Notes

X-Ray Crystal Structure of a Copper(II) Complex of the Neurotoxic Amino Acid, DL-α-Amino-β-methylaminopropionic Acid †

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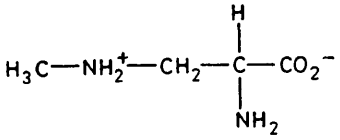
The *X*-ray crystal structure of a copper(II) complex of the neurotoxic amino acid DL-α-amino-β-methylaminopropionic acid is reported [space group $P2_1/a$, a = 9.893(1), b = 11.192(5), c = 8.367(1) Å, β = 101.62(1)°]. The copper atom lies at a centre of symmetry with N_2O_2 planar co-ordination, Cu–O 1.942 and Cu–N 1.976 Å. The complex is weakly axially co-ordinated by perchlorate, Cu–O 2.547 Å.

The non-protein amino acid L-α-amino-β-methylaminopropionic acid [1] (β-methylamino-L-alanine), L-L, has been detected in all *Cycas* species that have been examined.[2] The use of *Cycas circinalis* seed both as a foodstuff and in traditional medicine has been correlated with the incidence of chronic neurological disease, most notably the amyotrophic lateral sclerosis (motor neurone disease)/Parkinsonism dementia complex in Guam.[3,4]



L

Compound L induces a model motor neurone disease in experimental animals; macaques treated orally over a period of several weeks develop degenerative neurological changes associated with both upper and lower motor neurone dysfunction together with Parkinsonian features.[5]

The mechanisms by which compound L causes the death of neurones are unknown but a knowledge of its action may be crucial to understanding the aetiology of sporadic motor neurone disease in man. We have recently drawn attention to two distinct molecular mechanisms by which its toxicity may be mediated. First it forms unusually stable complexes with divalent metal ions such as copper(II) and zinc(II); some of the acute effects of its toxicity may involve such complexes.[6] Secondly, we have shown that it forms a stable α-carbamate,[7] the structure of which resembles that of the well known excitotoxin *N*-methyl-D-aspartate. Either, or both, of these observations may be important in explaining the neurotoxicity of this amino acid. In this note we report the *X*-ray crystal structure of a copper(II) complex of DL-L (only the DL isomer was available to us in sufficient quantity for synthetic work), and present the first structural information to be reported for this important amino acid.

Results and Discussion

Crystal data and details of the intensity measurements and refinement are given in Table 1, positional parameters in Table 2, and selected bond lengths and angles in Table 3. In the complex $[CuL_2(ClO_4)_2]$ the copper atom lies at a centre of symmetry with one L- and one D-amino acid in a *trans* CuN_2O_2 square-planar arrangement, Figure. The Cu–N (1.976 Å) and Cu–O (1.942 Å) distances are similar to those in other amino acid complexes.[8] The axial contacts are provided by oxygens from perchlorate anions at 2.54 Å. Since the copper atom lies at a centre of symmetry it is exactly in the N_2O_2 square plane.

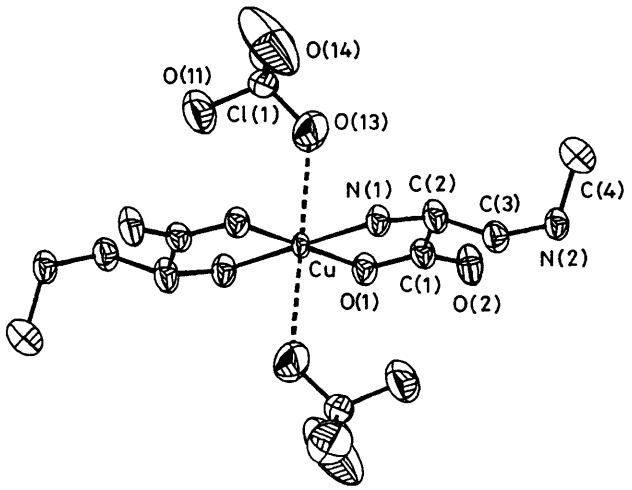


Figure. View of the copper complex

The structure resembles that of the related complexes of lysine precipitated either as the $[Hg_2I_6]^{2-}$ [9,10] or chloride salts,[11] in both of which the Cu–N and Cu–O bond distances are remarkably similar. However, there are some subtle differences; for example, in the chloro-complex of L-lysine and copper(II) the metal ion is 0.128 Å above the least-squares plane of the chelate rings.[11] In the present complex the amino acid side chain is located away from the metal with a hydrogen-bonding contact from a proton on the secondary nitrogen atom to the carbonyl oxygen of a neighbouring molecule [H(O2)···O(2′) 1.86 Å].

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1990, Issue 1, pp. xix—xxii.

Table 1. Crystallographic data for $[Cu(DL\text{-}L)_2(ClO_4)_2]$

Formula	$C_8H_{20}Cl_2CuN_4O_{12}$	M	498.73
Crystal system	Monoclinic	Space group	$P2_1/a$
a/Å	9.893(1)		
b/Å	11.192(5)	β/°	101.62(1)
c/Å	8.367(1)		
U/Å^3	907.43	$F(000)$	510
Z	2	D_c/g cm^{-3}	1.825
μ(Mo-K_α)/cm^{-1}	15.67	λ(Mo-K_α)/Å	0.710 69
T/K	219		
$\theta_{min.,max.}$/°	1.5, 30.0	hkl	0—13, 0—15, −11 to 11
Data measured	2 639	Data observed	2 137*
Absorption correction	ψ scans	Transmission	1.00—0.91
No. parameters	165	Weights	$[\sigma^2(F_o) + 0.000\,23F_o^2]^{-1}$
R	0.048	R'	0.074

* $F_o > 6\sigma(F_o)$.

