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Synthesis and characterisation of zinc(II) complexes of tripodal N_7 ligands involving pyridine and amine or amide nitrogen donors. Crystal structure of a zinc(II) complex

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Two tripodal heptadentate ligands tris[2-(2-pyridylmethyl)aminoethyl]amine (tpaa), and tris[2-picolinamidoethyl]amine (trenpicam) were synthesized as their hydrochloride salts and their protonation constants determined by potentiometry; variable pH ^{1}H NMR spectroscopy allows the determination of the order of protonation of their different basic nitrogen atoms. The stability constants of the zinc(II) chelates with these ligands, determined by potentiometry and UV spectrometry, show the formation of $[Zn(LH_2)]^{4+}$, $[Zn(LH)]^{3+}$ and $[ZnL]^{2+}$ species with tpaa, whereas amide group deprotonation of trenpicam permits the detection of the variable stoichiometry species $[ZnL]^{2+}$, $[ZnL_2]^{2+}$, $[Zn(L_2H_{-1})]^{+}$, $[Zn(L_2H_{-3})]^{-}$, $[Zn_2(LH_{-2})_2]$ and $[Zn_2(L_2H_{-5})]^{-}$, where LH_{-x} is an amide-deprotonated ligand. The zinc(II) complexes $[ZnL](ClO_4)_2$ (L = tpaa or trenpicam), and the dinuclear complex $[Zn_2(LH_{-2})Cl_2]$ (L = trenpicam) have been prepared and characterized by IR and mass spectroscopy. The crystal structure of the protonated ligand [Htrenpicam](ClO_4) and the complex $[Zn(tpaa)](ClO_4)_2$ are reported. $[Htrenpicam]^{+}$ contains one intra-molecular H-bond and in the cation $[Zn(tpaa)]^{2+}$ the geometry around the Zn^{2+} ion is distorted octahedral with one pyridyl nitrogen uncoordinated.

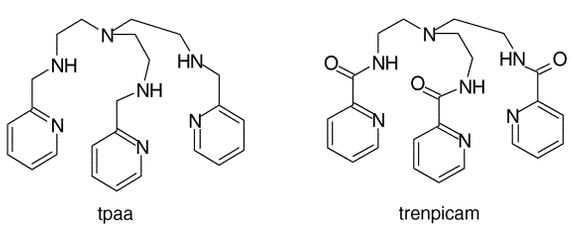
Introduction

The binding of metal ions by proteins and peptides is of fundamental interest due to the importance of metal ions in biological systems. Metals may be part of the active sites of enzymes, stabilize the macromolecular structure of proteins and affect enzymes or membranes to control cell metabolism.[1] Therefore, for many years there has been great interest in the study of complexes able to mimic the active sites of metalloproteins. These model complexes are generally obtained from bulky polydentate ligands in order to get an environment similar to the one found in proteins.

In previous papers we have described the complexation of different metal ions (Co^{2+}, Cu^{2+} and Zn^{2+}) with potentially hexadentate linear ligands involving two pyridyl groups and containing mixed heteroatom donors (N, O or S).[2] The structural, redox and thermodynamic properties of these complexes depend on the nature of the two central heteroatom donors. In addition, we have synthesized tripodal ligands which contain the well known tris(2-aminoethyl)amine (tren), in order to study their interactions with the following transition metal ions: Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}. The latter is the second most-abundant metal in biology and for instance, data on at least 34 enzymes suggest that the Zn^{2+} ion is present in numerous metalloenzymes, such as hydrolases where it may be involved as a necessary cofactor. Most of these zinc-containing enzymes are involved in hydrolysis reactions with the Zn^{2+} ion acting as a Lewis acid,[3] or playing a structural role.[4] Zinc(II) has the particularity of not being involved in any redox reactions. Indeed, this ion is often coordinated to several nitrogen atoms of His residues.[5]

The Fe(III),[6,7] Fe(II),[8] Mn(II)[9] complexes with the heptadentate tripod ligand tris[2-(2-pyridylmethyl)aminoethyl]amine (tpaa) have been previously reported as models of superoxide dismutase (SOD). Morgenstern-Baradau and co-workers[8,9] structurally characterized the $[Mn(tpaa)]^{2+}$ and $[Fe(tpaa)]^{2+}$ compounds having a coordination number of seven, achieved using only one ligand. Callhan and co-workers[10] reported a dinuclear compound obtained with Ni^{2+} and tpaa. Scrimin and co-workers[11] described the binding of tpaa with each pyridyl nitrogen donor in $[Zn(porphyrin)]^{2+}$, giving a molecular tris-(porphyrin) cage. To our knowledge no published data referring either to the acidity constants of tpaa or to the stability constants of its metallic ion complexes have been reported.

In order to expand on the role of the Zn^{2+} ion in the structural or catalytic functions of the model complexes, we report here the properties of two heptadentate ligands tris[2-(2-pyridylmethyl)aminoethyl]amine, (tpaa) and tris(2-picolinamidoethyl)amine, (trenpicam: tris[2-(2-pyridyl)amidoethyl]-amine) (Scheme 1) and their interactions with the Zn^{2+} ion. The



Scheme 1

syntheses of the two ligands and their zinc(II) complexes as well as the thermodynamic constants of the metal chelates formed by these ligands are described. The structure of the protonated ligand $[Htrenpicam]^{+}$ and the $[Zn(tpaa)]^{2+}$ complex have been investigated.

Experimental

Reagents

All the solvents were purified by conventional procedures[12] and

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distilled prior to use. All the chemicals commercially available (Aldrich) were used as supplied without further purification.

Synthesis of ligands

The syntheses of the two ligands tpaa[6,9] and trenpicam[13] are reported in the literature. However, we have developed a straightforward procedure for obtaining tpaa by modifying the reported procedure, and trenpicam was obtained from the procedure described by Vagg[14] and Mukherjee[15] for 1,2-bis-(pyridylamido)ethylene.

Tris(2-pyridylmethyl)-2-aminoethyl]amine pentahydrochloride monohydrate (tpaa·5HCl·H_2O). Tris(2-aminoethyl)amine (2.19 g, 15 mmol) dissolved in 40 mL of ethanol was added dropwise with stirring to a solution of 2-pyridinecarbaldehyde (4.80 g, 45 mmol) in 50 mL of ethanol and the mixture was refluxed for 2 h and allowed to cool at room temperature. $NaBH_4$ (0.57 g, 15 mmol) was added in small portions to the solution, and the mixture was stirred overnight. The reaction mixture was neutralized with concentrated HCl (pH ≈ 7) and evaporated to dryness. The residue was taken up in an aqueous 1 M solution of NaOH, and extracted with dichloromethane (3 × 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was rotoevaporated to give a yellowish oil which was taken up in methanol (30 mL). The solution was acidified with concentrated HCl (pH ≈ 1.5) and stirred at room temperature for about 2 h. The yellowish crude crystalline product which precipitated was filtered off, washed with methanol and dried *in vacuo* (yield *ca*. 75%); mp 206 °C. FAB MS: found, *m*/*z* 420 (20%); calc. for $[Htpaa]^+$, 420. Found: C, 46.4; H, 6.1; N, 15.5; Cl, 28.4. $C_{24}H_{40}N_7OCl_5$ requires C, 46.5; H, 6.5; N, 15.8; Cl, 28.6%. δ_H(250 MHz, D_2O), 8.65 (d, 3H), 8.20 (t, 3H), 7.80 (d, 3H), 7.70 (t, 3H), 4.80 (s, 4H), 4.50 (t, 2H), 3.35 (t, 6H), 2.95 (t, 6H). IR (KBr disk, ν/cm^{-1}): 3420 (s, $\nu_{N-H\,+\,OH}$); 3060–2700 (s or m, ν_{C-H}); 1640, 1616, 1546, 1465, 775 (vs, $\nu_{pyridine\ ring}$).

