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Cu^{2+} complexes of tetraazacyclododecanes functionalized with benzyl side chains carrying carboxylic or phenolic groups

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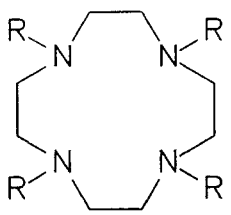
A series of tetra-*N*-functionalized 1,4,7,10-tetraazacyclododecanes with benzyl side chains carrying carboxylic or phenolic groups have been synthesized. All of these ligands form Cu^{2+} complexes, which have been characterized by elemental analysis, absorption spectra and in two cases (ligands 4 and 7) by an X-ray diffraction study. In both cases the Cu^{2+} is co-ordinated by the four nitrogens of the macrocycle folded in the *trans-I* configuration and an additional ligand. The additional ligand is Cl^- for the complex with 4, and a side chain carboxylate group for the complex with 7. In addition potentiometric and spectrophotometric equilibrium measurements of Cu^{2+} with 7 have been run. Three species CuL^{2-}, $CuLH^-$ and $CuLH_2$ have been identified and their stability constants determined.

INTRODUCTION

The functionalization of tetraaza macrocycles has produced a large number of interesting new ligands.[1] Generally, aliphatic side chains carrying functional groups such as carboxylates[2] or amines[3] have been attached to the nitrogens of the macrocycle to give *per*-substituted derivatives. Compared to the relatively rigid macrocyclic unit the side chains with functional groups are flexible and can therefore adapt themselves more easily to the geometrical requirements of the metal ion. The X-ray structure analyses of their metal complexes have shown that a large number of co-ordination geometries exist, depending on the co-ordination number of the metal ion, the ring size of the macrocycle, and the metal to ligand ratio.[4–6]

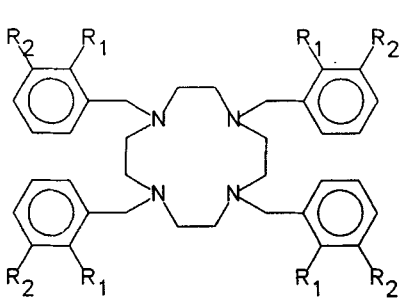
For metal ions with co-ordination number 6, only part of the groups are involved in binding the metal ion, and the structures can be very different. The 14-membered macrocyclic derivatives mostly give *trans*-octahedral co-ordination geometry, the macrocyclic cavity being ideal to bind a transition metal ion in the centre of the N_4 plane.[4,5] In contrast the 12-membered derivatives are more prone to induce *cis*-octahedral geometry,[5] since they have to fold in order to accommodate the four nitrogens of the macrocycle around the central ion. For larger metal ions such as the lanthanides the involvement of all donor groups has been observed.[6]



1 R = H
2 R = CH_2COOH

Many of the tetra-*N*-functionalized tetraazamacrocycles form metal complexes with high thermodynamic stability[7] and kinetic inertness,[8] and are ideal ligands for medical applications. Thus there has been a great deal of interest in compound **2** (DOTA), since it forms extremely stable complexes especially with trivalent metal ions. The Gd^{3+} complex of DOTA is already used as an NMR contrast agent.[9] Other derivatives of DOTA have also been proposed to label monoclonal antibodies for tumor diagnosis or therapy.[10]

In this study the tetra-*N*-substitution has been extended to benzyl side chains, which are less flexible and more hydrophobic than the side chains studied earlier. In addition to carboxylic groups, which are known to be good donors in this type of ligand, phenol and catechol units have also been included. Raymond *et al.*[11] have shown in their studies that macrocycles carrying catechols as functional groups are extremely good chelators for Fe^{3+}. Investigation of the metal complexes with the new ligands **3–8** is expected to give a better insight into the relationship between ligand structure and complex geometry.



3 R_1= OCH_3, R_2 = H
4 R_1 = OH, R_2= H
5 R_1 = R_2 = OCH_3
6 R_1 = R_2 = OH
7 R_1 = COOH, R_2= H
8 R_1 = CH_3, R_2 = H

EXPERIMENTAL SECTION

1,4,7,10-Tetraazacyclododecane **1**,[12] 2-methoxybenzylchloride,[13] 2,3-dimethoxybenzylchloride,[13] and 2-bromomethylbenzoic acid ethyl ester[14] were prepared according to the literature. NMR spectra were run on a Varian Gemini 300 using TMS and acetone as internal standards for $CDCl_3$ and D_2O solutions, respectively.