Table 2. Fractional atomic co-ordinates (×10^4) for $[Cu(DL\text{-}L)_2(ClO_4)_2]$

Atom	x	y	z
Cu	0*	0*	0*
N(1)	1 795(3)	−209(2)	−658(3)
O(1)	−734(2)	−924(2)	−1 945(3)
N(2)	2 606(3)	−1 750(3)	−4 377(3)
O(2)	−177(3)	−1 724(3)	−4 148(3)
C(1)	117(3)	−1 155(3)	−2 845(4)
C(2)	1 555(3)	−618(3)	−2 355(4)
C(3)	2 684(4)	−1 451(3)	−2 618(4)
C(4)	3 018(5)	−796(4)	−5 386(5)
Cl(1)	−507.8(9)	2 991.9(7)	−1 542.4(10)
O(11)	−1 144(4)	3 051(3)	−158(4)
O(12)	−1 360(5)	3 467(4)	−2 964(4)
O(13)	−231(6)	1 810(3)	−1 879(5)
O(14)	679(5)	3 648(6)	−1 193(5)

* Invariant parameter.

Table 3. Selected bond distances (Å) and angles (°) for $[Cu(DL\text{-}L)_2(ClO_4)_2]$

N(1)–Cu	1.976(5)	O(1)–Cu	1.942(4)
O(13)–Cu	2.547(6)	C(2)–N(1)	1.465(5)
C(1)–O(1)	1.264(5)	C(3)–N(2)	1.495(5)
C(4)–N(2)	1.469(6)	C(1)–O(2)	1.245(5)
C(2)–C(1)	1.523(6)	C(3)–C(2)	1.505(7)
O(11)–Cl(1)	1.427(4)	O(12)–Cl(1)	1.416(4)
O(13)–Cl(1)	1.391(5)	O(14)–Cl(1)	1.365(5)
O(1)–Cu–N(1)	84.8(2)	O(13)–Cu–N(1)	84.0(2)
O(13)–Cu–O(1)	86.2(2)	C(2)–N(1)–Cu	109.2(3)
C(1)–O(1)–Cu	115.2(3)	C(4)–N(2)–C(3)	116.0(4)
O(2)–C(1)–O(1)	124.0(4)	C(2)–C(1)–O(1)	117.2(4)
C(2)–C(1)–O(2)	118.6(4)	C(1)–C(2)–N(1)	110.1(3)
C(3)–C(2)–N(1)	110.9(4)	C(3)–C(2)–C(1)	113.4(4)
C(2)–C(3)–N(2)	113.0(4)	O(12)–Cl(1)–O(11)	112.3(4)
O(13)–Cl(1)–O(11)	110.2(3)	O(13)–Cl(1)–O(12)	107.2(3)
O(14)–Cl(1)–O(11)	107.6(4)	O(14)–Cl(1)–O(12)	108.6(4)
O(14)–Cl(1)–O(13)	111.0(5)	Cl(1)–O(13)–Cu	128.9(3)

Although we have suggested[6] that N_4 co-ordination of this amino acid may be important in solution, this structure shows the 'normal' N_2O_2 arrangement at the copper(II) centre. It is interesting to compare the properties of the present complex (**1**) with a complex (**2**) of the same empirical formula obtained by rapid precipitation from solution of DL-L and copper(II) with an excess of perchlorate.[6] There are small but significant differences between the i.r. spectra of these compounds. In particular the strong perchlorate stretch at *ca.* 1 100 cm^{-1} is not split in the case of (**1**) and there are more bands in the fingerprint region between 700 and 500 cm^{-1} than for (**2**). These differences suggest that the DL-L–Cu^{II} system is polymorphic, and also that various distinct solid phases may be obtained, depending upon the precise reaction conditions. This feature is not surprising in view of the complicated equilibria present in solutions of L-L and copper(II).[6] These results further emphasize that L has a rich and diverse co-ordination chemistry, which may be of direct relevance to a proper understanding of the toxicology of this natural product.

Experimental

Materials and Methods.—The compound DL-L was synthesized as reported previously,[12] all other reagents were used as supplied by B.D.H. Infra-red spectra were recorded as Nujol mulls between KBr plates using a Mattson Polaris FTIR spectrometer.

Preparation of the Complex.—The complex $[Cu(DL\text{-}L)(phen)][ClO_4]_2\cdot 3H_2O$ was prepared from the stoicheiometric reaction of DL-L, 1,10-phenanthroline (phen), and copper acetate monohydrate by the addition of a large excess of sodium perchlorate.[6] This compound (200 mg) was dissolved in water–methanol (50:50, *ca.* 40 cm^3), the solvent was allowed to evaporate slowly, and methanol was added to keep the quantity of solvent close to 5 cm^3. After several days, compound (**1**) had precipitated as well-formed rhombic crystals. These were easily separated from other complexes by hand.

Crystallography.—All measurements were made on a sample mounted in a glass capillary using a CAD4 diffractometer operating in the ω—2θ scan mode with graphite-monochromated Mo-K_α radiation as described previously.[13] The structure was solved *via* standard heavy-atom procedures and refined using full-matrix least-squares methods[14] with scattering factors calculated using data from ref. 15. All non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were identified in difference maps and included with isotropic thermal parameters.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom co-ordinates, thermal parameters, and remaining bond lengths and angles.

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