Tris(2-picolinamidoethyl)amine tetrahydrochloride hemihydrate (trenpicam·4HCl·0.5H_2O). To a mixture of picolinic acid (5.62 g, 46 mmol) in pyridine (15 mL) was added dropwise with stirring a solution of tris(2-aminoethyl)amine (2.19 g, 15 mmol) in pyridine (10 mL) at room temperature. The resulting emulsion was stirred for 60 min at 70 °C. To the solution obtained, triphenylphosphite (13.88 g, 45 mmol) was added dropwise with stirring. The mixture was refluxed overnight. After cooling the reaction mixture to room temperature and removal of the solvent under reduced pressure, the dark brown oil thus obtained was dissolved in dichloromethane (50 mL). The resulting solution was washed three times with water, three times with a saturated ammonium chloride solution, and then with brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was rotoevaporated to give a deep red-brown viscous liquid which was taken up in methanol (30 mL). The solution was acidified with concentrated HCl (pH ≈ 1.5) and kept in the refrigerator for 12 h. The pale brown crude crystalline product which precipitated was filtered off, washed with methanol and dried *in vacuo* (yield *ca.* 85%); mp 222 °C. FAB MS: found, *m*/*z* 462 (15%); calc. for $[Htrenpicam]^+$, 462. Found: C, 46.8; H, 4.8; N, 15.7; Cl, 22.7. $C_{24}H_{32}N_7O_{3.5}Cl_4$ requires C, 46.8; H, 5.2; N, 15.9; Cl, 23.0%. δ_H(250 MHz, D_2O), 8.65 (d, 3H), 8.40 (t, 3H), 8.00 (d, 3H), 7.90 (t, 3H), 3.90 (t, 6H), 3.70 (t, 6H). IR (KBr disk, ν/cm^{-1}): 3415, 3205 (s, $\nu_{N-H\,+\,OH}$); 3048–2750 (s or m, ν_{C-H}); 1680, 1605 (vs, $\nu_{C=O}$); 1565, 1450, 750 (s, $\nu_{pyridine\ ring}$); 1520 (s, ν_{C-N} and δ_{N-H}).

Synthesis of zinc(II) complexes

CAUTION! Although we have experienced no problems while handling any of the perchlorates described herein, readers are advised to handle these compounds with care.

[Zn(tpaa)]$(ClO_4)_2$ 1 and [Zn(trenpicam)]$(ClO_4)_2$ 2. A mixture of sodium acetate trihydrate (0.54 g, 4 mmol) and ligand hydrochloride, tpaa (0.62 g, 1 mmol) or trenpicam (0.62 g, 1 mmol), in absolute ethanol (30 mL) was stirred whilst boiling (10 min, water bath), then cooled and the sodium chloride which precipitated was filtered off. Zinc perchlorate hexahydrate (0.37 g, 1 mmol) in absolute ethanol (20 mL) was added dropwise to the filtrate and the solution was stirred for 2 h at room temperature. A colourless powder formed which was filtered off, washed with ethanol and dried *in vacuo*.

[Zntpaa]$(ClO_4)_2$ **1**: (yield *ca.* 70%); recrystallization from water–ethanol (1 : 1) gave colourless crystals suitable for X-ray structure determination, after three weeks; mp 220 °C. FAB MS: found, *m*/*z* 583, 484; calc. for $[Zn(tpaa)](ClO_4)^+$ and $[Zn(tpaa)]^{2+}$ 583 and 484 respectively. Found: C, 42.5; H, 4.6; N, 14.3; Zn, 9.3. $C_{24}H_{33}N_7O_8Cl_2Zn$ requires C, 42.2; H, 4.8; N, 14.3; Zn, 9.6%. IR (KBr disk, ν/cm^{-1}): 3325, 3291 (s, ν_{N-H}); 2940–2850 (m, ν_{C-H}); 1607, 1571, 1481, 1445 (s, $\nu_{pyridine\ ring}$) 1100 (vs, $\nu_{ClO_4^-}$).

[Zn(trenpicam)]$(ClO_4)_2$ **2**: (yield *ca.* 60%); mp 258 °C (decomp.). FAB MS: found, *m*/*z* 625 (15%), 526 (40%), calc. for $[Zn(trenpicam)](ClO_4)^+$ and $[Zn(trenpicam)]^{2+}$ 625 and 526 respectively. Found: C, 39.8; H, 3.3; N, 13.7; Zn, 8.7. $C_{24}H_{27}N_7O_{11}Cl_2Zn$ requires C, 39.7; H, 3.7; N, 13.5; Zn, 9.0%. IR (KBr disk, ν/cm^{-1}): 3350, 3100 (s, ν_{N-H}); 2950–2850 (m, ν_{C-H}); 1640, 1600 (vs, $\nu_{C=O}$); 1570, 1480, 750 (s and m, $\nu_{pyridine\ ring}$); 1520 (s, ν_{C-N} and δ_{N-H}); 1100 (vs, $\nu_{ClO_4^-}$).

[Zn_2(trenpicamH_{-2})Cl_2] 3. A solution of trenpicam·4HCl·0.5H_2O (0.62 g, 1 mmol) in 20 mL of sodium hydroxide was extracted with dichloromethane (3 × 10 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was rotoevaporated and a deep red-brown oil obtained was taken up in DMF (15 mL). Solid sodium hydride (0.050 g, 2 mmol) was added in small portions to the solution with stirring under N_2. A solution of zinc(II) chloride (0.27 g, 2 mmol) in DMF (10 mL) was added to the yellow solution obtained and the mixture was stirred at room temperature for 2 h. The solvent was removed by rotoevaporation. The crude crystalline product obtained was dissolved in hot acetone, cooled and filtered. The acetone solution was evaporated to give a yellowish powder (yield *ca.* 45%); mp 213 °C. FAB MS: found, *m*/*z* 663 (20%), 588 (40%), 524 (35%); calc. for $[Zn_2(trenpicamH_{-2})Cl_2]^+$, $[Zn_2(trenpicamH_{-2})]^{2+}$ and $[Zn(trenpicamH_{-2})]^{2+}$ 663, 588 and 524 respectively. Found: C, 43.4; H, 4.0; N, 14.5; Cl 10.3; Zn, 19.5. $C_{24}H_{25}N_7O_3Cl_2Zn$ requires C, 43.6; H, 3.8; N, 13.5; Cl 10.7; Zn, 19.8%. IR (KBr disk, ν/cm^{-1}): 3325, 3060 (s, ν_{N-H}); 2950–2750 (m, ν_{C-H}); 1670, 1605 (vs, $\nu_{C=O}$); 1570, 1480, 740 (s and m, $\nu_{pyridine\ ring}$); 1480 (s, ν_{C-N} and δ_{N-H}).

Measurements

Elemental analyses (C, H and N) were carried out on a Perkin-Elmer 2400 C, H, N element analyser in our University. The metal analyses were performed on an ICP AES Liberty Series II Varian apparatus and chloride ions were determined potentiometrically using silver nitrate.