1,4,7,10-Tetrakis(2-methoxybenzyl)-1,4,7,10-tetraazacyclododecane dihydrochloride (3·2HCl)

To **1** (1.21 g, 6.8 mmol) and KOH (1.64 g, 29.2 mmol) dissolved in absolute ethanol (15 ml) a solution of 2-methoxybenzylchloride (6.32 g, 40.4 mmol) in absolute ethanol (5 ml) was added over 2 h at 65°C. After complete addition the reaction mixture was kept for a further 3 h at 65°C, then cooled to r.t., filtered and the solvent evaporated. The oily residue was dissolved in acetone (100 ml), heated to 65°C and the hydrochloride was precipitated by addition of conc. HCl (2 ml). The precipitate was filtered, washed with acetone (20 ml) and recrystallized from acetone/water/HCl. The pure compound was filtered, washed with acetone (2 × 5 ml) and dried first in the desiccator, then at 60°C under high vacuum. Yield: 3.27 g (69%). Anal. calcd. for $C_{40}H_{54}Cl_2N_4O_4$ (725.81): C 66.19, H 7.50, Cl 9.77, N 7.72, O 8.82; found C 65.98, H 7.57, Cl 10.03, N 7.77, O 8.92. The free base was characterized by ^{1}H-NMR ($CDCl_3$): 2.74 (16H, s, CH_2-N), 3.50 (8H, s, CH_2-aromatic), 3.73 (12H, s, O-CH_3), 6.71 (4H, t, H5-aromatic), 6.77 (4H, d, H3-aromatic), 7.12 (4H, t, H4-aromatic), 7.82 (4H, d, H6-aromatic) and ^{13}C-NMR ($CDCl_3$): 53.37 (CH_2-aromatic), 53.99 (CH_2-N), 55.02 (O-CH_3), 109.48, 120.47, 126.85, 128.25, 129.86, 157.32 (C-aromatic).

1,4,7,10-Tetrakis(2-hydroxybenzyl)-1,4,7,10-tetraazacyclododecane dihydrochloride (4·2HCl)

To absolute CH_2Cl_2 (25 ml), cooled to 0°C and purged with dry N_2 for 30 min, **3**·2HCl (1.02 g, 1.4 mmol) and BBr_3 (2.9 ml, 31 mmol) were added. The mixture was left over night to reach r.t., then treated with H_2O (50 ml), conc. HCl (5 ml), and stirred for 1 h at 50°C. The precipitate was filtered, washed with cold H_2O (10 ml) and recrystallized twice from acetone/H_2O/HCl. The pure product was dried at 50°C under high vacuum. Yield: 0.76 g (78%). Anal. calcd. for $C_{36}H_{46}Cl_2N_4O_4 \cdot 1.3H_2O$ (693.11): C 62.39, H 7.07, Cl 10.23, N 8.08, O 12.23; found: C 62.47, H 7.09, Cl 10.27, N 7.92, O 12.13.

1,4,7,10-Tetrakis(2,3-dimethoxybenzyl)-1,4,7,10-tetraazacyclododecane dihydrochloride monohydrate (5·2HCl)

The compound was prepared as for **3**·2HCl. In absolute ethanol (15 ml) **1** (1.01 g, 5.9 mmol) and KOH (1.49 g, 26.6 mmol) were dissolved and treated with a solution of 2,3-dimethoxybenzylchloride (6.57 g, 35.4 mmol) in absolute ethanol (10 ml) at 65°C. Work up as for **3**·2HCl gave 4.23 g (83%). Anal. calcd. for $C_{44}H_{62}Cl_2N_4O_8 \cdot H_2O$ (861.93): C 61.31, H 7.48, Cl 8.22, N 6.50, O 16.70; found C 61.12, H 7.56, Cl 8.44, N 6.55, O 16.55. The free base was characterized by ^{1}H-NMR ($CDCl_3$): 2.72 (16H, s, CH_2-N), 3.53 (8H, s, CH_2-aromatic), 3.72 and 3.82 (24H, 2s, O-CH_3), 6.75 (4H, d, H4-aromatic), 6.88 (4H, t, H5-aromatic), 7.35 (4h, d, H6-aromatic) and ^{13}C-NMR ($CDCl_3$): 53.47 (CH_2-N), 55.64, 60.41 (O-CH_3), 110.34, 122.38, 123.67, 133.85, 147.26, 152.31 (C-aromatic).

1,4,7,10-Tetrakis(2,3-dihydroxybenzyl)-1,4,7,10-tetraazacyclododecane dihydrochloride (6·2HCl)

The compound was prepared as for **4**·2HCl. Yield: 0.86 g (75%). Anal. calcd. for $C_{36}H_{46}Cl_2N_4O_8$ (733.69): C 58.93, H 6.32, Cl 9.66, N 7.64; found C 58.81, H 6.35, Cl 9.48, N 7.95.

