The Effect of N[2]-Mono- and Dimethylation on the Crystal Structures of Bis[(S)-phenylalaninamidato]copper(II) Complexes

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Abstract: (S)-phenylalaninamide, N[2]-methyl-(S)-phenylalaninamide, and N[2],N[2]-dimethyl-(S)-phenylalaninamide co-ordinate to copper(II) as amidates, giving rise to trans bis(phenylalaninamidato) copper(II) complexes CuL_2H_{-2} respectively (1), (2), and (3). Their crystal structures were determined by X-ray crystallography. The striking feature is that in bis[N[2]-methyl-(S)-phenylalaninamidato]copper(II) complex (2), both methyl groups are on the axial positions and on the same side of the co-ordination plane. The knowledge of the crystal structures of complexes (1), (2), and (3) which are used successfully as chiral selectors in HPLC (reversed phase), provides very useful information on the stereochemical features of enantioselective species.

Copper(II) complexes of (S)-amino acid amides when used as additives to the mobile phase in HPLC (reversed phase) proved to be highly enantioselective for Dansyl-amino acids[1,2] and unmodified amino acids[3]. The mechanism of chiral discrimination is generally assumed to proceed *via* ligand exchange[4] between the initial Cu(II) complex and the enantiomers, leading to formation of diastereomeric ternary complexes of different stabilities and affinities for the column.

With the aim of investigating which factors mostly affect enantioselectivity, we first studied the complexation equilibria of Cu(II) with (S)-phenylalaninamide (Phe-NH2) , N[2]-methyl-(S)-phenylalaninamide (Me-Phe-NH2), N[2],N[2]-dimethyl-(S)-phenyl-alaninamide (Me2-Phe-NH2) and other amides in aqueous solution by potentiometry[5]. In this way we could detect the species potentially involved in the discrimination process and evaluate their formation constants. Several species are present in the pH range considered; however, CuL_2H_{-2}, which is present from pH 6.5 and reaches its maximum (100%) at pH 9, is the most relevant to the process. Thus, the knowledge of the crystal structure of these species can provide very useful informations about the stereochemical features of the chiral selectors.

Herein we report the preparation and the crystal structure determination by X-rays of the Cu(II) complex of unsubstituted (**1**), monomethylated (**2**), and dimethylated (S)-phenylalaninamide (**3**).

(**1**): R = R' = H

(**2**): R = CH$_3$; R' = H

(**3**): R = R' = CH$_3$
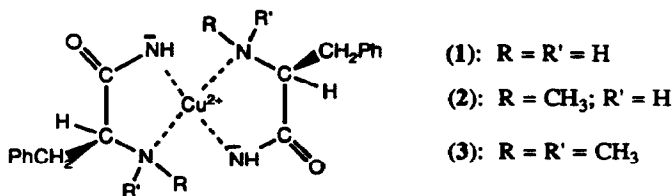
Since in the crystal structure of bis[(S)-phenylalaninamidato]Cu(II) (**1**) previously reported[6], one of the phenyl rings is approximately parallel to the basal plane of the metal co-ordination, it is very interesting to see how methylation of the amino group affects the stereochemistry of the complex and in particular the positioning of the amino acid side chain. Moreover, since during the complexation of Me-Phe-NH$_2$ to copper a new chiral center is being formed, it is very interesting to know its configuration.

Experimental

Syntheses -. The ligand (S)-phenylalaninamide hydrochloride was obtained from Sigma Chemical Co., while N^2-methyl-(S)-phenylalaninamide and N^2,N^2-dimethyl-(S)-phenylalaninamide hydrochlorides were prepared as described previously[5].

Bis[(S)-phenylalaninamidato]copper(II), [Cu(Phe-NH)$_2$] (**1**). 1M NaOH was added to an aqueous solution of (S)-phenylalaninamide hydrochloride (1.00 g, 5 mmol) and Cu(OAc)$_2$·H$_2$O (1.00 g, 5 mmol) to pH 11.6. After standing 24 h at room temperature deep violet crystals were obtained (m.p. 215-218 °C, decomp; Found : C, 55.6; H, 5.5 ; N, 14.5 %. Calc. for C$_{18}$H$_{22}$CuN$_4$O$_2$: C, 55.4 ; H, 5.7 ; N, 14.4 %)

Bis[N^2-methyl-(S)-phenylalaninamidato]copper(II) monohydrate, [Cu(Me-Phe-NH)$_2$]·H$_2$O (**2**). Freshly precipitated Cu(OH)$_2$, obtained from an aqueous solution of CuSO$_4$·5H$_2$O (62.42 mg,0.25mmol) brought to pH ~ 10, was added to dry Me-Phe-NH$_2$ obtained from the corresponding hydrochloride (107 mg, 0.5 mmol) by addition of 1M NaOH to pH ~ 10, extraction with chloroform and evaporation to dryness. The solid mixture was dissolved in absolute ethanol and dried. The violet powder obtained was filtered and then redissolved in (RS) methanol and allowed to evaporate very slowly in a capped flask (m.p. 156-158 °C decomp.; Found : C, 55.5 ; H, 6.9 ; N, 12.6 %. Calc. for C$_{20}$H$_{28}$CuN$_4$O$_3$: C, 55.1 ; H, 6.4 ; N, 12.9 %).