Protometric. Stock solutions of zinc(II) nitrate and zinc(II) perchlorate (Fluka) were standardized by H_4EDTA (pH = 10, Eriochrome Black T as an indicator). The basic (KOH) and strongly acidic (HNO_3) reactants were prepared from standardized 1 mol L^{-1} solutions (Prolabo).

Protometric titrations were performed at 25 °C using KOH 0.1 mol L^{-1} under a nitrogen stream, with a Metrohm 665 Dosimat. pH measurements were carried out with a Metrohm 654 pH-meter equipped with a combined glass electrode (filled with KCl 3 mol L^{-1}). HNO_3 0.01 mol L^{-1} solutions were used for the standardization. The ionic strength of the solutions was adjusted to 1 mol L^{-1} with KNO_3 (Fluka).

Table 1 X-Ray experimental data

Compounds	[Htrenpicam](ClO$_4$)	[Zn(tpaa)](ClO$_4$)$_2$
Formula	$C_{24}H_{28}N_7O_7Cl$	$C_{24}H_{33}N_7O_8Cl_2Zn$
M	561.99	683.85
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$ (no. 1)	$P2_1/c$ (no. 1)
a/Å	7.3724(1)	9.9115(2)
b/Å	27.1686(6)	16.1184(3)
c/Å	13.3039(3)	19.2407(5)
α/°	90	90
β/°	100.696(5)	103.543(5)
γ/°	90	90
U/Å^3	2618.44(9)	2988.4(1)
T/K	294	294
Z	4	4
F(000)	1176	1416
μ(Mo-Kα)/mm^{-1}	0.71073	0.71073
Reflections measured	10162	12287
Unique reflections collected	6140	7072
$wR(F^2)$	0.070	0.070
$R1(I > 2\sigma(I))$	0.056	0.047
R_{int}	0.04	0.04

Equilibrium constants were determined by fitting the titration curves with the least-squares refinement program PROTAF.[16] Furthermore, for some of the complexes occurring at high pH values, the determination of the ionic product of water under similar conditions was required. This was performed by refining the titration curves of acetic acid, a simple system which does not implicate equilibria above pH = 8. The solutions of both ligands used for the determination of the protonation and complexation constants were titrated with KOH 0.1 mol L^{-1}. Their concentrations ranged from 1.25×10^{-3} to 3.00×10^{-3} mol L^{-1}. The L–Zn ratios ranged from 1–10 : 1.

Spectroscopic. UV absorption spectra were recorded in quartz cells (1 cm path length) using a Shimadzu UV-2401-PC spectrophotometer equipped with a standard syringe sipper and a temperature-controlled cell holder TCC-240A. Solutions of both ligands were prepared without KNO_3 and titrated first with KOH and secondly with $HClO_4$ ($c_L = 7.5 \times 10^{-4}$ mol L^{-1} for tpaa and 5.3×10^{-5} mol L^{-1} for trenpicam). In the presence of Zn^{2+} (as its perchlorate salt) the ligand to metal ratio was adjusted to 1 : 1. The UV measurements required low pH values, so the electrode was calibrated in the range pH = 0–2 (where the response of the electrode is not linear) with increasing amounts of $HClO_4$ (pH = $-\log c_{HClO_4}$).

IR spectra were obtained in KBr pellets with a Nicolet Avatar 320. All NMR spectra were recorded in D_2O at room temperature with a Bruker AC 250 spectrometer. Chemical shifts (in ppm) for ^{1}H NMR spectra were referenced to residual protic solvent peaks. Mass spectra were obtained on a VG Instrument Autospec by the FAB technique. In all cases, the theoretical isotopic distributions of the relevant peaks were found to agree with the experimental spectrum.

Crystal structure determination

In Table 1 are summarized the pertinent crystallographic data together with the refinement details for [Htrenpicam](ClO$_4$) and [Zn(tpaa)](ClO$_4$)$_2$ **1**.

The crystal data were collected at 294 K on a Kappa CCD diffractometer using monochromated Mo-Kα 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 the positions expected for the hydrogen atoms. Hydrogen atoms were introduced as fixed contributors at calculated positions (C–H = 0.95 Å, B(H) = 1.3B_{eq}). Final difference maps revealed no significant maxima. All calculations were using the Nonius OpenMoleN package.[17] Neutral atom scattering factor coefficients and anomalous dispersion coefficients were taken from a standard source.[18]

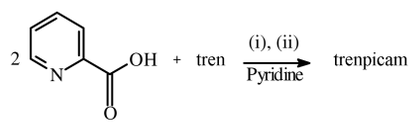
CCDC reference numbers 165086 and 165087.

See http://www.rsc.org/suppdata/dt/b1/b104777a/ for crystallographic data in CIF or other electronic format.

Results and discussion

Synthesis

The ligand tpaa described previously,[6,9] was easily prepared from commercially available tris(2-aminoethyl)amine (tren) by $NaBH_4$ reduction of the Schiff condensation product with 2-pyridinecarbaldehyde. The ligand trenpicam is obtained *via* a single-step synthesis of the amide from picolinic acid and tren, activated by triphenylphosphite (Scheme 2). The potentiometric



Scheme 2 (i) 100 °C, 60 min; (ii) + P(OPh)$_3$, reflux overnight.

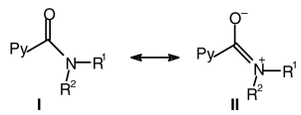
titration of ligands by silver nitrate confirmed that these compounds were isolated as penta- and tetra-hydrochloride salts respectively; five of the seven basic groups are likely to be protonated for tpaa and only four for trenpicam. The mass spectra gave clear molecular ion (M + H$^+$) peaks at m/z 420 for Htpaa and 462 for Htrenpicam.

The colourless complexes **1** and **2** were synthesized by treating an ethanolic suspension of the ligand hydrochloride salt and 5 or 4 equivalents of sodium acetate and the zinc(II) perchlorate hexahydrate. The binuclear complex **3** was obtained by the reaction of a DMF solution of the free ligand with 2 equivalents of sodium hydride and 2 equivalents of zinc(II) chloride. The three zinc(II) complexes were recrystallized from mixed water–ethanol (1 : 1) but complex **2** was dissociated. Therefore, suitable crystals for structure determination were only obtained for complex **1** and the protonated ligand [Htrenpicam](ClO$_4$).

As no suitable crystals for X-ray structure determination were obtained for complexes **2** and **3**, ^{1}H NMR studies for trenpicam and its zinc(II) complexes were performed. Unfortunately, these data offer little information other than showing the presence of the constituents. One reason for their limited value lies in the fact that complexes **2** and **3** require the highly polar DMSO as solvent. This solvent has the disadvantage of causing broad NMR resonances, thus obscuring the information obtainable from signal splitting or multiplet patterns.