1,4,7,10-Tetrakis(2-carboxybenzyl)-1,4,7,10-tetraazacyclododecane dihydrochloride monohydrate (7·2HCl)

The compound was prepared using 2-bromomethylbenzoic acid ethyl ester as for **3**·2HCl. After filtration of the hydrochloride the ester was hydrolysed in 18% HCl for 15 h at reflux temperature. The hydrochloric was then prepared and recrystallized as described for **3**. Yield: 2.55 g (55%). Anal. calcd. for $C_{40}H_{46}Cl_2N_4O_8 \cdot H_2O$ (799.76): C 60.07, H 6.05, Cl 8.86, N 7.00, O 18.00; found C 60.22, H 6.16, Cl 8.51, N 7.13, O 18.04. ^{1}H-NMR (D_2O, pD = 1.3): 3.09 (16H, s, CH_2-N), 4.01 (8H, s, CH_2-aromatic), 7.23 (4H, d, H6-aromatic), 7.37 (4H, t, H4-aromatic), 7.49 (4H, t, H5-aromatic), 7.73 (4H, t, H3-aromatic). ^{1}H-NMR (D_2O, pD = 14); 2.88 (16H, s, CH_2-N), 3.82 (8H, s, CH_2-aromatic), 7.42–7.53, 7.66 (12H, m, H-aromatic). ^{13}C-NMR (D_2O, pD = 14): 45.87 (CH_2-N), 53.20 (CH_2-aromatic), 123.34, 123.96, 125.36, 127.22, 131.05, 137.64 (C-aromatic), 174.89 (COOH).

1,4,7,10-Tetrakis(2-methylbenzyl)-1,4,7,10-tetraazacyclododecane trihydrochloride semihydrate (8·3HCl)

The compound was prepared as for **3**·2HCl using 2-methylbenzylchloride. Yield: 1.36 g (53%). Anal. calcd. for $C_{40}H_{55}Cl_3N_4 \cdot 0.5H_2O$ (707.27): C 67.93,

Table 1 Elemental analyses (upper line, calculated; lower line, found, in %) of the Cu^{2+} complexes with benzyl substituted 1,4,7,10-tetraazacyclododecanes

Compound (Molecular weight in k)	*Ligand*	*Elemental analysis—upper line calculated, lower line found (%)* C	H	Cl	Cu	N	*Yield (%)*
$C_{40}H_{52}N_4O_4CuCl_2 \cdot 0.5H_2O$ (796.34)	**3**	60.33	6.71	8.90	7.98	7.04	68
		60.40	6.72	8.86	7.79	7.14	
$C_{40}H_{52}N_4O_4CuCl(NO_3) \cdot H_2O$ (831.90)	**3**	57.75	6.54	4.26	7.64	8.42	57
		57.98	6.49	4.22	7.64	8.56	
$C_{40}H_{52}N_4O_4Cu(NO_3)_2 \cdot H_2O \cdot CH_3OH$ (890.50)[a]	**3**	55.30	6.57		7.13	9.44	74
		55.18	6.36		7.11	9.45	
$C_{36}H_{44}N_4O_4CuCl_2 \cdot 0.5H_2O \cdot CH_3OH$ (772.27)	**4**	57.55	6.40	9.18	8.23	7.25	68
		57.59	6.40	9.07	8.17	7.25	
$C_{36}H_{43}N_4O_4Cu(ClO_4) \cdot 1.3CH_3OH$ (800.42)[b]	**4**	55.97	6.07	4.43	7.94	7.00	38
		56.24	6.07	4.36	7.64	6.92	
$C_{44}H_{60}N_4O_8CuCl_2$ (907.43)	**5**	58.24	6.66	7.81	7.00	6.17	62
		58.08	6.73	7.80	6.92	6.18	
$C_{44}H_{60}N_4O_8Cu(NO_3)_2 \cdot H_2O$ (978.56)[a]	**5**	54.01	6.38		6.48	8.59	59
		54.17	6.33		6.49	8.74	
$C_{36}H_{44}N_4CuCl_2$ (795.22)	**6**	54.37	5.88	8.92	c	7.05	32
		54.47	5.64	8.60		6.89	
$C_{40}H_{43}N_4O_8CuCl \cdot 2H_2O$ (842.84)	**7**	57.00	5.62	4.20	7.54	6.65	68
		56.62	5.72	4.55	7.44	6.69	
$C_{40}H_{43}N_4O_8Cu(ClO_4) \cdot 2H_2O$ (906.84)	**7**	52.98	5.22	3.91	7.01	6.17	66
		52.62	5.20	4.24	7.01	6.19	
$C_{40}H_{44}N_4O_8Cu(ClO_4)_2 \cdot 1.5H_2O$ (998.29)[d,e]	**7**	48.13	4.75	7.10	6.36	5.61	84
		47.97	4.78	7.12	6.36	5.64	
$C_{40}H_{52}N_4CuCl(ClO_4) \cdot CH_3OH$ (819.37)	**8**	60.10	6.89	8.65	7.75	6.84	69
		60.11	6.92	8.66	7.77	6.88	

[a] An additional 1.0 g of $NaNO_3$ was added. [b] This solution was kept at alkaline pH; addition of 1.0 g of $NaClO_4$. [c] Not determined because of only a small amount of product. [d] An additional 1 g of $NaClO_4$ was added. [e] pH = 0.5.

