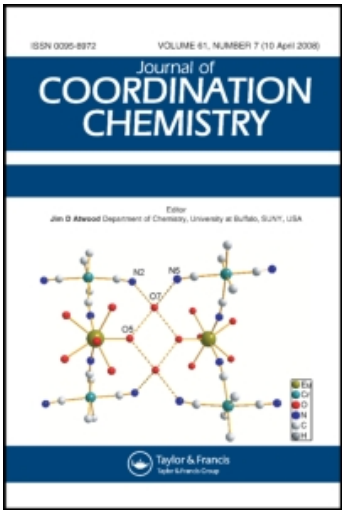

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Copper(II) Complexes with Chiral Diaminodiamido Ligands: Solution and Structural Studies

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COPPER(II) COMPLEXES WITH CHIRAL DIAMINODIAMIDO LIGANDS: SOLUTION AND STRUCTURAL STUDIES

FRANCESCO DALLAVALLE[a,*], GIUSEPPINA FOLESANI[a], GIORGIO PELOSI[a], MARISA BELICCHI FERRARI[a], GIANNI GALAVERNA[b], ROBERTO CORRADINI[b] and ROSANGELA MARCHELLI[b]

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Three diaminodiamido ligands (*S,S*)-*N,N'*-bis(prolyl)ethanediamine (ProNN-2), (*S,S*)-*N,N'*-bis(*N*-methylvalyl)ethanediamine (Me_2ValNN-2), and (*S,S*)-*N,N'*-bis(*N*-methylphenylalanyl)-ethanediamine (Me_2PheNN-2) were synthesised and their complex formation equilibria with copper(II) investigated in aqueous solution by potentiometry and, for ProNN-2, by electronic spectrophotometry. ProNN-2 forms the species $[CuLH]^{3+}$, $[Cu_2L_2]^{4+}$, $[Cu_2L_2H_{-2}]^{2+}$ and $[CuLH_{-2}]$, Me_2PheNN-2 forms the complexes $[CuLH]^{3+}$, $[Cu_2L_2H_{-2}]^{2+}$ and $[CuLH_{-2}]$, whereas Me_2ValNN-2 forms the monomer $[CuLH_{-1}]^{+}$ but not the dimer. The dimeric cation $[Cu_2L_2H_{-2}]^{2+}$, of Me_2PheNN-2 has severe steric requirements, as demonstrated by the X-ray crystal structure of the complex $[Cu_2L_2H_{-2}]Cl_2 \cdot 12H_2O$, of the corresponding non-methylated ligand. Since copper(II) complexes of the ligands examined are used as additives to the mobile phase to perform chiral resolution of *D,L*-amino acids in RP-HPLC, the present results provide valuable clues to an understanding of the mechanism of the enantiomeric separation.

Keywords: Diaminodiamido ligands; copper(II) complexes; formation constants; potentiometry; crystal structure; chiral recognition

INTRODUCTION

Earlier papers have reported the solution stabilities[1–4] and the solid state structures[5,6] of copper(II) complexes with chiral aminoamido ligands of

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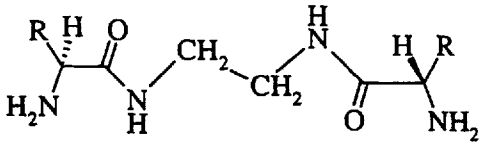
various denticities (bi-, tri-, and tetra-dentate). Some of these complexes were used in our laboratory to perform enantiomeric separation of amino acids and dansyl (Dns)-amino acids in RP-HPLC, when added to the mobile phase,[4,7-9] dynamically adsorbed,[10] or covalently bonded to the stationary phase of the column.[11] Chiral recognition is based in these cases on the formation of diastereomeric complexes between the metal ion, the chiral ligand and the enantiomers, which have different stabilities and/or different affinities for the stationary phase. Formation equilibria of the ternary copper(II) complexes of bidentate[3] and tridentate[4] aminoamido ligands with *D*- or *L*-amino acids allowed us to clarify some aspects of the recognition mechanism in chromatography. Indeed, with bidentate ligands (*L*-amino acid amides), ligand exchange occurs in the chromatographic system,[8,9] involving the displacement of one ligand molecule from an initial binary complex (Cu/L = 1/2) and the coordination of the enantiomer (Ligand Exchange Chromatography, L.E.C.[12]). In contrast, a tridentate diamino-amido ligand, *N*-(*S*)-phenylalanylethanediamine, forms a species $[CuLH_{-1}]^+$ and maintains its coordination sites around the copper(II) ion in the mixed complex, the bidentate enantiomer binding at the remaining equatorial position and eventually at the apical position.[4] In this case chiral discrimination is less efficient than with bidentate ligands. Copper(II) complexes of tetradentate ligands, ((*S*,*S*)-*N*,*N*′-bis(aminoacyl)ethanediamine), effect very good enantiomeric separations of Dns-amino acids.[7] Equilibrium studies[1] of the binary complexes with Cu^{2+} showed both the species $[Cu_2L_2H_{-2}]^{2+}$ and $[CuLH_{-2}]$ as potential selectors, but it is still a matter of discussion whether the enantiomeric separation occurs *via* partial ligand exchange or *via* formation of a supramolecular complex. The crystal structures of the ligand (*S*,*S*)-*N*,*N*′-bis(phenylalanyl)ethanediamine and of its complex $[Cu_2L_2H_{-2}]Cl_2 \cdot 12H_2O$ are reported here.

