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SYNTHESIS AND CRYSTAL STRUCTURE OF A COPPER(II) COMPLEX WITH A TETRADENTATE DITHIADIOXIME LIGAND

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Abstract—A neutral five-coordinate dithiadioxime complex of copper(II), chloro[3,3′-(1,3-propanedithia)bis(3-methyl-2-butanone oximato)(1-)-*S*,*S*′,*N*,*N*′]copper(II) (Cu(LH)Cl), was prepared by reaction of $CuCl_2$ with the [3,3′-(1,3-propanedithia)bis(3-methyl-2-butanone oxime)] ligand (LH_2) in methanol–acetone. The crystal structure of the Cu(LH)Cl monohydrate, $[CuCl(C_{13}H_{25}N_2S_2O_2)] \cdot H_2O$, reveals a square pyramidal geometry about the metal centre. The copper(II) ion is coordinated in an approximate square plane by the two oxime nitrogen atoms and two thioether sulphur atoms of the tetradentate dithiadioxime ligand, with the chlorine occupying an axial coordination site at a Cu—Cl distance of 2.3931(8) Å. The copper-to-nitrogen distances average 1.997 Å, while the copper-to-sulphur distances average 2.3279 Å. The least-squares S_2N_2 plane is situated 0.467(1) Å below the copper centre. A proton bridges the two oxime oxygen atoms of the complex in the fashion typical of metal complexes containing *cis*-oxime functions.

A number of copper radionuclides exhibit properties that make them attractive as radiolabels for diagnostic and therapeutic radiopharmaceuticals.[1] In an ongoing investigation of the potential role for ^{62}Cu radiopharmaceuticals in diagnostic imaging with positron emission tomography (PET),[2] we have been exploring the synthesis and properties of lipophilic radiocopper complexes with low molecular weight tetradentate chelating ligands.[3–5] We report here the synthesis and crystallographic structure of a copper(II) complex with a quasimacrocyclic dithiadioxime ligand, LH_2 (Fig. 1).

EXPERIMENTAL

Synthesis of [3,3′-(1,3-*propanedithia*)*bis*(3-*methyl*-2-*butanone oxime*)], LH_2

Nitrosyl chloride was synthesized by reacting sodium nitrite with concentrated HCl according to a literature procedure.[6] The 3-chloro-3-methyl-2-butanone oxime was prepared from nitrosyl chloride by the method of Murmann.[7] The 3,3′-(1,3-propanedithia)bis(3-methyl-2-butanone oxime) ligand (LH_2) was prepared by condensation of two equivalents of 3-chloro-3-methyl-2-butanone oxime with one equivalent of the sodium salt of 1,3-dithiolate under argon. Specifically, 0.69 g of sodium (30 mmol) was added to 10 cm^3 anhydrous ethanol

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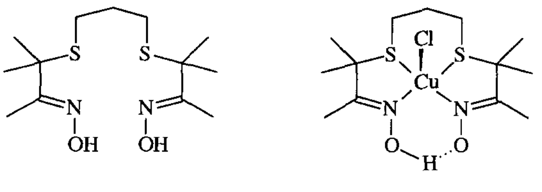
LH_2 **$Cu^{II}(LH)Cl$**

Fig. 1. Structural formulae of the dithiadioxime ligand (LH_2) and the $Cu^{II}(LH)Cl$ complex.

in a 100 cm^3 round-bottomed flask. A white suspension of sodium ethoxide was formed after stirring for 30 min. To this suspension, 1.6 g of 1,3-propanedithiol (15 mmol) was added slowly with vigorous stirring. The 3-chloro-3-methyl-2-butanone oxime (5 g, 37 mmol) dissolved in 10 cm^3 ethanol was then carefully added and stirred for 5 h. The ethanol was evaporated and the residue redissolved in 20 cm^3 diethyl ether, extracted with 20 cm^3 of water and the ethereal layer then dried over anhydrous sodium sulphate. On evaporation of ether and recrystallization from chloroform, the product was deposited as white plates. Yield : 1.2 g (26%) ; m.p. 170–172°C. ^1H NMR(300 MHz, in DMSO-d_6, TMS internal standard), δ (ppm) : 1.36 (12H, s, CH_3), 1.56 (2H, quintet, $J = 7.2$ Hz, CH_2), 1.82 (6H, s, CH_3), 2.32 (4H, t, $J = 7.2$ Hz, CH_2), 10.66 (2H, s, N—OH). FAB mass spectrum (DTT/DTE matrix) : $[M+H]^+$ at m/z 307.