H 7.98, Cl 15.04, N 7.92; found C, 68.00, H 7.98, Cl 14.86, N 8.20. The free base was characterized by ^{1}H-NMR ($CDCl_3$): 2.24 (12H, s, CH_3-), 2.72 (16H, s, CH_2-N), 3.37 (8H, s, CH_2-aromatic) 6.95–7.15 (12H, m, H-aromatic), 7.60 (4H, d, H6-aromatic) and ^{13}C-NMR ($CDCl_3$): 19.35 (CH_3-), 53.48 (CH_2-N), 57.97 (CH_2-aromatic), 125.60, 126.24, 129.28, 129.74, 136.47, 137.83 (C-aromatic).

Copper complexes

Equimolar (generally 0.28 mmol) amounts of ligand and Cu^{2+} salt were dissolved in water (25 ml) and heated to 60°C. After addition of methanol (25 ml) and acetone (25 ml) the pH was adjusted to 7–8 with 0.5 M NaOH. The hot solution was filtered and the pH adjusted to approximately 3–4 with HCl or HNO_3. Slow evaporation gave the crystalline compounds, which were filtered, washed with cold H_2O (3 × 5 ml) and dried at 70°C under high vacuum. The stoichiometry and analytical results are given in Table 1.

Potentiometric titrations

These were run on the automatic titrator previously described[15] at 25°C and $I = 0.5$ M (KNO_3) or $I = 0.1$ M (KCl) under N_2. Since ligand **7** is not very soluble in water it was dissolved in a little methanol and then diluted with water so that a 1% MeOH/water mixture resulted. Typical concentrations: ligand **7** = 8×10^{-4} M alone, or with $Cu^{2+} = 7 \times 10^{-4}$ M, and NaOH = 0.4 M as titrating agent. The titration curves were calculated using the programm TITFIT.[16]

Spectrophotometric titrations

These were run on the fully automated titration unit previously described[17] at 25°C and $I = 0.1$ M (KCl) between 260 and 350 nm in 1% MeOH/water solutions. Typical concentrations: ligand **7** = 6.2×10^{-5} M alone, or with $Cu^{2+} = 6 \times 10^{-5}$ M. In addition to the pH titrations the ligand was also titrated with Cu^{2+} at pH 5 to prove that a 1:1 complex is formed. The titrations were calculated using SPECFIT.[18] The spectra of the compounds, given in Table 2, were measured in aqueous solution at acidic and alkaline pH in a 1 cm cuvette.

X-ray diffraction

The crystal data and parameters of the data collection

Table 2 Effect of pH on the spectra of the Cu^{2+} complexes with tetra-*N*-substituted 1,4,7,10-tetraazacyclododecanes

Complex	*Axial group*	*Solvent*	λ_{max} (ε)[d] Acidic soln.	λ_{max} (ε)[d] Alkaline soln.
Cu(**1**)Cl_2[a]	H_2O	H_2O	615 (640)	
	Cl^-	CH_3OH	725 (510)	
Cu(**1**)$(NO_3)_2$[a]	H_2O	H_2O	614 (500)	
	CH_3OH	CH_3OH	625 (880)	
Cu(**8**)(Cl)(ClO_4)	Cl^-	H_2O/CH_3OH[b]	710 (636)	
Cu(**7**)(ClO_4)	$COOH/COO^-$	H_2O/CH_3OH[b]	607 (380)[c]	654 (525)
Cu(**4**)$(ClO_4)_2$	φ-OH/φ-O^-	H_2O/CH_3OH[b]	601 (340)[c]	687 (495)
Cu(**6**)$(ClO_4)_2$	φ-OH/φ-O^-	H_2O/CH_3OH[b]	590 (485)	680 (476)

[a] Ref 31. [b] H_2O/CH_3OH = 1:1. [c] Estimated value. [d] Molar absorptivity in μ^{-1} cm^{-1}/λ_{max} in nm.

