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Copper(II) complexes with lactamides: solution and solid state studies

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***Received** (in Montpellier, France) 15th December 2003, Accepted 19th February 2004*
First published as an Advance Article on the web 24th May 2004

Three functionalized ligands, S(−)-*N*-(pyridin-2-ylmethyl)lactamide (pml), S(−)-*N*-(2-dimethylaminoethyl)lactamide (dmael) and S(−)-*N*-(3-dimethylaminopropyl)lactamide (dmapl), were synthesized by the aminolysis of S(−)-methyl lactate with the corresponding primary amines. Their protonation constants and the stability constants of the chelates formed with copper(II) were determined by potentiometry. In all cases, we detected the formation of $CuLH_{-1}^{+}$, $CuLH_{-2}$ and $CuLH_{-3}^{-}$ species (L = free ligand). The copper(II) complexes prepared in the solid state were characterized by IR and UV-visible spectroscopies. The crystal structure of $[Cu(pmlH_{-1})X]$ (X = Cl, Br) shows that copper(II) is bound to the pyridyl and the deprotonated amidic nitrogen atoms, as well as to the oxygen atom of the hydroxyl group, which leads to a mono-chelated compound. The geometry around Cu^{2+} is square pyramidal.

Introduction

The chemistry of transition metal complexes of amide ligands has attracted much interest over the past decade because of their important role in various industrial and biological processes. Copper and nickel amide complexes also have applications in enantioselective catalysis[1,2] and metal ion therapeutics.[3–6] Studies of complexes with amide moieties are also of fundamental interest in order to understand the role of metalloproteins in the control of cell metabolism.[7]

The selectivity of amide moieties in the binding of metal ions strongly depends on the ease with which metal ions deprotonate the amidic nitrogen to form stable chelated compounds. The role of substituents appears essential to control the geometry and stability of the complexes formed, although it has not been thoroughly investigated.[8,9]

In order to further develop the coordination chemistry of the amide functionality, new ligands should be exploited. We have undertaken a program to explore the coordination chemistry of hydroxy acid-derived polyfunctionalized amides. These ligands seemed to be interesting target compounds: so far they have not been much studied and, moreover, the chirality, polyfunctionality and hydrosolubility properties of the parent acids are preserved in the amides. Consequently, such ligands are expected to present a wide field of potential applications in enantioselective catalysis,[1,2] molecular recognition,[10,11] selective complexation and metal ions extraction processes.[12]

As a first step towards this goal, we chose simple and easily synthesizable functionalized lactamides as model ligands and studied their complexation properties towards copper(II) ions. In this paper, we report the solution and solid coordination properties of copper(II) complexes with the different lactamides depicted in Fig. 1.

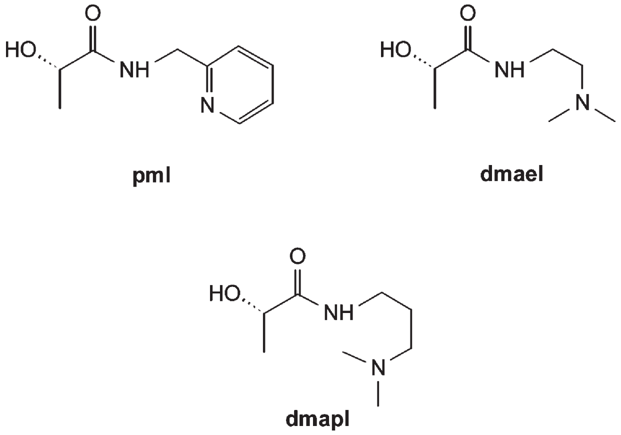

Fig. 1 Schematic structures of the lactamide ligands studied.

Experimental

General

All the solvents were purified by conventional procedures and distilled prior to use. All the chemicals commercially available (Aldrich) were used as supplied without further purification.

Elemental analyses (C, H and N) were carried out on a Perkin–Elmer 2400 C,H,N elemental analyzer in our university. The copper analyses were performed on an ICP-AES Liberty Series II Varian apparatus.

Syntheses

General procedure for the synthesis of ligands. The ligands were synthesized by the classical aminolysis of the S(−)-methyl lactate with the corresponding primary amine. A solution of S(−)-methyl lactate (1 equiv) and the amine (1.4 equiv) in THF was refluxed for 12 h. The solvent was then evaporated and the crude was dissolved in diethyl ether. Purification of the lactamides was performed by recrystallization in a petroleum ether–EtOAc mixture for the pml and dmael ligands. The ligand dmapl was purified by silica gel flash chromatography. Ligand pml[13] was previously reported; ligand dmapl[14]

DOI: 10.1039/b316393h

was previously reported but not fully characterized, whereas ligand dmael has not been described in the literature.

S(−)-(N-Pyridin-2-ylmethyl)lactamide (pml). White powder, yield 62%; mp 77 °C (lit.[13] mp 79 °C); $[\alpha]_D^{20} = -16.1$ ($c = 1$, EtOH) [lit.[13] $= -16.8$ ($c = 1$, EtOH)]. ^{1}H NMR ($CDCl_3$): $\delta = 1.47$ (d, 3H, $^3J = 6.9$ Hz, CH_3); 4.31 (q, 1H, $^3J = 6.9$ Hz, CHOH); 4.45–4.65 (m, 2H, CH_2); 7.18–7.30 (m, 2H, 2CH pyridine); 7.66 (td, 1H, $^3J = 9.1$ Hz, $^4J = 1.7$ Hz, CH pyridine); 7.92 (m, 1H, NH); 8.46–8.53 (m, 1H, CH pyridine). ^{13}C NMR ($CDCl_3$): $\delta = 21.6$ (CH_3); 44.4 (CH_2); 68.8 (CH); 122.8 (CH pyr); 123.0 (CH pyr); 137.6 (CH pyr); 149.3 (CH pyr); 157.0 (C_q pyr); 175.5 (C=O). IR (KBr): 3291 (ν_{OH}); 3163 (ν_{NH}); 1653 ($\nu_{C=O}$); 1123 ($\nu_{C\text{–}O}$). Anal calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55; found: C, 59.63; H, 6.78; N, 15.42.

S(−)-N-(2-Dimethylaminoethyl)lactamide (dmael). Oil, hygroscopic compound, yield 75%; $[\alpha]_D^{20} = -23.7$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (d, 3H, $^3J = 6.8$ Hz, CH_3); 2.27 [s, 6H, $N(CH_3)_2$]; 2.48 (t, 2H, $^3J = 5.7$ Hz, CH_2); 3.35–3.50 (m, 2H, CH_2); 4.23 (q, 1H, $^3J = 6.8$ Hz, CH); 7.60 (tl, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 22.1$ (CH_3); 36.4 (CH_2); 45.5 [$N(CH_3)_2$]; 59.2 (CH_2); 68.6 (CH); 175.5 (C=O). IR (KBr): 3347 (ν_{OH}); 1653 ($\nu_{C=O}$); 1125 ($\nu_{C\text{–}O}$). Anal. calcd for $C_7H_{16}N_2O_2 \cdot 0.2\ H_2O$: C, 51.27; H, 10.01; N, 17.10; found: C, 51.15; H, 10.28; N, 17.33.