Synthesis of chloro[3,3′-(1,3-*propanedithia*)*bis*(3-*methyl*-2-*butanone oximato*)(1-)-S,S′,N,N′]*copper*(II) *monohydrate*, $Cu(LH)Cl \cdot H_2O$

The dithiadioxime ligand, LH_2 (50 mg, 0.16 mmol), was dissolved in a warm mixture of 1.5 cm^3 methanol–1.5 cm^3 acetone and then slowly added to a solution of $CuCl_2 \cdot 2H_2O$ (27.8 mg, 0.16 mmol) in 0.5 cm^3 of warm methanol and stirred for 20 min. After cooling to room temperature, the resulting dark green solution was filtered and set in a freezer for 1 week to obtain the product as green crystalline needles. Yield : 29.6 mg (42.9%) ; m.p. 136–137°C (decomposed). Electronic absorption spectrum in methanol : $\lambda_{max} = 313$ nm ($\varepsilon = 3417$), 396 nm ($\varepsilon = 1725$) and 552 nm ($\varepsilon = 613$).

X-ray data collection and structure determination

A single crystal having approximate dimensions of 0.25 × 0.25 × 0.17 mm was selected for indexing. Summary information for crystal analysis, data collection and structure refinement is given in Table 1. Preliminary examination and data collection were performed with Cu-K_α radiation on an Enraf–Nonius CAD4 computer-controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the ranges $40 < \theta < 51°$, measured by the computer-controlled diagonal slit method of centring. The data were collected by using the ω–2θ scan technique to a maximum 2θ of 136.3°. The scan rate varied from 2 to 16° per min (in omega). A total of 3893 reflections were collected, of which 3504 were unique. Lorentz and polarization corrections were applied to the data. The agreement factors for the average of the 620 observed and accepted reflections was 2.2% based on intensity and 1.7% based on F_0. The structure was solved using the structure solution program SHELX-86.[8] The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but not refined. All calculations were performed on a VAX computer. Refinement was done using MolEN.[9]

RESULTS AND DISCUSSION

The dithiadioxime ligand LH_2 (Fig. 1) was obtained by reaction of 1,3-propanedithiol with two equivalents of 3-chloro-3-methyl-2-butanone

Table 1. Crystallographic data for the molecule $Cu(LH)Cl \cdot H_2O$

Empirical formula	$CuClS_2O_2N_2C_{13}H_{25} \cdot H_2O$
Formula weight	422.49
a (Å)	8.688(2)
b (Å)	22.739(3)
c (Å)	9.3997(9)
β (°)	90.93(1)
V (Å^3)	1856.6(7)
Z	4
Space group	$P2_1/n$ (No. 14)
T (K)	293
Wavelength (Å)	1.54184
D_{calc} (g cm^{-3})	1.511
Linear absorption coeff. (cm^{-1})	51.80
Transmission coeff.	1.000–0.681
R (F_0)[a]	0.031
R_w(F_0)[b]	0.046

[a] $R = \Sigma|F_0 - F_c|/\Sigma F_0$.

[b] $R_w = (\Sigma w(F_0 - F_c)^2/\Sigma w F_0^2)^{1/2}$.

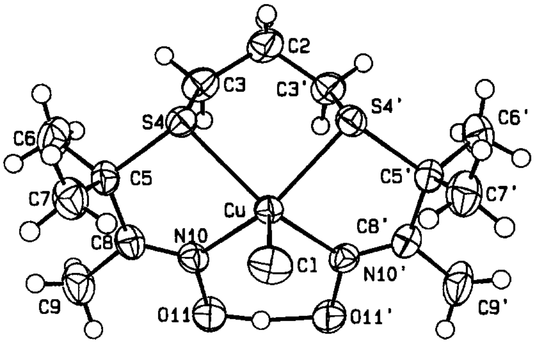

Fig. 2. ORTEP drawing showing the molecular structure of Cu(LH)Cl along with the atom numbering scheme.

Table 2. Selected bond distances (Å) for $Cu^{II}(LH)Cl\cdot H_2O$

Cu—Cl	2.3931(8)
Cu—S(4)	2.3373(7)
Cu—S(4′)	2.3185(7)
Cu—N(10)	2.000(2)
Cu—N(10′)	1.994(2)
O(11)—N(10)	1.378(3)
O(11)—H(11)	1.06(4)
O(11′)—N(10′)	1.376(3)
O(11′)—H(11)	1.38(4)
N(10)—C(8)	1.277(3)
N(10)—H(11)	1.92(4)
N(10′)—C(8′)	1.277(4)
N(10′)—H(11)	2.16(4)

oxime, analogous to a literature method for synthesis of the corresponding 1,3-propanediamine dioxime (H_2PnAO).[10] Upon reaction of $CuCl_2$ with the LH_2 dithiadioxime in methanol–acetone, the copper(II) complex of the singly deprotonated ligand ($Cu^{II}(LH)Cl$; Fig. 1) was readily isolated and crystallized.

