DALTON

Structure and stability of complexes of macrocyclic ligands bearing 2-hydroxycyclohexyl groups. Structure of the copper(II) complex of 1-(2-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane and the strontium(II) complex of 7,16-bis(2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane†

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The compound 1-(2-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane (L^1) and its complex $[CuL^1][ClO_4]_2$ **1** have been prepared, as well as the complex $[SrL^2(H_2O)][NO_3]_2$ **2** from the previously reported ligand L^2 (L^2 = D,L-7,16-bis(2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane). X-Ray studies of **1** and **2** gave for **1**, triclinic, space group $P\bar{1}$, $a = 8.632(1)$, $b = 14.677(2)$, $c = 17.797(4)$ Å, $\alpha = 86.80(2)$, $\beta = 78.71(2)$, $\gamma = 83.32(1)°$, $Z = 4$, $R = 0.0606$, while **2** gave monoclinic, space group *Cc*, $a = 16.809(6)$, $b = 8.889(2)$, $c = 21.232(6)$ Å, $\beta = 101.47(2)°$, $Z = 4$, $R = 0.0314$. The structure of **1** showed Cu–N and Cu–O bond lengths which were in the normal range. The structure shows some steric crowding of the co-ordinated ligand, with short H · · · H contacts between hydrogens on the cyclohexyl group and adjacent hydrogens on the macrocyclic ring. This acts to press the 2-hydroxycyclohexyl group towards the macrocyclic ring, and to have a compressive effect on the metal ion. The occurrence of **2** in space group *Cc* indicates spontaneous resolution of the complex into crystals with (*R*,*R*) or with (*S*,*S*) diastereomers of the ligand only. The Sr^{II} is nine-co-ordinate, with a water molecule occupying a co-ordination site. An extensive hydrogen-bonding network involving hydrogens from the co-ordinated water on Sr^{II} and nitrate oxygens, and hydrogens from the co-ordinated hydroxyls of the 2-hydroxycyclohexyl groups and nitrate oxygens, appears to be responsible for the spontaneous resolution. Ligands where ethylene bridges between donor atoms have been replaced by cyclohexanediyl bridges tend to show greater selectivity for smaller metal ions. This has been interpreted in terms of greater steric crowding on the outside of the ligand as the metal ion increases in size and decreases the curvature of the ligand. The structure of **2** shows six rather short H · · · H distances (2.05–2.2 Å) between hydrogens on the cyclohexyl group, and on the macrocyclic ring, which are much shorter than similar contacts in complex **1**, supporting this suggestion. The protonation constants (log *K*) of L^1 are 10.65, 9.51 and 4.03, while the formation constants ($\log K_1$) are 13.85 (Zn^{II}), 14.58 (Cd^{II}) and 11.40 (Pb^{II}), all in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C. The effect of the 2-hydroxycyclohexenyl bridge on the stability of complexes is discussed.

The finding of structural factors that can lead to design of ligands that are more selective is of importance[1] in areas ranging from medicine to design of detergents. Thus, for example, the observation[2] that six-membered chelate rings tend to promote selectivity for small metal ions, while five-membered chelate rings promote selectivity for larger metal ions, is of fairly general application in understanding the size-based selectivity displayed by a wide variety of ligands. An important aspect of ligand design is that of *preorganisation*. The more preorganised a ligand is[3] the more nearly are the ligand donor atoms arranged as required for co-ordination to the metal ion. Thus, macrocycles are generally more preorganised than open-chain ligands. It is, however, possible for open-chain ligands to have high levels of preorganisation. An early example of this was the ligand *trans*-H_4cdta (see Fig. 1 for key to ligand abbreviations), first investigated by Schwarzenbach *et al.*[4] The ligand *trans*-H_4cdta shows the properties associated with higher levels of preorganisation. Thus, compared to its analogue H_4edta, the complexes of *trans*-H_4cdta show formation constants, $\log K_1$, that are[4] up to five log units higher. The rates of metallation and demetallation of *trans*-H_4cdta complexes are also slower than those of the H_4edta analogues. The use of cyclohexanediyl bridges is thus a potentially useful factor in designing ligands with a higher level of preorganisation.

In spite of the interesting properties conferred on complexes of *trans*-H_4cdta by the presence of the cyclohexanediyl bridge between the two nitrogens of the ligand, the cyclohexanediyl bridge has not been extensively used in ligand design. Crown ethers containing cyclohexanediyl bridges have been studied,[5–7] and the reinforcement provided by the cyclohexanediyl bridges leads to enhanced thermodynamic stability as compared to the parent crown ethers with ethylene bridges only. Here the *cis*-cyclohexanediyl bridge leads to the more stable complexes, in contrast to the H_4edta family of ligands, where[8] the complexes of *cis*-H_4cdta show effectively no increase in complex stability relative to H_4edta itself. The *trans*-cyclohexanediyl bridge has also been very useful in complexes of Mn^{III} that show[9] enantioselective epoxidation of prochiral alkenes. Brechbiel and Gansow[10] have reported a ligand for the complexation of ^{212}Bi in cancer therapy, where a cyclohexanediyl bridge is present between two nitrogens of diethylenetriaminepentaacetic acid. Some of the present authors have reported[11] the complexing properties of L^2 and THECHDA, as well as making a preliminary report[12] of the synthesis of a range of ligands derived from reaction of cyclohexene oxide with amines, both open-chain and macrocyclic. The products obtained in the latter synthesis showed considerable selectivity, both in the number and position of 2-hydroxycyclohexyl groups that would attach to an amine and in the diastereomers obtained. Thus, ethylenediamine on reaction with cyclohexene oxide, even in large excess, gives[12] in 80% yield a crystalline product, which is all *N*,*N′*-disubstituted and which all appears to be the *meso* form.