S(−)-N-(3-Dimethylaminopropyl)lactamide (dmapl)[14]. Oil, hygroscopic compound, yield 89%; $[\alpha]_D^{20} = -11.6$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (d, 3H, $^3J = 6.8$ Hz, CH_3); 1.53 (m, 2H, CH_2); 2.05 [s, 6H, $N(CH_3)_2$]; 2.18 (t, 2H, $^3J = 7.0$ Hz, CH_2); 3.10 (m, 2H, CH_2); 3.98 (q, 1H, $^3J = 6.8$ Hz, CH); 7.44 (tl, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 20.8$ (CH_3); 26.5 (CH_2); 44.8 [$N(CH_3)_2$]; 56.7 (CH_2); 67.5 (CH); 175.4 (C=O). IR (KBr): 3323 (ν_{OH}); 1653 ($\nu_{C=O}$); 1125 ($\nu_{C\text{–}O}$). Anal. calcd for $C_8H_{17}N_2O_2 \cdot 0.2\ H_2O$: C, 54.00; H, 10.36; N, 15.75; found: C, 54.00; H, 10.22; N, 16.11.

General procedure for the synthesis of copper(II) complexes. The four copper(II) compounds were synthesized using the same procedure described here. To a solution of 10^{-3} mole of ligand dissolved in 40 mL of absolute ethanol was added dropwise a solution of 10^{-3} mole of copper(II) perchlorate hexahydrate in 10 mL of absolute ethanol (the precipitate that appears was dissolved with a few drops of water). The mixture was stirred for 10 min; the blue solution obtained was filtered and set aside at room temperature. Addition of a slight excess (1.5×10^{-3} mole) of tetraethylammonium chloride or bromide was added into these solutions. Blue crystals suitable for X-ray were obtained after three weeks only in the case of the Cu–pml system.

[Cu(pmlH$_{-1}$)Cl]·H$_2$O (**1**). Yield 60%. λ_{max}/nm (ε/mol^{-1} L cm^{-1}): 660 (solid state); 675 (93) (DMF). IR (KBr disk) ν/cm^{-1}: 3450–3280 (s, ν_{OH}); 3000–2650 (m, $\nu_{C\text{–}H}$); 1600 (vs, $\nu_{C=O}$); 1560, 1450 (s, $\nu_{\text{pyridine ring}}$); 1565, 1310 (s, $\nu_{C\text{–}N}$ and $\delta_{N\text{–}H}$). Anal calcd for $C_9H_{13}N_2O_3ClCu$: C, 36.6; H, 4.1; N, 9.5; Cu, 21.5; found C, 36.6; H, 4.3; N, 9.3; Cu, 21.4.

[Cu(pmlH$_{-1}$)Br]·H$_2$O (**2**). Yield 55%. λ_{max}/nm (ε/mol^{-1} L cm^{-1}): 660 (solid state); 675 (92) (DMF) . IR (KBr disk, ν/cm^{-1}): 3450–3280 (s, ν_{OH}); 3000–2650 (m, $\nu_{C\text{–}H}$); 1600 (vs, $\nu_{C=O}$); 1560, 1450 (s, $\nu_{\text{pyridine ring}}$); 1565, 1310 (s, $\nu_{C\text{–}N}$ and $\delta_{N\text{–}H}$). Anal calcd for $C_9H_{13}N_2O_3BrCu$: C, 31.7; H, 3.8; N, 8.2; Cu, 18.6; found: C, 31.5; H, 3.9; N, 8.1; Cu, 18.3

[Cu(dmaelH$_{-1}$)(H$_2$O)](ClO$_4^-$)·H$_2$O (**3**). Blue powder, yield 50%. λ_{max}/nm (ε/mol^{-1} L cm^{-1}): 630 (solid state); 642 (88) (DMF). IR (KBr disk, ν/cm^{-1}): 3400–3150 (s, $\nu_{N\text{–}H\,+\,O\text{–}H}$); 2940–2850 (m, $\nu_{C\text{–}H}$); 1615 (vs, $\nu_{C=O}$); 1565, 1460 (s, $\nu_{\text{pyridine ring}}$); 1570, 1310 (s, $\nu_{C\text{–}N}$ and $\delta_{N\text{–}H}$); 1091 (vs, $\nu_{ClO_4^-}$). Anal calcd for $C_7H_{19}N_2O_8ClCu$: C, 23.5; H, 5.3; N, 7.8; Cu, 17.8; found: C, 23.7; H, 5.6; N, 7.6; Cu, 17.5.

[Cu(dmaplH$_{-1}$)(H$_2$O)](ClO$_4^-$)·H$_2$O (**4**). Blue-green powder, yield 45%. λ_{max}/nm (ε/mol^{-1} L cm^{-1}): 640 (solid state); 606 (35) (DMF). IR (KBr disk, ν/cm^{-1}): 3450–3100 (s, $\nu_{N\text{–}H\,+\,O\text{–}H}$); 2940–2850 (m, $\nu_{C\text{–}H}$); 1610 (vs, $\nu_{C=O}$); 1570, 1474 (s, $\nu_{\text{pyridine ring}}$); 1565, 1310 (s, $\nu_{C\text{–}N}$ and $\delta_{N\text{–}H}$); 1090 (vs, $\nu_{ClO_4^-}$). Anal calcd for $C_8H_{21}N_2O_8ClCu$: C, 25.8; H, 5.7; N, 7.5; Cu, 17.1; found: C, 25.7; H, 5.6; N, 7.6; Cu, 17.3

Protometric measurements

Stock solutions of metal nitrates were prepared from commercially available reagents (Fluka) of the highest purity (>99%) and were used without further purification. Their concentrations were determined by EDTA titration at pH = 10, by using PAN [1-(2-pyridylazo)-2-naphthol] as an indicator for Cu^{2+}. Ionic strength was kept constant ($I = 0.1$) by addition of sodium nitrate (Prolabo) of the highest purity (>99%). The solutions of carbonate-free titrating base NaOH (0.1 mol dm^{-3}) were prepared from standardized 1 mol dm^{-3} solutions (Prolabo). All solutions were prepared in glass-distilled, deionized water that was deaerated with Ar gas for at least 30 min in order to remove dissolved CO_2 .

Protometric titrations were performed with a Metrohm 665 Dosimat and a Metrohm 654 pH-meter. The combined glass electrode was standardized with 10^{-2} mol dm^{-3} nitric acid (pH = 2.00) and the slope determined from a refinement of titration curves of nitric acid solutions. All measurements were performed at 25 °C under a nitrogen stream. For a classical titration, a total of 120 to 150 points (volume of NaOH + pH) was taken. For pml, neutralization curves were monitored in the presence of an excess of nitric acid (usually at a concentration of 6×10^{-3} mol dm^{-3}). For dmael and dmapl, oxalic acid was used instead of nitric acid because the complexation of copper ions by oxalate ions prevents the formation of a precipitate of $Cu(OH)_2$. Without oxalic acid, copper hydroxide began to precipitate above pH 6 and redissolved beyond pH 8 due to the complexation reaction with dmael and dmapl ligands.