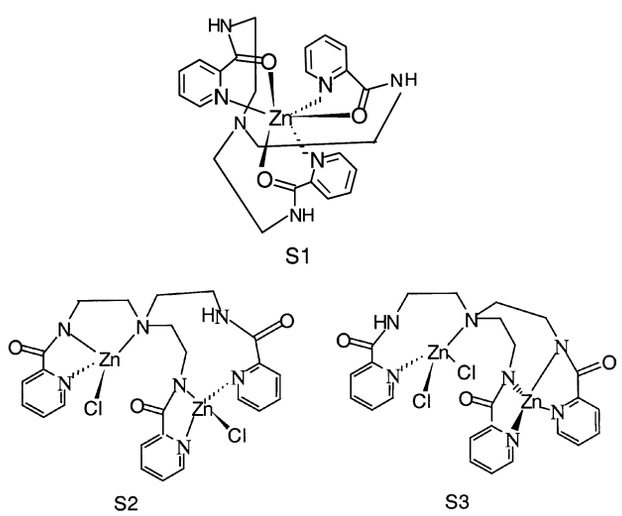
Positive-ion fast atom bombardment (FAB) mass spectra provide evidence for complex formation. The molecular peak for compounds **1** and **2** can be identified as [ZnL]ClO$_4^+$ at m/z 583 and 625 respectively, whereas complex **3** gives molecular peaks at m/z 663, 588 and 524 corresponding to $[Zn_2Cl_2(LH_{-2})]^+$, $[Zn_2(LH_{-2})]^{2+}$ and $[Zn(LH_{-2})]^+$ respectively. The dinuclear $[Zn_2Cl_2(LH_{-2})]^+$ ion exhibits isotope intensity patterns that closely match the calculated patterns, indicating the presence of two coordinated chloride ions in the complex.

IR spectra of these zinc(II) complexes are similar in pattern to those of the ligands. For all the three zinc(II) complexes, we observed small shifts in the lower energy for the characteristic secondary amine bands at 3400–3060 cm^{-1}, with a decrease in intensity. ClO$_4^-$ anions in the compounds **1** and **2** have a large band at *ca.* 1100 cm^{-1}. trenpicam has three amido groups and each group has the resonance structures[19] shown in Scheme 3; formula I predominates. Coordination through an oxygen atom increases the contribution of formula II. If coordination occurs through the nitrogen atom, its hybridization will be sp^3 and the C=O bond will become a complete double bond with loss of the resonance energy.[20]



Scheme 3

The amide I band consists mainly of $\nu_{C=O}$, and the amide II and III bands arise from ν_{C-N} as well as from δ_{N-H}, although these modes are coupled to one another.[21] Consequently for an amide group coordinated through the oxygen atom, the amide I band will shift to a lower frequency and the amide II and III to higher frequencies. On the other hand, if the amide-nitrogen atom coordinates, the amide I, II, III bands should shift in the opposite directions. Our experimental data (see Experimental section) revealed that the amide bands of complexes **2** and **3** shift in the direction expected for the amide-oxygen and amide-nitrogen coordination respectively; the coordination of the amide-nitrogen leads to its deprotonation. Thus, from mass and IR spectral data, it could be envisaged that the Zn^{2+} ion in complex **2** is hexacoordinated with three carbonyl-oxygen donor and three pyridyl-nitrogen donor atoms (Scheme 4: S1),



Scheme 4

whereas the neutral dinuclear complex **3** could be exemplified by two types of compound in which the ligand trenpicam is doubly deprotonated and the tetracoordination of zinc(II) is achieved by two chloride ions (Scheme 4: S2 and S3).

Solution equilibria

Ligand protonation constants. Protonation constants are expressed as follows:

$$LH_{h-1} + H \rightarrow LH_h \qquad K_{01h} = \frac{[LH_h]}{[LH_{h-1}][H]}$$

(charges omitted for clarity)

The strong acidic medium corresponding to the most protonated species required both protometric and spectrophotometric titrations. The ligand tpaa possesses seven potential protonation sites, but only five of the K_{01h} (Table 2) values have been determined by fitting the protometric titration curves (Fig. 1). Moreover the large standard deviation of K_{015} confirms the value obtained from UV spectrophotometric measurements. The distribution curves (Fig. 2) show that LH_3^{3+} is present in the pH range corresponding to the LH_5^{5+}/LH_4^{4+} equilibrium (pH < 2). However, the plot of the molar absorption coefficients as a function of pH (Fig. 3) exhibits a large plateau (pH = 2.5–5.5) indicating that LH_3^{3+} and LH_4^{4+} have the same absorption coefficient. So the value of K_{015} was determined from the method of Yatsimirski:[22] the protonation constant K_{015} and the absorption coefficient ε_5 of LH_5^{5+} are obtained from the slope and y-intercept in the linear relation, respectively.

Table 2 Logarithms of successive protonation constants of tpaa and trenpicam ($K_{01h} = [LH_h]/[L_{h-1}][H]$; $I = 1$ (KNO_3); 25 °C

	tpaa	trenpicam
$\log K_{011}$	9.12 (0.01)	6.21 (0.01)
$\log K_{012}$	8.14 (0.01)	2.30 (0.02)
$\log K_{013}$	6.91 (0.01)	
$\log K_{014}$	2.50 (0.01)	
$\log K_{015}$	1.0 (0.3)	
$\log K_{013}$ (UV)		1.0
$\log K_{015}$ (UV)	1.1	

[a] Values in parentheses refer to estimated standard deviations.

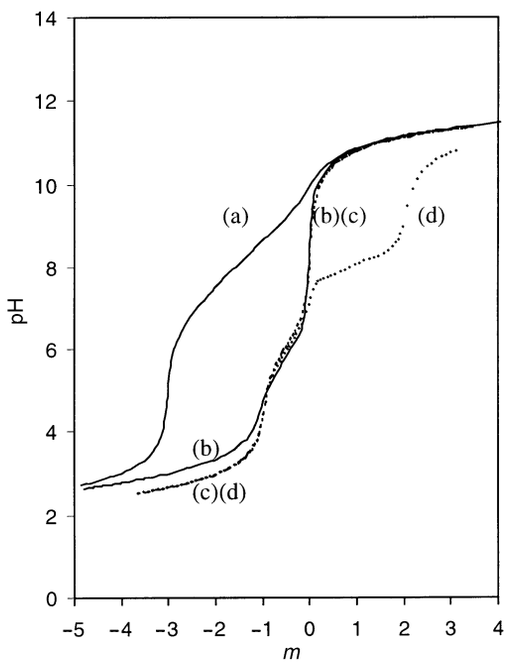


Fig. 1 Protometric titration curves for tpaa (solid lines, $c_L = 1.30 \times 10^{-3}$ mol L^{-1}) alone (a) and $c_L/c_{Zn} = 1$ (b); for trenpicam (dashed lines, $c_L = 1.22 \times 10^{-3}$ mol L^{-1}) alone (c) and $c_L/c_{Zn} = 1$ (d); m = mol of base added per mol of ligand (the origin corresponds to the neutral ligand); $I = 1$ (KNO_3); 25 °C.

$$\varepsilon = \varepsilon_5 + \frac{1}{K_{015}}\left[(\varepsilon_4 - \varepsilon)\left(\frac{1}{[H^+]} + \frac{1}{K_{014}[H^+]^2}\right)\right]$$

where ε is the mean molar absorption coefficient, ε_n the individual molar absorption coefficients of the species LH_h^{n+}. The value of K_{015} (Table 2) was estimated at 260 nm in the pH range 0.5–1.1. This value is very close to the one obtained from protometric titrations.

