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Structure of μ-Oxo-tetranuclear Copper(II) Complex Produced from Chlorpromazine (cpz) and Cu(II)Cl_2. An Alternative Binding Site of the cpz Molecule to Metal

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The structure of the complex $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$, produced from the reaction between chlorpromazine (cpz) and Cu(II)Cl_2 in the presence of a small amount of water, was determined by X-ray diffraction analysis. The complex crystallizes in the monoclinic space group $P2_1/a$ with $a=66.807(3)$, $b=16.767(2)$, $c=9.6484(4)$ Å, $\beta=95.725(3)°$, $V=10754(1)$ Å^3, and $Z=4$. Each copper atom in the core (Cu_4OCl_6) is coordinated by a cpz ligand through the terminal nitrogen atom of the side-chain.

Keywords chlorpromazine; copper(II) complex; μ-oxo-tetranuclear copper(II) complex; X-ray structural analysis

The metabolism of the antipsychotic drug, chlorpromazine (2-chloro-10-(3-dimethylaminopropyl)phenothiazine, cpz), seems complicated, and at least 77 metabolites have been observed by chromatographic analyses.$^{1)}$ The metabolic profiles were defined by two major categories$^{2)}$: oxidation of the phenothiazine ring *via* a cationic radical of the ring leading to formation of sulfoxide or hydroxylation of the aromatic rings; and oxidation on the terminal nitrogen of the side-chain on the 10-position of the phenothiazine nucleus. On the other hand, interactions between cpz and various metal ions have continued with a view to obtaining better understanding of the biochemical mechanisms by which the drug acts. As a matter of course, the reaction sites of cpz with metal ions will coincide with the reactive portions of the drug involved in its metabolism.

Several structural analyses have thus far been performed on the product of the reaction between cpz (or related phenothiazine drugs) and metal ions. However, the reaction site of the drugs with metal ions has been confined to the phenothiazine moiety: Cu(II)$Cl_4{}^{2-}$ salt of a cationic radical of cpz,$^{3)}$ promazine,$^{4)}$ and fenethazine,$^{5)}$ Pt(II) and Pd(II) complexes coordinated on the S atom of promethazine,$^{6)}$ and Co(II) and Cu(II) complexes coordinated on the O atom of sulfoxide of cpz-5-oxide.$^{7)}$ We prepared, for the first time, the coordination complex attached to metal at the terminal nitrogen atom of the side-chain of cpz, the structure of which is described in this paper. The complex obtained from the reaction between cpz and Cu(II)Cl_2 in the presence of a small amount of water was found to be a μ-oxo-tetranuclear copper(II) complex. This type of copper complex with the triphenylphosphine oxide ligand was first synthesized in 1966,$^{8)}$ the structures and properties of its homologs having been clarified since.$^{9)}$

Experimental

Absorption spectra in solution and diffuse reflection spectra in solid (using $BaSO_4$ as a reference and a diluent) were measured on a Shimadzu UV-3100 spectrophotometer. Magnetic susceptibilities were obtained with a Shimadzu torsion magnetometer MB-100 using $(NH_4)_2Fe(SO_4)_2$ as a standard. Infrared (IR) spectra (KBr disks) were obtained with a JASCO IR-810 spectrophotometer.

μ_4-Oxo-hexa-μ-chloro-tetrakis[(chlorpromazine-*N*)copper(II)] $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$ A solution of cpz (3.19 g, 10 mmol) in ethanol (30 ml) was added to a solution of $CuCl_2$ (1.35 g, 10 mmol) in ethanol (30 ml) at room temperature. The resulting ocher precipitate (3.86 g) was collected by filtration and dissolved in benzene (380 ml), followed by the addition of cyclohexane (570 ml). Yellow precipitate was gradually formed, collected by filtration after being allowed to stand for several hours, and dried *in vacuo* (1.32 g). The resulting precipitate was found to be $cpzH^+CuCl_3^-$, as identified by inspection of the IR and UV spectra, similar to those of $cpzH^+Cl^-$ and $(cpzH^+)_2CuCl_4{}^{2-}$, and elemental analysis. *Anal.* Calcd for $C_{17}H_{20}Cl_4CuN_2S$: C, 41.69; H, 4.12; N, 5.72. Found: C, 41.28; H, 4.11; N, 5.30. The yield was 80.4%, calculated on the basis of the added cpz (refer to the equation in the text). The filtrate from which $cpzH^+CuCl_3^-$ was removed was then evaporated *in vacuo* to give a brown powder. This powder was slowly crystallized from benzene and cyclohexane (1 : 1) to yield orange columnar crystals of the complex $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$ (2.28 g, 61.5% based on the added cpz). *Anal.* Calcd for $C_{104}H_{112}Cl_{10}Cu_4N_8OS_4$: C, 56.09; H, 5.07; N, 5.03. Found: C, 55.99; H, 5.10; N, 4.89.