Aquabis[N^2,N^2-dimethyl-(S)-phenylalaninamidato]copper(II), [Cu(Me$_2$-Phe-NH)$_2$(OH$_2$)] (**3**). The same procedure used for (**2**) was followed; (RS)-ethanol was utilized for recrystallization (m.p. 166-168°C; Found : C, 56.8 ; H, 7.2 ; N, 12.3 %. Calc. for C$_{22}$H$_{32}$CuN$_4$O$_3$: C, 57.0 ; H, 6.9 ; N, 12.1 %)

Structure Determination .- The ω–2θ scan mode of the Siemens AED single crystal computer controlled diffractometer was used for the recording of intensity data of all compounds. The intensity of a standard reflection was monitored after every 50 measurements and showed good stability of the crystal and the electronics. No correction for absorption was supplied. Details of data collection and processing are given in Table 1. Systematic absences (from survey of the complete data sets) allow the space groups to be determined uniquely. All data were corrected for Lorentz and polarization effects.

Table 1. Experimental data for the crystallographic analyses

Compound	[Cu(Phe-NH)$_2$] (1)	[Cu(Me-Phe-NH)$_2$]·H$_2$O (2)	[Cu(Me$_2$-Phe-NH)$_2$(OH$_2$)] (3)
Formula	C$_{18}$H$_{22}$CuN$_4$O$_2$	C$_{20}$H$_{28}$CuN$_4$O$_3$	C$_{22}$H$_{32}$CuN$_4$O$_3$
M	389.9	436.0	464.1
Space group	$P2_1$	$P3_2$	$P1$
a/Å	15.963(2)	12.735(2)	15.675(2)
b/Å	9.000(2)	12.735(2)	6.182(1)
c/Å	6.041(2)	11.590(2)	6.162(1)
α/°	90.0	90.0	77.71(1)
β/°	91.09(3)	90.0	83.77(2)
γ/°	90.0	120.0	78.93(1)
V/Å^3	867.4(4)	1627.7(5)	571.2(2)
Z	2	3	1
D_m/Mg m^{-3}	1.48	1.35	1.36
Dc/Mg m^{-3}	1.49	1.33	1.35
F (000)	406	687	245
Crystal size/mm	0.42x0.14x0.07	0.26x0.23x0.19	0.39x0.03x0.48
μ/mm^{-1}	18.9	16.0	15.5
θ - range/°	2.5 - 70	3.0 - 70	2.5 - 70
h range	-19 , 19	-15 , 7	-18 , 18
k range	0 , 10	0 , 15	-7 , 7
l range	0 , 7	0 , 14	0 , 7
Standard reflection	4 1 1	2 8 5	7 2 2
No. of measured reflections	1924	3395	2187
N. of unique reflections	1565	1964	2050
Conditions for obs.reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
No. of refined parametres	226	253	266
R	0.041	0.047	0.054
R_w **	0.054	0.053	0.056
Max.,min. height in final ΔF map,eÅ^{-3}	0.19,- 0.19	0.20, - 0.17	0.14, - 0.26

*Data common to three compounds:Cu-Kα radiation (λ=1.54178 Å); Siemens-AED diffractometer;
T=293±1K

**In all compounds unit weights are used.

The structures were solved by the heavy atom method for compound (1) and by direct methods (SHELX-86[7]) for (2) and (3) and refined by full matrix least-squares cycles using SHELX-76[8] system of computer programs. All hydrogen atoms were located on a difference map for the three compounds, but were not refined, except twelve of them in (1). In (3) the oxygen atom of water has very large thermal motion, so precluding the localization of the hydrogen atoms. The final atomic fractional co-ordinates are given in Tables 2, 3 and 4 for (1), (2) and (3) respectively. Atomic scattering factors were taken from ref. 9 .

All calculations were performed on the Gould-6040 Powernode computer of the Centro di Studio per la Strutturistica Diffrattometrica del C.N.R. (Parma), using the PARST[10] program for the geometrical description of the structures and ORTEP[11] and PLUTO[12] for the structure drawings.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom co-ordinates and thermal parameters.

Table 2. Fractional atomic co-ordinates ($\times 10^4$) for non-hydrogen atoms for (1).

Atom	X/a	Y/b	Z/c
Cu	1047(0)	2500(0)	2781(1)
N(1)	1324(3)	3240(5)	-116(6)
N(2)	1984(3)	3848(5)	3721(7)
N(3)	805(2)	1609(4)	5628(6)
N(4)	191(3)	1016(5)	1698(6)
O(1)	1857(2)	5215(5)	-1886(6)
O(2)	166(3)	-359(5)	7243(6)
C(1)	1740(3)	4458(6)	-202(8)
C(2)	2072(3)	5032(6)	2047(8)
C(3)	2936(3)	5703(7)	1934(10)
C(4)	3636(3)	4632(7)	1550(10)
C(5)	3750(4)	3956(9)	-495(11)
C(6)	4396(5)	2985(10)	-827(15)

Table 3 . Fractional atomic co-ordinates ($\times 10^4$) for non-hydrogen atoms for (2).