trenpicam possesses only four potential protonation sites (the tertiary amine and the three pyridine nitrogen atoms). The fitting of the protometric titration curves allowed the determination of two constants only. So, UV spectra were used for the evaluation of K_{013} (Table 2) in the pH range 0.25–1.1 at 265 nm. In this case ε_2 is not known and K_{013}, ε_2, ε_3 have to be determined simultaneously by a least-squares method:[23] in the presence of only two species LH_3^{3+} and LH_2^{2+} the expressions of the constant K_{013} and ε can be written as follows:

$$K_{013} = \frac{\alpha}{(1-\alpha)[H^+]}$$

$$\varepsilon = \varepsilon_2 + (\varepsilon_3 - \varepsilon_2)\alpha$$

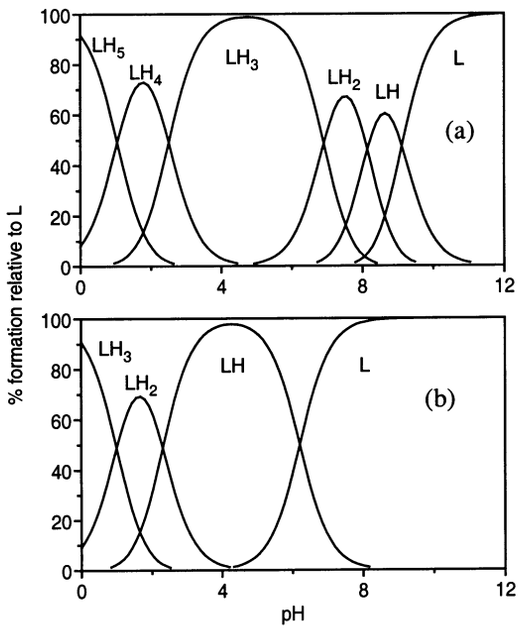


Fig. 2 Distribution curves of tpaa (a) and trenpicam (b); $c = 10^{-3}$ mol L^{-1}.

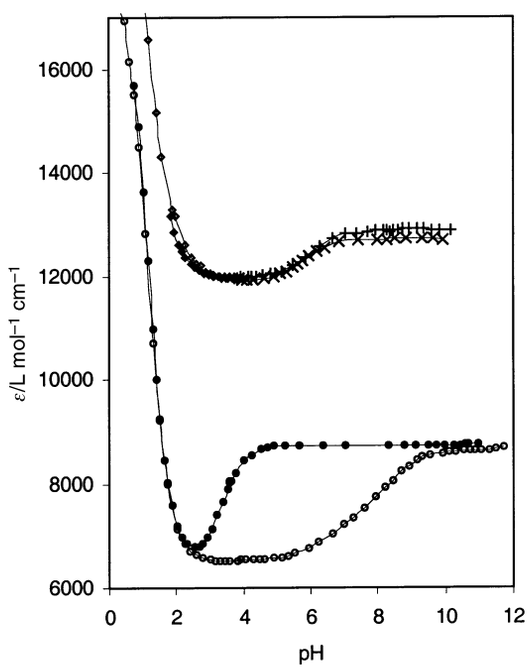


Fig. 3 Molar absorption coefficients at 264 nm as a function of pH; tpaa alone (○) and $c_L/c_{Zn} = 1$ (●); trenpicam alone (×) and $c_L/c_{Zn} = 1$ (+).

the best K_{013} value (Table 2) introduced in $a = K_{013}[H^+]/(1 + K_{013}[H^+])$ leads to the "best straight line" for $\varepsilon = f(a)$.

K_{013}, K_{014} and K_{015} for tpaa are very close to K_{011}, K_{012} and K_{013}, respectively, for trenpicam. This leads to analogous distribution curves of the corresponding species in the pH range 0–5 (Fig. 2).

UV spectra of the individual species (except for LH_2^{2+} of tpaa) were obtained from spectrophotometric titrations (Fig. 4). For trenpicam LH_3^{3+}, LH_2^{2+} and LH^+ species gave very similar spectra, while the spectrum of LH_3^{3+} is very different for the band around 265 nm as well as for the one around 220 nm. The behaviour of this ligand is analogous to that of picolinic acid. The main difference is that with trenpicam two pyridyl nitrogen atoms (not one) are protonated in LH_3^{3+}: the protonation of the first aromatic nitrogen as the pH decreases (LH_2^{2+} species)

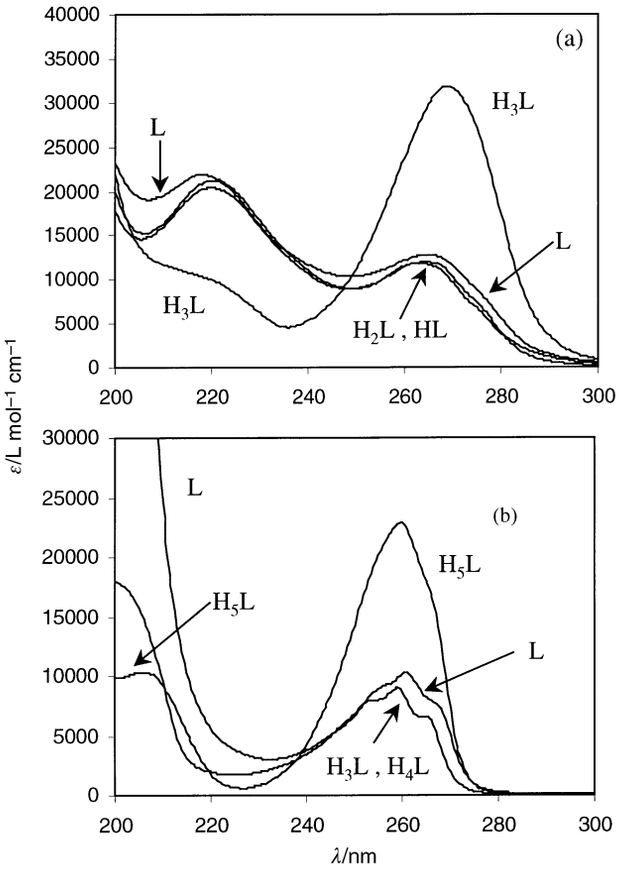


Fig. 4 UV spectra of trenpicam (a) and tpaa (b) individual species with various degrees of protonation in aqueous solution.

does not modify the UV spectra. For tpaa the spectra have the same appearance as the ones of pyridine. With decreasing pH, the molar absorption coefficient varies appreciably from the formation of LH_5^{5+}. The analogy with trenpicam (Fig. 2) suggests that in the LH_5^{5+} form of tpaa, two pyridyl nitrogen atoms are also protonated and consequently one of the secondary amines remains free at pH < 1. This phenomenon is also observed for the ligand tren for which only three pK_a values have been reported in the literature[24] (our own unpublished results for tren are logK_{01h} = 10.28, 9.86, 8.72 and ≈0).

^{1}H NMR spectra. Both ligands have seven basic groups, but it is not intuitively obvious which of the seven basic groups are protonated. Several authors[25] reported that the protonation of a basic site leads to a deshielding of the adjacent methylene groups and thus to a shift toward low field in the ^{1}H NMR spectrum. To extract complementary information on the order of protonation for the different basic groups in both ligands, variable pH-^{1}H NMR studies were performed. According to the distribution curves, every desired species was obtained by adjusting the pH of the aqueous ligand solutions (20 mL, 10^{-2} mol L^{-1}) by the addition of HCl or KOH 1 M (for pH ≈ 0, solid ligand was directly dissolved in HCl 1 M). The volume of the mixture was concentrated to a quarter and ethanol was added. The crude solid which precipitated was stirred, filtered off and dried *in vacuo*. The ^{1}H NMR spectrum of each species was obtained in D_2O. Chemical shift of both ligands as a function of the degree of protonation is given in Table 3.