Within a systematic project aimed at an understanding of the mechanism of chiral recognition, we report the synthesis of three new ligands, (*S*,*S*)-*N*,*N*′-bis(prolyl)ethanediamine (ProNN-2), (*S*,*S*)-*N*,*N*′-bis(*N*-methylvalyl)-ethanediamine (Me_2ValNN-2) and (*S*,*S*)-*N*,*N*′-bis(*N*-methylphenylalanyl)-ethanediamine (Me_2PheNN-2; Scheme 1) and the results of a potentiometric



SCHEME 1

and spectrophotometric investigation of their equilibria with Cu^{2+}. Copper(II) complexes of these ligands have been used for the separation of *D,L*-amino acids using HPLC.[13]

EXPERIMENTAL

Materials and Reagents

L-amino acids were obtained from SIGMA; Pd/C (10%), benzyl chloroformate and sodium hydride were obtained from Fluka Chemika-Biochemika; 1,2-diaminoethane, *N,N'*-dicyclohexylcarbodiimide and methyl iodide were purchased from Acros; *N*-hydroxysuccinimide was supplied by Aldrich; methanol (RCS-grade), ethyl ether (RCS-grade) and chloroform (RCS-grade) were obtained from Carlo Erba; 1,4-dioxane was purchased from Lab-Scan.

Instrumentation

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300 MHz and AMX 400 MHz spectrometers. Infrared spectra were recorded on Perkin Elmer Mod. 298 and Nicolet FT-IR 5PC spectrophotometers. Mass spectra were recorded on an API 150 Perkin Elmer Sciex spectrometer (ESI) or a Finnigan MAT SSQ 710 spectrometer using electron impact (70 eV, EI) or chemical ionization. Optical rotations were measured on an Autopol III Rudolph Research polarimeter, using a 10 cm cell.

Synthesis of the Ligands

(S,S)-N,N'-bis(prolyl)ethanediamine Dihydrochloride (ProNN-2 · 2HCl)

L-Proline (*L*-Pro) was *N*-protected to the *Z* (benzyloxycarbonyl) derivative,[14] esterified to the corresponding hydroxysuccinimidyl ester (OSu) by reaction with *N*-hydroxysuccinimide and *N,N*-dicyclohexylcarbodiimide in dry dioxane and recrystallized (chloroform : petroleum ether), according to the literature method.[15] 1,2-Ethanediamine (15 mmol, 1 cm^3) dissolved in dioxane (10 cm^3) was added dropwise to a solution of *Z*-Pro-OSu (30 mmol, 10.4 g) in dry dioxane (200 cm^3) at 0°C. The mixture was stirred at 0°C for 1 h, then at r.t. for 14 h. Z_2-ProNN-2 was precipitated as a white solid by addition of small amounts of water. It was then deprotected by hydrogenation in MeOH in the presence of Pd/C (10%) (20% w/w to the substrate) as

catalyst at 50°C for 20 h. The catalyst was removed by filtration and, after addition of HCl/MeOH to acid pH, the solvent was evaporated under vacuum. The product was obtained as a white solid by crystallisation from MeOH/Et_2O. Total yield: *ca.* 80%; m.p. 200°C; $[\alpha]_D^{25°C} = -74.0°$ (MeOH, $c = 1$); IR (KBr): ν 3360, 3200–2800, 1665, 1585, 1560, 1430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, free amine): δ 1.54 (m, 4H, CH_2–CH_2–$CH_{2proline}$), 1.69 (m, 2H, CH_2–CH_α), 1.96 (m, 2H, CH_2–CH_α), 2.25 (s, 2H, $NH_{proline}$), 2.81 (m, 4H, CH_2–$N_{proline}$), 3.21 (s, 4H, $CH_{2bridge}$), 3.55 (dd, 2H, CH_α), 7.79 (broad s, 2H, CONH) ppm; ^{13}C NMR (CD_3OD, free amine): δ 25.8, 31.5, 40.0, 40.8, 61.9, 170.4 ppm; MS (ESI) (*m/z*): 256($M + 2H^+$).

(S,S)-N,N'-bis(N-methylphenylalanyl)ethanediamine Dihydrochloride (Me₂PheNN-2 · 2HCl)

Z-Phe was *N*-methylated according to the McDermott and Benoiton procedure.[16] The desired product was prepared following the same procedure as for ProNN-2. Total yield 65%; m.p. 278–280°C; $[\alpha]_D^{25°C} = +91.16$ (EtOH 95%, $c = 1$); IR (KBr): ν 3240, 3200–2400, 1690, 1560, 800–700 cm^{-1}; ^1H NMR ($CDCl_3$, free amine): δ 1.50 (s, broad, 2H, NH_{amine}), 2.26 (s, 6H, N–CH_3), 2.50–2.80 (dd, 2H, CH_β), 3.10–3.25 (m, 4H, $CH_\beta + CH_\alpha$), 3.4 (m, 4H, $CH_{2bridge}$), 7.30 (m, 12H, $H_{arom.} + NH_{amide}$) ppm; ^{13}C NMR ($CDCl_3$, free amine): δ 35.4, 39.1, 39.4, 66.1, 126.8, 129, 137.6, 174.3 ppm; MS (EI) (*m/z*): 291(31), 277(31), 260(24), 249(24), 134(100), 119(16), 91(13), 71(13).

(S,S)-N,N'-bis(N-methylvalyl)ethanediamine Dihydrochloride (Me₂ValNN-2 · 2HCl)

The synthesis was totally analogous to the previous ligand. Total yield 60%; m.p. 295–298°C; $[\alpha]_D^{25°C} = +63.64$ (EtOH 95%, $c = 1$); IR (KBr): ν 3500–3400, 3300–2800, 1680–1670, 1580–1560 cm^{-1}; ^1H NMR ($CDCl_3$, free amine): δ 0.8 (d, 6H, $(CH_3)_2C$), 1.0 (d, 6H, $(CH_3)_2C$), 1.50 (s, broad, 2H, NH_{amine}), 1.9–2.2 (m, 2H, CH_β), 2.4 (s, 6H, NCH_3), 2.8 (d, 2H, CH_α), 3.4–3.5 (m, 4H, $CH_{2bridge}$), 7.6 (s, broad, 2H, NH_{amide}) ppm; ^{13}C NMR ($CDCl_3$, free amine): δ 18.1, 20.2, 32.0, 36.5, 39.5, 71.3, 175.1; MS (EI) (*m/z*): 286(3), 243(6), 201(37), 173(3), 128(6), 86(100), 71(10), 55(10).