X-Ray Crystal Structure Analysis of $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$ A single crystal with dimensions of $0.70 \times 0.30 \times 0.28$ mm^3 was mounted on a glass capillary and coated with epoxy glue. Intensity data in the range of $2° < 2\theta < 120°$ (h: $-78 \rightarrow 78$; k: $0 \rightarrow 19$; l: $-11 \rightarrow 0$) were collected on a Rigaku four circle AFC-5 diffractometer with graphite monochromated CuK_α radiation ($\lambda = 1.54173$ Å). The data were corrected for the Lorentz and polarization effects. Three standard reflections were monitored every 150 reflections, the maximum deviation being 1.8%. A total of 20358 reflections were measured, of which 12831 reflections with $|F_O| > 4\sigma(|F_O|)$ were employed for the structural determination. Crystal data: $C_{104}H_{112}Cl_{10}Cu_4N_8OS_4$, F.W. = 2227.08, monoclinic, space group $P2_1/a$, $a=66.807(3)$ Å, $b=16.767(2)$ Å, $c=9.6484(4)$ Å, $\beta=95.725(3)°$, $V=10754(1)$ Å^3, $Z=4$, $d_x=1.376$ g cm^{-3}, $d_m=1.37(1)$ g cm^{-3} (flotation).

The structure was solved by the direct method using the SHELX86 program$^{10)}$ and refined by the block-diagonal least squares approximations with the UNICSIII program.$^{11)}$ Non-hydrogen atoms were refined by the anisotropic factors, and the locations of hydrogen atoms were calculated. The atomic scattering factors were taken from the International Tables for X-ray Crystallography.$^{12)}$ The final R value converged to 0.076, the R_w value to 0.065 with $w=1/\sigma(F)$, and the final $|\Delta\rho|$ was less than 0.56 eÅ. Calculations were carried out on a FACOM M770/8 computer at this university and the molecular diagrams were drawn using the ORTEP program.$^{13)}$

Results and Discussion

The crystals of the complex studied here include six times mole of benzene as a solvent of crystallization, as represented by the formula $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$. The crystals are fairly stable, but on exposure to air for

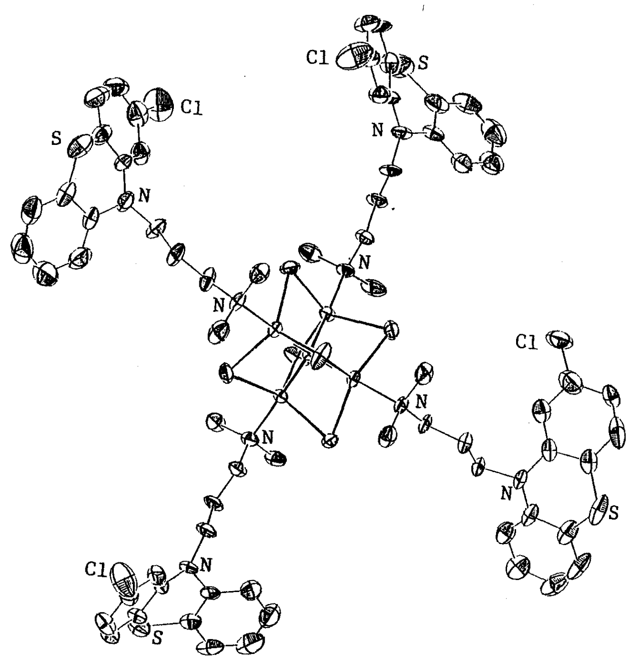

Fig. 1. The Molecular Structure of $[Cu_4OCl_6(cpz)_4]$ with the Thermal Ellipsoids of a 50% Probability Level

Benzene molecules in the crystals and all the hydrogen atoms are omitted for clarity.

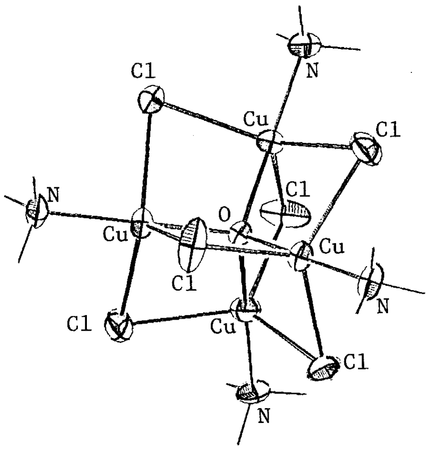

Fig. 2. The Structure of the Core of $[Cu_4OCl_6(cpz)_4]$ with the Thermal Ellipsoids of a 50% Probability Level

The N atoms are in the cpz ligands.

several days a slight turbidity appears on their surfaces, presumably due to partial loss of benzene. This necessitated the coating of the crystal with epoxy glue during the data collection in the X-ray analysis. The reaction is stoichiometrically expressed by the following equation,

$$6cpz + 6CuCl_2 + H_2O \rightarrow [Cu_4OCl_6(cpz)_4] + 2cpzH^+CuCl_3^-$$

where water was supposed to come from the air moisture and the solvent being used.