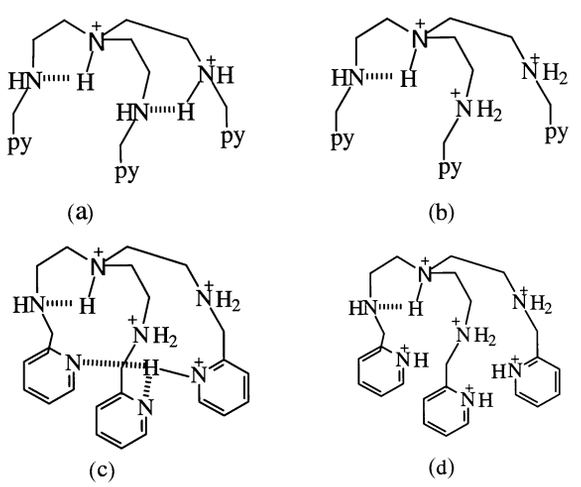
tpaa. According to the close proximity of the values of logK_{011} and logK_{012} and that the concentration of LH^+ is around 50% of the total amount of the ligand, only LH_2^{2+} was isolated. The first two equivalents of acid added (pH = 8.2) to tpaa become attached to two amino groups. ^{1}H NMR spectrum of

Table 3 ^{1}H NMR chemical shifts of tpaa and trenpicam as a function of the degree of protonation

	δ^a							
	pH		pyridyl			methylene	ethylene	
tpaa	>10	8.40 d	7.70 t	[7.25 m]		3.75 s	2.65 t	2.55 t
H_2tpaa^{2+}	8.2	8.50 d	7.95 t	[7.45 m]		4.40 s	3.30 t	3.00 t
H_3tpaa^{3+}	5.0	8.55 d	7.95 t	7.55 d	7.45 t	4.45 s	3.40 t	3.00 t
H_4tpaa^{4+}	2.0	8.65 d	8.35 t	7.75 d	7.65 t	4.50 s	3.40 t	3.00 t
H_6tpaa^{6+}	≈0	8.85 d	8.60 t	8.15 d	8.05 t	4.70 s	3.40 t	3.00 t
trenpicam	>10	8.10 d	7.75 t	7.70 d	7.35 t	—	3.45 t	2.85 t
Htrenpicam$^+$	4.5	8.45 d	7.80 t	7.55m	7.45 d	—	3.90 b	3.60 b
H_4trenpicam^{4+}	≈0	8.60 d	8.00 t	7.70 t	7.60d	—	4.00 t	3.80 t

^{a} Values in ppm relative to residual solvent; s = singlet, t = triplet, m = multiplet, b = broad.

LH_2^{2+} shows the significant shift in the methylene and ethylene group proton signals; there is also a slight shift in the ring proton signals, but the splitting pattern remains largely the same. However, the spectral data obtained indicate that the diprotonated ligand retains the same symmetry as free tpaa (each of the different methylenic group protons gives only one signal); this suggests that these methylenic and ethylenic group protons have the same environment. Thus, we deduce that of the two protons added one is attached to the tertiary apical nitrogen (more basic) and one to one of the three secondary amino groups, and each proton forms a two-center chelate H-bond [13] with each of the two remaining secondary amino nitrogens (Scheme 5a), as described by Micheloni and co-workers [26] for alkylpolyamines.



Scheme 5

At pH = 5.0, the LH_3^{3+} species was isolated and the distribution curves show that its concentration is almost 100%. The third proton added induces a slight shift in the methylene protons signal (+0.05 ppm) and one of the –CH_2– signals (+0.10 ppm) of the three ethylene groups; the multiplet obtained for two ring protons with free and diprotonated tpaa is now well separated. This implies the protonation of one more amino group, replacing the two-center chelate H-bond [13] between the two secondary amino groups obtained with LH_2^{2+} (Scheme 5b).

When the fourth proton is added (pH = 2.0, LH_4^{4+} species), the pyridyl and methylene proton signals are shifted downfield, but the ethylene proton signals remain the same as for LH_3^{3+}. Thus, we conclude that protonation occurs on the aromatic nitrogen atom. However, the symmetry of the three pyridyl and methylene groups (one signal obtained for each kind of proton) leads us to believe that the three pyridylmethyl groups have the same environment. This implies the formation of three-centered bifurcated H-bonds [13] (Scheme 5c), which explains the anomalous variation of the absorption of the aromatic groups in the UV studies (the strong variation of the absorbance is observed only from the fifth proton attached: LH_5^{5+}). The non-protonation of the third secondary amino group can be attributed to electrostatic repulsion which favors the widest possible separation of charges.[27]

Under more acidic conditions (pH ≈ 0) the LH_6^{6+} species was isolated. Compared with free tpaa we note a considerable downfield shift of ring (average +0.70 ppm) and methylene (+0.95 ppm) proton signals and all pyridyl or methylene groups resonate as one aromatic or one methylene signal. This implies the equivalence of the three pyridyl and three methylene groups. Thus, we can conclude that the three ring nitrogens are protonated (Scheme 5d).

It seems that the order of protonation of the basic groups in the tpaa ligand with decreasing pH is N_{apical}, N_{amine} and N_{amine} and $N_{pyridyl}$, $N_{pyridyl}$, and $N_{pyridyl}$.

trenpicam. The potentiometric study of this ligand (trenpicam), which also has seven nitrogen donors like tpaa, shows that only four sites are protonated over the pH range examined. According to the distribution curves, two solid compounds were isolated at pH = 4.5 and pH ≈ 0 corresponding to the mono- and tetra-protonated species. ^{1}H NMR spectral data (Table 3) for these LH^+ and LH_4^{4+} species indicate a significant downfield shift for ethylene (LH^+) and pyridyl (LH_4^{4+}) proton signals; this is consistent with the protonation of the apical nitrogen atom (confirmed by X-ray crystal structure) and three ring nitrogens (in more acidic conditions) respectively. Thus, the order of protonation of the basic groups in the trenpicam ligand with decreasing pH is N_{apical}, and $N_{pyridyl}$, $N_{pyridyl}$ $N_{pyridyl}$.

Metal chelate formation constants. The protometric titration curves are represented in Fig. 1 for both ligands alone and with 1 : 1 ligand–zinc ratios. The splitting of the tpaa and tpaa/Zn^{2+} curves from pH = 2.6 indicates strong complexation. The curve in the presence of metal ions presents two steps which indicate the nearly complete formation of $[ZnLH]^{3+}$ ($m = -1$) and ZnL^{2+} ($m = 0$). No more species appear above pH = 8. Furthermore, the best fitting of the curves (5 titrations with L–Zn ratios from 1–10 : 1) means that the minor species $[ZnLH_2]^{4+}$ has to be taken into consideration. The behaviour of trenpicam is different: a significant role of the Zn^{2+} ion appears only from pH = 5 and especially for pH > 7. The third step which appears for 2 equivalents of OH^- at pH = 9 indicates the involvement of two amide-nitrogen atoms in the complexation. In the pH range 7.5–8.5 the slope of the curve is unusually low, and this could mean the formation of a condensed species or even a precipitate. Therefore, we have verified that equilibrium was effectively reached in the solutions by varying the duration of the titrations and the ratios L–Zn. Analysis of the curves with the program PROTAF [16] results in the fact that the dimeric species $[Zn_2L_2H_{-4}]$ has to be taken into consideration (Fig. 5). In addition, the best fitting of curves requires the introduction of its deprotonated form $[Zn_2L_2H_{-5}]^-$, as well as the 2 : 1 species ($[ZnL_2]^{2+}$, $[ZnL_2H_{-1}]^+$, $[ZnL_2H_{-3}]^-$) for the solutions of L : Zn

Table 4 Logarithms of equilibrium constants of tpaa and trenpicam complexes with Zn^{2+} ($\beta_{01h} = [Zn_mL_lH_h]/[Zn]^m[L]^l[H]^h$; $I = 1$ (KNO_3); 25 °C

	tpaa	trenpicam
$\log\beta_{112}$	23.92 (0.04)	
$\log\beta_{111}$	21.38 (0.01)	
$\log\beta_{110}$	15.62 (0.02)	2.4 (0.1)
$\log\beta_{22-4}$		−22.30 (0.04)
$\log\beta_{22-5}$		−33.7 (0.1)
$\log\beta_{120}$		5.91 (0.04)
$\log\beta_{12-1}$		−2.26 (0.05)
$\log\beta_{12-3}$		−20.46 (0.04)

[a] Values in parentheses refer to estimated standard deviations.

