

# Preparation, Characterization and Complexation of 4,6-Dimethyl-1,3-bis{methyl-[1-(2-hydroxyethyl)piperazyl]}benzene and 2,6-Di{methyl-[1-(2-hydroxyethyl)piperazyl]}pyridine

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4,6-Dimethyl-1,3-bis{methyl[1-(2-hydroxyethyl)piperazyl]}benzene ( $L_1$ ) and 2,6-di-{methyl[1-(2-hydroxyethyl)piperazyl]}pyridine ( $L_2$ ) were synthesized and their complex formation equilibria with alkaline-earth(II), Pr<sup>III</sup>, Ni<sup>II</sup>, Cu<sup>II</sup> and Zn<sup>II</sup> ions were studied with potentiometric techniques over the pH range 2.1–9.3 in 0.10 mol dm<sup>-3</sup> NaCl at 25 °C. The data indicate that whereas  $L_1$  forms only  $[ML]^{2+/3+}$  complexes,  $L_2$  forms  $[M(H_xL_y)]^{(2+x)+}$  ( $X=0-2$ ,  $Y=1, 2$ ) and the hydrolysed  $[M(OH)_xL]^{1+/0}$  ( $X=1, 2$ ) transition-metal(II) complexes. With Pr<sup>III</sup>  $L_2$  forms only  $[M(HL)]^{4+}$  and  $[M_2L_2]^{6+}$  complexes.  $L_2$  contains the pyridine unit and is a much better complexing agent than  $L_1$ . The protonation of the ligands was studied by <sup>1</sup>H NMR in aqueous solution of 0.10 mol dm<sup>-3</sup> NaCl at 24 °C.  $L_2$  crystallizes in a monoclinic space group  $P2_1/a$ ,  $a=9.998(2)$ ,  $b=15.476(3)$ ,  $c=12.957(3)$  Å,  $\beta=92.64(2)^\circ$ . The ligand shows a planar structure. Upon complexation, however, the 1-(2-hydroxyethyl)piperazine fragments may rotate around the bonds C15–C17 and C10–C11 by ca. 180° to create a pocket containing three nitrogen donor atoms the orientation of which is suitable for the coordination with metal ions.

Piperazine is frequently used for the design of various ligands, since it contains two nitrogen atoms that can coordinate to metal ions.<sup>1</sup> It is less rigid than aromatic rings but more rigid than secondary amines when it acts as a double-bridged building block.<sup>2</sup> Piperazine and its *N*-substituted derivatives have pharmacological applications as anthelmintics, sedatives and local anaesthetics.<sup>3</sup> Au<sup>III</sup>, Os<sup>IV</sup>, Pd<sup>II</sup>, Pt<sup>IV</sup> and Pt<sup>II</sup> *N,N'*-bis(2-hydroxyethyl)piperazine complexes have antitumoral activity against lymphoid leukemia L1210.<sup>4</sup> In this work 4,6-dimethyl-1,3-bis{methyl[1-(2-hydroxyethyl)piperazyl]}benzene ( $L_1$ ) and 2,6-di{methyl[1-(2-hydroxyethyl)piperazyl]}pyridine ( $L_2$ ) were prepared as potential reagents for the design of larger structures. There are some crystal structures and NMR data about complexes containing this type of pyridine–piperazine ligand,<sup>1,2,5</sup> but no thermodynamic data have been reported. Crystal structures can be used to discuss the ability of the ligand to form complexes with metal ions, but they do not give

information about the thermodynamics or the selectivity of the complex formation.

Ligands  $L_1$  and  $L_2$  are water soluble and therefore suitable for traditional potentiometric titration in a constant ionic medium. Transition-metal ions, praseodymium and alkaline-earth metal ions were chosen to establish the differences in coordination.

## Experimental

*4,6-Dimethyl-1,3-bis{methyl[1-(2-hydroxyethyl)piperazyl]}benzene.* 4,6-Dimethyl-1,3-bis(bromomethyl)benzene (4.0 g, 13.67 mmol), 1-(2-hydroxymethyl)piperazine (3.0 g, 22.72 mmol) and NaHCO<sub>3</sub> (9 g, 107 mmol) were refluxed in acetonitrile (100 cm<sup>3</sup>) for 3 h. After cooling, filtration and evaporation of the solvent, the residue was recrystallised from ethyl acetate. Yield 3.0 g (56%).  $\delta_H$  (CD<sub>3</sub>OD, 270 MHz, SiMe<sub>4</sub>): 2.47 (s, 6 H, CH<sub>3</sub>-Ar), 2.70 (t+s, 16+4 H, piperazine and -CH<sub>2</sub>-CH<sub>2</sub>-OH), 3.61 (s, 4 H, Ar-CH<sub>2</sub>-piperazine), 3.85 (t, 4 H, -CH<sub>2</sub>-CH<sub>2</sub>-OH), 5.04 (s, 2 H, -OH), 7.12

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(s, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H).  $\delta_C$  (CD<sub>3</sub>OD, 67 MHz, SiMe<sub>4</sub>): 19.38, 54.03, 54.78, 60.09, 61.51, 133.53, 133.75, 134.28, 137.74. MS:  $m/z = 390$  ( $M^+$ ).

*2,6-Di{methyl[1-(2-hydroxyethyl)piperazyl]}pyridine.* 2,6-Bis(chloromethyl)pyridine (4.0 g, 22.72 mmol), 1-(2-hydroxymethyl)piperazine (5.92 g, 45.44 mmol) and NaHCO<sub>3</sub> (9 g, 107 mmol) were refluxed in acetonitrile (100 ml) for 3 h. After cooling, filtration and evaporation of the solvent, the oily residue was let to stand at room temperature for 70 h. The product crystallised during this time and it was recrystallised from ethyl acetate. Yield 6.0 g (73%). M.p. 68 °C.  $\delta_H$  (CD<sub>3</sub>OD, 270 MHz, SiMe<sub>4</sub>): 2.53 (t+s, 16+4 H, piperazine and -CH<sub>2</sub>-CH<sub>2</sub>-OH), 3.66 (t, 4 H, -CH<sub>2</sub>-CH<sub>2</sub>-OH), 4.81 (s, 4 H, Pyr-CH<sub>2</sub>-piperazine), 7.39 (d, 2 H, Py-H), 7.76 (t, 1 H, Py-H).  $\delta_C$  (CD<sub>3</sub>OD, 67 MHz, SiMe<sub>4</sub>): 53.87, 54.35, 59.84, 61.29, 64.74, 123.46, 138.63, 158.67. MS:  $m/z = 363$  ( $M^+$ ).