Computations

Protonation constants of the ligands and overall stability constants (β_{mlh}) of the copper(II) complexes were calculated with the general computation program HYPERQUAD[15,16] where:

$$m\mathrm{M} + l\mathrm{L} + h\mathrm{H} \rightleftharpoons \mathrm{M}_m\mathrm{L}_l\mathrm{H}_h \qquad \beta_{mlh} = \frac{[\mathrm{M}_m\mathrm{L}_l\mathrm{H}_h]}{[\mathrm{M}]^m[\mathrm{L}]^l[\mathrm{H}]^h}$$

The concentration of metal ions C_M ranged from 1–4 × 10^{-3} mol dm^{-3}, the concentration of the ligand C_L ranged between 4–8 × 10^{-3} mol dm^{-3} and the ratio R, defined as C_L/C_M , varied from 1 to 5.

Spectroscopic studies

NMR data were recorded on a Bruker 250 MHz apparatus operating near 250 (^{1}H) or 62.5 (^{13}C) MHz. Chemical shifts were relative to TMS. Visible spectra of copper(II) complexes were recorded in aqueous solutions using a Shimadzu UV-2401-PC spectrophotometer equipped with a standard syringe sipper and a temperature-controlled TCC-240A cell holder. The experiments were monitored in the same concentration range as used for the pH titration; an average of 40 spectra were recorded in the pH range from 2.5 to 11.5. Anisotropic X-band electron paramagnetic resonance (ESR) of frozen solutions were recorded at 100 K using a Bruker ESP 300 spectrophotometer; 20% ethylene glycol was used to ensure the formation of glasses. The g values were measured relative to diphenylpicrylhydrazyl (dpph; $g = 2.0037$).

Electrospray ionization mass spectrometry (ESI-MS)

Experiments were performed using a Micromass (Manchester, UK) Quattro II tandem mass spectrometry of QhQ geometry equipped with an atmospheric pressure ionization (API) source operating in the nebulizer-assisted electrospray mode. The electrospray potential was set to 3 kV in positive ion mode and the extraction cone voltage was usually varied between 30–60 V in order to obtain optimized mass spectra. In negative ion mode the same voltages with opposite sign were used. Solutions of copper(II) nitrate and pml ligand in the ratios 1:1 and 2:1 L/M were prepared under conditions similar to the ones set out for the potentiometric study. The ligand concentration was equal to 4×10^{-3} mol dm^{-3}.

Crystal structure determination

In Table 1 are summarized the pertinent crystallographic data together with refinement details for compounds **1** and **2**.† The crystal data for both compounds were collected at 173 K on a Kappa CCD diffractometer using monochromated Mo K$_\alpha$ radiation ($\lambda = 0.71073$ Å). The structures were solved using direct methods. After refinement of the non-hydrogen atoms, difference Fourier maps revealed maxima of residual electron density close to positions expected for the hydrogen atoms. Hydrogen atoms were introduced as fixed contributors at calculated positions [C–H = 0.95 Å, B(H) = 1.3 Beqv]. Final difference maps revealed no significant maxima. All calculations used the Nonius OpenMoleN package.[17] Neutral atom scattering factor coefficients and anomalous dispersion coefficients were taken from a standard source.[18]

Results and discussion

Potentiometry and UV-visible spectrophotometry

Protometric titrations are depicted as curves of $\bar{h}$ *vs.* pH, where $\bar{h}$ is the average number of protons bound per mole of ligand:

$$\bar{h} = \frac{1}{C_L}(nC_L - [H^+] + [OH^-] - C_B + C_H)$$

(n = number of protons in the neutral form of the ligand; C_B = concentration of the strong base added; C_H = concen-concentration of the strong acid present in the solution of the neutral form of the ligand). Fig. 2 represents the $\bar{h}$ variation for solutions of ligands alone and for solutions with added copper ions, R equal to 2 (pml and dmael) or 3.33 (dmapl). The relatively strong acidity of the pyridinium group of pml is completely neutralized at pH 5.5, whereas higher pH are required to neutralize the acidity of the tertiary amine in the case of dmael and dmapl (pH 9.5 and 10.5, respectively). For the three ligands, the deprotonation of the amidic nitrogen is not observed (plateau at $\bar{h} = 0$).

Table 1 X-Ray experimental data for compounds [Cu(pmlH$_{-1}$)Cl]·H$_2$O and [Cu(pmlH$_{-1}$)Br]·H$_2$O

	[Cu(pmlH$_{-1}$)Cl]·H$_2$O	[Cu(pmlH$_{-1}$)Br]·H$_2$O
Formula	$C_9H_{13}ClCuN_2O_3$	$C_9H_{13}BrCuN_2O_3$
Molecular weight	296.21	339.64
Crystal system	Monoclinic	Monoclinic
Space group	$P1\,2_1$	$P1\,2_1$
a/Å	4.0185(1)	4.0535(1)
b/Å	19.4997(6)	19.3293(7)
c/Å	7.2382(3)	7.3828(2)
β/deg	92.118(5)	92.357(5)
U/Å^3	566.79(3)	577.96(3)
Z	2	2
μ/mm^{-1}	2.155	5.338
T/K	173	173
Number of data measured	2585	3182
Number of data collected	2486	2507
R_{int}	0.040	0.050
$wR2$	0.029	0.041
$R1$	0.021	0.033

For pml, the comparison of $\bar{h}$ *versus* pH curves for the ligand alone and in the presence of copper ions (R = 2) shows that complexation occurs above pH 4. The curve presents three plateaus for $\bar{h}$ = −0.5, −1, and −1.5 corresponding to the release of 1, 2, and 3 protons by the complexes. The three equivalent points are attributed to the successive formation of CuLH$_{-1}$$^+$, CuLH$_{-2}$ and CuLH$_{-3}$$^-$ species. For the Cu(II)-dmael and Cu(II)-dmapl systems, complexation occurs above pH 7.5 and 8.5, respectively. With dmael (R = 2), the curve $\bar{h}$ *vs.* pH shows only one plateau ($\bar{h}$ = −1.5), corresponding to the release of 3 protons per Cu(II), attributed to the formation of the CuLH$_{-3}$$^-$ species. For dmapl (R = 3.33), the curve