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† *Non-SI unit employed:* 1 cal = 4.184 J.

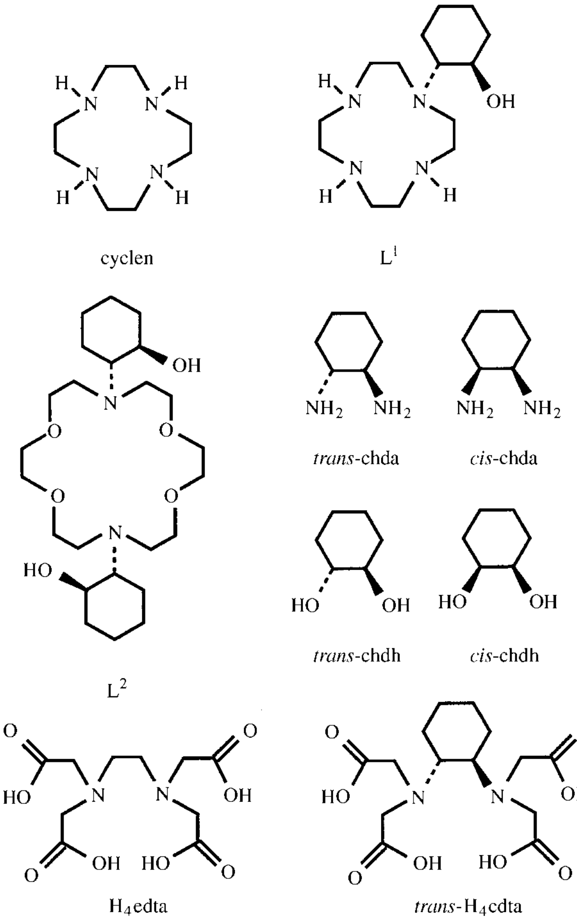

Fig. 1 Ligands discussed in this paper

The tetraaza macrocycle cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) adds on a single cyclohexene oxide to give L^1, even in large excess of cyclohexene oxide. This is a useful result, as it leaves three nitrogen donors free for substitution with donor groups such as acetates. Such a ligand with three acetate groups gives a neutral complex with trivalent Gd^{III}, which is desirable in MRI (Magnetic Resonance Imaging) applications. In MRI relatively large quantities of the gadolinium(III) imaging agent must be administered, and charged complexes run the possibility of producing osmotic shock in the patient. Ligands such as *N*-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-*N′*,*N″*,*N‴*-triacetate have been synthesized as MRI agents,[13] and are currently in use. However, reaction of cyclen with propylene oxide gives a mixture of products and it is therefore necessary to protect[14,15] three of the nitrogens of the cyclen to ensure a maximum yield of the mono-substituted 2-hydroxypropyl derivative. Such syntheses can involve several steps, so that a one-step synthesis that yields a monosubstituted cyclen is potentially useful.

In this paper is reported the synthesis of L^1, its complex with copper(II) perchlorate, the structure of the latter complex, and the protonation constants of L^1, as well as its formation constants with Zn^{II}, Cd^{II} and Pb^{II}. Also reported is the synthesis of the complex of L^2 with the large ion Sr^{II}, which allows for examination of the idea that larger metal ions will cause greater steric crowding between the cyclohexyl groups and the rest of the ligand. Some molecular orbital (MO) calculations on complexes of Li$^+$ using the MOPAC package[16] are reported. These are aimed at understanding the effect on complex stability of the placement of the donor atoms *cis* or *trans* on the cyclohexane ring and why neutral oxygen donors appear to lead to greater stabilisation when they are placed in a *cis* position on the cyclohexane ring, and why neutral nitrogen donors should do so when they are placed *trans* to each other.

Experimental

Syntheses

1-(2-Hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane (L^1). The macrocycle cyclen (2.3 g, 0.012 mol) was dissolved in anhydrous ethanol (100 cm^3). To this was added cyclohexene oxide (1.1 g, 0.12 mol), and the mixture was refluxed for 48 h at 80 °C. On removing the solvent, a pale yellow oil was obtained, which solidified on drying under reduced pressure. Dissolving this residue in acetone, and cooling in a refrigerator for 24 h gave a colourless crystalline solid. Yield = 83% (Found: C, 62.60; H, 11.90; N, 19.95. Calc. for $C_{14}H_{30}N_4O$: C, 62.20; H, 11.20; N, 20.70%).