Table 3 Crystal data and parameters of data collection for $[CuL]Cl_2 \cdot CH_3OH \cdot H_2O$ (L = 4) **A** and $[CuL](ClO_4) \cdot 4H_2O$ (L = 7)**B**

Compound	*A*	*B*
Formula	$C_{37}H_{50}Cl_2CuN_4O_6$	$C_{40}H_{51}ClCuN_4O_{16}$
Relative molecular weight	781.275	442.853
Crystal system	Monoclinic	Monoclinic
Space group	*Ia*	$P2_1/n$
a (Å)	19.220(4)	8.978(10)
b (Å)	8.899(6)	34.994(18)
c (Å)	21.924(5)	13.863(7)
β (deg)	93.78(6)	98.77(6)
Z	4	4
Volume (Å^3)	3741.5	4308.5
Density (kg/dm^3)	1.387	1.453
Temperature	R.t.	R.t.
Θ_{max}	25	28
Radiation	Mo K_α (λ = 0.71069 Å)	Mo K_α (λ = 0.71069 Å)
Scan type	$\omega/2\Theta$	$\omega/2\Theta$
No. of independent reflections	3278	10,345
No. of reflections in refinement	2156	5390
No. of variables	445	597
Final *R*	0.0710	0.0472
Final R_w	0.041	0.042

R.t. = room temperature.

for the two complexes $[CuL]Cl_2 \cdot CH_3OH \cdot H_2O$ (L = 4) and $[CuL](ClO_4) \cdot 4H_2O$ (L = 7) are given in Table 3. Unit cell parameters were determined by accurate centring of 25 independent strong reflections by the least-squares method. Four standard reflections monitored every hour during data collection showed no significant variation of the intensity. The raw data set was corrected for polarization effects. The structures were determined by Patterson techniques using the program SHELXS-86.[19] Absorption correction was calculated using DIFABS.[20] Anisotropic least-squares refinements were carried out on all non-H atoms, using the program CRYSTALS.[21] H atoms are in calculated positions with C–H distances of 1.0 Å and fixed isotropic thermal parameters. Scattering factors are taken from the International Tables for Crystallography.[22] Fractional co-ordinates are deposited at the Cambridge Crystallographic Data Centre.

Only small crystals were available for the complex with **4**. In order to get an acceptable ratio between observations and variables, reflections with a high standard deviation had to be included in the refinement. To compensate the lack of data, restraints for bond lengths and anisotropic temperature factors were applied.

The centrosymmetric space group $I2/a$ was excluded by the following considerations. $I\,2/a$ would imply the molecule to be located on a special position of the unit cell (Z = 4), either a centre of symmetry or a 2-fold axis. The first can be excluded because of the molecular geometry of the cation. The second requires the molecule to produce its image by the 2-fold axis. Rotating the molecule around the axis through Cu(1) and Cl(1) using the method described by Kabsch,[23] formally equivalent positions reveal distances of up to 0.8 Å. Moreover this 2-fold axis

should be perpendicular to the glide plane along *a*. But the calculated angle between the molecular axis and the crystallographic glide plane was 61.2°. These considerations have been confirmed by a search for additional crystallographic symmetry[24] using the program PLATON.[25] The complex with **4** has a single water of crystallization and a CH_3OH molecule in arbitrary positions. The shortest distance (2.61 Å) which could indicate a hydrogen bond is between O(31) of the cation and O(50) of the solvent molecule CH_3OH.

In the complex of **7** water of crystallization occupies a contiguous space of approximately 300 $Å^3$. The solvent accessible area has been found with the program PLATON.[25] Several contacts with less than 3 Å from the oxygen atoms of the cation [O(2), O(3), O(6)] can be observed with the waters of crystallization. Since the protons of the water molecules could not be localized, no exact information can be given on possible hydrogen bonding.

RESULTS AND DISCUSSION

The synthesis of the ligands is straightforward. The macrocycle **1** is alkylated with a benzyl halogenide derivative, in which the functional group, if present, is protected either by an ether function for the phenolic oxygen, or by an ester function for the carboxylic group. The products of the alkylation can easily be isolated by crystallization as hydrochlorides. The deprotection of the functional groups in the tetra-alkylated products is done using BBr_3 for the phenolic ethers, or through acid hydrolysis for the ester. All of the final products are stable except the catechol derivative **6**, which even as a solid slowly oxidizes on contact with air.

Ligands **3**–**8** form Cu^{2+} complexes which can be isolated and characterized as solids (Table 1). This indicates that the tetra-*N*-substitution of the 12-membered ring does not hinder the co-ordination of the metal ion. Even ligand **8** with an *ortho*-methyl substituent, which presents an additional steric hindrance, is able to bind Cu^{2+}.

