

단 신

L-Methionine Ethyl Ester 유도체의 구리 이가 착물 합성 및 구조 분석

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Synthesis and Structural Characterization of Cu(II) Complex of a *L*-Methionine Ethyl Ester Derivative

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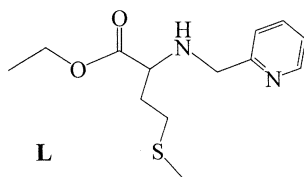
Recent interest in transition metal complexes with chiral ligands originates from applications to asymmetric catalysis,^{1,2} biomarkers³ and metal pharmaceuticals,⁴⁻⁶ and modeling metalloproteins.⁷⁻⁸ Since natural amino acids have an inherent chiral center and are relatively inexpensive, they have been extensively used as sources of chiral functionality.⁹ Furthermore, amino acids can be easily modified as multidentate ligands by standard organic reactions such as conversion of the C-termini to amide and alkylation or reductive amination of the N-termini.⁹ Due to the growing interest in the Cu coordination chemistry of sulfur containing amino acids in relation to copper proteins like dopamine β hydroxylase (DBH) and peptidylglycine α -hydroxylating monooxygenase (PIIM),¹⁰⁻¹¹ and possibly in Alzheimer's or prion peptides,¹²⁻¹³ we have decided to investigate the coordination chemistry of a new chiral

multidentate ligand derived from *L*-methionine ethyl ester (**L**). We have found that the chelate forms a stable copper (II) complex in N₂O fashion and maintains its chirality upon coordination.

EXPERIMENTAL

Materials and Methods. Reagents and solvents used were of commercially available reagent grade quality unless otherwise stated. Anhydrous diethyl ether was distilled from sodium/benzophenone under argon.

Elemental analysis (C, H, N) were performed by the Elemental Analysis Laboratory of the Korean Basic Science Institute. Chemical ionization mass spectra were obtained on a double-focusing Vacuum Generator 70-S (VG-70S) gas chromatography/mass spectrometer. Infrared spectra were recorded on a KBr plate with a PE Biosystem FT-IR spectrometer. ¹H and ¹³C NMR spectra were obtained in CDCl₃ on a JEOL (400MHz) spectrometer. X-band EPR measurements were taken using a Varian E-4 spectrometer equipped with a liquid nitrogen Dewar insert. Electronic absorption spectra were taken with Shimadzu UV-160 using a quartz cuvette (1 cm).



Synthesis of N-pyridylmethyl-L-methionine ethyl ester (L). To a solution of L-methionine ethyl ester (2.5 g, 14.1 mmol) in 100 mL of DMF was added 2-picoyl chloride (2.2 g, 17.2 mmol) with stirring. To this mixture was then added sodium bicarbonate (7.2 g, 85.7 mmol). The resulting solution was stirred at 80 °C for 1 day after which it was filtered and the filtrate was rotary evaporated to give crude oil product, which was chromatographed on silica gel using a 97/3 (v/v %) mixture of ethyl acetate/hexane. The purified ligand was obtained as a brown oil in 67 % yield (2.5 g). IR (KBr, cm^{-1}): 3315, 2727, 1739 (C=O), 1482, 1229, 1297, 1150. ^1H NMR (CDCl_3 , δ): 8.48 (d, 1H), 7.58 (m, 1H), 7.28 (d, 1H), 7.09 (m, 1H), 4.20 (q, 2H), 3.82 (m, 2H), 3.38 (t, 1H), 2.55 (t, 2H), 2.02 (s, 3H), 1.882.04 (m, 2H), 1.22 (t, 3H). ^{13}C NMR (CDCl_3 , δ): 174.6, 159.2, 149.1, 136.3, 122.1, 121.9, 60.8, 59.9, 53.4, 32.7, 30.4, 15.2, 14.2. Mass spectrum (CI) (m/z) 269 (M+1) $^+$.

Synthesis of $[\text{Cu}^{\text{II}}(\text{L})_2](\text{ClO}_4)_2$ (I). The ligand L (0.31 g, 1.16 mmol) was dissolved in 10 mL of argon saturated CH_3OH and added to dropwise to 0.21 g (0.56 mmol) of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ while stirring for 25 minutes. To the resulting blue solution was added diethyl ether until the solution became cloudy. The solution was then filtered through a medium porosity frit and the complex precipitated by addition of 40 mL of diethyl ether. The supernatant was decanted and the complex was washed with 50 mL of additional ether. The resulting solid was recrystallized from methanol/ether twice and dried under vacuum giving 0.40 g (89.5 % yield) blue powder. IR (KBr, cm^{-1}): 3235, 2035, 1695 (C=O), 1614, 1297, 1093 (ClO_4). UV/Vis (DMF, λ_{max} , nm (ϵ , $\text{M}^{-1} \text{cm}^{-1}$): 329 (7100), 676 (245). Anal. $\text{CuC}_{26}\text{H}_{40}\text{N}_4\text{O}_{12}\text{S}_2\text{Cl}_4$: Calcd.: C, 39.08; H, 5.04; N, 7.01. Found: C, 38.81; H, 5.56; N, 7.24. Well shaped blue crystals suitable for X-ray diffraction analysis were grown by layering of diethyl ether over the concentrated methanol solution.