[CuL^1][ClO$_4$]$_2$. $Cu(ClO_4)_2 \cdot 6H_2O$ (Aldrich) (0.8 g, 0.022 mol) was added to deionised water (15 cm^3). An aqueous solution of KOH (10 ml, 0.54 mol dm^{-3}) was added with constant stirring on an ice-bath. The macrocycle (0.5 g, 0.0019 mol) was dissolved in deionised water (10 cm^3) and added to the copper solution, forming a purple precipitate on stirring. The solution was warmed to 60 °C and 12 mol dm^{-3} $HClO_4$ added dropwise until a clear solution was obtained. The solvent was removed under reduced pressure and the residue was dissolved in acetone, filtering off the solid which did not dissolve. A further 25 cm^3 of deionised water was added and on slow evaporation crystals of the copper complex were deposited. Mass collected = 0.71 g, yield = 72% (Found: C, 31.25; H, 5.45; N, 10.05. Calc. for $C_{14}H_{30}Cl_2CuN_4O_9$: C, 31.55; H, 5.65; N, 10.50%).

[SrL^2(H$_2$O)][NO$_3$]$_2$. The ligand L^2 was synthesized as described previously.[11] The complex was synthesized by mixing 1 equivalent of $Sr(NO_3)_2$ and 1 equivalent of the ligand in water, and allowing the mixture to stand. On slow evaporation, colourless crystals of $[SrL^2(H_2O)][NO_3]_2$ were deposited.

X-Ray crystallography

Crystals of $[CuL^1][ClO_4]_2$ **1** and $[SrL^2(H_2O)][NO_3]_2$ were mounted on glass fibres at room temperature. Preliminary examination and data collection were performed on a Rigaku AFC5 (oriented graphite monochromator; Mo-Kα radiation) at 293(2) K. Cell parameters were calculated from the least-squares fitting for 25 high-angle reflections ($2 < \theta < 15°$). Omega scans for several intense reflections indicated acceptable crystal quality. Data were collected in the range $1.79 < 2\theta < 25.05°$ and $5.0 < 2\theta < 50°$ for **1** and **2** respectively, at 298(2) K. Scan width for data collection for **1** was 1.68° + 0.3 tan θ in ω with a variable scan rate of 4–16° min^{-1}; for **2** the scan width was 1.0° with a scan speed of 2.0° min^{-1}. Weak reflections were rescanned (maximum of two rescans) and the counts for each scan were accumulated. The three standards, collected every 150 reflections for **1**, and every 97 reflections for **2**, showed no significant trends. Background measurement was by stationary crystal and stationary counter technique at the beginning and end of each scan for half the total scan time. Lorentz and polarisation corrections were applied. A total of 7779 unique observed reflections for **1** and 2435 for **2** were used in further calculations. A semi-empirical absorption correction was applied.[17] The structures were solved by direct methods.[18] Full-matrix least-squares anisotropic refinement for all non-hydrogen atoms yielded $R = 0.0614$ at convergence for **1**, and $R = 0.0405$ for **2**.[19a] Neutral atom scattering factors and anomalous scattering factors were taken from ref. 19(*b*). The structure of **1** is shown in Fig. 2, and of **2** is shown in Fig. 3. The crystal data and details of structure refinement for **1** and **2** and selected bond lengths and angles are given in Tables 1–3.

Atomic coordinates, thermal parameters, bond lengths and

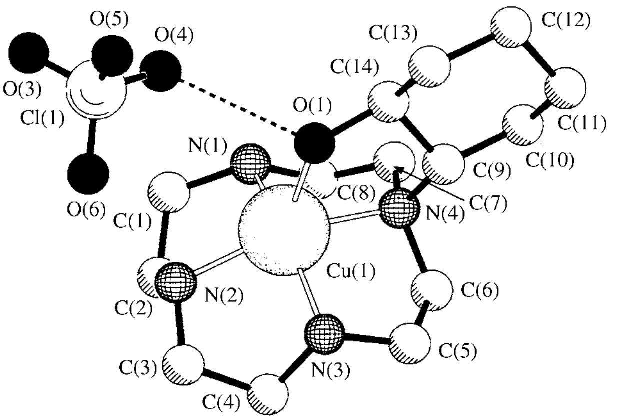

Fig. 2 The structure of [CuL^1][ClO$_4$]$_2$ showing the atom numbering scheme. Only one perchlorate is shown, with a hydrogen bond holding it to the hydroxyl from the cyclohexyl group indicated as a broken line. The O(1)···O(4) hydrogen bonding distance is 2.91 Å

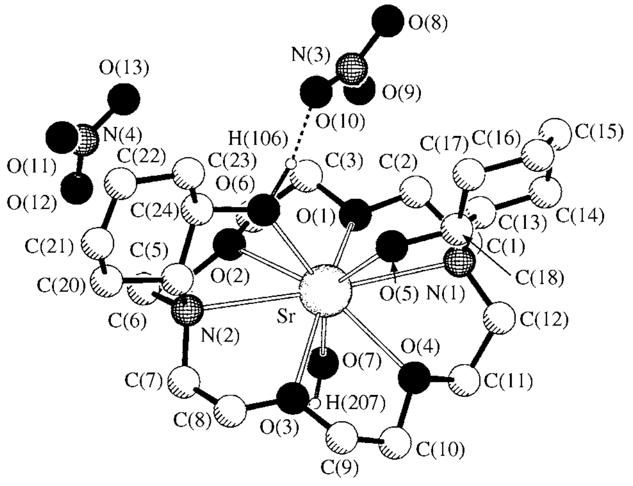

Fig. 3 The structure of [SrL^2(H$_2$O)][NO$_3$]$_2$ showing the atom numbering scheme

angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/383.