Potentiometric Measurements

The ligand hydrochlorides were dried *in vacuo* over P_4O_{10} and stock solutions (*ca.* 0.02 mol dm^{-3}) were prepared by weight and their titre was checked by means of potentiometric titration with KOH. HCl, KOH and $CuCl_2 \cdot 2H_2O$

solutions were prepared and standardised by usual procedures as previously reported.[2–4] Freshly boiled, bi-distilled water was used throughout. The titrations were carried out at $T = 25 \pm 0.1$°C and $I = 0.1$ mol dm^{-3} (KCl) under an N_2 stream, using 50 cm^3 samples. Potentiometric measurements were performed with our automatic apparatus previously described.[2–4] The ORION Ross 8102SC combined electrode was calibrated in terms of $[H^+]$ by titrating HCl solutions (*ca.* 0.01 mol dm^{-3}) in a starting volume of 50 cm^3 with standard KOH solutions (*ca.* 0.2 mol dm^{-3} in 0.1 mol dm^{-3} KCl). The PC program BEATRIX,[17] based on the Gran method, was used to calculate the equivalence volume (V_e), the electrodic chain standard potential ($E°$), and pK_w (13.76(1)). Protonation constants were determined by alkalimetric titration of three samples ($3–5 \times 10^{-3}$ mol dm^{-3}) of each ligand dihydrochloride. For the Cu^{II} complexation equilibria, 5–6 titrations for each system were performed with ligand/metal ratios 1/1 and 2/1 for ProNN-2 ($C_{Cu} = 1.5–3.0 \times 10^{-3}$ mol dm^{-3}) and Me_2PheNN-2 ($C_{Cu} = 1.0–2.0 \times 10^{-3}$ mol dm^{-3}). In the case of Me_2ValNN-2 precipitation of hydrolysis products occurred with 1/1 and 2/1 ratios at pH *ca.* 6.0, so only 3/1 to 5/1 ratios and lower copper concentrations were used ($C_{Cu} = 0.4–1.0 \times 10^{-3}$ mol dm^{-3}). The pH range explored was between 3 and 10.5 in all cases.

Spectrophotometric Measurements

Absorption spectra for the system Cu^{2+}/ProNN-2 were recorded on a UVIKON 941 Plus KONTRON spectrophotometer using matched quartz cells of 1 cm pathlength against a 0.1 mol dm^{-3} KCl solution as reference. The solutions were passed from the potentiometric vessel to the spectrophotometric cell by a peristaltic pump. Fourteen spectra, at appropriate pH, were recorded between 400 and 800 nm at 2 nm intervals. For Me_2ValNN-2 and Me_2PheNN-2 the features ($\lambda_{max}/\varepsilon$) of $[CuLH_{-2}]$ were obtained by recording the spectra at pH > 9 where this species represented 100% of copper(II).

Calculations

Stability constants were calculated using the computer program HYPERQUAD[18] employing the sum of the weighted squares of the residuals between observed and calculated *e.m.f.* values as the optimisation function. The weighting of the experimental observations takes into account the errors of *e.m.f.* and titrant volume, estimated as 0.2 mV and 0.008 cm^3, respectively. For each system, data from different titrations were treated as a unique batch. Spectroscopic data ($A = f(\lambda)$) were processed by the program

SQUAD[19] and molar absorptivities (ε) as a function of λ were calculated for each species by using the formation constants obtained by potentiometry.

X-ray Data Collection and Processing

Crystals of compound (1) were obtained as previously described[1] while those of its copper(II) complex (2) were prepared from a 5×10^{-3} mol dm^{-3} solution of $Cu(NO_3)_2 \cdot 3H_2O$ and PheNN-2 · 2HCl · $2H_2O$ (molar ratio 1 : 1) in a water/acetonitrile mixture 50 : 50 (v/v) after adjusting the pH value to *ca.* 7 with KOH.

The crystal and instrumental parameters used in data collection are summarised in Table I. All cell parameters were calculated by least-squares refinements on diffractometer angles for 30 automatically centred reflections ($\theta > 13°$). Diffraction data for ligand (1) and complex (2) were collected on a Siemens AED single-crystal computer-controlled diffractometer (θ–2θ scan) with CuKα radiation (Ni-filtered). Crystals of 2 were affected by serious twinning problems and only after several attempts a suitable specimen was

TABLE I Relevant crystal data collection and refinement parameters

Compound	1	2
Formula	$C_{20}H_{30}Cl_2N_4O_4$	$C_{40}H_{74}Cl_2Cu_2N_8O_{16}$
Molecular weight	461.387	1121.067
Space group	$P2_12_12_1$	$I23$
a (Å)	9.175(5)	31.538(7)
b (Å)	10.516(5)	31.538(7)
c (Å)	25.277(7)	31.538(7)
α, β, γ (°)	90.0	90.0
V (Å^3)	2439(2)	31369(12)
Z	4	24
F(000)	976	14160
$D_{calc.}$ (Mg/m^3)	1.26	1.25
μ (cm^{-1})	26.58	25.49
λ (Å)	1.54056	1.54056
Radiation	CuKα	CuKα
θ range (°)	3–60	3–60
hkl ranges	0–10, 0–12, 0–29	0–33, 0–35, 0–31
Standard reflection	−1, 2, 2	7, −3, 14
Crystal size (mm)	0.7 × 0.5 × 0.8	0.8 × 0.8 × 0.8
Crystal colour	Colourless	Violet-blue
No. meas. reflections	2404	4304
No. unique reflections	2365	1642
No. refined parameters	385	408
Max and min height in final ΔF map/eÅ^{-3}	0.44, −0.29	0.72, −0.34
$R = \sum\|\|Fo\| - \|Fc\|\|/\sum\|Fo\|$	0.078	0.098
$Rw2$	0.203	0.241
Goodness-of-fit	0.942	1.047
Weights	0.1000	0.1685

found that gave acceptable data. Intensities were measured using a modified version[20] of the profile analysis method of Lehman and Larsen[21] and were corrected for Lorentz and polarisation effects. The structures of the two compounds were solved by direct methods using SHELX86[22] and SIR92.[23] Successive Fourier syntheses allowed assignment of atoms to the electron density peaks, and the coordinates were refined by full-matrix least-squares methods using SHELXL97.[24] Anisotropic thermal parameters were used for all non-hydrogen atoms. Hydrogen atoms were located from a Fourier difference synthesis. The final refinement converged to $R = 0.078$ for the ligand and $R = 0.098$ for the complex. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[25] All calculations were performed on an IBM-RISC 6000 computer. Geometrical parameters were calculated using PARST97[26] and ORTEP[27] was used for the structure drawings.