X-ray Structure Determinations. X-ray quality crystals of (I) were grown by adding diethyl ether over methanol solution of the copper complex and allowing the solution to stand several days at room temperature. These crystals were mounted on glass fibers. All measurements were made on a Bruker

SMART CCD Detector single crystal diffractometer with a graphite monochromated Mo K α source ($\lambda(\text{MoK}\alpha)=0.71073 \text{ \AA}$) at -80 °C. Preliminary unit cell constants were determined with a set of 45 narrow frames (0.3 in ω) scans. Data sets collected consist of 1286 frames of intensity data collected with a frame width of 0.3 in ω and counting time of 25 seconds/frame at a crystal to detector distance of 5.0 cm. The double pass method of scanning was used to exclude any noise. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. SMART and SAINT software packages (Bruker Analytical X-ray, Madison, WI, 1997) 11 were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by a global refinement of 8192 reflections ($\theta < 25.0^\circ$). Collected data were corrected for absorbance using SADABS 15 based upon the Laue symmetry using equivalent reflections. Structure solution and refinement of the structure were carried out using the SHELXTL-PLUS (5.03) software package. 16 Tables of crystal data, data collection methods, and refinement procedures are provided in Table 1.

RESULTS AND DISCUSSION

The ligand was prepared enantiomerically pure from the reaction of L-methionine ethyl ester with picoyl chloride in the presence of sodium bicarbonate as base. The copper(II) complex has been synthesized from reacting 2 equivalents of L and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in methanol and obtained as a blue powder. Based on the elemental analysis (C, H, N) the complex was formulated as $[\text{Cu}^{\text{II}}(\text{L})_2](\text{ClO}_4)_2$ (I). An attempt to isolate 1:1 ligand/Cu(II) complex failed, probably because the cupric ion could not be stabilized with three or four donor atoms available in the ligand L. A very distinct band in the solid state IR spectrum at 1695 cm^{-1} is attributed to the stretching frequency of the C=O (at 1739 cm^{-1} in uncoordinated L). This decrease in frequency might be due to some interaction between the copper(II) ion and the carbonyl oxygen, as is indeed seen in the X-ray crystal structure (*vide infra*). Signals for

Table 1. Crystal data and structure refinement for $[\text{Cu}^{\text{II}}(\text{L})_2](\text{ClO}_4)_2$ (1).

Empirical formula	$\text{C}_{26}\text{H}_{40}\text{Cl}_2\text{CuN}_4\text{O}_{12}\text{S}_2$
Formula weight	799.18
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Rhombohedral
Space group	R3
Unit cell dimensions	a=21.2504(11) Å $\alpha=90^\circ$ b=21.2504(11) Å $\beta=90^\circ$ c=21.3274(15) Å $\gamma=120^\circ$
Volume	8340.7(8) Å ³
Z	9
Density (calculated)	1.432 Mg m ⁻³
Absorption coefficient	0.906 mm ⁻¹
F(000)	3735
Crystal size	0.45 0.43 0.28 mm ³
θ range for data collection	1.92 to 28.28 $^\circ$
Index ranges	-12 \leq h \leq 28, -28 \leq k \leq 26, -28 \leq l \leq 27
Reflections collected	17286
Independent reflections	8533 [R(int)=0.0195]
Completeness to $\theta=28.28$	97.5%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7856 and 0.6861
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	8533/1/489
Goodness-of-fit on F ²	1.092
Final R indices [I \geq 2sigma(I)]	R ₁ =0.0403, wR ₂ =0.1142
R indices (all data)	R ₁ =0.0452, wR ₂ =0.1184

$$R_1 = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}; \quad wR_2 = \left[\frac{\sum w(F_o^2 - F_c^2)^2}{\sum wF_o^4} \right]^{1/2}$$

the perchlorate anion appear in the region between 1050 and 1150 cm⁻¹ as expected.