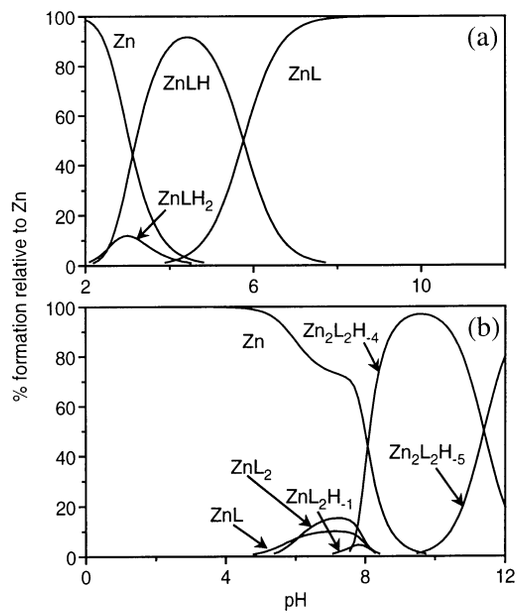


Fig. 5 Distribution curves for zinc(II) complexes ($c_L = c_M = 10^{-3}$ mol L^{-1}); tpaa (a) and trenpicam (b).

more than one to one. These complexes play a minor role in the pH range 5–8 (5 to 15% of Zn at pH = 7 for $c_L/c_{Zn} = 1$). Stability constants determined by refining the protometric titration curves (Table 4) are expressed as follows:

$$mM + lL + hH \rightarrow M_mL_lH_h \qquad \beta_{mlh} = \frac{[M_mL_lH_h]}{[M]^m[L]^l[H]^h}$$

the negative values of *h* refer to amide-deprotonated ligands.

The variations of the UV spectra as a function of pH in the presence of Zn^{2+} (Fig. 3) are consistent with the protometric titration curves. On the other hand, the formation of the main complexes of trenpicam occurs in a pH range where the tertiary amine is deprotonated (pH ≈ 7.5–8), so their spectra are not different from those of the ligand alone. In addition, the curves of tpaa alone and in the presence of Zn^{2+} split from pH = 2 corresponding to the onset of formation of $[ZnLH_2]^{4+}$ and $[ZnLH]^{3+}$.

X-Ray diffraction studies

The crystal structure of compounds [Htrenpicam](ClO_4) and [Zn(tpaa)](ClO_4)$_2$ **1**, were determined by single crystal X-ray diffraction.

[Htrenpicam](ClO_4). The crystal structure determination reveals that colourless crystals of [Htrenpicam](ClO_4) consist of $[Htrenpicam]^+$ cations which are well separated from the perchlorate anions. The disordered perchlorate anion can be described as a hexagon in which two of the oxygen atoms each occupy two sets of positions (Fig. 6a). A view of the cation with the labelling scheme is shown in Fig. 6b. Principal bond distances and angles are listed in Table 5.

Table 5 Selected bond lengths (Å) and angles (°) for [Htrenpicam]-(ClO_4) and [Zn(tpaa)](ClO_4)$_2$

[Htrenpicam](ClO_4)			
N(2)–C(3)	1.334(5)	C(3)–O(1)	1.242(5)
N(4)–C(11)	1.342(5)	C(19)–O(2)	1.217(5)
N(6)–C(19)	1.346(6)	C(11)–O(3)	1.234(5)
N(1)–H(01)	1.116(8)	O(1)–H(01)	1.7394
N(2)–C(3)–C(4)	116.0(4)	N(6)–C(19)–C(20)	116.2(4)
N(4)–C(11)–C(12)	115.6(4)	N(1)–H(01)–O(1)	149.99
Complex **1**			
Zn–N(1)	2.117(3)	Zn–N(5)	2.126(3)
Zn–N(2)	2.198(3)	Zn–N(6)	2.274(3)
Zn–N(4)	2.194(3)	Zn–N(7)	2.243(3)
N(1)–Zn–N(2)	82.2(1)	N(2)–Zn–N(7)	92.1(1)
N(1)–Zn–N(4)	80.2(1)	N(4)–Zn–N(5)	78.0(1)
N(1)–Zn–N(5)	157.3(1)	N(4)–Zn–N(6)	95.7(1)
N(1)–Zn–N(6)	79.5(1)	N(4)–Zn–N(7)	171.7(1)
N(1)–Zn–N(7)	102.1(1)	N(5)–Zn–N(6)	96.8(1)
N(2)–Zn–N(4)	96.1(1)	N(5)–Zn–N(7)	98.7(1)
N(2)–Zn–N(5)	105.8(1)	N(6)–Zn–N(7)	77.0(1)
N(2)–Zn–N(6)	156.2(1)		

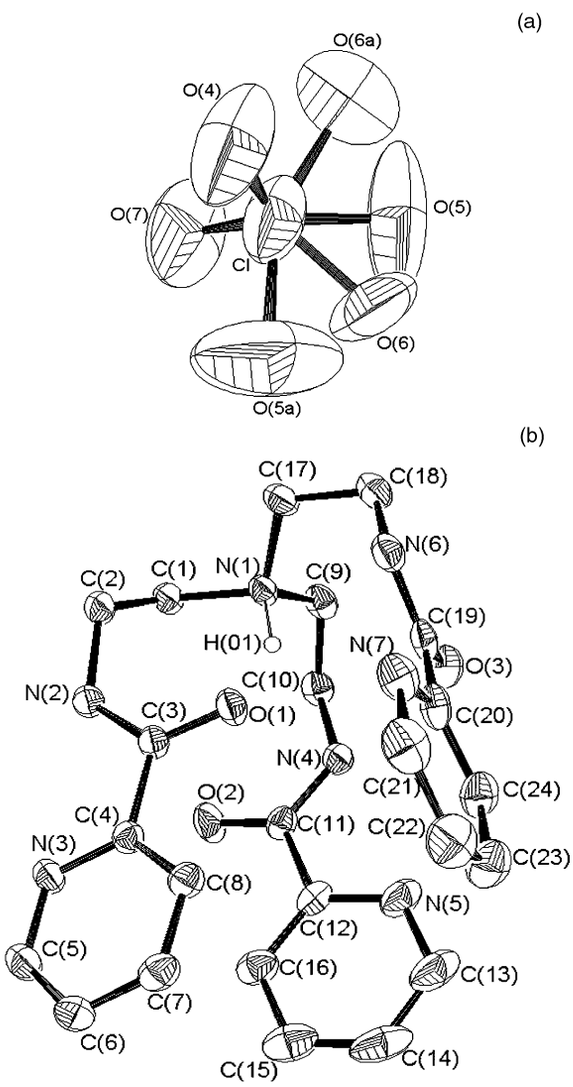


Fig. 6 An ORTEP[31] drawing of the ClO_4^- anion (a) and the cation $[Htrenpicam]^+$ (b) showing 30% probability ellipsoids and the atom labelling scheme. Other hydrogen atoms are omitted for clarity.