Stability constant determination

Potentials were recorded for the solutions using a Radiometer PHM 84 pH meter and type GK 2402B or GK 2401C glass electrodes. Measurements were made with the solutions in a water-jacketted cell connected to a Haake G thermostatted water bath. The protonation constants of L^1 were determined by routine methods in 0.1 mol dm^{-3} NaNO$_3$ at 25.0 ± 0.1 °C. Equilibration of metal–ligand solutions was very slow, and necessitated an 'out-of-cell' approach.[20] The complexes of L^1 with Cu^{II} and Ni^{II} were too inert to allow for determination of the formation constants in a reasonable amount of time, so that only the complexes of Zn^{II}, Cd^{II} and Pb^{II} were studied. For each metal ion sets of solutions containing 1:1 ratios of ligand and metal ion and differing amounts of acid were prepared. These were kept in a thermostatted bath at 25 ± 1 °C, and periodically the pH values of the sets were recorded to see whether equilibrium had been attained. Equilibrium was attained for all the solutions in under one month. The formation constants were calculated from the potentiometric data using the program ESTA.[21]

Table 1 Crystal data and structure refinement for [CuL^1][ClO$_4$]$_2$ **1** and [SrL^2(H$_2$O)][NO$_3$]$_2$

Complex	**1**	**2**
Empirical formula	$C_{14}H_{30}Cl_2CuN_4O_9$	$C_{24}H_{48}N_4O_{13}Sr$
M	532.86	688.3
T/K	298(2)	298(2)
λ/Å	0.710 73	0.710 73
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	*Cc*
a/Å	8.632(1)	16.809(6)
b/Å	14.677(2)	8.889(2)
c/Å	17.797(4)	21.232(6)
α/°	86.80(2)	
β/°	78.71(2)	101.47(2)
γ/°	83.32(1)	
U/Å^3	2194.8(6)	3109(2)
Z	4	4
μ/mm^{-1}	1.292	1.470
F(000)	1108	1448
Crystal size/mm	0.1 × 0.4 × 0.4	0.5 × 0.4 × 0.3
Crystal colour, habit	Blue plate	Colourless plate
Scan type	ω–2θ	ω (Wyckoff)
Scan speed/° min^{-1}	Variable, 4.0–16.0	2.0
Scan width	1.68 + 0.3 tan θ	1.0
θ Range for data collection/°	1.79–25.05	5.00–50.00
Index ranges	$-10 \leqslant h \leqslant 10$, $-17 \leqslant k \leqslant 0$, $-21 \leqslant l \leqslant 21$	$0 \leqslant h \leqslant 19$, $0 \leqslant k \leqslant 10$, $-25 \leqslant l \leqslant 24$
Reflections collected	8115	2842
Independent reflections	7779 (R_{int} = 0.0345)	2435
R_1[a]	0.0606	0.0314
wR_2[b]	0.1386	0.0771
R_1 (all data)	0.1445	0.0405
wR_2 (all data)	0.3217	0.0863
Largest peak, hole/e Å^{-3}	0.783, −0.506	0.232, −0.229

[a] $R_1 = \Sigma|F_o| - |F_c|/\Sigma|F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{\frac{1}{2}}$.

Table 2 Selected bond lengths (Å) and angles (°) for **1**. Corresponding lengths and angles in the two individual cations present in the unit cell are given as pairs

Cu(1)–N(1)	2.009(5)	Cu(2)–N(5)	1.996(5)
Cu(1)–N(2)	1.999(5)	Cu(2)–N(6)	2.002(6)
Cu(1)–N(3)	2.018(5)	Cu(2)–N(7)	2.008(6)
Cu(1)–N(4)	2.022(5)	Cu(2)–N(8)	2.031(6)
Cu(1)–O(1)	2.197(5)	Cu(2)–O(2)	2.130(5)
N(1)–Cu(1)–N(2)	87.0(2)	N(5)–Cu(2)–N(6)	86.9(2)
N(1)–Cu(1)–N(3)	150.4(2)	N(5)–Cu(2)–N(7)	150.2(2)
N(1)–Cu(1)–N(4)	87.3(2)	N(5)–Cu(2)–N(8)	86.7(2)
N(2)–Cu(1)–N(3)	86.8(2)	N(6)–Cu(2)–N(7)	86.8(2)
N(2)–Cu(1)–N(4)	156.0(2)	N(6)–Cu(2)–N(8)	154.9(2)
N(3)–Cu(1)–N(4)	86.9(2)	N(7)–Cu(2)–N(8)	86.7(2)
N(1)–Cu(1)–O(1)	105.5(2)	N(5)–Cu(2)–O(2)	103.1(2)
N(2)–Cu(1)–O(1)	122.0(2)	N(6)–Cu(2)–O(2)	123.8(2)
N(3)–Cu(1)–O(1)	102.3(2)	N(7)–Cu(2)–O(2)	104.5(2)
N(4)–Cu(1)–O(1)	81.9(2)	N(7)–Cu(2)–N(8)	81.3(2)