Atom	X/a	Y/b	Z/c
Cu	-3335(1)	-1399(1)	0
N(1)	-1656(5)	-320(6)	-16(5)
N(2)	-3178(5)	-617(5)	1613(5)
N(3)	-5057(5)	-2551(7)	3(5)
N(4)	-3478(5)	-1777(5)	-1716(5)
O(1)	32(4)	952(4)	1072(4)
O(2)	-6606(4)	-3884(5)	-1150(4)
O(3)	-7861(6)	-2875(6)	-12(5)
C(1)	-1086(6)	238(6)	950(6)
C(2)	-1931(6)	-98(6)	1989(6)
C(3)	-1790(7)	-1008(7)	2784(6)
C(4)	-2004(8)	-2160(8)	2215(6)
C(5)	-1019(9)	-2265(9)	1899(8)
C(6)	-1209(14)	-3355(14)	1352(10)

C(7)	-2324(17)	-4256(12)	1123(11)
C(8)	-3317(13)	-4156(9)	1445(11)
C(9)	-3148(9)	-3092(8)	1986(9)
C(10)	-5509(6)	-3154(7)	-957(7)
C(11)	-4569(7)	-2952(7)	-1888(6)
C(12)	-4326(8)	-3997(8)	-1866(7)
C(13)	-3698(7)	-4145(7)	-2915(7)
C(14)	-3358(8)	-5017(9)	-2874(9)
C(15)	-2865(10)	-5278(12)	-3837(12)
C(16)	-2691(10)	-4638(13)	-4823(12)
C(17)	-3011(14)	-3754(12)	-4887(10)
C(18)	-3537(11)	-3534(10)	-3924(9)
C(19)	-3537(8)	305(8)	1423(9)
C(20)	-3506(8)	-795(8)	-2318(8)

Table 4. Fractional atomic coordinates (x10^4) for non hydrogen atoms for (3).

Atom	X/a	Y/b	Z/c
Cu	0	0	0
O(1)	1244(4)	-4366(9)	4920(9)
O(2)	-1250(3)	5679(9)	-3524(10)
O(3)	-8(7)	-2387(18)	-2361(18)
N(1)	208(5)	-2397(13)	2543(16)
N(2)	1327(4)	-73(9)	70(10)
N(3)	-1339(4)	864(10)	775(10)
N(4)	-201(5)	2674(15)	-2235(14)
C(1)	1007(6)	-3128(13)	3118(16)
C(2)	1692(6)	-2409(14)	1341(16)
C(3)	1369(6)	1680(12)	1378(16)
C(4)	1799(6)	385(17)	-2149(16)
C(5)	2592(5)	-2626(13)	2180(14)
C(6)	3186(5)	-4842(13)	1934(14)
C(7)	3595(7)	-5134(21)	-130(16)
C(8)	4132(8)	-7188(28)	-341(23)
C(9)	4247(8)	-8852(23)	1417(32)
C(10)	3860(7)	-8638(17)	3464(25)
C(11)	3309(6)	-6617(15)	3706(17)
C(12)	-1699(6)	2312(16)	-1277(14)
C(13)	-1014(6)	3715(15)	-2482(14)
C(14)	-1389(6)	2160(16)	2574(12)
C(15)	-1798(6)	-1108(16)	1478(17)
C(16)	-2607(4)	3744(13)	-948(12)
C(17)	-3171(5)	4021(13)	-2879(13)
C(18)	-3542(5)	2228(14)	-3155(15)
C(19)	-4080(6)	2504(18)	-4899(18)
C(20)	-4246(6)	4462(20)	-6325(16)
C(21)	-3864(6)	6256(17)	-6139(16)
C(22)	-3326(6)	6027(15)	-4404(15)

Results and Discussion

The syntheses of the ligands were achieved as previously described.While the complex [Cu(Phe-NH)$_2$] (1) was easily obtained as deep violet crystals directly from an aqueous solution of the ligand and copper acetate at basic pH, crystals of the other two complexes [Cu(Me-Phe-NH)$_2$]·H$_2$O (2) and [Cu(Me$_2$-Phe-NH)$_2$(OH$_2$)] (3) were difficult to obtain. Both ligands had to be converted into their basic forms and treated with freshly prepared copper hydroxyde. Purple reddish crystals of complex (2) were obtained from methanol, light blue crystals of complex (3) were obtained from ethanol.

X-Ray Crystallography and Description of Structures .- Bond distances and angles for compounds (1), (2) and (3) are reported in Tables 5, 6 and 7 respectively.