Crystallographic data for the structures are available from the authors upon request.

RESULTS AND DISCUSSION

Synthesis of the Ligands

The synthesis of the ligands ProNN-2, Me_2ValNN-2, Me_2PheNN-2 was performed following the general rules of peptide synthesis. The α-amino function of the amino acids was protected with the benzyloxycarbonyl (Z) group[14] and successively methylated for Z-phe and Z-val.[16] The carboxyl group was activated as hydroxysuccinimidyl ester[15] and reacted with ethanediamine (2 : 1 ratio). By carefully controlling the reaction conditions and the stoichiometry, bis-acylation of ethanediamine was obtained. Final deprotection was accomplished by hydrogenation. The products were obtained as crystalline solid dihydrochlorides. No racemisation was observed during the synthesis. Full characterisation of the ligands is reported in the Experimental section.

Solution Equilibria Studies

We have already reported[1] the formation constants of Cu^{2+} complexes with (*S,S*)-*N,N'*-bis(aminoacyl)ethanediamine ligands (alanyl, AlaNN-2; valyl, ValNN-2; phenylalanyl, PheNN-2) and we proposed a four species model, namely $[CuLH]^{3+}$, $[CuL]^{2+}$, $[Cu_2L_2H_{-2}]^{2+}$ and $[CuLH_{-2}]$. Previous studies of similar ligands showed quite complicated equilibria, the existence of some

species being questionable. In fact, Briellman and Zuberbuehler[28] proposed two more species for GlyNN-2, *i.e.* $[CuL_2H_2]^{4+}$ and $[Cu_2L_2]^{4+}$, whereas Bai and Martell[29] found only the complexes $[CuL]^{2+}$, $[Cu_2L_2H_{-2}]^{2+}$, and $[CuLH_{-2}]$, in agreement with Muir and Rechani[30] for AlaNN-2.

Protonation and Cu^{2+} complexation constants obtained for the three ligands ProNN-2, Me_2ValNN-2 and Me_2PheNN-2 are reported in Table II. As expected, the increased basicity of the amino groups of Me_2ValNN-2 and Me_2PheNN-2 with respect to those of ValNN-2 and PheNN-2 may be ascribed to the inductive effect of the methyl substituents.

The final speciation model obtained for the Cu^{2+}/ProNN-2 system involves the complexes $[CuLH]^{3+}$, $[Cu_2L_2]^{4+}$, $[Cu_2L_2H_{-2}]^{2+}$ and $[CuLH_{-2}]$. Inclusion of two more species, $[CuL]^{2+}$ and $[CuLH_{-1}]^{+}$, did not give a significant decrease of sample variance and led to $\log\beta$ values with large standard deviations and negligible amounts of the two complexes ($[CuL]^{2+}$, 7.74(19), max. 5% of total copper; $[CuLH_{-1}]^{+}$, 2.00(11), max. 8%). On the other hand, the difficulty of defining unambiguously monomer/dimer couples like $[CuL]^{2+}/[Cu_2L_2]^{4+}$ and $[CuLH_{-1}]^{+}/[Cu_2L_2H_{-2}]^{2+}$ was outlined for GlyNN-2 by Briellman and Zuberbuehler[28] who detected the monomer $[CuL]^{2+}$ only through spectroscopic data, but with low precision (see Table II). A speciation diagram for ProNN-2 is presented in Figure 1.

A visible (400–800 nm) spectrophotometric study was also carried out in order to characterise the complexes and as a check of the potentiometric model. Molar absorptivities (ε) as a function of λ were calculated for each species using the constants listed in Table II. The spectroscopic parameters ($\lambda_{max}/\varepsilon$) thus obtained are presented in Table III and are in agreement with those reported for the corresponding GlyNN-2 complexes.[28,29] On the basis of these results the structures reported in Scheme 2 may be proposed for the various complexes. The species $[CuLH]^{3+}$ could have structure (I), as suggested by the $\log K$ value of the equilibrium

$$Cu^{2+} + HL^{+} = [CuLH]^{3+}$$

which is lower (5.36) than that of the corresponding complex, $[CuL]^{2+}$, of (*S*)-prolinamide ($ProNH_2$, 5.74)[2] and in agreement with those observed for AlaNN-2 (4.48)[1] and $AlaNH_2$ (5.07),[31] ValNN-2 (4.24)[1] and $ValNH_2$ (4.55),[2] PheNN-2 (3.93)[1] and $PheNH_2$ (4.42).[2]

As regards the species $[Cu_2L_2]^{4+}$, its $\lambda_{max} = 644$ nm is comparable with that of $[CuL_2]^{2+}$ for $ProNH_2$ (625 nm),[32] suggesting that Cu^{2+} coordination could be the same in the two complexes (two amine nitrogen and two carbonyl oxygen donors) (II). Analogous behaviour has been reported for

TABLE II Logarithms of protonation and Cu^{II} complex formation constants ($\beta_{pqr} = [Cu_pL_qH_r]/[Cu]^p[L]^q[H]^r$) of ProNN-2, Me_2ValNN-2 and Me_2PheNN-2, and related ligands. $T = 25°C$, $I = 0.1\ mol\ dm^{-3}$ (KCl). Standard deviations are given in parentheses