Electronic absorption spectrum of (1) obtained from *N,N*-Dimethylformamide (DMF) solution exhibits absorption ascribable to d-d transitions at 676 nm with their typically weak extinction coefficient ($\epsilon=245$). An EPR spectrum obtained from frozen solution in DMF exhibits a spectral pattern characteristic of an axial symmetric complex with $g_{\parallel}=2.243 > g_{\perp}=2.067$, and $A=157 \times 10^{11}$ cm⁻¹. This result indicates the copper ion is in a $d_{3,2,2}$ ground state, which is in good agreement with the structure suggested by the crystal structure (*vide infra*).

An ORTEP plot of the copper complex is shown in Fig. 1 including the atom labeling scheme. Selected bond lengths and angles are listed in Table 2. The copper ion is four coordinate with ligation to two pyridyl nitrogen atoms and two nitrogen atoms

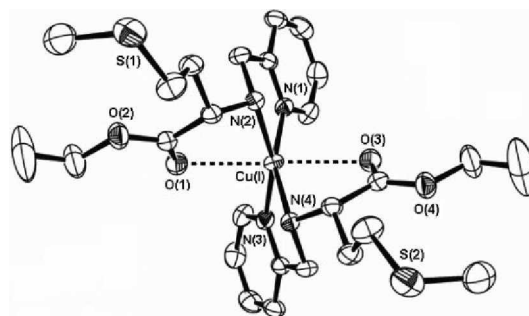


Fig. 1. An ORTEP drawing of the cationic portion of $[\text{Cu}^{\text{II}}(\text{L})_2](\text{ClO}_4)_2$. Hydrogen atoms have been omitted for clarity.

from the two secondary amines. In addition to the four Cu(1)-N bonds, the metal ion seems to have weak interactions with two ester carbonyl oxygens with an average distance of 2.5 Å. The average C-O distance (1.2 Å) of the two carbonyl oxygens is

Table 2. Selected Bond Distances (Å) and Angles (°) for [Cu^{II}(L₂)₂](ClO₄)₂ (1).

Bond lengths			
Cu(1)-N(1)	1.978 (3)	Cu(1)-N(4)	2.044 (2)
Cu(1)-N(2)	2.045 (2)	Cu(1)-O(1)	2.502 (2)
Cu(1)-N(3)	1.976 (2)	Cu(1)-O(3)	2.500 (2)
Bond angles			
N(3)-Cu(1)-N(1)	99.19 (10)	O(1)-Cu(1)-N(2)	72.03 (9)
N(3)-Cu(1)-N(4)	83.27 (10)	O(1)-Cu(1)-N(3)	88.49 (9)
N(1)-Cu(1)-N(4)	160.21 (9)	O(1)-Cu(1)-N(4)	95.35 (10)
N(3)-Cu(1)-N(2)	160.30 (9)	O(3)-Cu(1)-N(1)	88.49 (10)
N(1)-Cu(1)-N(2)	83.27 (10)	O(3)-Cu(1)-N(2)	95.23 (9)
N(4)-Cu(1)-N(2)	101.07 (10)	O(3)-Cu(1)-N(3)	104.35 (9)
O(1)-Cu(1)-O(3)	160.33 (8)	O(3)-Cu(1)-N(4)	71.94 (10)
O(1)-Cu(1)-N(1)	104.33 (9)		

almost identical with that of the free carbonyl group seen in other related complexes.¹⁸ However, a lone pair of electrons on each carbonyl oxygens points in the direction of the empty axial positions of the metal ion with $\angle C_{=O}-O_{C=O}-Cu=106^\circ$, indicating the carbonyl oxygen coordination to the Cu ion. The geometry around Cu(1), therefore, can be best described as an irregular octahedron with atoms N(1), N(2), N(3), N(4) as the basal plane. In the basal plane, the two pyridyl nitrogens, N(1) and N(3), are *trans* to the aliphatic amine nitrogens, N(4) and N(2), respectively. The Cu(1)-N (Cu(1)-N(1), Cu(1)-N(2), Cu(1)-N(3) and Cu(1)-N(4)) bond lengths are in the range expected for other related cupric compounds containing aliphatic amine and pyridine.¹⁷ One notable feature of the structure is that the chiral carbons locate the ester and pyridyl functionalities such that they might form a small chiral pocket, which can be potentially useful for some applications such as asymmetric synthesis.

In summary, a *L*-methionine ethyl ester with covalently attached synthetic polydentate chelator and its Cu(II) complex have been prepared and characterized. The structural and spectroscopic results indicate that the ligand coordinates to the cupric ion through the carbonyl oxygens as well as pyridyl and amino nitrogens. Further studies will focus on application of these metal complexes in modeling metalloenzymes and asymmetric organic synthesis.

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Supporting Information Available: Details about the X-ray structure determination of [Cu^{II}(L₂)₂](ClO₄)₂ are available from the author upon request.

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