[Cu(Phe-NH)$_2$] (1). The crystal structure of this complex has been previously reported.[6] Copper co-ordination is square planar tetrahedrally distorted, completed to give a very elongated pyramid by a long interaction   [2.732(5) Å] between copper and the O(2) carbonyl atom of an adjacent molecule. The benzyl groups are on the same side with respect to the co-ordination plane and one of them is approximately parallel to it (Figure 1)(in fact two of its carbon atoms are closer than the others to copper: Cu...C(14) = 3.173(7) and Cu...C(13) = 3.314(5) Å). The dihedral angles between the co-ordination plane and the phenyl groups are 25.0(2) and 95.7(2)° respectively.

Table 5. Selected bond distances (Å) and angles (°) for (1)

Co-ordination polyhedron

Cu-N(1)	1.932(4)	Cu-N(3)	1.943(4)
Cu-N(2)	2.000(5)	Cu-N(4)	2.011(5)
Cu...O(2^i)	2.732(5)	Cu...C(14)	3.173(7)
		Cu...C(13)	3.314(5)
N(3)-Cu-N(4)	82.4(2)	N(1)-Cu-N(2)	82.2(2)
N(2)-Cu-N(3)	99.2(2)	N(1)-Cu-N(4)	95.7(2)
N(2)-Cu-N(4)	174.3(2)	N(1)-Cu-N(3)	175.6(2)

i = - x, 1/2- y, 1- z

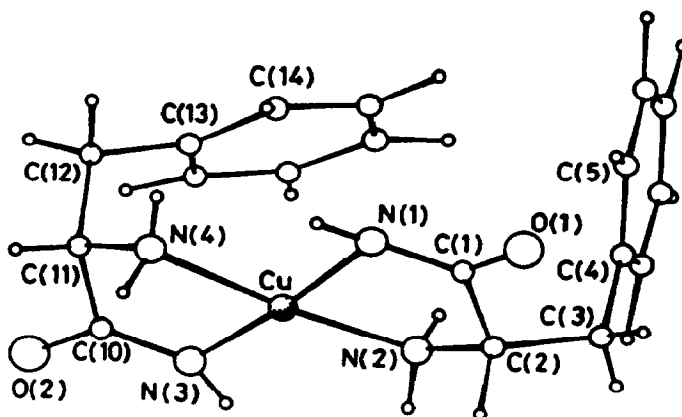| Molecule 1		Molecule 2	
O(1)-C(1)	1.241(6)	O(2)-C(10)	1.255(6)
N(1)-C(1)	1.283(7)	N(3)-C(10)	1.282(6)
N(2)-C(2)	1.478(7)	N(4)-C(11)	1.483(7)
C(1)-C(2)	1.538(7)	C(10)-C(11)	1.521(7)
C(2)-C(3)	1.508(7)	C(11)-C(12)	1.546(8)
C(3)-C(4)	1.497(8)	C(12)-C(13)	1.505(8)
Cu-N(1)-C(1)	117.3(3)	Cu-N(3)-C(10)	117.0(3)
Cu-N(2)-C(2)	108.9(3)	Cu-N(4)-C(11)	107.6(3)

Figure 1. X-Ray molecular structure of [Cu(Phe-NH)₂] (1).

[Cu(Me-Phe-NH)₂]·H₂O (2). The structure consists of discrete molecular units (Figure 2). The Cu(II) ion has an approximate square planar environment involving the four nitrogen atoms from two Me-phenylalaninamidato molecules which are *trans* to each other as found in (1). The Cu atom deviates by 0.1349(11) Å towards C(9) from the mean plane containing the co-ordinated atoms, while in (1) Cu is only 0.0804(4) Å out of the similar co-ordination plane towards O(2). The N(1)-Cu-N(3) angle of 178.2(3)° is greater than N(2)-Cu-N(4) of 165.5(2)° owing to the steric hindrance of the methyl groups on the amino nitrogen atoms N(2) and N(4). The corresponding angles in the unmethylated [Cu(Phe-NH)₂] are 175.6(2) and 174.3(2)° respectively, since the system may achieve a better planarity. Also in (2) the benzyl groups are on the same side of the co-ordination plane as it has been found so far only in [Cu(N-Bz-L-Pro)₂][13] and in (1). One of the phenyl rings is bent towards the co-ordination plane (Figure 2) but the interaction with the metal is weaker than that found in (1). In this case only one carbon atom is close to copper [Cu...C(9) = 3.24(1) Å].

