178(2) Å) indicates that the O(1) atom is not involved in coordination. The cyclohexane rings and the six-membered chelate rings have stable chair conformations.

The selected bond distances and angles of the complex are listed in Table 2. As expected, the Cu-N(2) (tertiary) and Cu-N(3) (tertiary) distances (2.061(3) and 2.093(3) Å, respectively) are considerably longer than the Cu-N(1) and Cu-N(4) distances (2.023(2) and 2.025(3) Å, respectively) involving the secondary nitrogen atoms. The Cu-O(2) distance (2.471(2) Å) indicates that the oxygen atom is coordinated to the metal ion. The metal ion lies *ca.* 0.047(1) Å above the mean CuN₄ plane in the direction of the O(2) atom. This may be resulted from the formation of the Cu-O(2) bond. The O(2)-C(24) distance (1.428(5) Å) and C(23)-O(2)-C(24) angle (112.8(3)^o) are slightly longer and larger, respectively, than the O(1)-C(21) distance (1.414(5) Å) and C(20)-O(1)-C(21) angle (111.3(3)^o). The angles of N(2)-Cu-N(4) (175.9(2)^o) and N(1)-Cu-N(3) (175.8(2)^o) are distorted from 180^o. The N(2)-Cu-N(3) angle (97.7(1)^o) involving the methoxymethyl groups is considerably larger than the N(1)-Cu-N(4) angle (91.3(2)^o).

The infrared spectrum of **1** shows two peaks of ν_{N-H} of the coordinated secondary amines at 3220 and 3200 cm⁻¹. The electronic absorption spectra of **1** measured in various solvents show the *d-d* band at 524-533 nm, which is *ca.* 30-40 nm longer than that of [CuL¹]²⁺ measured in each solvent.²⁷ The spectra are comparable with those of other related square-pyramidal copper(II) complexes.^{6,7} The infrared and electronic spectral data of the complex are in accordance with the crystallographic results. The molar conductance values (245 Ω⁻¹mol⁻¹cm²) of **1** measured in

acetonitrile indicate that the complex is a 1:2 electrolyte.

The copper(II) complex is extremely stable in the solid state and in various solvents. It is relatively stable even in low or high pH; visible absorption spectra of **1** (2.0×10^{-3} M) measured in 0.1 M HClO₄ or 0.1 M NaOH solutions showed no apparent decomposition during 5 h at room temperature. However, all our attempts to isolate the free macrocycles L² from the reaction of **1** with NaCN were unsuccessful; the only macrocyclic compound isolated from the attempts was L¹. This means that the pendant *N*-CH₂-O-CH₃ group of L² is stable when the macrocycle is coordinated to the metal ion.

Conclusion

The macropolycycle L³ containing two 1,3-diazacyclopentane rings can be prepared in good yield by the reaction of L¹ with formaldehyde at room temperature. This may be closely related to the observation that L³ is thermodynamically more stable than L⁴. The preparation of **1**, in which one of the two *N*-CH₂OCH₃ groups is coordinated to the copper(II) ion, shows that the reaction of L³ with methanol is promoted by the metal ion. Furthermore, the pendant *N*-CH₂OCH₃ groups of L² in **1** are stabilized by the coordination of the macrocycle to the metal ion.

Supplementary material. Crystallographic data of **1** are available from the Cambridge Structural Database, CCDC reference number 621230. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (<http://www.ccdc.cam.ac.uk>; fax: +44-1223-336-033, or e-mail: deposit@ccdc.cam.ac.uk).

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