*Reagents and solutions.* Stock solutions of alkaline-earth metal(II), Cu<sup>II</sup>, Zn<sup>II</sup> and Ni<sup>II</sup> ions were prepared from chlorides (Merck) and Pr<sup>III</sup> from Pr<sub>6</sub>O<sub>11</sub> (Typpi OY) dissolved in hydrochloric acid. These stock solutions were standardized by titration with EDTA as well as by cation-exchange chromatography.<sup>6</sup> The purity of the compounds L<sub>1</sub> and L<sub>2</sub> was determined by <sup>1</sup>H NMR spectroscopy and by titration with standardized NaOH solution. Hydrochloric acid (Baker) was standardized by titration with tris(hydroxymethyl)aminomethane (TRIS) using bromocresol green-methyl red (3:2) as an indicator. The NaOH stock solution was prepared by dissolving NaOH granules (Merck) in boiling distilled water. It was stored in high-density polyethylene bottle fitted with a carbon dioxide (soda lime) trap. The NaOH stock solution was standardized by titration against potassium hydrogen phthalate using phenolphthalein as an indicator.

*Potentiometric studies.* The potentiometric studies were carried out in an inert atmosphere [commercial argon passed through 10% (w/w) H<sub>2</sub>SO<sub>4</sub>, 10% (w/w) NaOH and background electrolyte] at 25 ± 0.1 °C using a locally constructed automatic titration system (TIT5 program)<sup>7</sup> involving a Metrohm 665 piston burette as well as an Orion 91-01sc glass electrode and an Orion 9002 Ag/AgCl (s) double-junction reference electrode. Every titration was started with the calibration of the electrode system by titration of 30 or 40 cm<sup>3</sup> of E<sub>0</sub>-solution (0.090 and 0.010 mol dm<sup>-3</sup> with respect to NaCl and HCl) with CO<sub>2</sub>-free 0.10 mol dm<sup>-3</sup> NaOH solution. These data were employed to obtain the value of E<sub>0</sub> in the Nernst equation

$$E = E_0 + 59.16 \log h + E_j \quad (1)$$

The liquid junction potentials [ $E_j = j_{ac}h + (j_{alk}k_w)/h$ ] were determined by separate titrations and the obtained values [ $j(\text{acid}) = -512 \pm 8$  mV M<sup>-1</sup>,  $j(\text{alk}) = 239 \pm 10$

mV M<sup>-1</sup> and  $pK_w = 13.775$ ] were similar to the literature values.<sup>8</sup>  $E_j$ , however, assumed a significant value only at pH < 2.5. The titrations were mainly carried out in conditions where the liquid junction potential is negligible.

The acidified solutions of the ligands (H<sub>4</sub>L<sup>4+</sup>) were titrated with NaOH to obtain the protonation constants and the exact ligand concentrations. Solutions containing the acidified ligand and the metal ion were titrated with NaOH to high pH to determine the stability constants of the metal complexes.

*<sup>1</sup>H NMR studies.* The protonation measurements were carried out on a Bruker AM 200 spectrometer operating at 200.13 MHz for <sup>1</sup>H at 24 ± 1 °C. In order to reach a sufficiently good signal-to-noise ratio, 128 FIDs were accumulated by applying a pulse width of 2.5 μs (nuclear tip angle of ca. 30°), a pulse delay of 5.7 s and spectral width of 3.5 kHz leading to a resolution of 0.365 Hz/point. The protonation constants were determined using the batch technique. The pH of each sample solution (standardized stock solution) was adjusted with concentrated HCl and NaOH solutions and monitored with a combination electrode and Metler Toledo 320 pH meter [pH 4.01 and 6.87 buffers (TAMRO)] at ca. 24 °C. The spectra were measured in a 5 mm tube directly from the water solution within a day after the pH adjustment to mimic the potentiometric titration. C<sub>6</sub>D<sub>6</sub> was used as a <sup>2</sup>H lock and TMS as an external reference. Solvent peak suppression was carried out by the presaturation method.

*Crystal structure determination of 2,6-di{methyl[1-(2-hydroxyethyl)piperazyl]}pyridine (L<sub>2</sub>).* Colourless platelike crystals suitable for the X-ray measurement were obtained by slow concentration of the ethyl acetate solution. Diffraction data were collected on an Enraf-Nonius CAD4 diffractometer at 293 K using graphite monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). Crystal data and experimental details of the data collection are shown in Table 1. The unit-cell parameters were determined by the least-squares refinement of 25 automatically centered reflections. Two reference reflections were used to monitor the stability of the crystal. Their intensities were recorded periodically after each batch of 98 data. The decay of the crystal was negligible during the data collection. The total number of 3217 reflections were collected in the 2 $\theta$  range 4.1–45.96°. The reflection data were corrected for Lorentz and polarization effects. No absorption correction was applied.

The structure was solved by direct methods using the SHELXS97<sup>9</sup> system and refined using SHELXL97.<sup>10</sup> After the full-matrix least-squares refinement against  $F^2$  of the non-hydrogen atoms with anisotropic thermal parameters the hydrogen atoms were placed in calculated positions. Hydroxyl hydrogen atom positions were calculated by the method in which the maximum electron density synthesis is calculated around the circle which

Table 1. Crystal data and structure refinement for L<sub>2</sub>.