[Cu(Me₂-Phe-NH)₂(OH₂)] (3). As shown in Figure 3 the copper atom has an approximate square pyramidal environment . The four nitrogen atoms form a square base with tetrahedral distortion, while the apical position is occupied by the water oxygen atom O(3). The Cu-O(3) line forms an angle of 0.7(3)° with the normal to the co-ordination plane . The copper ion is displaced of 0.3172(4) Å from the base plane towards the pyramid top. The N(1)CuN(4) and N(2)CuN(3) angles are respectively 171.7(4)° and 158.3(2)°. Contrary to what had been observed in (1) and (2) and in bis(L-tyrosinato)copper(II) complex [14], in complex (3) the benzyl groups stretch out and away from the co-ordination sphere and do not interact with the copper atom. The two methyl groups on the amino nitrogen atoms probably enforce the different orientation of the benzyl moieties, which are, however, on the same side of the co-ordination plane. In contrast, in bis(L-phenylalaninato)copper(II)[15] the benzyl groups are on the opposite sides.
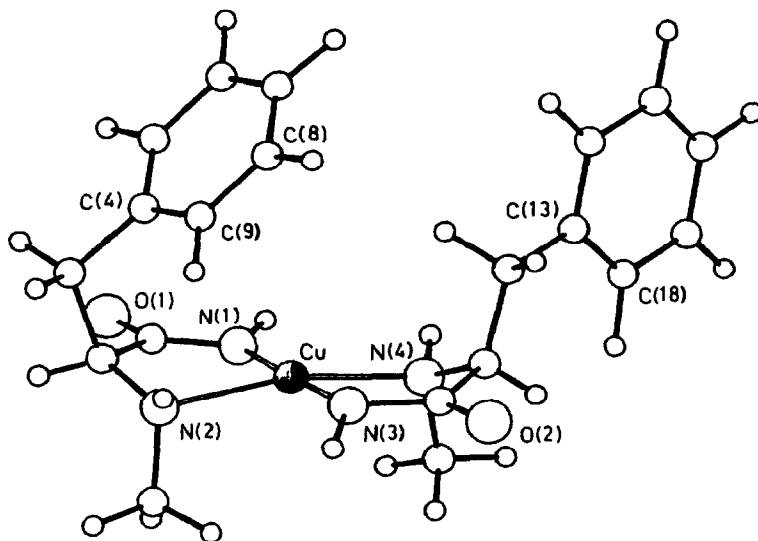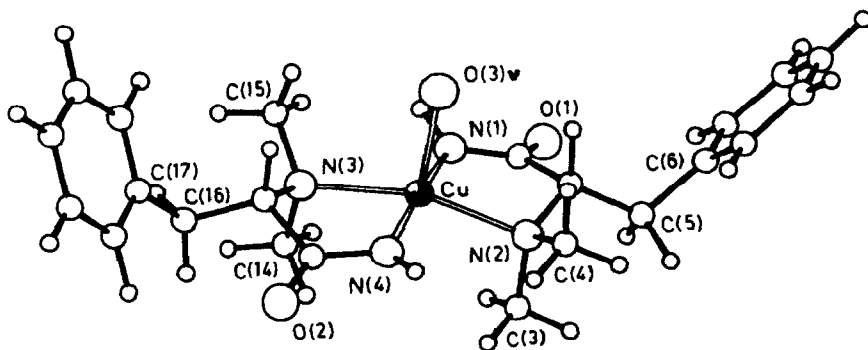
Figure 2. X-Ray molecular structure of [Cu(Me-Phe-NH)$_2$].H$_2$O (2).

Figure 3. X-Ray molecular structure of [Cu(Me$_2$-Phe-NH)$_2$(OH$_2$)] (3).

Table 6. Selected bond distances (Å) and angles (°) for (2)

Co-ordination polyhedron

Cu- N(1)	1.877(5)	Cu- N(3)	1.934(5)
Cu- N(2)	2.080(6)	Cu- N(4)	2.033(6)
Cu...C(9)	3.244(11)		

N(1) -Cu -N(2)	81.8(2)	N(2) -Cu -N(3)	99.3(3)
N(3) -Cu -N(4)	83.6(3)	N(1) -Cu -N(4)	95.6(2)
N(1) -Cu -N(3)	178.2(3)	N(2) -Cu -N(4)	165.5(2)

Molecule 1		Molecule 2	
O(1)- C(1)	1.256 (8)	O(2)- C(10)	1.252 (8)
N(1)- C(1)	1.330 (9)	N(3)- C(10)	1.311(10)
N(2)- C(2)	1.450 (9)	N(4)- C(11)	1.459 (8)
N(2)- C(19)	1.474(15)	N(4)- C(20)	1.448(13)
C(1)- C(2)	1.527(10)	C(10) - C(11)	1.535(11)
C(2)- C(3)	1.559(13)	C(11) - C(12)	1.509(15)
C(3)- C(4)	1.505(13)	C(12) - C(13)	1.519(13)

Cu -N(1) -C(1)	120.1(5)	Cu -N(3) -C(10)	116.3(6)
Cu -N(2) -C(19)	104.7(5)	Cu -N(4) -C(20)	107.8(5)
Cu -N(2) -C(2)	108.0(5)	Cu -N(4) -C(11)	107.6(4)
C(2) -N(2) -C(19)	112.8(6)	C(11) -N(4) -C(20)	113.4(7)

Table 7. Bond distances (Å) and angles (°) for (3)