	$[HL]^+$	$[H_2L]^{2+}$	$[CuLH]^{3+}$	$[CuL]^{2+}$	$[Cu_2L_2]^{4+}$	$[CuLH_{-1}]^+$	$[Cu_2L_2H_{-2}]^{2+}$	$[CuLH_{-2}]$	S^{2a}	n^a
ProNN-2	8.92(1)	17.07(1)							0.50	127
			14.28(1)		20.45(1)		8.54(1)	−4.19(1)	2.82	423
Me_2ValNN-2	8.25(1)	15.64(1)							2.70	183
			11.96(5)			−0.99(2)		−7.91(3)	4.88	327
Me_2PheNN-2	7.70(1)	14.48(1)							0.31	159
			11.02(1)				1.89(1)	−6.92(1)	1.17	259
ValNN-2[b]	8.12(1)	15.27(1)								
			12.36(3)	6.78(2)			4.90(3)	−6.38(2)		
PheNN-2[b]	7.58(1)	14.24(1)								
			11.51(5)	6.32(6)			5.78(4)	−5.87(2)		
GlyNN-2[c]	8.27(1)	15.88(1)								
			13.40(1)	7.68(20)	19.26(16)		6.17(6)	−6.25(2)		

[a] $S^2 = \sum w_i(E_i^{obs} - E_i^{calc})^2/(n-m)$ = sample variance; $w_i = 1/\sigma_i^2$, where σ_i is the expected error for each experimental observation (E_i^{obs}); n = number of observations; m = number of parameters refined. [b] Ref. [1]. [c] Ref. [28].

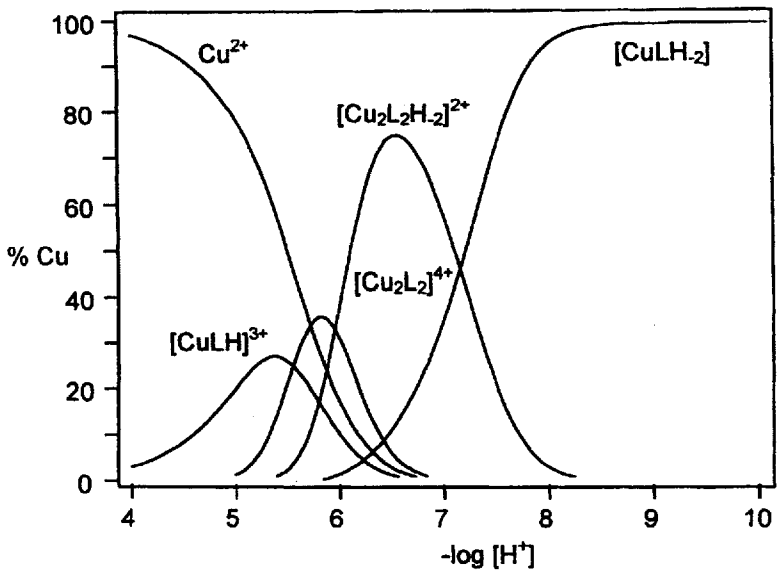


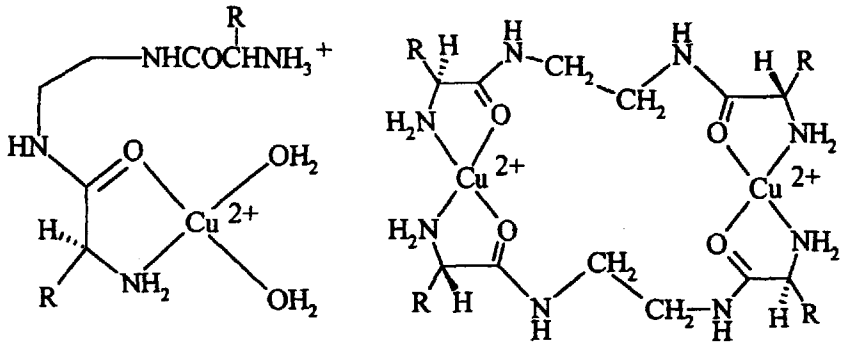
FIGURE 1 Species distribution for the Cu^{II}/ProNN-2 (1 : 1) system. $C_{Cu} = 2 \times 10^{-3}$ mol dm^{-3}.

TABLE III Spectroscopic parameters, $\lambda_{max}/\varepsilon$ (nm/M^{-1} cm^{-1}), for copper(II) complexes of diaminodiamido ligands in the visible region

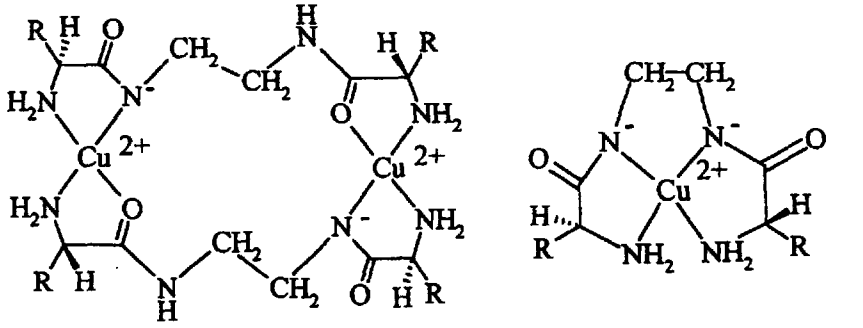
	ProNN-2	*Me*$_2$*ValNN*-2	*Me*$_2$*PheNN*-2	*GlyNN*-2		*ValNN*-2[a]	*PheNN*-2[a]
				b	c		
$[CuLH]^{3+}$	738/45			≫680			
$[CuL]^{2+}$					685/60		
$[Cu_2L_2]^{4+}$	644/131			662/84			
$[Cu_2L_2H_{-2}]^{2+}$	586/147			597/108	590/108	584/136	579/107
$[CuLH_{-2}]$	506/210	492/227	503/208	513/163	518/166	506/194	510/164

[a] Ref. [1]. [b] Ref. [28]. [c] Ref. [29].