Compound	C <sub>19</sub> H <sub>33</sub> N <sub>5</sub> O <sub>2</sub>
Formula weight	363.5
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>a</i> <sup>a</sup>
Unit cell dimensions	<i>a</i> = 9.998(2) Å <i>b</i> = 15.476(3) Å <i>c</i> = 12.957(3) Å $\beta$ = 92.64(2) <sup>c</sup>
Volume	2002.7(7) Å <sup>3</sup>
Z	4
Density (calculated)	1.206 Mg m <sup>-3</sup>
Absorption coefficient	0.080 mm <sup>-1</sup>
<i>F</i> (000)	792
Crystal size	0.3 × 0.3 × 0.4 mm
Θ-Range for data collection	2.05–22.98°
	0 ≤ <i>h</i> ≤ 10, −1 ≤ <i>k</i> ≤ 16, −14 ≤ <i>l</i> ≤ 14
Index ranges	
Reflections collected	3217
Independent reflections	2773 [ <i>R</i> (int) = 0.0322]
<i>I</i> > 2σ( <i>I</i> )	1042
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>
Data/restraints/parameters	2773/0/237
Goodness-of-fit on <i>F</i> <sup>2</sup>	0.880
<i>R</i> -indices [ <i>I</i> > 2σ( <i>I</i> )] <sup>b</sup>	<i>R</i> <sub>1</sub> = 0.0591, <i>wR</i> <sub>2</sub> = 0.1079
<i>R</i> -indices (all data) <sup>b</sup>	<i>R</i> <sub>1</sub> = 0.1836, <i>wR</i> <sub>2</sub> = 0.1347
Max. shift/error	< 0.01.
Largest diff. peak and hole	0.236 and −0.169 e Å <sup>-3</sup>

<sup>a</sup>Non-standard setting of *P*2<sub>1</sub>/*c* (No. 14).<sup>b</sup>*w* = 1/[σ<sup>2</sup>(*F*<sub>o</sub><sup>2</sup>) + (0.0535*P*)<sup>2</sup>] where *P* = (*F*<sub>o</sub><sup>2</sup> + 2*F*<sub>c</sub><sup>2</sup>)/3.

represents the locus of possible hydrogen positions in a rigid O–H structure (fixed O–H distance and C–O–H angle). In the final refinement the hydrogen atoms were allowed to ride on the atom to which they were bonded. The isotropic thermal parameters of the hydrogen atoms were fixed at 1.2 times that of the corresponding carbon or oxygen atom. The scattering factors for the neutral atoms were those incorporated with the programs. Fractional coordinates and isotropic thermal parameters are listed in Table 2 and the bond lengths in Table 3. The anisotropic thermal parameters, calculated hydrogen atom positions and structure factor tables can be obtained from the authors upon request.

### Calculations

Potentiometric titrations and <sup>1</sup>H NMR measurements were carried out with the ligand concentration range indicated in Table 4. The protonation constants of the ligand and the stability constants of complexes were calculated from the potentiometric data with the program LETAGROPVRID, version ETITR,<sup>11–13</sup> and from the <sup>1</sup>H NMR data with the program SIGMAPLOT.<sup>14</sup> The modelling of the protonation equilibria on the basis of <sup>1</sup>H NMR data was carried out as described previously.<sup>15</sup> The hydrolysis of nickel and copper ions were taken into account by assuming the constants log β<sub>Ni(OH)<sup>+</sup></sub> = −10.11 ± 0.03 and log β<sub>Cu<sub>2</sub>(OH)<sub>2</sub><sup>2+</sup></sub> = −10.61 ± 0.05.<sup>16</sup> The best fit to the experimental data was determined by minimizing the error square sum  $U = \sum (H_{\text{calc}} - H_{\text{exp}})^2$ ,

Table 2. Atomic coordinates (× 10<sup>4</sup>) and equivalent isotropic displacement parameters (Å<sup>2</sup> × 10<sup>3</sup>) for L<sub>2</sub>.<sup>a</sup>

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
O1	1859(4)	2396(3)	15274(2)	83(1)
O26	14737(4)	1581(3)	5614(3)	120(2)
N4	2822(3)	1856(2)	12617(3)	44(1)
N7	4422(3)	1329(2)	10938(3)	46(1)
N16	6900(4)	1369(2)	8927(3)	46(1)
N18	9942(4)	950(2)	7523(3)	46(1)
N21	12442(4)	844(3)	6521(3)	50(1)
C2	2475(5)	2518(3)	14317(3)	66(2)
C3	2349(5)	1731(3)	13649(3)	54(1)
C5	2500(4)	1106(3)	11971(4)	55(1)
C6	2978(4)	1204(3)	10896(3)	57(2)
C8	4739(5)	2097(3)	11553(3)	54(1)
C9	4265(4)	2002(3)	12630(3)	53(1)
C10	4925(4)	1381(3)	9907(3)	57(1)
C11	6414(4)	1234(3)	9859(4)	46(1)
C12	7178(4)	943(3)	10685(3)	45(1)
C13	8518(4)	781(3)	10559(3)	48(1)
C14	9036(5)	904(3)	9605(4)	49(1)
C15	8203(5)	1194(3)	8807(3)	44(1)
C17	8618(5)	1296(3)	7699(3)	57(1)
C19	11010(4)	1576(3)	7725(3)	52(1)
C20	12351(4)	1170(3)	7570(3)	52(1)
C22	11356(5)	242(3)	6311(3)	60(2)
C23	10021(5)	646(3)	6467(3)	58(2)
C24	13718(5)	401(3)	6362(4)	75(2)
C25	14916(5)	968(4)	6389(4)	77(2)

<sup>a</sup>*U*(eq) is defined as one third of the trace of the orthogonalized *U*<sub>*ij*</sub> tensor.

Table 3. Bond lengths (in Å) and angles (in °) for L<sub>2</sub>.