Molecular orbital calculations

The program MOPAC (version 6.00)[16] is available in the CACHE suite of programs,[22] with parameters at the MNDO level available for lithium. The model building facility of the CACHE system was used to construct complexes of Li$^+$ to test the ability of the program to reproduce structures of these complexes. A crucial factor here is the observation[23] that in complexes of metal ions co-ordinated to unidentate ethers the oxygen is co-ordinated in such a way that it lies in the plane formed by the Li and the two carbons attached to the oxygen, as though the oxygen were sp^2 hybridised. A typical structure showing this feature is the [Li(thf)$_4$]$^+$ cation[24] (thf = tetrahydrofuran). It was found that MOPAC reproduces the structures of Li$^+$ complexes well, reproducing the planar co-ordination about

Table 3 Selected bond lengths (Å) and angles (°) for **2**

Sr–O(1)	2.658(9)	Sr–O(6)	2.562(8)
Sr–O(2)	2.793(9)	Sr–O(7)	2.542(3)
Sr–O(3)	2.618(8)	Sr–N(1)	2.944(9)
Sr–O(4)	2.664(9)	Sr–N(2)	2.98(1)
Sr–O(5)	2.533(7)		
O(1)–Sr–O(2)	60.0(3)	O(4)–Sr–O(5)	75.4(3)
O(1)–Sr–O(3)	155.4(1)	O(4)–Sr–O(6)	136.9(3)
O(1)–Sr–O(4)	112.0(3)	O(4)–Sr–O(7)	74.3(4)
O(1)–Sr–O(5)	102.0(3)	O(5)–Sr–O(6)	67.9(1)
O(1)–Sr–O(6)	97.7(3)	O(5)–Sr–O(7)	146.3(4)
O(1)–Sr–O(7)	76.5(4)	O(6)–Sr–O(7)	145.7(4)
O(2)–Sr–O(3)	111.9(3)	N(1)–Sr–N(2)	175.2(2)
O(2)–Sr–O(4)	147.8(1)	N(1)–Sr–O(1)	60.3(3)
O(2)–Sr–O(5)	135.5(3)	N(1)–Sr–O(2)	120.2(3)
O(2)–Sr–O(6)	74.3(3)	N(1)–Sr–O(3)	121.0(2)
O(2)–Sr–O(7)	73.5(3)	N(1)–Sr–O(4)	60.1(3)
O(3)–Sr–O(4)	61.1(3)	N(1)–Sr–O(5)	61.6(2)
O(3)–Sr–O(5)	98.8(3)	N(1)–Sr–O(6)	116.1(2)
O(3)–Sr–O(6)	102.6(3)	N(1)–Sr–O(7)	90.4(3)
O(3)–Sr–O(7)	78.9(3)	N(2)–Sr–O(2)	58.9(2)

the neutral oxygen donor co-ordinated to Li^+, whether this involves ethers such as thf, or alcohols such as methanol, or co-ordinated water.

Results and Discussion

The structures of **1** and **2** are shown in Figs. 2 and 3. In the unit cell of **1** two slightly different individual $[CuL^1]^{2+}$ cations are present, which are essentially mirror images of each other. In Fig. 2 is shown only the individual Cu(1). The structure of **1** shows that the oxygen donor of L^1 is co-ordinated to Cu^{II}. The Cu–O distance is 2.197 Å for the Cu(1)–O(1) distance and 2.130 Å for the Cu(2)–O(2) distance in the other molecule. The latter is fairly short for a bond between Cu^{II} and an axially co-ordinated oxygen which are usually in the vicinity of 2.25 Å. The fact that the Cu–O distances to the axially co-ordinated oxygen can differ quite significantly in the two individuals, without significantly affecting the Cu–N distances, which average 2.01(1) Å for both individuals, indicates the weakness of the axial interaction. The copper is raised some 0.47 Å above the plane of the four nitrogen donors.

The complex $[SrL^2(H_2O)][NO_3]_2$ crystallises in the optically active space group *Cc*. All individuals in any one crystal have the ligand as the (*R*,*R*) or as the (*S*,*S*) diastereomer. Spontaneous resolution of mixtures of enantiomers on crystallisation is fairly unusual,[25] so this is of some interest. The spontaneous resolution of the complex appears to be due to an extensive network of hydrogen bonding running throughout the crystal, as seen in Fig. 4. The Sr^{II} is nine-co-ordinate, with a water molecule co-ordinated on the side of the complex away from the 2-hydroxycyclohexyl substituents. The nitrates are hydrogen bonded to this water molecule, and to the hydroxyl groups of the complex cation below, with the nitrates oriented by their interaction with the cyclohexyl groups. It is this interaction that communicates the chirality of the cyclohexyl groups throughout the crystal, and leads to the spontaneous resolution of the complex. This resembles the role of the hydrogen bonding network throughout the crystals of complexes such as *cis*-$[Co(en)_2(NO_2)_2]Cl$ (en = ethylenediamine), that also undergo spontaneous resolution on crystallisation.[25] The hydrogen bonds from the co-ordinated water molecule of $[SrL^2(H_2O)][NO_3]_2$ to the pair of nitrates below the complex cation lead to O · · · O distances of 2.78 and 2.82 Å, and those from the co-ordinated oxygens of the 2-hydroxycyclohexyl groups to nitrate oxygens lead to O · · · O distances of 2.77 and 2.83 Å. Bernal and Kauffman[25] observed that in complexes such as *cis*-$[Co(en)_2(NO_2)_2]Cl$ the co-ordinated nitro groups provide paddle shaped parts of the complex cation that project from it and interact with neighbouring complex cations by hydrogen bonding, promoting the spontaneous resolution observed. Here the similarly shaped nitrates provide the effect entirely through hydrogen bonding without being strongly co-ordinated to Sr^{II}.