An ORTEP drawing illustrating the structure of $Cu^{II}(LH)Cl$ is given in Fig. 2 along with the atom numbering scheme. Selected intramolecular bond distances and bond angles are listed in Tables 2 and 3, respectively. The X-ray study reveals a five-coordinate copper(II) centre ligated in a square pyramidal geometry by the two thioether sulphur atoms and two oxime nitrogen atoms of the tetradentate dithiadioxime ligand, with the chlorine atom in the apical position. The two sulphur and two nitrogen atoms of the ligand are nearly coplanar, with a maximum deviation of 0.013 Å from their least-squares plane. The copper atom is displaced 0.467(1) Å above the least-squares S_2N_2 plane toward the chloride anion. The three methylene carbon atoms of the propane backbone [C(3), C(2) and C(3′)] are positioned below the N_2S_2 plane, due to the chair configuration of this six-membered chelate ring.

The overall geometry about the metal centre is similar to that observed in related $Cu^{II}PnAO$ complexes.[11] The Cu—N bond lengths (1.997 Å average) in $Cu^{II}(LH)Cl$ are in the range of metal–oxime nitrogen bond distances (1.97–2.09 Å) observed in other copper(II) oxime complexes;[11,12] however, they are somewhat longer than the Ni—N distances (1.900 Å) observed in the recently reported square-planar $[Ni^{II}Dtdo]^{1+}$ dithiadioxime complex isolated as its perchlorate salt.[13] The Cu—S separations in $Cu^{II}(LH)Cl$ (2.3279 Å average) are typical of copper–thioether sulphur bonds[14] and are also similar to the Cu—S distances (2.234–2.269 Å) observed in tetradentate N_2S_2 bis(thiosemicarbazone) complexes of copper(II).[15] As with the metal–nitrogen distances, the Cu—S bond lengths in the five-coordinate $Cu^{II}(LH)Cl$ are significantly longer than those found in the four-coordinate $[Ni^{II}Dtdo][ClO_4]$ dithiadioxime complex (Ni—S distances of 2.163 and 2.145 Å).[13]

Table 3. Selected bond angles (°) for $Cu^{II}(LH)Cl\cdot H_2O$

Cl—Cu—S(4)	101.35(3)	Cu—N(10)—O(11)	118.7(2)
Cl—Cu—S(4′)	102.02(3)	Cu—N(10)—C(8)	124.9(2)
Cl—Cu—N(10)	103.88(7)	O(11)—N(10)—C(8)	116.2(2)
Cl—Cu—N(10′)	102.97(7)	O(11)—N(10)—H(11)	33(1)
S(4)—Cu—S(4′)	87.31(3)	C(8)—N(10)—H(11)	148(1)
S(4)—Cu—N(10)	82.27(7)	Cu—N(10′)—O(11′)	118.3(2)
S(4)—Cu—N(10′)	155.15(7)	Cu—N(10′)—C(8′)	124.2(2)
S(4′)—Cu—N(10)	153.51(7)	Cu—N(10′)—H(11)	80(1)
S(4′)—Cu—N(10′)	82.74(7)	O(11′)—N(10′)—C(8′)	117.0(2)
N(10)—Cu—N(10′)	96.71(9)	O(11′)—N(10′)—H(11)	38(1)
N(10)—O(11)—H(11)	103(2)	C(8′)—N(10′)—H(11)	155(1)
N(10′)—O(11′)—H(11)	103(2)	O(11)—H(11)—O(11′)	167(4)

As is typical of metal complexes containing two oxime units in a *cis*-configuration, a single proton is found to bridge the two oxime oxygen atoms. The short O(11) ··· O(11′) separation [2.425(3) Å] is even shorter than most of those observed in metal complexes containing tetradentate (2.42–2.54 Å)[11] or bidentate oxime ligands (2.42–2.69 Å),[12] and is consistent with the occurrence of strong hydrogen bonding interaction between two oxygen atoms. There is also a hydrogen bond between O(11) and the single water of hydration (not shown in Fig. 2).

Supplementary data

Final values of all refined atomic coordinates, thermal parameters, bond lengths, and bond angles have been deposited.