O1–C2	1.422(5)	N21–C20	1.457(5)
O26–C25	1.387(5)	N21–C24	1.471(5)
N4–C3	1.452(5)	C2–C3	1.496(6)
N4–C5	1.458(5)	C5–C6	1.500(5)
N4–C9	1.460(5)	C8–C9	1.502(5)
N7–C10	1.452(5)	C10–C11	1.510(6)
N7–C6	1.455(5)	C11–C12	1.362(5)
N7–C8	1.457(5)	C12–C13	1.380(5)
N16–C11	1.339(5)	C13–C14	1.375(5)
N16–C15	1.346(5)	C14–C15	1.373(5)
N18–C23	1.453(5)	C15–C17	1.521(6)
N18–C17	1.456(5)	C19–C20	1.502(5)
N18–C19	1.457(5)	C22–C23	1.496(6)
N21–C22	1.447(5)	C24–C25	1.484(6)
C3–N4–C5	110.5(4)	N4–C9–C8	111.0(4)
C3–N4–C9	112.0(4)	N7–C10–C11	114.5(4)
C5–N4–C9	108.8(3)	N16–C11–C10	114.4(4)
C6–N7–C8	108.6(4)	N16–C11–C12	123.2(4)
C6–N7–C10	111.0(4)	C10–C11–C12	122.4(4)
C8–N7–C10	112.4(4)	C11–C12–C13	118.6(4)
C11–N16–C15	117.7(4)	C12–C13–C14	119.3(4)
C17–N18–C23	110.8(4)	C13–C14–C15	118.8(4)
C17–N18–C19	113.0(4)	N16–C15–C14	122.4(4)
C19–N18–C23	108.3(3)	N16–C15–C17	113.3(4)
C20–N21–C22	108.6(3)	C14–C15–C17	124.2(4)
C20–N21–C24	112.6(4)	N18–C17–C15	113.5(4)
C22–N21–C24	108.7(4)	N18–C19–C20	110.4(4)
O1–C2–C3	111.6(4)	N21–C20–C19	111.4(4)
N4–C3–C2	113.8(4)	N21–C22–C23	111.9(4)
N4–C5–C6	112.4(4)	N18–C23–C22	110.4(4)
N7–C6–C5	109.7(4)	N21–C24–C25	115.1(4)
N7–C8–C9	111.0(4)	O26–C25–C24	108.1(4)

where  $H$  is the total hydrogen ion concentration or the  $^1\text{H}$  chemical shift in the case of potentiometric titrations and NMR measurements, respectively. Every metal ion–ligand system has been modelled by the computer program SOLGASWATER.<sup>17</sup> Theoretical  $Z(A/B)$  (the aver-

age number of protons bound to each ligand) versus  $-\log[\text{H}^+]$  curves were calculated to evaluate the correctness of the model.<sup>18</sup>

## Results and discussion

**Molecular structure of L<sub>2</sub>.** The molecular structure and numbering of the atoms in L<sub>2</sub> is presented in Fig. 1. There is no symmetry element in the molecule, and the ligand has adopted a long, linear conformation (total length ca. 19 Å) in the crystalline state. The C–C and C–N bond lengths (1.36–1.38 and 1.34 Å, respectively) in the pyridine ring show typical values for those expected in the aromatic rings. The corresponding bond lengths (C–C = 1.48–1.50 Å and C–N = 1.45–1.47 Å) in piperazine and 2-hydroxyethyl chains are typical for the aliphatic compounds. Upon complexation, however, the 1-(2-hydroxyethyl)piperazine fragments may rotate around the bonds C15–C17 and C10–C11 by ca. 180° to create a pocket containing three nitrogen donor atoms the orientation of which is suitable for the coordination with metal ions. The ligands have been linked together via intermolecular hydrogen bonds from O26–O1 and O26–N4 [O...O, O1–O26, 2.699(5) Å, O1–H26–O26, 168.8°, symmetry element  $x+3/2, -y+1/2, z-1$ ; O26–O1, 3.155(5) Å, O26–H26–O1, 128.0°, symmetry element  $x-1, y, z+1$ ; O26–N4, 2.938(5) Å, O26–H26–N4, 158.0°, symmetry element  $x-1, y, z+1$ ] forming a net-type packing structure.

**Protonation.** The logarithms of the protonation constants are presented in Table 5. The potentiometric and  $^1\text{H}$  NMR data lead to similar protonation constants, although the pH measurements were performed in the concentration and activity scales in the case of potentiometric titrations and NMR experiments, respectively.

Table 4. Experimental parameters:  $n_T$  = number of titrations,  $n_P$  = number of titration points,  $C_L$  = ligand concentration,  $C_M$  = metal ion concentration,  $M/L$  = metal to ligand concentration ratio.

Compound	$n_T/n_P$	$M/L$	$C_L/\text{mmol dm}^{-3}$	$C_M/\text{mmol dm}^{-3}$	pH range
L <sub>1</sub> , protonation, pot	2/101	—	2.146–3.477	—	2.2–9.4
L <sub>1</sub> , protonation, $^1\text{H}$ NMR	1/13	—	9.150	—	2.5–9.0
Mg <sup>II</sup>	3/118	1:1, 2:1, 5:1	1.466–1.779	1.945–8.923	2.8–9.0
Ca <sup>II</sup>	2/78	2:1, 5:1	1.466–1.929	2.889–9.502	2.8–8.9
Sr <sup>II</sup>	2/78	2:1, 5:1	1.466–1.929	3.429–9.650	2.8–8.9
Ba <sup>II</sup>	2/78	2:1, 5:1	1.466–1.929	3.252–9.630	2.8–8.9
Pr <sup>III</sup>	3/98	1:1, 2:1	1.466–1.745	1.780–2.990	2.8–7.5
Ni <sup>II</sup>	3/103	1:1, 2:1, 5:1	1.466–1.929	1.847–7.333	2.8–8.1
Cu <sup>II</sup>	1/20	1:1	1.779	1.757	2.8–4.6
Zn <sup>II</sup>	2/58	1:1, 2:1	1.514–1.779	1.732–2.949	2.8–7.5
L <sub>2</sub> , protonation, pot	3/262	—	2.265–3.773	—	2.1–9.3
L <sub>2</sub> , protonation, $^1\text{H}$ NMR	1/14	—	3.400	—	2.0–8.9
Mg <sup>II</sup>	2/112	1:1, 2:1	1.585–1.887	1.943–3.268	2.4–9.2
Ca <sup>II</sup>	3/148	1:1, 5:1	1.683–2.028	1.753–9.502	2.4–9.3
Sr <sup>II</sup>	1/52	5:1	2.028	10.125	2.4–9.2
Ba <sup>II</sup>	1/52	5:1	2.028	10.180	2.4–9.2
Pr <sup>III</sup>	2/78	1:1, 2:1	1.541–1.731	1.815–2.990	2.4–7.5
Ni <sup>II</sup>	4/193	1:2, 1:1, 2:1	1.683–3.349	1.526–3.408	2.4–8.6
Cu <sup>II</sup>	3/173	1:2, 1:1, 2:1	1.540–3.131	1.471–3.217	2.4–9.1
Zn <sup>II</sup>	3/126	1:2, 1:1, 2:1	1.541–3.081	1.586–3.172	2.6–7.6