GlyNN-2 (662 nm)[28] and $GlyNH_2$ (658 nm).[32] The structure of $[Cu_2L_2H_{-2}]^{2+}$ (**III**) can be inferred by the crystal structure data of GlyNN-2[33] and PheNN-2 (see below) and by comparison of its spectroscopic features ($\lambda_{max} = 586$ nm) with those of similar ligands (Table III). Finally, $[CuLH_{-2}]$ most probably has a square planar geometry with three fused 5,5,5-chelate rings (**IV**). In fact, it displays an absorption band with $\lambda_{max} = 506$ nm, which indicates the presence of two amine and two deprotonated amide nitrogens around the copper(II) ion. This value is very close to those reported in Table III for this type of ligand and is in agreement with data reported for the corresponding complex $[CuL_2H_{-2}]$ of $ProNH_2$ (513 nm),[2,32] for which the crystal structure has been determined.[6]



(I) $[CuLH]^{3+}$ (II) $[Cu_2L_2]^{4+}$



(III) $[Cu_2L_2H_{-2}]^{2+}$ (IV) $[CuLH_{-2}]$

SCHEME 2

For the dimethylated ligands various sets of species were tested in the calculations and the best fit to the potentiometric data was obtained with the set $[CuLH]^{3+}$, $[CuLH_{-1}]^{+}$, $[CuLH_{-2}]$ for Me_2ValNN-2, and with the set $[CuLH]^{3+}$, $[Cu_2L_2H_{-2}]^{2+}$, $[CuLH_{-2}]$ for Me_2PheNN-2. A speciation diagram for the Me_2ValNN-2/Cu^{2+} system is reported in Figure 2. It is remarkable that the ligand containing phenylalanine forms the dimer $[Cu_2L_2H_{-2}]^{2+}$, whereas that containing valine forms the monomer $[CuLH_{-1}]^{+}$. The formation of the monomer could be justified considering that only low copper concentrations and high ligand/metal ratios ($\geq 3/1$), *i.e.*, conditions unfavourable to dimer formation, were accessible to measurements owing to hydrolysis, with L/M = 1 or 2 at pH *ca.* 6.0. Dimer

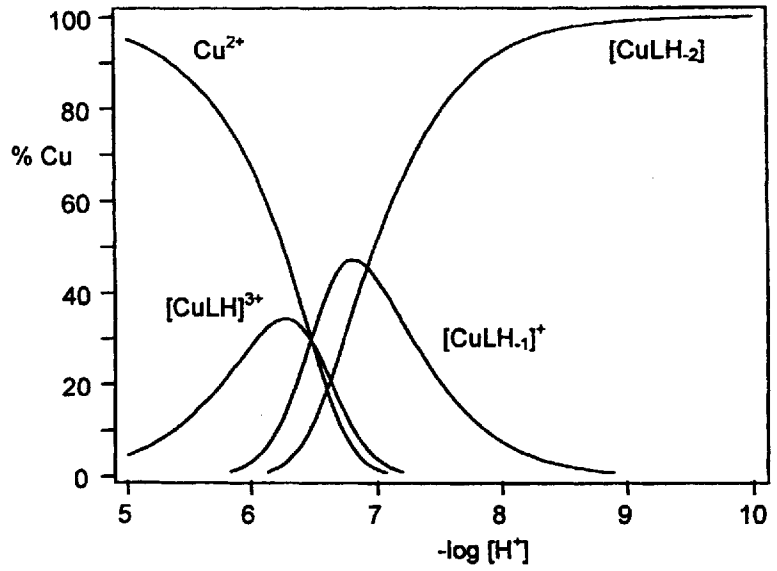


FIGURE 2 Species distribution for $Cu^{II}/Me_2ValNN\text{-}2$ (1:3) system. $C_{Cu} = 0.8 \times 10^{-3}$ mol dm^{-3}.

formation may be prevented by steric hindrance of the isopropyl side chains. Actually, the main differences between the complexing capacity of the methylated and the corresponding non-methylated ligands ValNN-2 and PheNN-2 are represented by the absence of the complex $[CuL]^{2+}$ and by the lower stability of the common species, particularly $[Cu_2L_2H_{-2}]^{2+}$ ($Me_2PheNN\text{-}2$, $\log\beta = 1.89$; PheNN-2, 5.78), most probably on account of the bulkiness of the methyl groups. In contrast, the stability of the complex $[CuLH_{-2}]$ is much less affected, $\Delta \log\beta$ being 1.53 for $Me_2ValNN\text{-}2$ and 1.05 for $Me_2PheNN\text{-}2$.

Spectroscopic features of $[CuLH_{-2}]$ are slightly different for the methylated and non-methylated ligands, *i.e.*, $\lambda_{max} = 492$ nm for $Me_2ValNN\text{-}2$ and 506 nm for ValNN-2; 503 nm for $Me_2PheNN\text{-}2$ and 510 nm for PheNN-2. This is consistent with what is observed for the complex $[CuL_2H_{-2}]$ of amino acid amides (MeVal-NH_2, 497 nm,[34] Val-NH_2, 513 nm,[2,32] MePhe-NH_2, 504 nm,[32] Phe-NH_2, 520 nm[2,32] and also for the species $[CuL]^{2+}$ of two tetraamines (3,6-diaza-1,8-diaminooctane, trien, $\lambda_{max} = 580$ nm;[35] 1,4,7,10-tetraazadodecane, Me_2trien, 570 nm[36]). We suggest that the lower absorption wavelengths of the methylated complexes may be due to the more hydrophobic environment surrounding the copper(II) ion.

These results provide valuable clues for an understanding of the mechanism of separation of *D,L*-amino acids in RP-HPLC performed by the copper(II) complexes of these ligands. In fact, preliminary chromatographic experiments carried out in the pH range 6–7.5, in which the potential selectors are either $[Cu_2L_2H_{-2}]^{2+}$ or $[CuLH_{-2}]$ for Me_2PheNN-2 and either $[CuLH_{-1}]^{+}$ or $[CuLH_{-2}]$ for Me_2ValNN-2, showed quite different behaviour with respect to that of the non-methylated ligands. The discrepancy might be due to the remarkable stability decrease of the dimer for Me_2PheNN-2 and to the formation of the monomer $[CuLH_{-1}]^{+}$ in the case of Me_2ValNN-2. Chromatographic results will be published in detail elsewhere.[13]

X-ray Studies

Analysis by single crystal X-ray diffraction allowed structure determinations of the ligand PheNN-2 dihydrochloride dihydrate (**1**) and of its complex $[Cu_2L_2H_{-2}]Cl_2 \cdot 12H_2O$ (**2**). An ORTEP plot of each is shown in Figures 3 and 4, respectively. A list of relevant interatomic distances and angles is reported in Table IV.