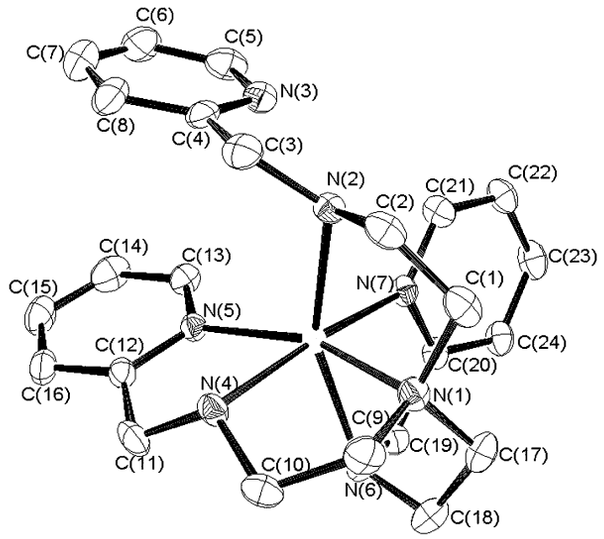
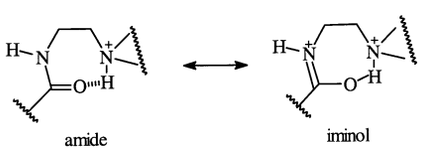


Fig. 7 ORTEP drawing of the cation $[Zn(tpaa)]^{2+}$. Details as in Fig. 6.

The structure of the $[Htrenpicam]^{+}$ cation demonstrates that protonation of the apical nitrogen N(1) causes an intramolecular H-bond with one of the oxygen donors O(1) of the three aromatic amides. Following the nomenclature of H-bonding geometry[13] the type of interaction which is present in this cation is two-center (chelate), with the H-bond well identified within the H(01)···O(1) distance criterion [H(01)···O(1) 1.739 Å].

In each arm of the cation, the picolinamide moiety is held practically planar, due to the extended π network of the aromatic amide linkage. However, we note a significant shortening of N(2)–C(3) bond to 1.334(5) Å and a lengthening of the C(3)–O(1) bond to 1.242(5) Å, due to the intramolecular H-bond [H(01)···O(1)]. The concomitant increase in C=O (*ca.* +0.022 Å) and decrease in C–N (*ca.* −0.010 Å) bond lengths reflect the fact that the iminol form is present for this picolinamide group (Scheme 6).



Scheme 6

$[Zn(tpaa)](ClO_4)_2$ 1. The molecular structure of complex **1** consists of $[Zn(tpaa)]^{2+}$ cations which are well separated from ordered and well behaved ClO_4^- anions. A perspective drawing of the cation with atom labelling is illustrated in Fig. 7, relevant bond lengths and angles in Table 5.

The structure shows the presence of two independent molecules. Although tpaa is a potentially heptadentate ligand, the zinc(II) ion has a coordination number of six in each complex; thus, one of the three pyridyl nitrogen atoms remains uncoordinated. The zinc(II) center is coordinated by the apical nitrogen atom [N(1)], two aromatic nitrogen atoms [N(5) and N(7)] and three secondary amine nitrogen atoms [N(2), N(4) and N(6)]. The coordination sphere is distorted octahedral with N(1)–Zn–N(5) = 157.3(1)°, N(2)–Zn–N(6) = 156.2(1)°, N(4)–Zn–N(7) = 171.7(1)°. The bond lengths involving two nitrogen atoms (pyridyl and secondary amine) of the same arm of the tpaa ligand [Zn–N(6) = 2.274(3) Å and Zn–N(7) = 2.243(3) Å] are longer than the others, whereas the apical nitrogen bond is the shortest [Zn–N(1) = 2.117(3) Å]. The formation of this latter bond induces some strain in the molecule; thus, the angle N(1)–Zn–N(7) is quite enlarged (mean value 102.1°) and N(1)–Zn–N(6) contracted (mean value 79.5°) with respect to an octahedral geometry (90°). The structure of complex **1** is surprisingly different from the hexacoordinated N_6 $[Zn(py)_3(tren)]^{2+}$ compound,[28] containing a ligand similar to tpaa, but possessing HC=N bonds instead of H_2C–NH. This latter complex does not exhibit coordination of the tripodal nitrogen atom to the zinc center; Morgenstern-Baradau and co-workers[9] explain this kind of difference as being a stronger chelating effect of the α-imine linkage present in $(py)_3$tren.

Conclusion

The protometric and UV spectrophotometric results reveal that the two tripodal ligands show five and three species for tpaa and trenpicam respectively. The main difference in the behaviour of these ligands with decreasing pH is due to the three amidic nitrogens present in trenpicam. Several investigators[29] estimated the protonation constant of an amide nitrogen to be $pK_a = -8$, whereas the pK_a value of the amide hydrogen falls outside the upper pH limit of this measurement ($pK_a \approx 15$); thus the chelation of metal ions by the amidic nitrogen promotes the latter amide hydrogen ionization.[30] In addition, variable pH ^{1}H NMR spectrometry is a powerful tool when used in conjunction with pH potentiometry to study the more stable protonated ligand species; this combination of methods allows the determination of the order of protonation of the different basic sites of these ligands.

A comparison of the ligating properties in aqueous solution of both these ligands with zinc(II) ions clearly shows that tpaa gives three complexes $[ZnLH_2]^{4+}$, $[ZnLH]^{3+}$ and $[ZnL]^{2+}$, but only the latter compound has been isolated in the solid state. An X-ray crystal analysis of the $[Zn(tpaa)](ClO_4)_2$ complex, shows that the geometry around the zinc(II) ion is octahedral and one of the three pyridyl nitrogens of tpaa remains uncoordinated, in contrast to Fe(II) and Mn(II) complexes with the same ligand which are all heptacoordinated.[8,9] On the other hand, trenpicam forms, in aqueous solution, a series of complexes with variable stoichiometry $[ZnL]^{2+}$, $[ZnL_2]^{2+}$, $[ZnL_2H_{-1}]^{+}$, $[ZnL_2H_{-3}]^{-}$, $[Zn_2(LH_{-2})_2]$ and $[Zn_2L_2H_{-5}]^{-}$; the two complexes isolated in the solid state are the monomeric $[ZnL](ClO_4)_2$ and the dinuclear $[Zn_2(LH_{-2})Cl_2]$ as shown by IR and mass spectrometry measurements. Surprisingly, the major dimeric $[Zn_2(LH_{-2})_2]$ species (*ca.* 100%) detected in the protometric study is completely different from the dinuclear compound isolated in the solid state. This difference can be explained by the fact that the low concentration of chloride ions used in protometry does not favour the formation of chloro-complexes.

It seems to us worthwhile to get a more complete picture of the factors influencing the nature of the species obtained (aqueous solution and solid state) and the metallic ion effect on the ionization of the amidic group by studying the chelating effect of other cations. Further work along these lines is in progress.

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