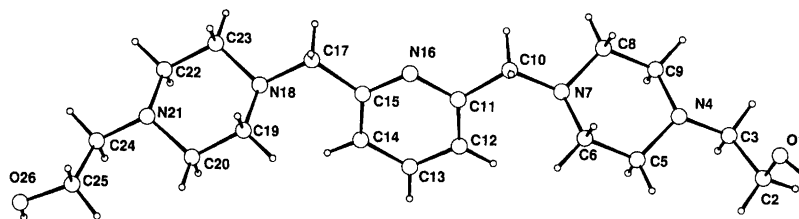


Fig. 1. The molecular structure of the  $L_2$  indicating the numbering of the atoms.

Table 5. The protonation constants  $\beta_{qr} \pm \sigma^a$  and  $K_{qr}^a$  of  $L_1$  and  $L_2$  at 25 °C and  $I=0.10 \text{ mol dm}^{-3}$  NaCl, as determined using potentiometric titration and  $^1\text{H}$  NMR spectroscopy (activity constants).<sup>b</sup>

	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{13}$	$\log \beta_{14}$	$U^c$
$L_1$ , potentiometric	8.10 (0.004)	15.41 (0.004)	19.13 (0.004)	21.91 (0.004)	$3.6 \times 10^{-3}$
$L_1$ , $^1\text{H}$ NMR	8.06 (0.10)	15.40 (0.20)	19.07 (0.02)	21.93 (0.06)	0.58
$L_2$ , potentiometric	7.82 (0.004)	14.82 (0.004)	18.32 (0.004)	20.30 (0.004)	$2.3 \times 10^{-3}$
$L_2$ , $^1\text{H}$ NMR	7.81 (0.08)	14.77 (0.19)	18.34 (0.03)	20.39 (0.06)	0.21
	$\log K_{11}$	$\log K_{12}$	$\log K_{13}$	$\log K_{14}$	$U^c$
$L_1$ , potentiometric	8.10 (0.004)	7.31 (0.004)	3.72 (0.004)	2.78 (0.004)	$3.6 \times 10^{-3}$
$L_1$ , $^1\text{H}$ NMR	8.06 (0.10)	7.34 (0.20)	3.67 (0.02)	2.86 (0.06)	0.58
$L_2$ , potentiometric	7.82 (0.004)	7.00 (0.004)	3.50 (0.004)	1.98 (0.004)	$2.3 \times 10^{-3}$
$L_2$ , $^1\text{H}$ NMR	7.81 (0.08)	6.96 (0.19)	3.57 (0.03)	2.05 (0.06)	0.21

<sup>a</sup> $\beta_{qr}$  refers to reaction  $qL + rH = L_qH_r$  and  $K_{qr}$  refers to reactions  $L + H = LH$ ,  $LH + H = LH_2$ ,  $LH_2 + H = LH_3$  and  $LH_3 + H = LH_4$ .  
<sup>b</sup> $^1\text{H}$  NMR spectroscopic measurements have been carried out at 24 °C. <sup>c</sup>Potentiometric,  $U/\text{mol}^2 \text{ dm}^{-6}$  and NMR,  $U/\text{Hz}^2$ .

The first and second protonations take place in piperazine nitrogen atoms near the 2-hydroxyethyl chains and the third and the fourth protonations in piperazine nitrogen atoms near the aromatic units in the case of  $L_1$ . The first, second and third protonations of  $L_2$  are analogous to  $L_1$ , but the  $^1\text{H}$  NMR data indicate that the fourth protonation in  $L_2$  possibly takes place at the pyridine nitrogen atom instead of the piperazine nitrogen atom. In the case of  $L_1$  the fourth protonation can only take place at the piperazine nitrogen. This is also indicated by the difference in  $\log K_{14}$  values of  $L_1$  and  $L_2$  (2.78 and 1.98, respectively). The  $\log K_{11}$ ,  $\log K_{12}$  and  $\log K_{13}$  values of  $L_1$  and  $L_2$  do not differ significantly (for example  $\log K_{11}$  values of  $L_1$  and  $L_2$  are 8.10 and 7.82, respectively).

On the other hand, the protonation constant of 2,6-di(aminomethyl)pyridine is  $-0.9$ .<sup>19</sup> This suggests that the protonation of the pyridine group in  $L_2$  does not take place at pH 2, and therefore the fourth protonation of  $L_2$  may preferably take place at the piperazine nitrogen atom, as in the case of  $L_1$ . The presence of the nitrogen heteroatom in the aromatic ring may render pyridine more electrophilic than benzene. This could explain the lower  $\log K_{14}$  value in  $L_2$  than in  $L_1$ .

$\log \beta_{11}$  and  $\log \beta_{12}$  were calculated using the methylene proton resonance **a** (Fig. 2) of the 2-hydroxyethyl chains. Similarly,  $\log \beta_{13}$  and  $\log \beta_{14}$  were calculated using the methylene proton resonance **b**. The protonation constant  $\log \beta_{14}$  is 21.91 and 20.30 for  $L_1$  and  $L_2$ , respectively. These values indicate that the two ligands are equally good complexing agents or that  $L_1$  is slightly

better than  $L_2$ . The stability constants, however, do not agree with this trend (Table 6). This can be explained by the consideration of the molecular structures of the ligands  $L_1$  and  $L_2$ .  $L_2$  has a pyridine ring between the two piperazine moieties [Fig. 2(b)]. The three close-lying nitrogen atoms can coordinate to the same metal ion, and the ligand can therefore be tridentate. In contrast, in  $L_1$  the two piperazine fragments are connected by a benzene ring. In this case there are only two nitrogen donor atoms suitable for coordination. In fact the C–H fragment may sterically hinder the coordination of the metal ion to the two nitrogen atoms.