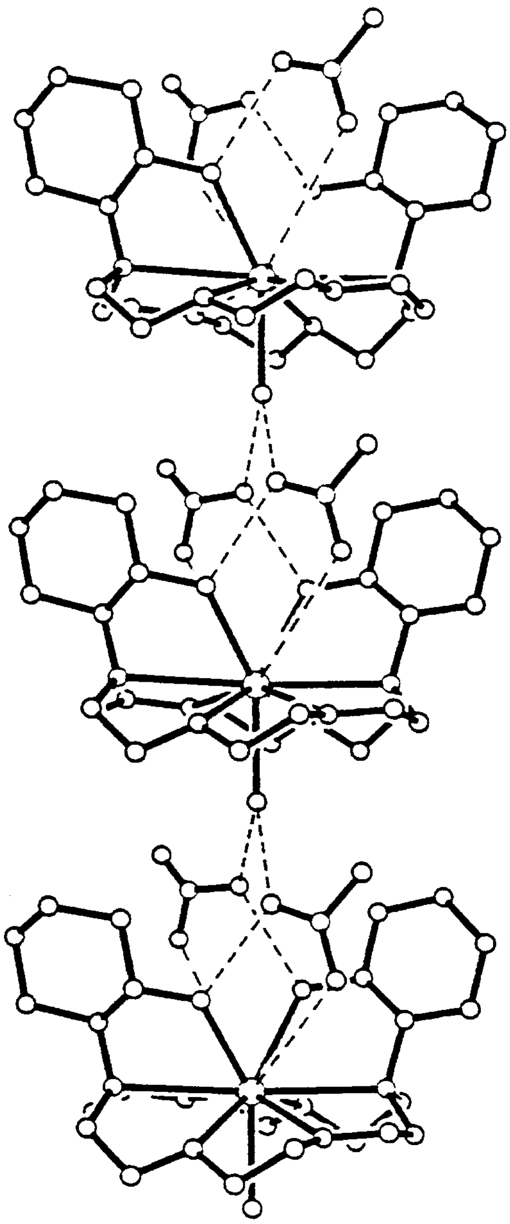

Fig. 4 The hydrogen bonding between adjacent $[SrL^2(H_2O)]^{2+}$ cations and nitrates, shown as broken lines. Also shown are the long contacts (*ca.* 4.3 Å) between Sr and oxygens from nitrates

The fact that introduction of cyclohexanediyl bridges into ligands leads to lower selectivity for larger metal ions has been interpreted[11,12] in terms of greater steric crowding on the outside of the ligand as ligand curvature decreases with increasing metal ion size. This idea can be examined with the structure of the strontium(II) complex of L^2, since Sr^{II} is a large metal ion of radius[26] 1.17 Å. Examination of the structure shows that some hydrogens on the cyclohexanediyl bridges of the ligand are distances from hydrogens on the macrocycle part of the ligand of only 2.05 [H(24A) · · · H(6B)], 2.11 [H(13A) · · · H(2B)], 2.13 [H(12B) · · · H(18A)] and 2.20 Å [H(1A) · · · H(14A), H(7A) · · · H(20B) and H(8B) · · · H(19A)]. These short H · · · H separations are considerably shorter and more numerous than the short H · · · H separations found in the copper(II) complex of L^1 discussed below, lending support to the idea that there is much

Table 4 Heats of formation (ΔH_f, kcal mol^{-1}) of *cis* and *trans* forms of the lithium complexes of chda (primary amine donors) and chdh (alcoholic oxygen donors), from the elements in their standard states, as calculated using MOPAC.[16] Also shown are the strain energies (*U*) computed for the same complexes using the MM2 force field.[a] The differences calculated are for pairs of *cis* and *trans* complexes

Complex	ΔH_f (MOPAC)/ kcal mol^{-1}	Difference (*cis/trans*)/ kcal mol^{-1}	U(MM2)/ kcal mol^{-1}	Difference (*cis/trans*)/ kcal mol^{-1}
[Li(*cis*-chda)(H_2O)$_2$]$^+$	−79.32	+3.43	21.02	+2.47
[Li(*trans*-chda)(H_2O)$_2$]$^+$	−82.75		18.55	
[Li(*cis*-chdh)(H_2O)$_2$]$^+$	−173.82	+0.43	20.08	+0.03
[Li(*trans*-chdh)(H_2O)$_2$]$^+$	−174.25		20.05	

[a] For key to ligand abbreviations, see Fig. 1.