The absorption spectra of the Cu^{2+} complexes with several of these ligands measured at acidic and alkaline pH are given in Table 2. Two different behaviours can be observed. Ligands with no additional donor group in the side chains give spectra which do not depend on the pH, whereas those of the derivatives with carboxylic and phenolic groups change with pH. The absorption maxima of the complexes, which have no axial ligand except the solvent, all absorb at 615–625 nm. With Cl^- as axial ligand the absorption maxima shift to 710–725 nm. The macrocycles with an additional donor group in the benzyl side chains have absorption maxima between 590 and 607 nm in acidic solution, where the carboxylic or phenolic groups are protonated and therefore are only weakly bound (if at all) to the metal ion. In alkaline solution, however, the λ_{max} values are shifted to longer wavelengths, as expected when the donor group axially binds to Cu^{2+}.[26]

The protonation and complexation equilibria of **7** and Cu^{2+} were studied potentiometrically and spectrophotometrically. To fit all the measures eqns 1–9 were taken into account. The results are given in Table 4.

$$L + H \rightleftharpoons LH;\ K_{H,1} \quad (1)$$

$$LH + H \rightleftharpoons LH_2;\ K_{H,2} \quad (2)$$

Table 4 Protonation and Cu^{2+} stability constants of **7** and **2** (DOTA) at 25°C

	Ligand 7			*Ligand 2*	
	potentiometric[a]	potentiometric[b]	spectrophotometric[b]	Ref 32[b]	Ref 7[c]
Log $K_{H,1}$	11.81(2)	11.89(7)		11.36	12.09
Log $K_{H,2}$	9.42(7)	9.60(8)	9.63(2)	9.73	9.68
Log $K_{H,3}$	4.39(7)	4.47(8)	4.42(2)	4.54	4.55
Log $K_{H,4}$	3.43(7)	3.46(7)	3.10(2)	4.41	4.13
Log $K_{H,5}$	2.66(8)	2.72(7)		<2	<2
Log $K_{H,6}$	<2.5	<2.5		<2	<2
Log K^{M}_{ML}	19.78(1)		20.10(5)		22.21
Log K^{M}_{MLH}	3.95(2)		3.92(5)		4.30
Log $K^{M}_{MLH_2}$	3.12(2)		2.94(6)		3.58

[a] I = 0.5 M (KNO_3).
[b] I = 0.1 M (KCl).
[c] I = 0.1 M $(CH_3)_4N(NO_3)$.

$$LH_2 + H \rightleftharpoons LH_3;\ K_{H,3} \quad (3)$$

$$LH_3 + H \rightleftharpoons LH_4;\ K_{H,4} \quad (4)$$

$$LH_4 + H \rightleftharpoons LH_5;\ K_{H,5} \quad (5)$$

$$LH_5 + H \rightleftharpoons LH_6;\ K_{H,6} \quad (6)$$

$$Cu + L \rightleftharpoons CuL;\ K^{M}_{ML} \quad (7)$$

$$CuL + H \rightleftharpoons CuLH;\ K^{H}_{MLH} \quad (8)$$

$$CuLH + H \rightleftharpoons CuLH_2;\ K^{H}_{MLH_2} \quad (9)$$

The protonation constants log $K_{H,1}$ and log $K_{H,2}$ of **7** are similar to those found for DOTA (**2**), for which *trans*-diprotonation of two nitrogens was observed.[27] The sudden drop in log $K_{H,3}$ is also typical and due to the protonation of a carboxylate side chain.

Comparison of the stability constants of the Cu^{2+} complexes with **7** and DOTA (**2**) indicates that the more flexible acetate side chains of DOTA are better ligands than the *ortho*-toluilic acid of **7**. Protonation of CuL^{+} to give $CuLH^{2+}$ and $CuLH_2^{3+}$ probably takes place at carboxylate groups, which are not involved in the co-ordination to Cu^{2+}, since no spectral change in the Cu^{2+} chromophore occurs at pH > 2. For the other compounds equilibrium measurements in aqueous solution are prevented by the low solubility of the ligands. Measurements in water/dioxane (1/1) were run, but were difficult to interpret, because of the many protonation and complexation possibilities and the lack of data to compare with.

The two structures here solved are good examples for the different possibilities these tetra-*N*-substituted ligands have in regard to the complexation of their side chains with a metal ion such as Cu^{2+}.

In the structure of the Cu^{2+} complex with **4**, which was obtained from acidic solution, the Cu^{2+} is pentaco-ordinated by the four nitrogens of the macrocycle and by a chloride ion (Fig 1 and Table 5).

The phenolic oxygens are not involved in any

Table 5 Selected bond lengths and angles for $[CuL(Cl)]Cl \cdot CH_3OH \cdot H_2O$ ($L = 4$)

Bond	*Bond lengths (Å)*		*Angles (°)*
Cu–N(1)	2.076(7)	N(1)–Cu–N(3)	148.3(3)
Cu–N(2)	2.068(7)	N(2)–Cu–N(4)	146.7(3)
Cu–N(3)	2.066(7)	N(1)–Cu–N(2)	85.8(3)
Cu–N(4)	2.092(7)	N(2)–Cu–N(3)	85.8(3)
Cu–Cl(1)	2.393(4)	N(3)–Cu–N(4)	85.7(3)
		N(4)–Cu–N(1)	84.8(3)
		Cl(1)–Cu–N(1)	105.1(2)
		Cl(1)–Cu–N(2)	107.8(3)
		Cl(1)–Cu–N(3)	106.6(2)
		Cl(1)–Cu–N(4)	105.5(3)