Co-ordination polyhedron

Cu- N(1)	1.922 (8)	Cu- N(3)	1.912 (8)
Cu- N(2)	2.077 (6)	Cu- N(4)	2.092 (6)
Cu- O(3)	2.284(12)		

N(3) - Cu - N(4)	82.8(3)	N(2) - Cu - N(4)	96.0(3)
N(2) - Cu - N(3)	158.4(2)	N(1) - Cu - N(4)	171.5(4)
N(1) - Cu - N(3)	95.8(3)	N(1) - Cu - N(2)	82.2(3)
O(3) - Cu - N(4)	94.9(4)	O(3) - Cu - N(3)	100.2(3)
O(3) - Cu - N(2)	101.4(3)	O(3) - Cu - N(1)	93.6(4)

Molecule 1		Molecule 2	
O(1)- C(1)	1.256(10)	O(2)- C(13)	1.253(10)
N(1)- C(1)	1.307(12)	N(4)- C(13)	1.321(12)
N(2)- C(2)	1.525 (9)	N(3)- C(12)	1.482 (9)
N(2)- C(3)	1.496(12)	N(3)- C(14)	1.487(11)
N(2)- C(4)	1.481(11)	N(3)- C(15)	1.496(12)
C(1)- C(2)	1.507(12)	C(12)- C(13)	1.539(13)
C(2)- C(5)	1.527(12)	C(12)- C(16)	1.543(11)
C(5)- C(6)	1.527(11)	C(16)- C(17)	1.520(11)

Cu - N(1) - C(1)	118.8	(7)	Cu - N(4) - C(13)	118.0	(7)
Cu - N(2) - C(4)	114.7	(5)	Cu - N(3) - C(15)	114.0	(5)
Cu - N(2) - C(3)	103.8	(5)	Cu - N(3) - C(14)	103.8	(5)
Cu - N(2) - C(2)	105.9	(5)	Cu - N(3) - C(12)	105.8	(6)
C(3) - N(2) - C(4)	111.2	(6)	C(14) - N(3) - C(15)	112.0	(6)
C(2) - N(2) - C(4)	110.4	(6)	C(12) - N(3) - C(15)	109.5	(6)
C(2) - N(2) - C(3)	110.7	(6)	C(12) - N(3) - C(14)	111.3	(6)
O(1) - C(1) - N(1)	127.1	(9)	O(2) - C(13) - N(4)	126.1	(8)

In all three compounds the orientation of the aromatic groups with respect to the co-ordination plane is shown by the following torsion angles: N(2)C(2)C(3)C(4) =55.8(6), 65.6(9)°, N(4)C(11)C(12)C(13) = 68.5(6)° , -73.8(9)° respectively for (1) and (2); N(2)C(2)C(5)C(6) = -139.8(6), N(3)C(12)C(16)C(17) = -144.8(6)° for (3). In (1) the benzyl ring which interacts with the copper atom is assessed in an axial position [CuN(4)C(11)C(12) = -89.2(4)°] and the other in the equatorial one [CuN(2)C(2)C(3) = -154.3(4)°]; in (2) both the benzyl rings are in the axial positions [CuN(2)C(2)C(3) = -95.6(6); CuN(4)C(11)C(12) = -92.6(7)°] whereas in (3) are both in an equatorial arrangement [CuN(2)C(2)C(5) = 162.8(5), CuN(3)C(12)C(16) = -162.2(5)°]. In [Cu(Me-Phe-NH)$_2$]·H$_2$O the methyl groups bonded to N(2) and N(4) amino atoms respectively are in the axial positions [C(19)N(2)C(2)C(1) = -88.6(8); C(20) N(4) C(11) C(10) = -89.7(8)°]. When two methyl groups are present at N(2) and N(3), as in [Cu(Me$_2$-Phe-NH)$_2$(OH$_2$)], the former is axial and the latter equatorial [C(3)N(2)C(2)C(1) = 75.8(7); C(4)N(2)C(2)C(1) = -159.2(6)°; C(14)N(3)C(12)C(13) = 77.7(7), C(15)N(3)C(12)C(13) = -157.0(6)°].

The absolute configuration of the structures were established in the early stages of the refinement by assigning the (S) configuration to the phenylalaninamide ligand. In (2) a new chiral center is formed on the amino nitrogen : the absolute configuration of the N(2) and N(4) atoms is (R).

The Cu-N bond lengths in all complexes range from 2.000 to 2.092 Å for the amino nitrogen, the longest distance being observed between copper and the dimethylated amino groups and from 1.877 to 1.943 Å for the anionic amidates (Tables 5, 6 and 7)[16]. In general, the dimensions of the two phenylalaninamide moieties are very similar and fall in the usual range of values reported for other amino acid derivatives.

The five membered chelate ring on the side of the benzyl group which interacts with the copper atom is in an envelope conformation both in (1) and in (2), while the one on the other side is twist in (1) and shows an intermediate stereochemistry between an envelope and a twist conformation (or better a twist-envelope (C$_2$) conformation)[17] in (2). In (3) both chelating rings are in the twist conformation (Table 8).