**Complexation.** Logarithms of overall stability constants are presented in Table 6.  $Z(A/B)$  versus  $-\log[H^+]$  for  $[\text{Cu}^{\text{II}}-L_2]$  is presented in Fig. 3. The potentiometric data for  $L_2$  indicate that when  $Z(A/B) \geq 2$ , the  $[\text{M}(\text{H}_2\text{L})]$  complex is predominant in the solution, when  $2 < Z(A/B) \leq 1$ , the  $[\text{M}(\text{HL})]$  complex is the main component in solution, and when  $Z(A/B) < 1$ ,  $[\text{ML}]$ ,  $[\text{ML}_2]$  and possible hydrolysed complexes exist in solution. As expected  $L_2$  is a better complexing agent than  $L_1$ .  $L_1$  forms only  $[\text{ML}]$  complexes. Its alkaline-earth(II) complexes are very weak ( $\log \beta$  values are ca. 1–1.4).  $\text{Ni}^{\text{II}}$  and  $\text{Zn}^{\text{II}}$  complexes of  $L_1$  are stronger ( $\log \beta$  values are 2.01 and 2.32) but weaker than the  $\text{Pr}^{\text{III}}$  complex ( $\log \beta = 2.80$ ). This stability order is unexpected because the transition-metal ions normally form more stable complexes with nitrogen donor ligands than the lanthanoid ions. Lanthanoid(III) ions are hard ions, and their binding is mainly ionic with negligible covalent contribu-

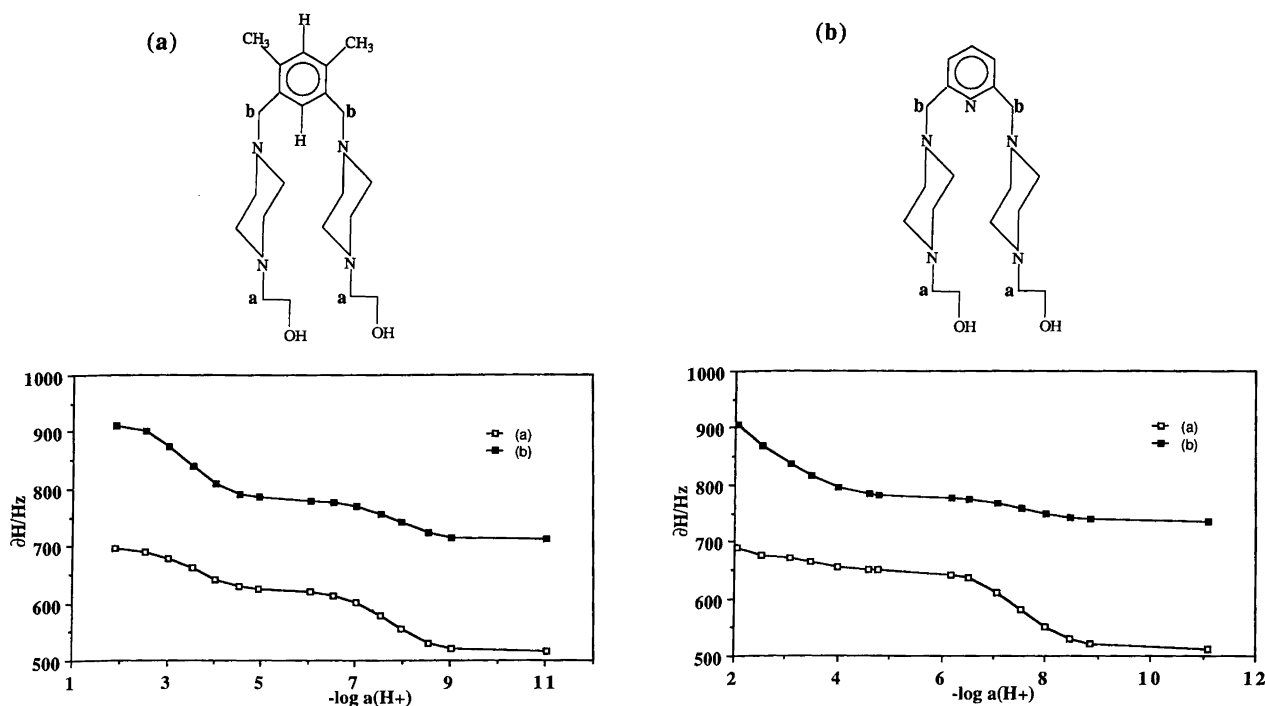


Fig. 2. Experimental chemical shift (in Hz) versus  $-\log a_{\text{H}^+}$  of (a)  $L_1$  and (b)  $L_2$  at  $24^\circ\text{C}$  and  $I=0.10 \text{ mol dm}^{-3}$  NaCl.

Table 6. The overall stability constants,  $\beta_{pqr} \pm \sigma$ ,<sup>a</sup> of alkaline-earth(II), Pr<sup>III</sup>, Ni<sup>II</sup>, Cu<sup>II</sup>, Zn<sup>II</sup>  $L_1$  and  $L_2$  complexes at  $25^\circ\text{C}$  and  $I=0.10 \text{ mol dm}^{-3}$  NaCl.