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REFERENCES

1. A. M. Emram (Ed.), *New Trends in Radiopharmaceutical Synthesis, Quality Assurance, and Regulatory Control*, pp. 119–127. Plenum, New York (1991); K. J. Jankowski and D. Parker, *Adv. Met. Med.* 1993, **1**, 29.
2. M. A. Green, *Adv. Met. Med.* 1993, **1**, 75; M. A. Green, *J. Nucl. Med.* 1990, **31**, 1641.
3. E. E. van der Wall, H. Sochor, A. Righetti and M. G. Niemeyer (Eds), *What's New in Cardiac Imaging?*, pp. 165–177. Kluwer, Dordrecht (1992).
4. M. A. Green, *Nucl. Med. Biol.* 1987, **14**, 59; M. A. Green, D. L. Klippenstein and J. R. Tennison, *J. Nucl. Med.* 1988, **29**, 1549; M. E. Shelton, M. A. Green, C. J. Mathias and M. J. Welch, *J. Nucl. Med.* 1989, **30**, 1843; E. K. John and M. A. Green, *J. Med. Chem.* 1990, **33**, 1764; M. A. Green, C. J. Mathias, M. J. Welch, A. H. McGuire, D. Perry, F. Fernandez-Rubio, J. S. Perlmutter, M. E. Raichle and S. R. Bergmann, *J. Nucl. Med.* 1990, **31**, 1989; C. J. Mathias, M. J. Welch, M. E. Raichle, M. A. Mintun, L. L. Lich, A. R. McGuire Zinn, E. K. John and M. A. Green, *J. Nucl. Med.* 1990, **31**, 351; M. E. Shelton, M. A. Green, C. J. Mathias and M. J. Welch, *Circulation* 1990, **82**, 990; C. J. Mathias, M. J. Welch, M. A. Green, H. Diril, C. F. Meares, R. J. Gropler and S. R. Bergmann, *J. Nucl. Med.* 1991, **32**, 475; P. Herrero, J. Markham, C. J. Weinheimer, C. J. Anderson, M. J. Welch, M. A. Green and S. R. Bergmann, *Circulation* 1993, **87**, 173; C. J. Mathias, M. A. Green, W. B. Morrison and D. W. Knapp, *Nucl. Med. Biol.* 1994, **21**, 83.
5. E. K. John, A. J. Bott and M. A. Green, *J. Pharm. Sci.* 1994, **83**, 587.
6. J. R. Morton and H. W. Wilcox, in *Inorganic Syntheses*, Vol. IV, p. 48. McGraw-Hill, New York (1953).
7. R. K. Murmann, *J. Am. Chem. Soc.* 1957, **79**, 521.
8. G. M. Sheldrick, Institut fur Anorganische Chemie der Universitat Gottingen, Germany (1986).
9. C. K. Fair, MolEN Structure Determination System. Delft Instruments, Delft, The Netherlands (1990).
10. E. G. Vassian and R. K. Murmann, *Inorg. Chem.* 1967, **6**, 2043; R. K. Murmann, *J. Am. Chem. Soc.* 1958, **80**, 4174.
11. J. W. Fraser, G. R. Hedwig, H. K. J. Powell and W. T. Robinson, *Aust. J. Chem.* 1972, **25**, 747; C. Kay Fair, D. E. Troutner, E. O. Schlemper, R. K. Murmann and M. L. Hoppe, *Acta Cryst.* 1984, **C40**, 1544; I. B. Liss and E. O. Schlemper, *Inorg. Chem.* 1975, **14**, 3035; J. A. Bertrand, J. H. Smith and D. G. VanDerveer, *Inorg. Chem.* 1977, **16**, 1484; Y.-M. Wang, C.-C. Wang, S.-L. Wang and C.-S. Chung, *Acta Cryst.* 1990, **C46**, 1770.
12. A. Vaciago and L. Zambonelli, *J. Chem. Soc. A* 1970, **55**, 218; R. Ruiz, J. Sanz, B. Cervera, F. Lloret, M. Julve, C. Bois, J. Faus and M. Carmen Munoz, *J. Chem. Soc., Dalton Trans.* 1993, 1623; R. Ruiz, J. Sanz, F. Lloret, M. Julve, J. Faus, C. Bois and M. Carmen Munoz, *J. Chem. Soc., Dalton Trans.* 1993, 3035.
13. V. V. Pavlishchuk, A. W. Addison, R. J. Butcher and R. P. F. Kanters, *Inorg. Chem.* 1994, **33**, 397; A. W. Addison, V. V. Pavlishchuk and R. J. Butcher, *Abstr. Pap. Am. Chem. Soc.* 1992, **204**, INOR 73.
14. E. Bouwman, W. L. Driessen and J. Reedijk, *Coord. Chem. Rev.* 1990, **104**, 143.
15. E. John, P. E. Fanwick, A. T. McKenzie, J. G. Stowell and M. A. Green, *Nucl. Med. Biol.* 1989, **16**, 791; M. R. Taylor, J. P. Glusker, E. J. Gabe and J. A. Minkin, *Bioinorg. Chem.* 1974, **3**, 189; G. W. Bushnell and A. Y. M. Tsang, *Can. J. Chem.* 1979, **57**, 603.