Table 8. Puckering parameters (q$_2$ in Å and φ in °) for (1), (2) and (3).

Compound	CuN(2)C(2)C(1)N(1)		CuN(4)C(11)C(10)N(3)		CuN(4)C(13)C(12)N(3)	
	q2	φ2	q2	φ2	q2	φ2
(1)	0.314(4)	-20.8(8)	0.325(4)	36.2(7)	---------	--------
(2)	0.281(6)	34(1)	0.292(7)	44(1)	---------	--------
(3)	0.349(7)	-55(1)	---------	-------	0.342(6)	-52(1)

In (1) the packing is determined by the long interactions between copper and the O(2) carbonyl atom of an adjacent molecule and, therefore, infinite chains are formed around the two-fold screw axes[6]. In (2) a crystallization water molecule O(3) is present and affects the packing, that is different around the three-fold screw axes along the z direction. The complexes are linked by O(3)-H···O(2) hydrogen bonds

in the chains around the threefold screw axes at x=1/3 and y=2/3 and by two hydrogen bonds N-H···O(1) around the screw axes at x=0, y= 0, while only van der Waals interactions between the phenyl rings are present around the screw axes at x=2/3, y=1/3 (Figure 4). In (3) the packing is determined by possible hydrogen bonds involving the water molecule in the apical position and the carbonylic oxygen atoms [O(3)···O(2) (x, y-1, z) = 2.70(1) and O(3)···O(1) (x, y, z-1) = 2.72(2) Å] and by weak N(1)-H···O(2)(x, y-1, z+1), N(4)-H···O(1)(x, y+1, z-1) interactions of 3.34(1), 3.31(1) Å respectively. Therefore, infinite layers of complexed molecules parallel to the (1 0 0) planes are formed. These layers are linked by van der Waals interactions between the phenyl rings (Figure 5 and Table 9).
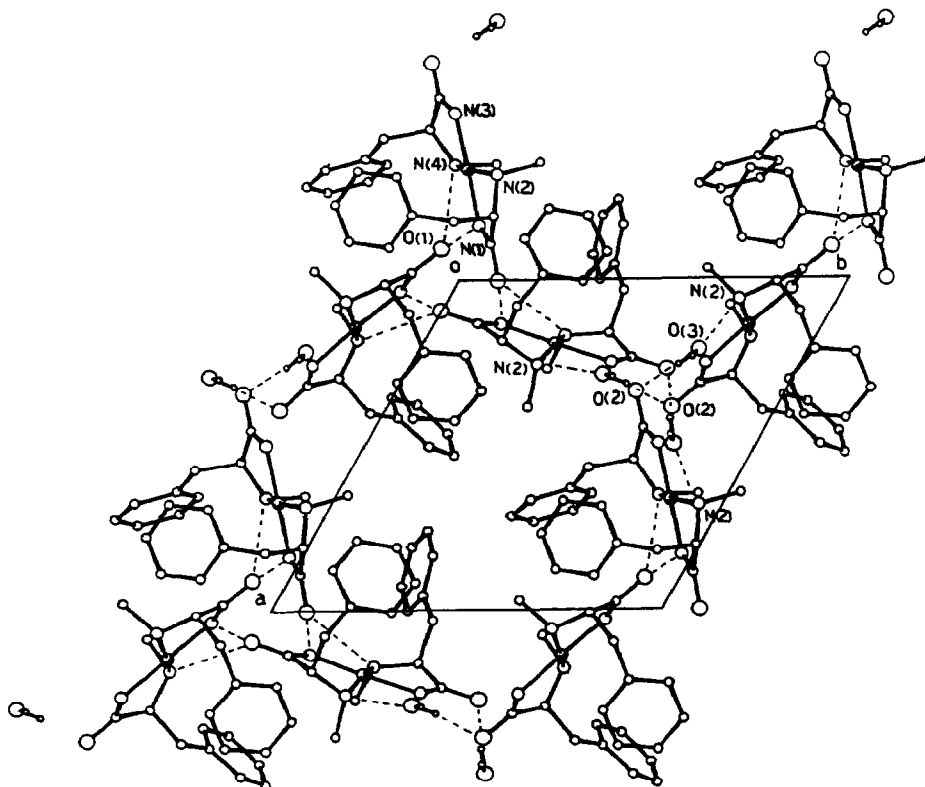