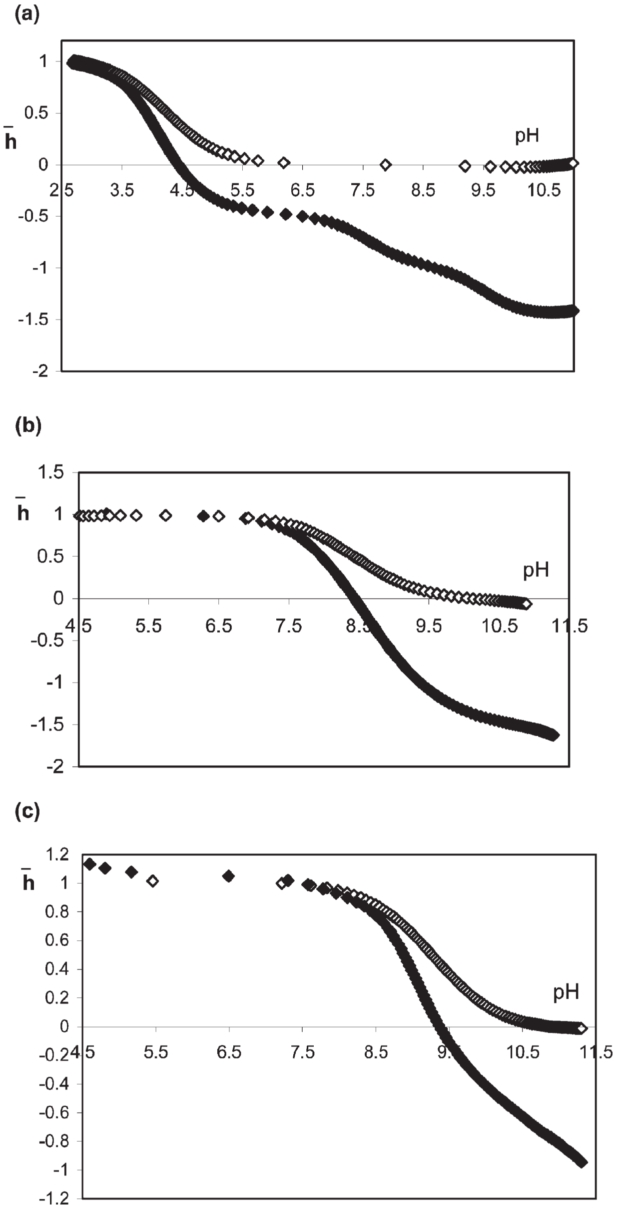

Fig. 2 Average number $\bar{h}$ of protons bound per mole of ligand as a function of pH: (a) Cu-pml, R = 2; (b) Cu-dmael, R = 2; (c) Cu-dmapl, R = 3.33. (◇) ligand alone ($C_L = 4 \times 10^{-3}$ mol dm^{-3}), (◆) in the presence of Cu^{2+}.

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† CCDC reference numbers 219411 (**1**) and 228293 (**2**). See http://www.rsc.org/suppdata/nj/b3/b316393h/ for crystallographic data in .cif or other electronic format.

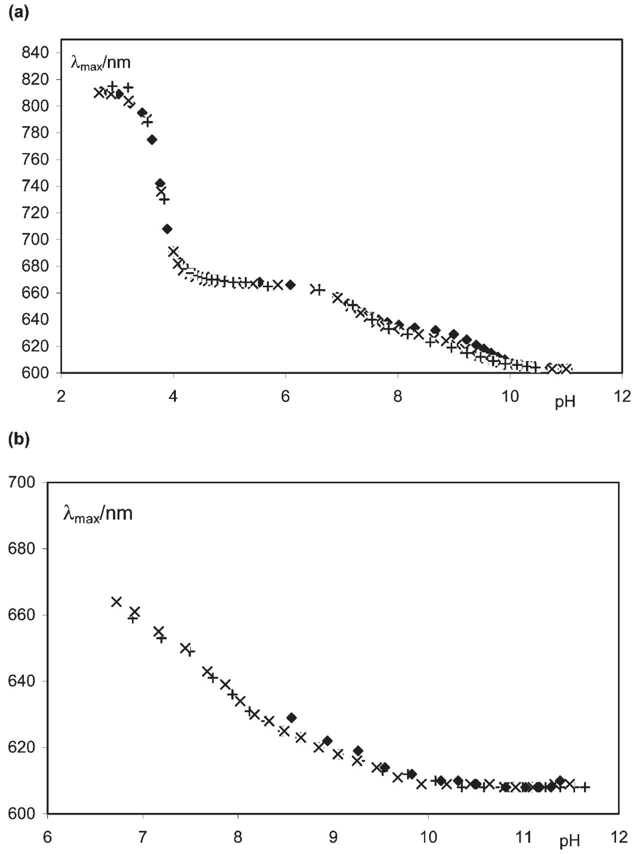

Fig. 3 Variation of λ_{max} as a function of pH for (a) Cu-pml and (b) Cu-dmael solutions of variable [L]/[M] ratio R: (◆) 1, (×) 2, (+) 4.

$\bar{h}$ *vs.* pH shows a rapid decrease of $\bar{h}$ above pH 8, leading to an average value of −0.9, indicating the release of approximately three protons per Cu(II) in agreement with the probable formation of the $CuLH_{-3}^{-}$ species.

Fig. 3 shows the variation of λ_{max} as a function of pH for the Cu-pml and Cu-dmael systems. For a given ligand, whatever the [L]/[M] ratio may be, the curves show nearly the same variation of λ_{max}. There is a strong evidence that in both systems only 1:1 species are formed. For R values below 1, precipitation of copper hydroxide occurs above pH 6.

Mass spectrometry

Further analysis of Cu-pml solutions by ESI-MS allowed us to determine the stoichiometry of the Cu-pml complexes. Figs. 4 and 5 give the positive and negative ion mass spectra, respectively, of a Cu-pml solution at pH 6.5 with R equal to 1. The accurate mass and elemental composition of the main ions are given in Table 2. In the positive mode, the spectrum is rather complicated due to the formation of adducts[19,20] between monocharged complexes and electrolyte or neutral ligand or neutral complex molecules. To make an effective identification between the complexes formed and the adducts generated by the spray, we based our interpretation on the coherence of the adduction mechanism as well as on the similarities observed when the pH and the C_L/C_M ratio vary. In Fig. 4, the ligand can be detected as a protonated ion at m/z 181 and as a sodiated species at m/z 203 (Fig. 4 and Table 2). The peaks related to the copper complexes were identified by analyzing their specific isotopic profile due the different Cu isotopes (*e.g.*, ^{63}Cu and ^{65}Cu). The copper complexes were detected through peaks at m/z 242, 327, 422, 483, 546, 568 and 724 (the mass indicated corresponds to the first peak of the isotopic clump and the ^{63}Cu species). The peak at m/z 242 can be directly ascribed to the species $CuLH_{-1}^{+}$ formed to a large extent at pH 6.5; the peaks at m/z 327 and 422 correspond to the same ionic complex with adducts of sodium nitrate and a neutral ligand molecule, respectively. It is noteworthy that the same species are detected at the same pH with the solution C having a C_L/C_M ratio equal to 2 (see Table 2).