Ligand	Metal ion	Species/ $pqr$ <sup>b</sup>	$\log \beta_{pqr}$	$U/\text{mol}^2 \text{ dm}^{-6}$
$L_1$	Mg <sup>II</sup>	1 1 0	1.41 (0.07)	$2.4 \times 10^{-3}$
$L_1$	Ca <sup>II</sup>	1 1 0	1.1 (0.1)	$7.0 \times 10^{-5}$
$L_1$	Sr <sup>II</sup>	1 1 0	1.0 (0.1)	$1.8 \times 10^{-4}$
$L_1$	Ba <sup>II</sup>	1 1 0	1.35 (0.03)	$7.3 \times 10^{-5}$
$L_1$	Pr <sup>III</sup>	1 1 0	2.80 (0.04)	$3.5 \times 10^{-3}$
$L_1$	Ni <sup>II</sup>	1 1 0	2.01 (0.03)	$1.2 \times 10^{-3}$
$L_1$	Cu <sup>II</sup>	—	—	—
$L_1$	Zn <sup>II</sup>	1 1 0	2.32 (0.08)	$2.8 \times 10^{-3}$
$L_2$	Alkaline-earth <sup>II</sup>	—	—	—
$L_2$	Pr <sup>III</sup>	1 1 1	9.79 (0.02)	$1.6 \times 10^{-4}$
		2 2 0	8.62 (0.01)	
$L_2$	Ni <sup>II</sup>	1 1 0	3.93 (0.01)	$9.5 \times 10^{-4}$
		1 1 1	10.91 (0.01)	
		1 1 2	17.06 (0.01)	$2.8 \times 10^{-4}$
		1 2 0	6.77 (0.02)	$6.2 \times 10^{-3}$
		1 1 - 1	-5.00 (0.02)	
$L_2$	Cu <sup>II</sup>	1 1 0	8.08 (0.01)	$6.9 \times 10^{-3}$
		1 1 1	14.54 (0.01)	
		1 1 2	20.37 (0.01)	
		1 2 0	9.96 (0.04)	$1.4 \times 10^{-3}$
		1 1 - 1	-0.10 (0.01)	
		1 1 - 1	-0.01 (0.02)	
		1 1 - 2	-10.21 (0.05)	
$L_2$	Zn <sup>II</sup>	1 1 0	2.93 (0.01)	$9.7 \times 10^{-4}$
		1 1 1	10.19 (0.02)	
		1 1 2	16.88 (0.01)	
		1 2 0	5.85 (0.03)	$4.0 \times 10^{-3}$

<sup>a</sup> $\beta_{pqr}$  refers to the reaction  $pM + qL + rH = M_pL_qH_r$ . <sup>b</sup>\*  $M/L = 1/2$ ; \*\*  $M/L = 1/1$ .

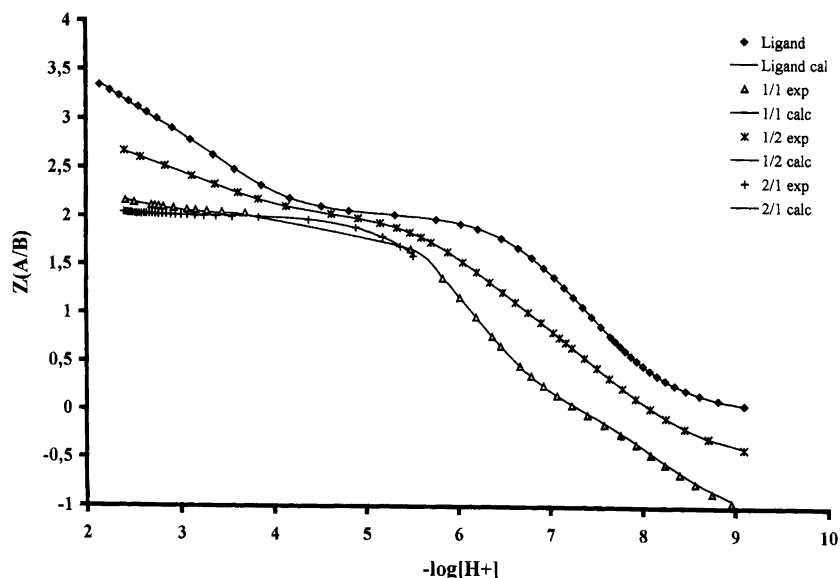
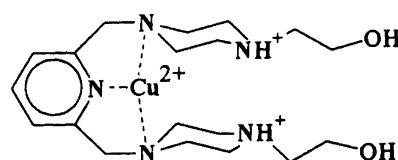


Fig. 3.  $Z(A/B)$  (the average number of protons bound to each ligand) versus  $-\log[H^+]$  for  $Cu^{II}-L_2$ .

tions. The stronger complex formation of  $Pr^{III}$  with  $L_1$  as compared to that of  $Ni^{II}$  and  $Zn^{II}$  may be explained by the larger size of  $Pr^{III}$  that renders the didentate coordination through the piperazine nitrogen atoms next to 2-hydroxyethyl chains sterically more facile than in the case of smaller  $Ni^{II}$  and  $Zn^{II}$  ions.  $Cu^{II}$  does not form complexes with  $L_1$ . Only the hydrolysis of uncomplexed  $Cu^{II}$  ion was observed in the aqueous solution.

$L_2$  does not form alkaline-earth(II) complexes.  $Pr^{III}$  shows  $[M(HL)]$  and dimeric  $[M_2L_2]$  species, but no  $[ML]$  or  $[M(H_2L)]$  complexes, which are observed for the transition-metal ions. The stronger complex formation of the transition-metal ions compared to  $Pr^{III}$  (see  $[M(HL)]$  stability constants in Table 6) originates from different acceptor abilities of the metal ions and the larger size of  $Pr^{III}$ . In contrast to the transition-metal ions the  $Pr^{III}$  ion is possibly too large to fit in the space defined by the three close-lying nitrogen atoms of  $L_2$ .  $[M(HL)]$  and dimeric  $[M_2L_2]$  do not impose as severe steric limitations.

The logarithms of pyridine  $[ML]$  complexes are  $Zn^{II}$  1.10,  $Ni^{II}$  2.08 and  $Cu^{II}$  2.58.<sup>20</sup> The stabilities of our  $L_2$  complexes are greater than the stabilities of the corresponding pyridine complexes. It can be inferred that the piperazine nitrogen donor atoms are essential in the coordination and the pyridine unit alone does not dominate in the complexation. A possible coordination scheme in the present transition-metal  $[M(H_2L_2)]^{4+}$  complexes is exemplified by the  $Cu^{II}$  complex. The suggested structure (I) is analogous to a known cyclic  $Cu^I$  complex.<sup>1a</sup> The deprotonation of the protonated complex in neutral and basic solutions increases the amount of the complex with a tridentate coordination through the piperazine and the pyridine nitrogen atoms and enables the formation of the hydrolysed  $[M(OH)_xL]^{1+/0}$  ( $X=1, 2$ ) complexes.



