

Enantiopure Chiral Macrocyclic Lanthanide Complexes Derived from (*R*)-2,2'-Diamino-1,1'-binaphthyl and 2,6-Diformylpyridine

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Abstract

The template condensation of (*R*)-2,2'-diamino-1,1'-binaphthyl and 2,6-diformylpyridine leads to lanthanide(III) complexes of the new chiral hexaaza macrocycle L that adopts highly twisted conformation in [LnL](NO₃)₃ complexes. The complexes have been characterised by ESI MS spectrometry and NMR spectroscopy. The analogous N₂O₄ chiral crown ether L2 that has the same carbon skeleton as L does not exhibit tendency to bind lanthanide(III) ions. The X-ray crystal structure of L2 exhibit squeezed conformation of the macrocycle and spatial disposition of donor atoms that does not predispose it for coordination of lanthanide(III) ions.

Introduction

Macrocyclic lanthanide(III) complexes exhibit exceptional thermodynamic and kinetic stability that is strongly related to their successful application as contrast enhancement agents for magnetic resonance imaging, luminescent labels and catalysts for hydrolytic cleavage of RNA and DNA. Suitable modifications of the structure of the macrocyclic ligands allow to tune the properties of their lanthanide complexes. In particular, when the chiral macrocycles are applied then enantiopure lanthanide complexes can be obtained. Enantiopure lanthanide complexes [1] attract increasing attention as enantioselective catalysts [2] and spectroscopic probes. In particular, lanthanide(III) complexes of chiral crown ethers containing two pyridine groups are stable enough to act as enantioselective catalysts in aqueous media [2b, c]. However, enantiopure macrocyclic lanthanide(III) complexes, such as DOTA derivatives [3], chiral crown ethers [2b, c], or hexaazamacrocycles [4–6] are relatively rare. Since many successful chiral systems are based on chiral binaphthyl fragment [7], we turned our attention to chiral macrocycles L and L2 (Scheme 1) as potential ligands for coordination of lanthanide(III) ions. L is a new hexaaza Schiff base macrocycle that is expected to be sterically more crowded than analogous macrocycles L3 derived from 1,2-diaminocyclohexane [4] or 1,2-diphenylethylenediamine [5] (Scheme 1). L2 is a chiral azacrown

synthesised by Cram *et al.* [8], which coordination chemistry has not been explored so far. In this paper we report the synthesis and characterisation of enantiopure La(III), Ce(III) and Eu(III) complexes of the new chiral hexaazamacrocyclic L (Scheme 1) derived from binaphthyl. We also compare the difference between L and L2 in complexation of lanthanide(III) ions and present the X-ray crystal structure of the macrocycle L2.

Experimental

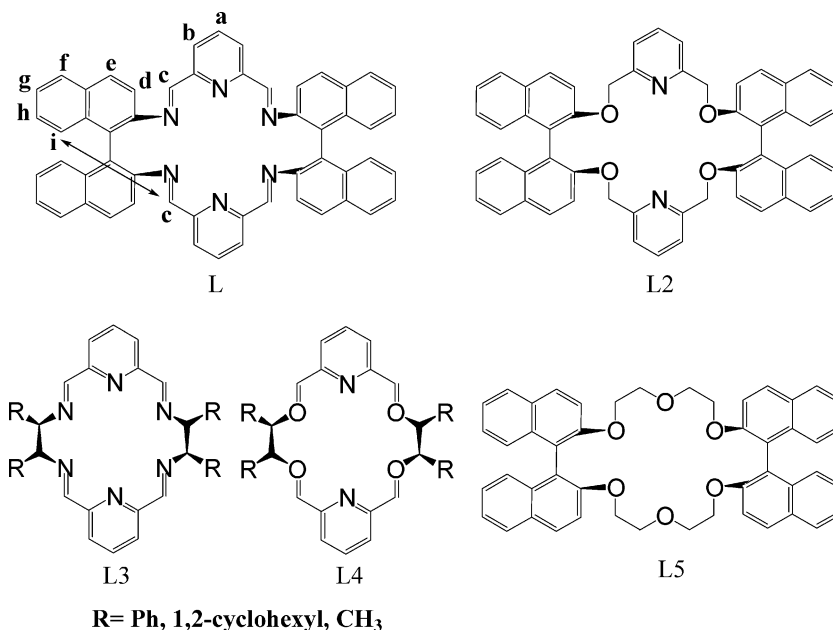
(*R*)-2,2'-diamino-1,1'-binaphthyl and lanthanide salts (99.9%) were purchased from Aldrich, 2,6-diformylpyridine was synthesised according to literature method [9].