In addition, for solution A, the peaks observed at m/z equal to 483, 546 and 568 result from associations between the $CuLH_{-1}^{+}$ species and adducts of the neutral complex $CuLH_{-2}$ alone (m/z 483) or with nitric acid (m/z 546) or sodium nitrate (m/z 568). The highest peak (m/z 724) can be the result of the

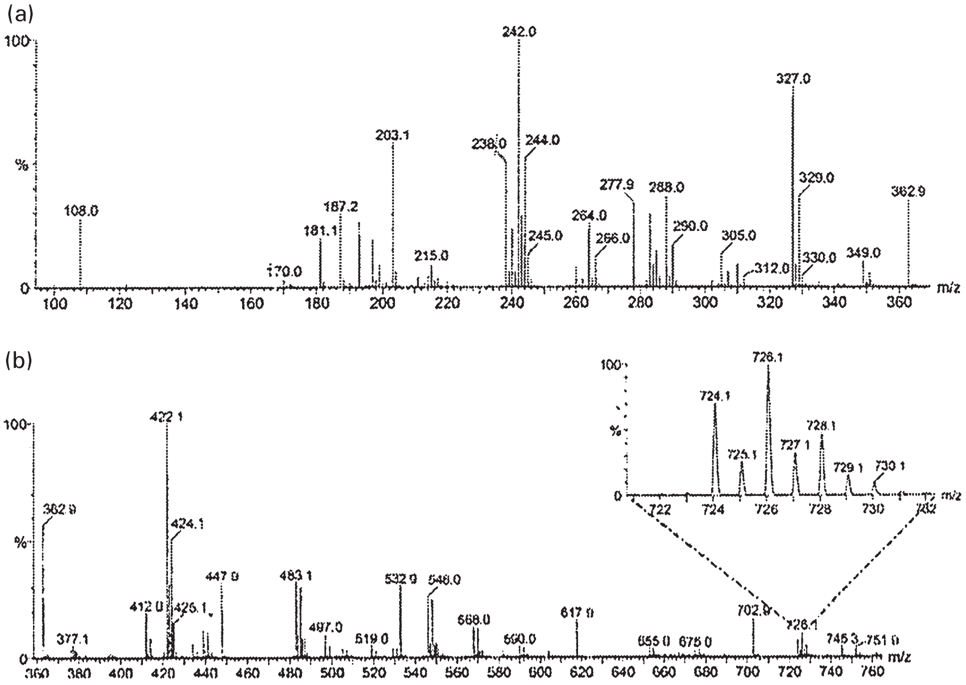

Fig. 4 High resolution mass spectrum of a copper(II)-pml solution at pH 6.5: (a) in the range of m/z = 0–350; (b) in the range of m/z = 350–800; R = 1; $C_L = 4 \times 10^{-3}$ mol dm^{-3}.

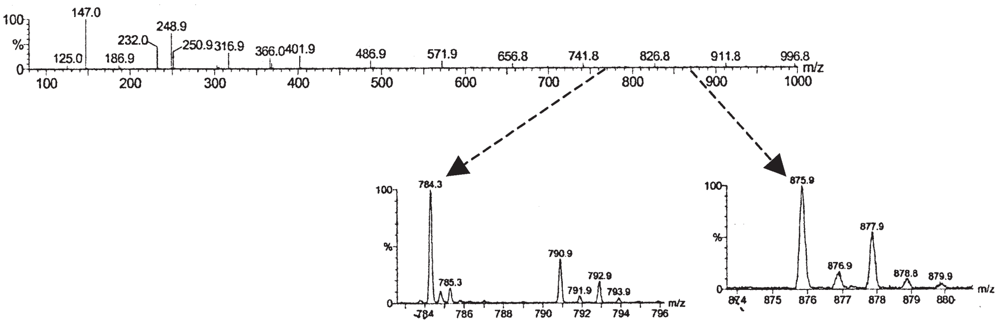

Fig. 5 Negative ion electrospray ionization mass spectrum of a copper (II)-pml solution. $R = 1$; $C_L = 4 \times 10^{-3}$ mol dm^{-3}.

association of one monocharged $CuLH_{-1}^{+}$ species and two neutral complexes $CuLH_{-2}$. All the other peaks in the spectrum correspond to cluster ions of sodium nitrate or nitric acid.

The interpretation of the solution A spectrum were confirmed by analysis of the mass spectrum of the same solution in the negative mode. Although less sensitive, negative mode provides a less complicated spectrum and a more direct determination of complex stoichiometry.[21] The main peaks detected in the spectrum correspond to cluster ions formed with sodium nitrate (m/z 147, 232, 317, 402, 487, 572, 657, 912 and 997); additionally, copper nitrate adducts are observed at m/z 187 and 249. The ions related to copper-ligand associations are detected with low abundance at m/z 303, 366, 791 and 876. The peak at m/z 303 corresponds to the association of the $CuLH_{-2}$ species with a nitrate ion. The species at m/z 366, 791 and 876 can be correlated to the $CuLH_{-1}^{+}$ species associated with two nitrate ions and 5 or 6 sodium nitrate molecules. It is important to note that there are no polymetallic ions detected in the negative mode, which confirms that only monomeric species are formed.

At pH 8.5, the positive mode spectrum of solution B (ratio $R = 1$) reveals the presence of copper complexes at m/z 505, 590, 675. The peak at m/z 505 corresponds to the association of a sodium ion and two neutral $CuLH_{-2}$ complexes. The peaks at m/z 590 and 675 correspond to the same species with sodium nitrate adducts.

Stability of copper complexes

Protonation constants of the ligands and overall stability constants of the copper(II) complexes are summarized in Table 3. Computations were done by taking into account the $CuLH_{-1}^{+}$, $CuLH_{-2}$, $CuLH_{-3}^{-}$ species and the soluble hydroxo species $CuOH^{+}$, $Cu(OH)_2$, and $Cu_2(OH)_2^{2+}$. The formation constants of the hydroxo species are available in a compilation.[22] For the three copper-ligand systems, the low values of the estimated standard deviation σ_{mlh} of each constant β_{mlh} and of the global standard deviation σ_t confirm the validity of the chemical model used in the fitting procedure. Introduction of 1:2 and 1:3 complexes into the computational model did not provide a better fit. In addition, spectral parameters were also in agreement with the exclusive formation of 1:1 species (see Fig. 3). For the Cu-dmael and Cu-dmapl systems, we included in the computation the formation constants of two copper-oxalate complexes, CuC_2O_4 and $Cu(C_2O_4)_2^{2-}$ [$\log\beta_{110} = 5.51(2)$; $\log\beta_{120} = 9.28(2)$] and the protonation constant of the oxalate ion [$\log\beta_{011} = 3.81(2)$]. These three constants were determined under our experimental conditions [$T = 25\,°C$ and $I = 0.1$ ($NaNO_3$)] by protometric and

Table 2 Singly charged ions observed in the ESI-MS spectra of copper-pml solutions