Thermodynamic data are exemplified for the  $[Cu^{II}-L_2]$  (1:1) system. The distribution diagram is shown in Fig. 4. The  $[Cu(H_2L_2)]^{4+}$  complex is relatively abundant when  $pH < 3$ . The order of the stability of the transition-metal complexes of  $L_2$  is  $Zn^{II} < Ni^{II} < Cu^{II}$ , is in agreement with the Irving-Williams order.<sup>21,22</sup> The value of  $\log \beta$  of  $[CuL_2]^{2+}$  is about four orders of magnitude higher than that of the next stable  $[NiL_2]^{2+}$  complex.

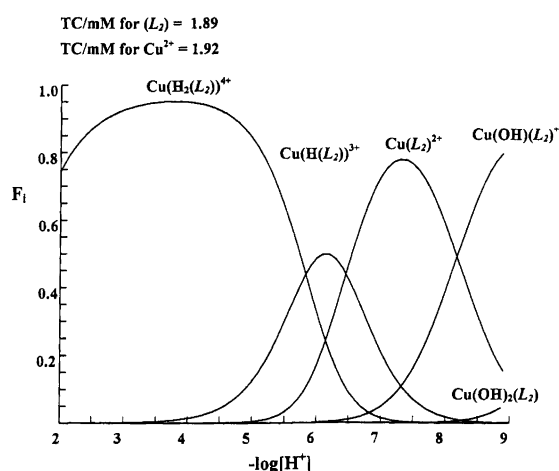


Fig. 4. The distribution diagram for individual  $[Cu^{II}-L_2]$  complexes when the metal-ligand concentration ratio is 1:1.

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## References

- (a) Rissanen, K., Breitenbach, J. and Huuskonen, J. *J. Chem. Soc., Chem. Commun.* (1994) 1265; (b) Allinger, N. L., Carpenter, J. G. D. and Karkowski, F. M. *J. Am. Chem. Soc.* 87 (1965) 1232; (c) Schneider, H. J. *Angew. Chem., Int. Ed. Engl.* 30 (1991) 1417; (d) Wade, P. W. and Hancock, R. D. *J. Chem. Soc., Dalton Trans.* (1990) 1323; (e) Hancock, R. D., Ngwenya, M. P., Evers, A., Wade, P. W., Boyens, J. C. A. and Dobson, S. M. *Inorg. Chem.* 29 (1990) 264; (f) Hancock, R. D., Dobson, S. M., Evers, A., Wade, P. W., Ngwenya, M. P., Boyens, J. C. A. and Wainwright, K. P. *J. Am. Chem. Soc.* 110 (1988) 2788; (g) Wade, P. W., Hancock, R. D., Boyens, J. C. A. and Dobson, S. M. *J. Chem. Soc., Dalton Trans.* (1990) 483.
- (a) Huuskonen, J., Schulz, J. and Rissanen, K. *Liebigs Ann.* (1995) 1515; (b) Larkins, H. L. and Hamilton, A. D. *Tetrahedron Lett.* 27 (1986) 2721; (c) Krakowiak, K. E., Bradshaw, J. S., Jiang, W., Dalley, N. K., Wu, G. and Izatt, R. M. *J. Org. Chem.* 56 (1991) 2675; (d) Saigo, K. *Chem. Lett.* (1989) 1289; (e) Ramasubbu, A. and Wainwright, K. P. *J. Chem. Soc., Chem. Commun.* (1982) 277; (f) Chenevert, R. and Plate, R. *Synthesis* (1983) 847; (g) Bazzicalupi, C., Benzini, A., Fusi, V., Micheloni, M. and Valtancoli, B. *J. Chem. Soc., Chem. Commun.* (1994) 1119.
- Kushner, S. *J. Org. Chem.* 13 (1948) 144.
- Doadrio, A., Craciunescu, D., Ghirvu, C. and Nuno, J. C. *An. Quim.* 73 (1977) 1220.
- Ratilainen, J., Airola, K., Kolehmainen, E. and Rissanen, K. *Chem. Ber.* 130 (1997) 1353.
- Jeffery, G. H., Bassett, G., Mendham, J. and Denney, R. C. *Vogel's Textbook of Quantitative Chemical Analysis*, 5th edn., Longman, Avon 1989, pp. 186 and 311.
- Ginstrup, O. *Chem. Instrum.* 4 (1973) 141.
- Sjöberg, S., Hägglund, Y., Nordin, A. and Ingri, N. *Marine Chem.* 13 (1983) 35.
- Sheldrick, G. M. *SHELXS97*, University of Göttingen, Germany 1997.
- Sheldrick, G. M. *SHELXL97*, University of Göttingen, Germany 1997.
- Ingri, N. and Sillen, L. G. *Ark. Chem.* 23 (1964) 97.
- Arnek, R., Sillen, L. G. and Wahlberg, O. *Ark. Chem.* 31 (1969) 353.
- Brauner, P., Sillen, L. G. and Whiteker, R. *Ark. Chem.* 31 (1969) 365.
- Sigmaplot Scientific Graphing System Version 4.0, Jandel Corporation, 1986–89.
- Hietapelto, V., Laitinen, R.S., Pursiainen, J. and Rahkamaa, E. *Acta Chem. Scand.* (1998). *In press.*
- Baes, C. F. and Mesmer, R. E. *The Hydrolysis of Cations*, 1st edn., Wiley, New York 1976, pp. 246 and 274.
- Eriksson, G. *Anal. Chim. Acta* 112 (1979) 375.
- Rossotti, H. S. *Talanta* 21 (1974) 809.
- Couturier, Y. and Petitfaux, C. *Bull. Soc. Chim. Fr.* (1975) 141.
- Israeli, M., Laing, D. K. and Pettit, L. D. *J. Chem. Soc., Dalton Trans.* (1974) 2194.
- Irwing, H. and Williams, R. J. P. *Nature* 162 (1948) 746.
- Irwing, H. and Williams, R. J. P. *J. Chem. Soc.* (1953) 3192.

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