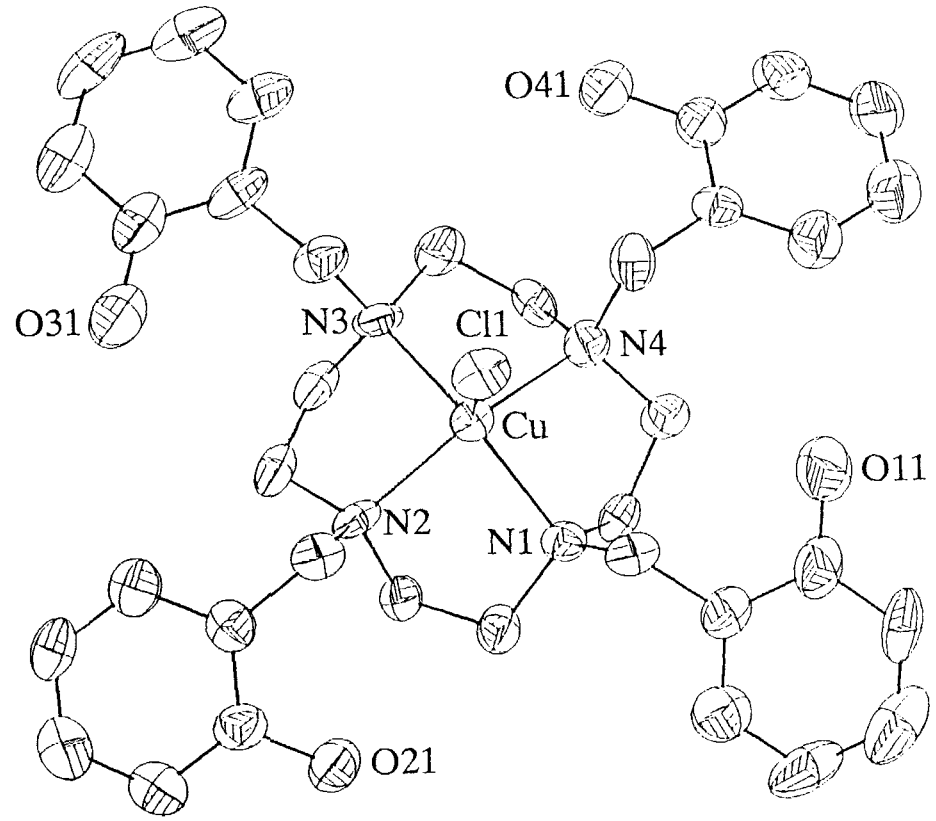


Figure 1 Plot of the structure of $[CuL]Cl_2 \cdot CH_3OH \cdot H_2O$ ($L = 4$).

interaction with the metal ion and point away from it. As in most complexes of tetra-*N*-substituted tetraazacyclododecanes the macrocycle is folded[28] and adopts the *trans-I* configuration.[29] The geometry of the complex is square pyramidal, the four nitrogens forming a nearly perfect plane (± 0.015 Å). The Cu^{2+} is displaced out of this plane by 0.58 Å in the direction of the chloride ion. The four Cu–N bonds are not exactly equal but are in the normal range (2.07–2.09 Å). The Cu–Cl bond (2.39 Å) is shorter than that generally found for axial bonds (2.73–3.19 Å) in square planar complexes,[30] but is similar to Cu–Cl bonds found in tetra-*N*-benzyl derivatives (2.37–2.42 Å).[28] A second chloride Cl(2) is situated *trans* to Cl(1) at 4.88 Å with a Cl(1)–Cu–Cl(2) angle of 175.5°, very close to the ideal value of 180°. However, the long distance excludes any interaction between Cu and Cl(2). This chloride probably cannot come closer to the metal ion since the 12-membered ring, being folded in order to be able to complex the metal ion, blocks the sixth co-ordination position.

In the complex with **7** the macrocycle is also in the *trans-I* configuration and the Cu^{2+} is pentaco-ordinated, but now all five donors stem from the ligand: four nitrogens from the macrocyclic ring and one carboxylate from a side chain (Fig 2 and Table 6).