Compound (**1**) presents the two chloride ions hydrogen-bonded to the protonated amino nitrogens (distances range between 2.81(1) and 3.09(1) Å). The Cl1 anion is disordered over two positions with a site occupancy factor

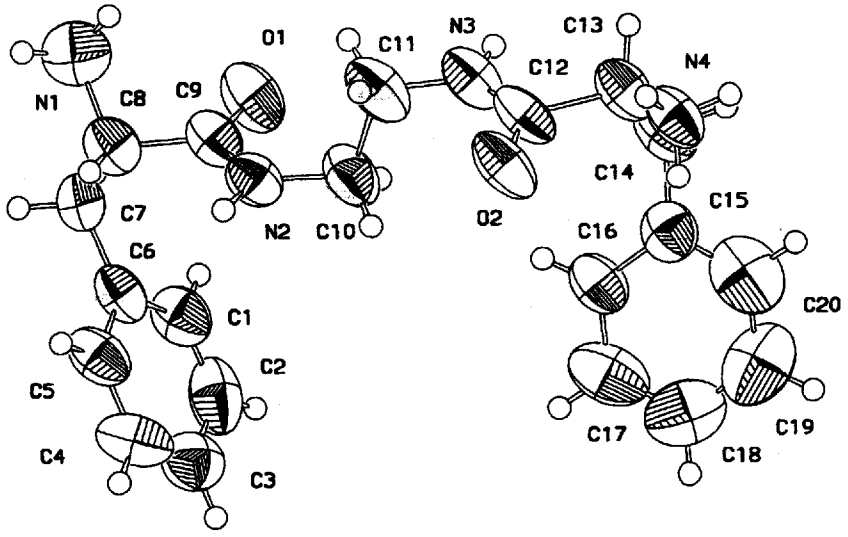


FIGURE 3 An ORTEP diagram (40% ellipsoids) of compound (**1**).

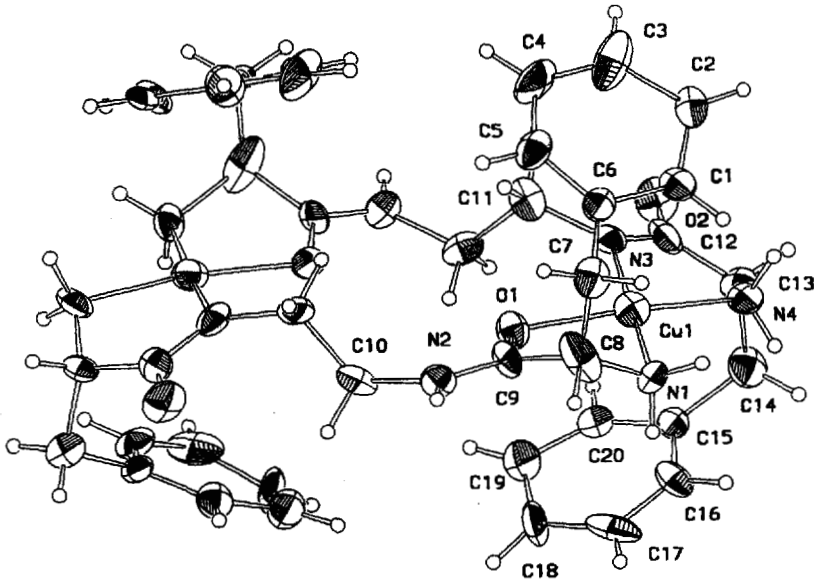


FIGURE 4 An ORTEP diagram (30% ellipsoids) of the cationic molecular unit of compound (2).

of 0.65 and 0.35. The conformation of the whole system is determined by an extended network of hydrogen bonds connecting the amide and ammonium hydrogens to the chloride ions and to the crystallisation waters. Moreover, very weak stacking interactions are observed between the aromatic rings with values in the range 3.42(2)–3.65(2) Å.

In the dinuclear copper(II) complex (2), each bridging ligand chelates on one side through the deprotonated amido nitrogen and the amino nitrogen, while on the other side it binds through the carbonyl oxygen and the amino nitrogen, as already observed for the analogous complex of *N,N'*-diglycylethanediamine, $[Cu_2L_2H_{-2}(H_2O)_2](ClO_4)_2 \cdot 4H_2O$.[33] In contrast with the cited paper, where the two copper ions were correlated by a centre of symmetry allowed by the lack of chirality of glycine, in this case the two halves are correlated by a twofold crystallographic axis. As already observed in other phenylalanine[37,38] and phenylalanine amide complexes,[5] the copper centre coordinates in a square planar (slightly distorted) geometry with the phenyl ring of the amino acid side chain hindering the apical positions. The chelate rings in the former copper atom (Cu1) present a conformation between E and T with puckering parameters $q_2 = 0.45(3)$ Å, $\phi_2 = 44(3)°$ $q_2 = 0.33(2)$ Å, $\phi_2 = 153(5)°$; the latter copper (Cu2) has puckering parameters $q_2 = 0.36(4)$ Å, $\phi_2 = 129(6)°$ and $q_2 = 0.34(3)$ Å, $\phi_2 = 22(6)°$, corresponding