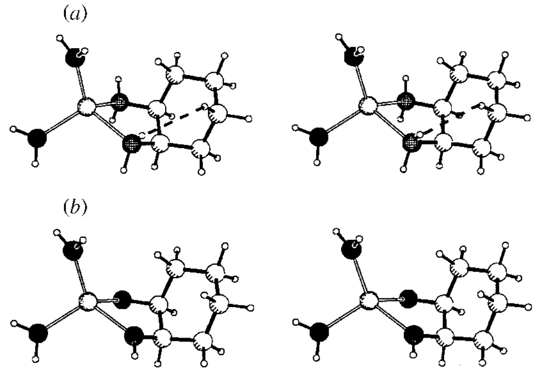

Fig. 5 Stereoviews of structures of (*a*) [Li(*cis*-chda)(H_2O)$_2$]$^+$ and (*b*) [Li(*cis*-chdh)(H_2O)$_2$]$^+$ as generated by MOPAC.[16] The broken lines show the short H···H distances (2.2 Å) in [Li(*cis*-chda)(H_2O)$_2$]$^+$ that destabilise it relative to its *trans* isomer, that are absent in [Li(*cis*-chdh)(H_2O)$_2$]$^+$ because the co-ordinated oxygens lack these hydrogens. A major part of the strain energy in [Li(*cis*-chda)(H_2O)$_2$]$^+$ is also caused by torsional contributions to strain energy due to the H–N–C–C torsion angles of the axial amino groups that are rather small. Note the planar co-ordination around the oxygens of the co-ordinated waters, and co-ordinated alcohols of the 2-hydroxycyclohexyl groups, which is an important feature[23] observed in structures of complexes of ethers with metal ions

greater steric crowding on the outside of complexes of large metal ions when cyclohexanediyl bridges are present.

A further point of interest is the Sr–O distance to the nearer oxygens of the nitrates that are on the side of the complex where the two 2-hydroxycyclohexyl groups are co-ordinated to the Sr^{II}. These oxygens [O(9) and O(12)] are 4.34 and 4.39 Å from the Sr^{II}, which contacts are shown as broken lines in Fig. 4. Ordinarily this would be regarded as being too long to be considered as a bond. However, it is of interest to consider such long, potentially very weak, interactions. In the complexes of metal ions such as Hg^{II} of co-ordination number two there are usually four much longer interactions to other donor atoms,[27] creating a distorted octahedron. Metal ions such as Pb^{II} and Bi^{III} with stereochemically active lone pairs often show[28] M–L separations of about 3.5 Å to donor atoms placed directly above the supposed position of the lone pair. These oxygens at about 4.3 Å from the Sr^{II} may simply be held in place by packing forces in the crystal, or these may represent very long and weak electrostatic interactions.

The structures of [Li(*cis*-chda)(H_2O)$_2$]$^+$ and [Li(*cis*-chdh)(H_2O)$_2$]$^+$ as generated by MOPAC[16] are shown as stereoviews in Fig. 5. The MOPAC calculations give enthalpies of formation of the *cis* and *trans* forms of the chda and chdh complexes from the constituent elements in their standard states at 25 °C, shown in Table 4. The calculations show that the energies of formation of the *cis* and *trans* form of chdh, with its oxygen donors to Li, are essentially identical. For the chda analogues, with nitrogen donors instead of oxygen donors, the energy of formation of the *trans* form is 3.43 kcal mol^{-1} more favourable than the *cis* form. Examination of Fig. 5 suggests a reason for this difference. Co-ordination to Li of the NH_2 which is in an axial position on the *cis*-chda rotates an N–H hydrogen around so as to produce a steric clash with an axial hydrogen on the cyclohexyl ring. This interaction is shown as a broken line in Fig. 5. In the free *cis*-chda ligand this hydrogen is free to rotate away from steric interaction with the axial hydrogen on the cyclohexyl ring. In the chdh complexes, the oxygen donors have only one hydrogen on them instead of two, and the steric clash is avoided as seen in Fig. 5. Since the MOPAC calculations had suggested a steric explanation of the poor co-ordinating abilities of *cis*-chda compared to *trans*-chda, the strain energies (*U*) of the same four complexes were calculated using the MM2 force field.[29]

The CACHE suite of programs generates parameters for modelling sp^3 hybridised Li using the MM2 force field, and these were used without further modification. The calculated strain energies for the four complexes shown in Table 4 support the steric interpretation of the origin of the weaker complexing ability of *cis*-chda. The strain energies of the pair of chdh complexes are virtually identical, while that of the *cis*-chda complex is 2.47 kcal mol^{-1} higher than that of *trans*-chda. The strain energy calculations show that the higher strain energy in [Li(*cis*-chda)(H_2O)$_2$]$^+$ arises from H···H repulsion, and also from the small H–N–C–H torsion angles of 28.8 instead of 60° produced in co-ordination of the ligand to Li. The corresponding H–O–C–H torsion angle in the *cis*-chdh complex is 68.7°, which should produce little strain. The difference in complex stability[8] of metal ions such as Ni^{II} with *cis*-chda (log $K_1 = 7.12$) and *trans*-chda (log $K_1 = 7.74$) are quite small. However, for *cis*-cdta and *trans*-cdta differences in log K_1 become[8] large, with, for example, log K_1 with Mg^{II} being 8.38 (*cis*) and 11.07 (*trans*). This can be understood in terms of the present calculations as arising from the fact that in the *cis*-chda complex the steric clash is between two hydrogens, and so is not severe. For the *cis*-cdta complex the steric clash will involve a hydrogen from the cyclohexyl group, and a more bulky methylene from an acetate group, which steric effect should be much larger.