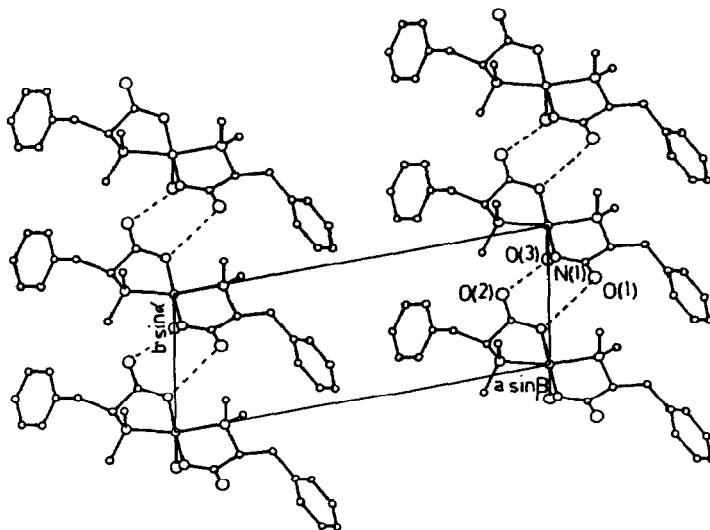Figure 4. Projection of the structure of (2) on the (0 0 1) plane

Figure 5. Projection of the structure of (3) on the (0 0 1) plane.

Table 9. Relevant hydrogen bonds.

Compound (2)

Bond	Distance/Å	Angle/°
D-H⋯A	D ⋯ A	D-H⋯A
O(3)-H(1O)⋯O(2)	2.83(1)	159.7(4)
O(3)-H(2O)⋯O(2^I)	2.82(1)	171.1(6)
N(1)-H(1N)⋯O(1^{II})	2.97(1)	134.7(4)
N(4)-H(4N)⋯O(1^{II})	2.90(1)	152.9(3)
N(2)-H(2N)...O(3^I)	2.94(1)	152.9(3)

Symmetry Operations

I $-x +y$-1, $-x$ -1, z +1/3   II $-y, x-y, z$ -1/3

Compound (3)

Bond	Distance/Å	Angle/°
D-H⋯A	D ⋯ A	D-H⋯A
O(3)⋯O(1^I)	2.72(1)	-
O(3)⋯O(2^{II})	2.70(1)	-
N(4)-H(4)⋯O(1^{III})	3.30(1)	153.6(6)
N(1)-H(1)⋯O(2^{IV})	3.34(1)	148.4(5)

Symmetry Operations

I x, y, z -1   II x, y -1, z III x, y +1, z -1   IV x, y -1, z +1

Crystallographic data may be well correlated to those obtained in solution[5] : (1) is more stable than (2) (log β 1-5.45; log β_2 -6.10) whereas (3) is so unstable that it does not prevent copper(II) hydrolysis in alkali aqueous solution. Absorption maxima at 520 nm for (1), 504 for (2) and 518 for (3) are consistent with a coplanar CuN_4 chromophore; the strongest ligand field is experienced by (2), which shows the shortest amidato to copper bond Cu-N(1). Instead, the binding of the anchoring group does not seem to depend upon basicity, but rather on steric hindrance due to methylation. This holds true also in the solid state , where the longest distances between copper and the amino nitrogen are observed in the order Phe-NH$_2$< Me-Phe-NH$_2$<Me$_2$PheNH$_2$. The equilibrium constants observed in solution for the reaction :

$$CuL_2^{2+} = CuL_2H_{-1}^+ + H^+$$

were higher for the phenylalanine containing ligands than for the other amides [5].This was attributed to the possibility of apical interaction between copper(II) and one of the two phenyl rings . Indeed, the crystal structures of (1) and (2) may confirm this hypothesis, since in both complexes a tilting of the phenyl ring towards the metal ion is observed.

Negative CD bands, observed at 555 nm for complex (1), 540 for (2) and 546 for (3), are not consistent with the chelate ring puckering observed in the solid state which is $\delta\lambda$ for (1), $\lambda\lambda$ for (2) and $\delta\lambda$ for (3), but rather with the position of the benzyl groups relatively to the Cu^{2+} chromophore.

Another band at shorter wavelengths appears for the complexes of amides containing N-substituted amino nitrogen (Pro-NH$_2$ = prolinamide and Me-Phe-NH$_2$) which can be correlated to the formation of a new chiral centre directly bound to the copper (II) chromophore. The configuration of the centre is (R) for Me-Phe-NH$_2$, whereas it is (S) for Pro-NH$_2$ (as deduced from its crystal structure)[18]
In the crystal structure of the former both methyl groups are placed in an axial position on the same side of the co-ordination plane and opposite to the benzyl moieties. Correspondingly, a positive CD band is observed for (2) at 453 nm and a negative one for [Cu(ProNH)$_2$] at 465 nm.

Finally, the knowledge of the crystal structures of (1), (2), and (3) sheds some light on the enantioselectivity displayed by these copper complexes in HPLC. First of all, the affinities of complex (1) and specially (2) for the C$_{18}$-column might well be accounted for by the lipophilic interaction of the phenylalanine side chains, which are always on the same side of the copper co-ordination plane. Moreover, the different elution order observed for D- and L-Dns-amino acids with (1) (D < L for polar and D > L for apolar amino acids)[2] and (2) (always D < L)[19] may be explained by the presence of the N^2-methyl group on the axial position, which could prevent the same co-ordination mode in the diastereomeric complexes responsible for chiral discrimination.

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