Solution and mode	m/z	Elemental composition	Formula[a]
A[b]; positive mode	181.1	$C_9H_{13}N_2O_2$	$pml + H^+$
	203.08	$C_9H_{12}N_2O_2Na$	$pml + Na^+$
	242.01	$C_9H_{11}N_2O_2Cu$	$Cu(pmlH_{-1})^+$
	326.99	$C_9H_{11}N_3O_5CuNa$	$Cu(pmlH_{-1})^+ + NaNO_3$
	422.10	$C_{18}H_{23}N_4O_4Cu$	$Cu(pmlH_{-1})^+ + L$
	483.02	$C_{18}H_{21}N_4O_4Cu_2$	$Cu(pmlH_{-1})^+ + Cu(pmlH_{-2})$
	546.01	$C_{18}H_{22}N_5O_7Cu_2$	$Cu(pmlH_{-1})^+ + Cu(pmlH_{-2}) + HNO_3$
	567.99	$C_{18}H_{21}N_5O_7Cu_2Na$	$Cu(pmlH_{-1})^+ + Cu(pmlH_{-2}) + NaNO_3$
	724.02	$C_{27}H_{31}N_6O_6Cu_3$	$Cu(pmlH_{-1})^+ + 2Cu(pmlH_{-2})$
A[b]; negative mode	186.90	N_2O_6Cu	$Cu(NO_3)_2^-$
	248.89	N_3O_9Cu	$Cu(NO_3)_3^-$
	302.99	$C_9H_{10}N_3O_5Cu$	$Cu(pmlH_{-2}) + NO_3^-$
	365.98	$C_9H_{11}N_4O_8Cu$	$Cu(pmlH_{-1})^+ + 2NO_3^-$
	790.88	$C_9H_{11}N_9O_{23}CuNa_5$	$Cu(pmlH_{-1})^+ + 2NO_3^- + 5NaNO_3$
	875.85	$C_9H_{11}N_{10}O_{26}CuNa_6$	$Cu(pmlH_{-1})^+ + 2NO_3^- + 6NaNO_3$
B[c]	504.99	$C_{18}H_{20}N_4O_4Cu_2Na$	$2Cu(pmlH_{-2}) + Na^+$
	589.98	$C_{18}H_{20}N_5O_7Cu_2Na_2$	$2Cu(pmlH_{-2}) + NaNO_3 + Na^+$
	674.95	$C_{18}H_{20}N_6O_{10}Cu_2Na_3$	$2Cu(pmlH_{-2}) + 2NaNO_3 + Na^+$
C[d]	242.01	$C_9H_{11}N_2O_2Cu$	$Cu(pmlH_{-1})^+$
	326.99	$C_9H_{11}N_3O_5CuNa$	$Cu(pmlH_{-1})^+ + NaNO_3$
	422.10	$C_{18}H_{23}N_4O_4Cu$	$Cu(pmlH_{-1})^+ + pml$

[a] For copper complexes the m/z values correspond to the species formed with the ^{63}Cu isotope. [b] Solution A: [L] $= 4 \times 10^{-3}$ mol dm^{-3}; [M^{2+}] $= 4 \times 10^{-3}$ mol dm^{-3}; pH = 6–6.5. [c] Solution B: [L] $= 4 \times 10^{-3}$ mol dm^{-3}; [M^{2+}] $= 4 \times 10^{-3}$ mol dm^{-3}; pH = 8–8.5. [d] Solution C: [L] $= 4 \times 10^{-3}$ mol dm^{-3}; [M^{2+}] $= 2 \times 10^{-3}$ mol dm^{-3}; pH = 6–6.5.

Table 3 Logarithmic values of the protonation constant of the ligands (β_{011}) and of the overall stability constants of the copper(II) complexes determined by potentiometric titrations[a][b]

						Log($[Cu^{2+}]/C_M$)	
	log β_{011}	logβ_{11-1}	logβ_{11-2}	logβ_{11-3}	σ_t	pH 9	pH 11
pml	4.26(1)	−1.47(1)	−8.98(1)	−18.61(2)	1.25	−5.60	−10.88
dmael[c]	8.46(1)	−1.81(2)	−10.44(1)	−19.96(1)	1.32	−4.17	−9.53
dmapl[c]	9.21(1)	−1.80(3)	−11.46(2)	−21.81(3)	1.39	−3.35	−7.47

[a] $I = 0.1$ mol dm^{-3} (NaNO$_3$), $T = 298$ K. [b] Values in parentheses refer to estimated standard deviations for the last significant digit. [c] For the Cu-dmael and Cu-dmapl systems, computations are done by taking into account the overall formation constants of copper-oxalate complexes (logβ_{110} = 5.51; logβ_{120} = 9.28) and the protonation constant of the oxalate ion (logβ_{011} = 3.81).

complexometric titrations. For both systems, refinement of the experimental titration curves monitored with the five metal complexes, CuC_2O_4, $Cu(C_2O_4)_2^{2-}$, $CuLH_{-1}^{+}$, $CuLH_{-2}$, $CuLH_{-3}^{-}$, provided good fits with low σ_{mlh} and σ_t. Acceptable refinements were also obtained by taking into account the formation of a mixed complex $[Cu(LH_{-1})(C_2O_4)]^{-}$ [instead of $Cu(LH_{-1})^{+}$]; however, the comparison of the UV-visible spectra with and without the oxalate ions did not provide experimental evidence for the formation of such a complex.

In order to make the stability constant values more explicit, the complexing abilities of the three ligands towards copper (II) were compared. Table 3 contains the molar fraction (on a logarithmic scale) of free metal ions at pH 9 and 11 for the three systems. The value of log($[Cu^{2+}]/C_M$) clearly shows the difference in the chelating ability of the three ligands. Complexation occurs above pH 3 with pml, but only above pH 6 with dmael and pH 7 with dmapl. At pH 11, the free copper concentration is 3.4 log units smaller with pml than with dmapl. The strong affinity of pml towards Cu(II) compared to dmael and dmapl is due to the pyridinic nitrogen atom while the higher affinity of copper(II) towards dmael compared to dmapl is in accordance with the higher stability of a five-membered chelate ring compared to a six-membered one.

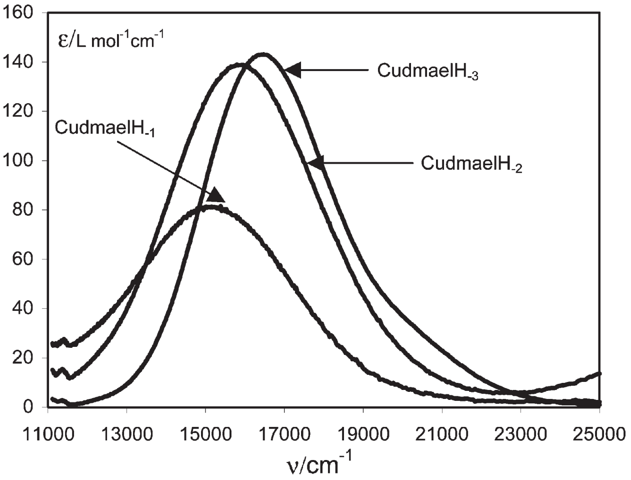

Fig. 6 Electronic spectra computed from the spectrophotometric titrations and the stability constants of the Cu(II)-dmael complexes.