Formation constants

The protonation and formation constants of L^1 determined here are given in Table 5. In previous studies it had been found[11,12] that substitution of ethylene bridges by *trans*-cyclohexenyl bridges leads to a metal-ion size related change in complex stability, such that the smaller the metal ion was the larger the increase in complex stability. This can be seen in comparing *trans*-cdta complexes with their edta analogues for Ca^{II}, Sr^{II} and Ba^{II} (Table 6).

The dependence on metal-ion size of the stabilisation produced by adding cyclohexenyl bridges is quite general.[11,12] In using it as a ligand design tool to discriminate between metal ions of different sizes, one should be aware, however, that with decreasing metal ion size there *may* come a point[11,12] where general steric crowding produced by the bulky cyclohexanediyl groups will overwhelm the geometric effects of the cyclohexanediyl bridge. Thus, although Be^{II} and Mg^{II} are smaller than Ca^{II}, there is not a larger stabilisation in passing from edta

Table 5 Formation constants and protonation constants of L^1 in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C[a]

Lewis acid	Equilibrium	log *K*
H^{+}[b]	$H^+ + OH^- \rightleftharpoons H_2O$	13.78
	$L^1 + H^+ \rightleftharpoons [HL^1]^+$	10.65(2)
	$[HL^1]^+ + H^+ \rightleftharpoons [H_2L^1]^{2+}$	9.51(2)
	$[H_2L^1]^{2+} + H^+ \rightleftharpoons [H_3L^1]^{3+}$	4.03(2)
Zn^{II}	$Zn^{2+} + L^1 \rightleftharpoons [ZnL^1]^{2+}$	13.85(5)
Cd^{II}	$Cd^{2+} + L^1 \rightleftharpoons [CdL^1]^{2+}$	14.58(5)
Pb^{II}	$Pb^{2+} + L^1 \rightleftharpoons [PbL^1]^{2+}$	11.40(5)

[a] This work unless otherwise stated. [b] Ref. 8.

Table 6 Formation constants for edta and *trans*-cdta complexes[a]

Metal ion	Be^{II}	Mg^{II}	Ca^{II}	Sr^{II}	Ba^{II}
Ionic radius[26] (Å)	0.45	0.72	1.00	1.17	1.36
log K_1 (edta)	9.2	8.83	10.61	8.68	7.80
log K_1 (*trans*-cdta)	11.51	11.07	13.15	10.58	8.6
Stabilisation[b]	2.3	2.24	2.46	1.90	0.80

Ionic radii for six-co-ordination. [a] log K_1 values from ref. 8. [b] Stabilisation = difference in log K_1.

Table 7 Formation constants for L^1 and cyclen

Metal ion	Zn^{II}	Cd^{II}	Pb^{II}
log K_1 (cyclen)[8]	16.2	14.3	15.9
log K_1 (L^1)	13.85	14.58	11.40

to *trans*-cdta, because general steric crowding dominates the more specific steric effects of the cyclohexanediyl bridge. For Be^{II}, in particular, it seems probable that the four-co-ordination preferred by the metal ion[26] might lead to non-co-ordination of some of the donor groups of edta and *trans*-cdta, further complicating the size related effects on complex stability expected from the introduction of a cyclohexanediyl bridge. In applying rules that have been identified[1] for controlling selectivity for metal ions on the basis of their size, one should always pay attention to whether the denticity of the ligand is appropriate to the co-ordination number of the target metal ion. This might seem obvious, but comments received by the present authors have made it clear that not all researchers have paid attention to this factor, and also the question of overall steric crowding with small metal ions such as Be^{II} or Al^{III}.

Unfortunately, with log K_1 values for only three metal ions, it is not possible to draw any general conclusions about the complexing properties of L^1. The effect of the 2-hydroxycyclohexyl group is for Zn^{II} and Pb^{II} to cause considerable drops in log K_1, as seen in comparing log K_1 for L^1 and the parent amine, cyclen (Table 7).

The 2-hydroxycyclohexyl group of L^1 has a limited ability to be moved upwards as metal ions increase in size, and acts rather like the metal bar of a mouse trap bearing down on the metal ion. The restricted movement of the 2-hydroxycyclohexyl group appears to be due to van der Waals repulsion between hydrogens on the cyclohexyl group and adjacent hydrogens on the cyclen ring. The H···H distance between one hydrogen on C(10) and one on C(7) is 2.20 Å, while the distance between the second H on C(10) and one on C(6) is 2.4 Å. Such fairly short van der Waals contacts between two hydrogens will produce modest strain energies in the copper(II) complex, but these will increase rapidly as the cyclohexyl group is forced to rotate towards the outside of the ligand by increasing metal ion size. These van der Waals contacts act as the spring in the mousetrap analogy, forcing the cyclohexyl group down on to the cyclen ring of L^1. It seems probable that it is this effect that causes the low stability of the lead(II) complex of cyclen. The stability of the zinc(II) complex of L^1 may be low for the same reason. The shorter H···H contacts observed in the L^2 complex of the larger metal ion Sr^{II}, noted above, support the idea that the steric crowding between C substituents on the outside of complexes will increase with decreasing curvature of the ligand accompanying larger metal ion size. The high stability of the cadmium(II) complex of L^1 is puzzling. It may be that the hydroxy group on the cyclohexyl ring is not co-ordinated to the Cd^{II} at all, and is rotated out of the way. Further studies would be necessary to check this suggestion.

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