Figure 1 shows the molecular structure of the complex which has crystallographically no symmetry element in one molecule.[14)] Figure 2 demonstrates the central core of the molecule. Four copper atoms in the core are located at the corners of a slightly distorted tetrahedron around the central oxygen atom with the Cu–O bond lengths of 1.895(5)— 1.930(5) Å (average 1.920 Å) and the Cu–O–Cu angles of 108.0(2)— 111.2(2)° (average 109.5°). Two adjacent copper atoms are bridged by a chlorine atom, all forming a cluster. Each cpz ligand is coordinated to the copper atom through the terminal nitrogen atom of the side-chain with the Cu–N bond lengths of 2.038(6)—2.051(6) Å (average 2.042 Å). The configuration around each copper atom is found to be trigonal bipyramidal with three chlorine atoms within the equatorial plane: the lengths of the Cu–Cl bonds are 2.378(3)—2.423(3) Å (average 2.399 Å) and the angles of the Cl–Cu–Cl bonds 113.4(1)—122.2(1)° (average 119.1°). All the copper atoms are displaced toward the cpz ligand by 0.232(2)—0.237(2) Å from the plane formed by the three chlorine atoms. Although the bond lengths or angles belonging to the same category in a molecule have small differences as mentioned above, their average values are in close agreement with those of other μ-oxo-tetranuclear copper(II) complexes with various ligands. Four cpz ligands in the complex also hold slightly different configurations from that of free cpz. For instance, the dihedral angles between the lateral benzene rings in the tricyclic system are 132.2(4)—143.3(3)° (average 137.7°): the angle of a free cpz molecule is 139.4°.[15)] Benzene molecules in the crystals seem to have little interaction with the complex because they are far from it (the shortest distance between the benzene molecule and the complex is 3.59(2) Å).

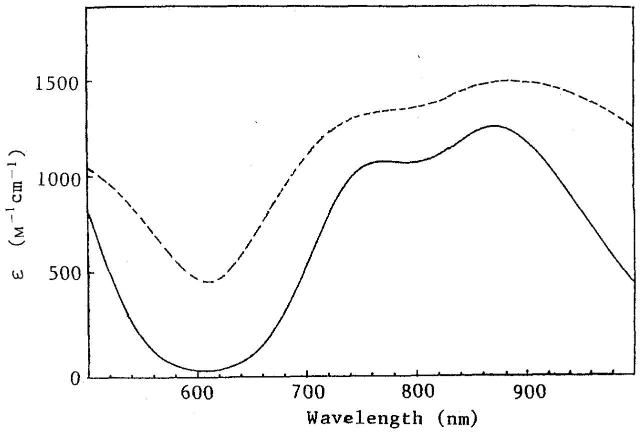

Fig. 3. Diffuse Reflection Spectrum of $[Cu_4OCl_6(cpz)_4](C_6H_6)_6$ in Solid Using $BaSO_4$ as a Reference (Broken Line), and Absorption Spectrum in Benzene (Solid Line)

The molar extinction coefficients refer to the solution spectrum; the solid spectrum is on an arbitrary scale.

The intramolecular distances between the copper atoms are 3.10— 3.16 Å, the existence of the metal–metal interactions being anticipated. Magnetic susceptibility measurements showed the effective magnetic moment (μ_{eff}) per gram atom copper(II) to be 1.89 B.M. at 20.5 °C. This value is close to that of ordinary single nuclear copper(II) complexes and within the range of a group with relatively low μ_{eff} values, as classified by Wong *et al.* for tetranuclear copper(II) complexes.[16)] These facts imply that the metal–metal interactions in the present complex might, if present at all, be weak.

Figure 3 illustrates the diffuse reflection spectrum of the *d–d* transition region in solid using $BaSO_4$ as a reference, together with the absorption spectrum in benzene. The two spectra manifest a similar appearance, consisting of a broad, two-component band with the peaks centered at *ca.* 750 and 883 nm in solid and at *ca.* 760 nm ($\varepsilon = 1100$) and 874 nm ($\varepsilon = 1270$) in solution. The solid spectrum exhibits broader peaks and a wider peak interval than those of the solution spectrum, which is attributable to the well-known perturbations of the transitional energies in the crystal state. At any rate, the similarity between the two spectra obtained for different phases indicates that the cluster structure remains intact whilst in solution. Examination of the IR spectrum of the complex reveals the presence of two new bands in addition to the bands originating from the cpz ligand. The broad band of medium intensity at *ca.* 560 cm^{-1} is associated with the $\nu_{\mathrm{Cu-O}}$ frequency in the Cu_4O core and the relatively sharp band of medium intensity at 686 cm^{-1} is thought to be associated with the $\nu_{\mathrm{Cu-N}}$ frequency. These assignments were obtained by comparison of the IR absorption frequencies to those of other Cu_4O core complexes.[17)]

The present complex, produced for the first time by combining cpz with metal ions through the terminal nitrogen atom in the side-chain, was found to possess a known core structure as previously cited. Nevertheless, this complex suggests the possible interaction of the side-chain of cpz and metals in a living body, and may provide a clue to understanding the detailed action of the drug.

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