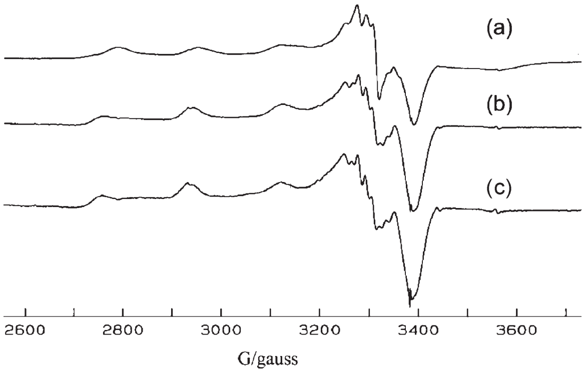

Fig. 7 Low-temperature (100 K) ESR spectra of the species formed in Cu(II)-dmael solution ($C_M = 2 \times 10^{-3}$ mol dm^{-3}; $C_L = 4 \times 10^{-3}$ mol dm^{-3}) at different pH: (a) 11, (b) 9, (c) 7.

Structure of complexes in aqueous solutions

In order to understand more clearly the complexation process of copper with lactamide compounds, we examined the spectral features of copper(II) complexes. Figs. 6 and 7 show the electronic and ESR spectra of Cu-dmael complexes. The electronic spectra were computed from the spectrophotometric titrations and the formation constants reported in Table 3. The ESR spectra are anisotropic and typical of axially symmetric monomeric copper(II) with three of the expected four hyperfine transitions in the parallel region visible while the fourth transition is masked by overlap with perpendicular features of the spectrum. The spectra exhibit a tetragonal distortion with $g_{\parallel} > g_{\perp}$ and a d_{x2-y2} ground state.[23] The hyperfine coupling constant and the g values (Table 4) are very close to those found for the copper-bleomycin complex[24] and are in agreement with a square pyramidal geometry[25–27] for all complexes. The value of $A_{\parallel}$ is thus indicative of a low-distortion square pyramidal geometry and the strong in-plane ligand strength is corroborated by the large $A_{\parallel}$ values. The appearance of a five-line superhyperfine splitting in the parallel region of the ESR spectra for all complexes indicates the presence of two nitrogen atoms in the coordination sphere of the copper(II) ion. The absorption spectra for these complexes essentially exhibit similar patterns in the 250–450 nm region, with strong bands that may be due to intraligand[28] and charge transfer transitions. In the visible region, the spectra of copper complexes exhibit only one single d-d transition. The symmetrical shape of the bands and the values of the molar extinction coefficient ε, ranging between 75 and 143 L mol^{-1} cm^{-1}, are characteristic of a square-based pyramidal geometry around the Cu^{2+} ion.[28–30] The range of λ_{max} values of the Cu-dmael complexes (between 608 and 660 nm) confirms the

Table 4 Spectral parameters of various copper(II) complexes

	pml			dmael			dmapl		
	$CuLH_{-1}$	$CuLH_{-2}$	$CuLH_{-3}$	$CuLH_{-1}$	$CuLH_{-2}$	$CuLH_{-3}$	$CuLH_{-1}$	$CuLH_{-2}$	$CuLH_{-3}$
λ_{max}/nm	650	620	605	660	630	608	–	655	613
ε/L mol^{-1} cm^{-1}	80	127	120	80	138	143	–	75	80
$g_{\parallel}$	2.26	2.24	2.24	–	–	2.24	–	–	2.23
$g_{\perp}$	2.06	2.05	2.05	–	–	2.05	–	–	2.05
$A_{\parallel}/10^{-4}$ cm^{-1}	173	193	188	–	–	198	–	–	173

2N coordination according to the Billo equation[31] and is comparable to that reported by several authors for copper-peptide complexes.[32–35]

In Table 4, we report the ESR and electronic spectral parameters for all 3 ligand complexes. For Cu(II)-pml solutions, ESR parameters were determined at pH values corresponding to the maximum predominance of $CuLH_{-1}^{+}$ $CuLH_{-2}$, and $CuLH_{-3}^{-}$. ESR parameters were determined on Cu(II)-dmael and Cu(II)-dmapl solutions above pH 11, which corresponds to the maximum formation of $CuLH_{-3}$ species. The comparison of the spectral parameters shows clearly that copper(II) ion has the same coordination mode in the $CuLH_{-1}^{+}$ species. The structure of $CuLH_{-1}^{+}$ species in aqueous solution can also be compared with those reported for isolated solid compounds (see below). The loss of one proton on the ligand in $CuLH_{-1}^{+}$ is attributed to deprotonation of the amidic nitrogen atom upon complexation to form two five-membered chelate rings with the ligands pml and dmael, and both five- and six-membered rings in the case of dmapl. These facts are in full agreement with the X-ray structure of the complex $[Cu(pmlH_{-1})Cl]\cdot H_2O$ and shows that the structural arrangement is identical in the solid state and in solution. Similar data for all complexes and other copper-bleomycin models[36,37] show that the coordination structures of these complexes are about the same as for the carboxamido complexes.[38,39]

Steric hindrance does not allow the fixation of a second ligand, so that the five coordination number of copper(II) is achieved by two water molecules. ESR and visible spectra parameters are in good agreement with a pentacoordination for all the copper-lactamide systems.[24–26] The further deprotonation of $CuLH_{-1}^{+}$ to form $CuLH_{-2}$ and $CuLH_{-3}^{-}$ species corresponds likely to loss of a proton from the hydroxyl group and/or from a coordinated water molecule. This interpretation is corroborated by the weak variation of λ_{max} for the three different $CuLH_{-1}^{+}$, $CuLH_{-2}$ and $CuLH_{-3}^{-}$ species as well as the similarities of their ESR parameters in the case of the ligand pml. However, potentiometric and spectroscopic data do not allow to specify the exact sequence of the second and third deprotonation steps.