The geometry is square pyramidal, the four nitrogens forming a nearly perfect plane (± 0.019 Å) with the Cu^{2+} displaced 0.49 Å out of this plane towards the axial donor group. The Cu–N bonds are in the normal range (1.99–2.08 Å), Cu–N(1) being the shortest and Cu–N(2) the longest. Whether this has to do with interactions of the benzyl side chain with the atoms of the macrocycle is difficult to prove, but as Figure 2

Table 6 Selected bond lengths and angles for $[CuL](ClO_4)\cdot 4H_2O$ ($L = 7$)

Bond	*Bond length (Å)*		*Angles (°)*
Cu–N(1)	2.013(3)	N(1)–Cu–N(3)	152.9(1)
Cu–N(2)	2.063(3)	N(2)–Cu–N(4)	151.3(1)
Cu–N(3)	2.018(3)	N(1)–Cu–N(2)	86.7(1)
Cu–N(4)	2.056(3)	N(2)–Cu–N(3)	87.2(1)
Cu–O(5)	2.079(2)	N(3)–Cu–N(4)	86.6(1)
		N(4)–Cu–N(1)	86.3(1)
		O(5)–Cu–N(1)	105.5(1)
		O(5)–Cu–N(2)	97.9(1)
		O(5)–Cu–N(3)	101.5(1)
		O(5)–Cu–N(4)	110.7(1)

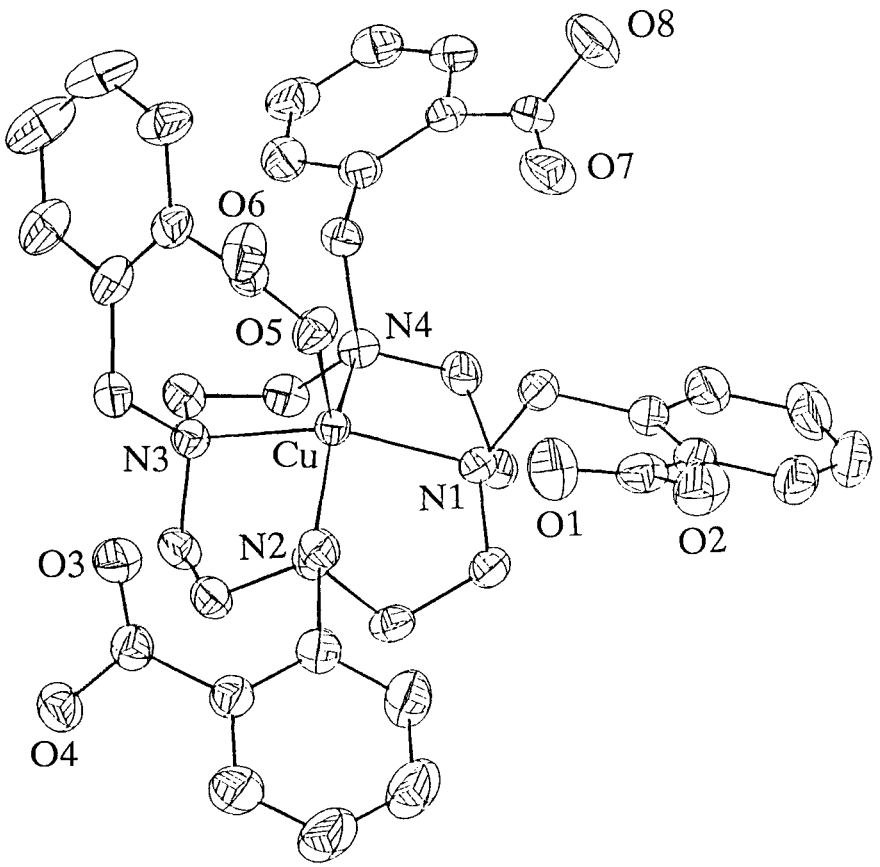


Figure 2 Plot of the structure of $[CuL](ClO_4)\cdot 4H_2O$ ($L = 7$).

shows the aromatic ring of the co-ordinated side chain is bent over the macrocycle towards N(2), which could cause some repulsion and thus increase the Cu–N(2) bond length. The Cu–O bond with 2.08 Å is relatively short for an axial bond. In this ligand the carboxylate oxygen is not completely free to take any position since it is part of a relatively rigid side chain, which determines the optimal distance between the Cu^{2+} and the carboxylate oxygen.

A comparison of the structures of the Cu^{2+} complex with **2** and **7** shows that although in both cases the macrocycle is folded in the *trans-I* configuration, in the complex with **2** two carboxylates bind to the metal ion thus giving a *cis*-octahedral geometry, whereas in the complex with **7** only one carboxylate is co-ordinated in a square-pyramidal structure. This might stem from the different sterical requirements of the two types of side chains and their reciprocal interactions.

In conclusion we can say that benzyl side chains attached to the four nitrogen atoms of the 12-membered tetraazacyclododecane do not prevent the co-ordination of a metal ion such as Cu^{2+}. The macrocycle being folded in the *trans-I* configuration leaves enough space for the *N*-substituents, so that sterical interactions remain small. If the side chain contains a donor group it can additionally bind to the metal ion.

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