TABLE IV Bond distances (Å) and angles (°) for compounds 1 and 2

Compound **1**					
O1–C9	1.266(13)	C1–C6	1.380(15)	C12–C13	1.562(15)
O2–C12	1.212(13)	C2–C3	1.39(2)	C13–C14	1.478(17)
N1–C8	1.505(16)	C3–C4	1.362(20)	C14–C15	1.547(17)
N2–C9	1.297(15)	C4–C5	1.403(18)	C15–C16	1.338(17)
N2–C10	1.479(16)	C5–C6	1.392(15)	C15–C20	1.37(2)
N3–C11	1.451(15)	C6–C7	1.519(15)	C16–C17	1.41(2)
N3–C12	1.288(16)	C7–C8	1.495(16)	C17–C18	1.31(3)
N4–C13	1.522(17)	C8–C9	1.550(15)	C18–C19	1.36(3)
C1–C2	1.34(2)	C10–C11	1.513(18)	C19–C20	1.39(3)
C9–N2–C10	122.2(10)	N1–C8–C9	107.6(9)	C12–C13–C14	115.7(9)
C11–N3–C12	121.6(10)	C7–C8–C9	113.3(9)	C13–C14–C15	116.0(10)
C2–C1–C6	122.9(12)	O1–C9–N2	124.6(10)	C14–C15–C16	124.1(10)
C1–C2–C3	121.3(13)	O1–C9–C8	116.9(9)	C14–C15–C20	120.6(13)
C2–C3–C4	117.6(13)	N2–C9–C8	118.3(10)	C16–C15–C20	115.3(12)
C3–C4–C5	121.5(12)	N2–C10–C11	110.7(10)	C15–C16–C17	120.6(12)
C4–C5–C6	119.9(11)	N3–C11–C10	109.8(10)	C16–C17–C18	122.2(16)
C1–C6–C5	116.7(9)	O2–C12–N3	127.0(11)	C17–C18–C19	119.8(18)
C1–C6–C7	120.6(10)	O2–C12–C13	120.6(9)	C18–C19–C20	116.8(18)
C5–C6–C7	122.7(10)	N3–C12–C13	112.4(10)	C15–C20–C19	124.9(17)
C6–C7–C8	113.6(9)	N4–C13–C12	106.3(9)		
N1–C8–C7	109.5(9)	N4–C13–C14	111.0(10)		
Compound **2**					
Cu1–O1	1.993(19)	C8–C9	1.47(5)	N5–C28	1.45(5)
Cu1–N1	2.01(2)	C7–C8	1.50(6)	N6–C29	1.35(6)
Cu1–N3	1.94(3)	C6–C7	1.43(5)	N6–C30	1.48(6)
Cu1–N4	1.95(2)	C12–C13	1.43(5)	N7–C32	1.22(7)
O1–C9	1.26(4)	C13–C14	1.54(4)	N7–C31	1.53(7)
O2–C12	1.21(5)	C14–C15	1.49(4)	N8–C33	1.41(6)
N1–C8	1.53(5)	Cu2–O4	2.03(3)	C26–C27	1.61(5)
N2–C9	1.23(4)	Cu2–N5	1.95(3)	C27–C28	1.46(6)
N2–C10	1.47(4)	Cu2–N6	1.94(4)	C28–C29	1.47(7)
N3–C11	1.46(4)	Cu2–N8	1.95(4)	C32–C33	1.56(8)
N3–C12	1.32(5)	O3–C29	1.25(6)	C33–C34	1.51(6)
N4–C13	1.44(4)	O4–C32	1.24(6)	C34–C35	1.39(5)
O1–Cu1–N1	81.1(9)	C13–C12–N3	110(3)	Cu2–N6–C30	124(3)
O1–Cu1–N4	172.3(9)	C12–C13–C14	115(3)	C29–N6–C30	122(4)
O1–Cu1–N3	97.3(10)	C12–C13–N4	114(3)	Cu2–N8–C33	111(3)
N1–Cu1–N4	101.6(10)	C14–C13–N4	107(2)	C32–N7–C31	130(5)
N1–Cu1–N3	176.7(10)	C13–C14–C15	112(2)	O3–C29–N6	121(4)
N4–Cu1–N3	80.3(11)	C14–C15–C16	121(3)	O3–C29–C28	125(5)
Cu1–O1–C9	112.1(20)	C14–C15–C20	129(3)	N6–C29–C28	114(4)
Cu1–N1–C8	106.0(18)	O4–Cu2–N5	171.2(12)	N5–C28–C29	112(4)
C9–N2–C10	128(3)	O4–Cu2–N6	95.4(14)	N5–C28–C27	111(3)
O1–C9–N2	119(3)	O4–Cu2–N8	81.4(14)	C29–C28–C27	109(4)
O1–C9–C8	120(3)	N5–Cu2–N6	83.4(15)	C28–C27–C26	114(3)
N2–C9–C8	120(3)	N5–Cu2–N8	100.4(14)	O4–C32–N7	120(5)
N1–C8–C9	102(3)	N6–Cu2–N8	174.4(15)	O4–C32–C33	117(5)
N1–C8–C7	114(3)	Cu2–O4–C32	112(3)	N7–C32–C33	123(6)
C9–C8–C7	115(3)	Cu1–N4–C13	107.8(20)	N8–C33–C32	104(4)
C8–C7–C6	114(3)	Cu1–N3–C12	118(3)	N8–C33–C34	114(3)
C7–C6–C1	118(3)	Cu1–N3–C11	121(2)	C32–C33–C34	115(4)
C7–C6–C5	124(3)	C12–N3–C11	120(3)	C33–C34–C35	114(3)
O2–C12–C13	124(4)	Cu2–N5–C28	108(3)	C34–C35–C40	124(3)
O2–C12–N3	125(4)	Cu2–N6–C29	113(3)	C34–C35–C36	119(3)

to more regular twisted conformations.[39] The four phenyl rings form angles with the coordination planes ranging between 22.1(8)° and 31.2(9)°, the distances of the medium points of the four rings from the metal centres being respectively 3.388(4) and 3.434(4) Å for Cu1 and 3.477(5) and 3.579(5) Å for Cu2. The shortest contact between a copper centre and an aromatic carbon is 2.95(3) Å, a value that lies significantly beyond the upper limit [2.751 Å] of the Cu–C bond length distribution obtained with the CSD.[40] The overall structure presents a system of cavities that host several water molecules connected by an extended network of hydrogen bonds that also involve the two chloride ions.

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