Molecular structures of $[Cu(pmlH_{-1})Cl]\cdot H_2O$ (1) and $[Cu(pmlH_{-1})Br]\cdot H_2O$ (2)

Compounds **1** and **2** are isostructural and the corresponding selected bond parameters are listed in Table 5. The asymmetric unit of compounds **1** and **2** includes one $Cu(pmlH_{-1})X$ (X = Cl or Br) fragment and one water molecule. The structure reveals that the copper(II) ion is surrounded by one pyridyl nitrogen [N(1)], one deprotonated amido nitrogen [N(2)], one alcohol oxygen [O(2)] while the fourth site of the equatorial plane around the metal ion is occupied by a chloride or a bromide ion. The molecular structure of $[Cu(pmlH_{-1})Cl]\cdot H_2O$ O (**1**) is illustrated in Fig. 8(a). The chelate bite angles of the two five-membered rings formed by the pyridyl-N, the amido-N and the alcohol-O are 82.41° and 80.64°. The $Cu–N_{amido}$ (1.911 Å) bond distance, slightly shorter than that of $Cu–N_{pyridyl}$ (1.988 Å) is consistent with the deprotonated form of the amide group.[40] The Cu–Cl bond length (2.2226 Å), longer than the three others, is in agreement with those found for copper(II) complexes that contain a tridentate coligand.[41]

In the crystalline structure, compound **1** forms a one-dimensional chain of copper(II) ions *via* equatorial-apical bridges [Fig. 8(b)], giving a polymeric species. The $Cu\cdots Cl_{apical}$ and inter-monomer $Cu\cdots Cu$ distances are 2.996 and 4.018 Å, respectively. The Cu–Cl–Cu bridge angle is 99.65°. The four equatorial coordinating atoms N(1), N(2), O(2) and Cl are nearly coplanar. In the lattice, the water molecule of crystallization forms two kinds of H-bonds: the oxygen atom O_w is H-bonded with the hydrogen of the alcohol group ($O_w\cdots H–O$ = 2.600 Å) and each of the two H_w is H-bonded with

Table 5 Selected bond lengths (Å) and bond angles (°) for $[Cu(pmlH_{-1})X]$ complexes with X = Cl and Br

	$[Cu(pmlH_{-1})Cl]\cdot H_2O$ (**1**)	$[Cu(pmlH_{-1})Br]\cdot H_2O$ (**2**)
Cu–N(1)	1.988(2)	1.991(4)
Cu–N(2)	1.911(2)	1.903(4)
Cu–O(2)	1.985(2)	1.993(3)
Cu–X	2.222(5)	2.3646(6)
N(1)–Cu–N(2)	82.41(7)	82.7(2)
N(1)–Cu–O(2)	162.44(6)	162.2(1)
N(1)–Cu–X	100.62(5)	100.6(1)
N(2)–Cu–X	167.15(5)	165.9(1)
N(2)–Cu–O(2)	80.64(7)	80.4(1)
X–Cu–O(2)	94.98(4)	94.51(4)

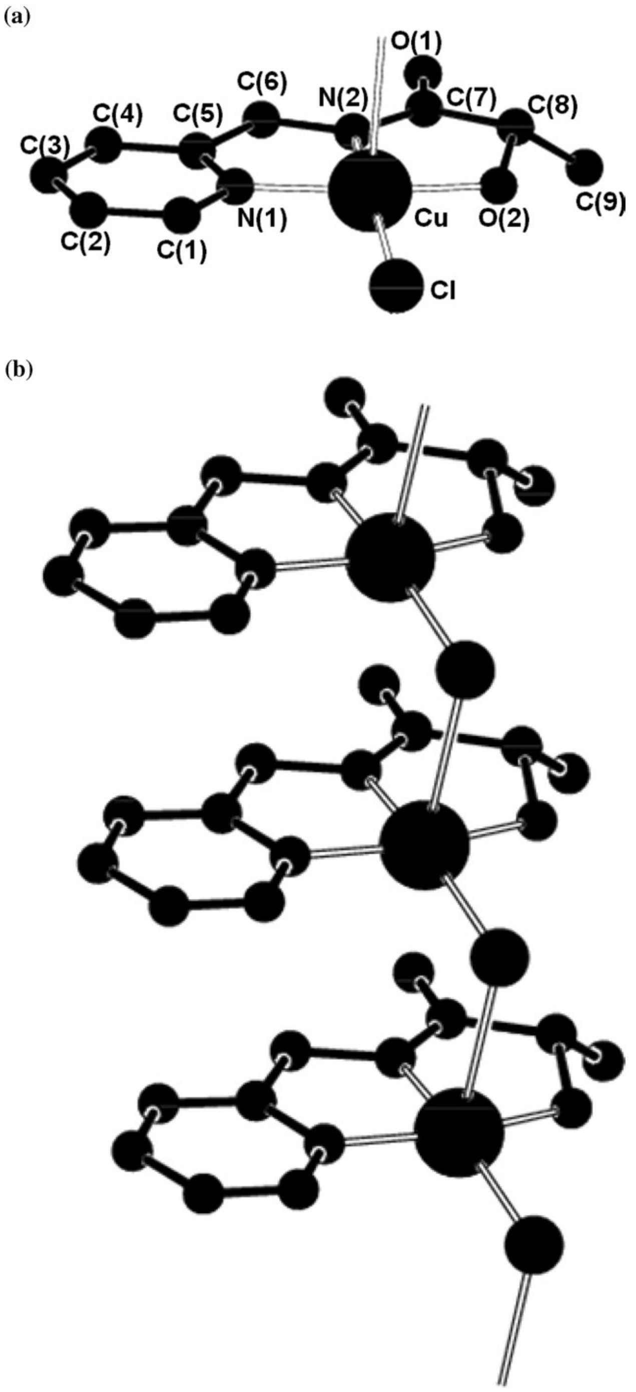

Fig. 8 (a) Molecular structure with atom labelling and (b) chain structure of $[Cu(pmlH_{-1})Cl]\cdot H_2O$. For clarity, hydrogen atoms and water molecule are omitted.

the neighbouring molecule *via* the oxygen of the C=O group, which leads to the formation of a polymeric species.

Spectroscopic properties

To investigate whether or not the solid state structure is retained in solution, the UV-visible spectral behaviour was investigated in solution (DMF) as well as in the solid state. The overall pattern for both spectra corresponding to each complex is closely similar. The electronic spectra of these complexes display an absorption in the range 600–675 nm (see Experimental). In this region, absorptions observed for other square-planar or square-pyramidal copper(II) complexes of similar ligands have been assigned to d-d transitions.[41]

Conclusion

For the three ligands studied, the potentiometric and UV-visible spectrophotometric results reveal the formation of $CuLH_{-1}^{+}$, $CuLH_{-2}$ and $CuLH_{-3}^{-}$ species. The determination of the overall formation constants of the complexes indicates that the chelating power of the ligands towards copper ions decreases in the order pml > dmael > dmapl. The coordination mode of the ligands in aqueous solutions was specified by ESR and UV-visible spectrophotometry. The copper(II) complexes formed with the three ligands have a square-pyramidal geometry with two nitrogen atoms and one oxygen atom in the first coordination sphere. This coordination mode was confirmed by the structures of the solid compounds $[Cu(pmlH_{-1})X]\cdot H_2O$ (X = Cl or Br).

Acknowledgements

This work has been supported by a BQR grant of the Université de Reims-Champagne Ardenne. We are grateful to Dr A. De Cian (Université Louis Pasteur, Strasbourg, France) for the single-crystal X-ray analyses. We thank Dr S. Brandes for ESR spectra recording and helpful discussions. We also thank P. Gans, A. Sabatini and A. Vacca for the free distribution of the HYSS program.

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