Synthesis

67.6 mg (0.5 mmol) of 2,6-pyridine-dicarboxaldehyde and 142.2 mg (0.5 mmol) of (*R*)-2,2'-diamino-1,1'-binaphthyl were refluxed in ethanol with 0.25 mmol of appropriate lanthanide nitrate hexahydrate. The resulting yellow precipitate was filtered and purified by fractional recrystallisation from methanol/chloroform mixture. Yields 64%, 30%, 25% for La(III), Ce(III), Eu(III) complexes, respectively.

[LaL(NO₃)₃]*4H₂O: ¹H NMR (298 K, CD₃OD/CDCl₃ 1:2 v/v, see Scheme 1 for the labelling of signals) δ 8.63 (4H, s, c), 8.11 (2H, t, a), 8.03 (4H, d, e), 7.90 (4H, d, f), 7.86 (4H, d, b), 7.44 (4H, t, g) 7.23 (4H, t, h), 7.11

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Scheme 1. Structure and labelling scheme of the discussed macrocycles. Arrow indicate “long-range” NOESY correlation observed for complexes of L.

(4H, d, d), 6.82 (4H, d, i). ¹³C NMR (298 K, CD₃OD/CDCl₃ 1:2 vv) δ 166.69, 151.89, 145.34, 141.89, 133.38, 133.02, 131.45, 130.87, 128.87, 127.96, 126.68, 125.65, 124.23, 120.64. ESI MS *m/z*: 1028 ([LaL(NO₃)₂]⁺), 483 ([LaLNO₃]²⁺). C₅₄H₄₂N₉O₁₃La requires: C 55.73, H 3.60, N 10.80%, found: C 55.78, H 3.20, N 10.71%.

[CeL(NO₃)₂]₃[Ce(NO₃)₆]*CHCl₃*4H₂O: ¹H NMR (298 K, CD₃OD/CDCl₃ 1:2 vv) δ 13.08, 12.76, 12.54, 6.35, 6.24, 5.82, 5.46, 3.56, 2.00. ESI MS *m/z*: 1030 ([CeL(NO₃)₂]⁺), 484 ([CeLNO₃]²⁺). C₁₆₃H₁₀₅N₃₀O₄₀Cl₃Ce₄ requires: C 51.65 H 2.79 N 11.09%, found: C 51.76 H 2.84 N 10.94%.

[EuL(NO₃)₂]₃[Eu(NO₃)₆]*3CHCl₃*3H₂O: ¹H NMR (298 K, CD₃OD/CDCl₃ 1:2 vv) δ 17.43 (4H, d, i), 11.15 (4H, t, h), 10.50 (4H, d, f), 10.27 (4H, t, g), 10.13 (4H, d, e), 9.04 (4H, d, d), 0.38 (2H, t, a), -1.16 (4H, d, b), -11.23 (4H, s, c). ¹³C NMR (298 K, CD₃OD/CDCl₃ 1:2 vv) δ 186.20, 179.28, 156.18, 150.56, 139.68, 139.53, 139.08, 134.84, 134.49, 133.77, 129.52, 125.86, 108.19, 97.22. ESI MS *m/z*: 1043 ([EuL(NO₃)₂]⁺), 490.5 ([EuLNO₃]²⁺). C₁₆₅H₁₀₅N₃₀O₃₉Cl₉Eu₄ requires: C 48.83 H 2.61, N 10.35%, found: C 48.70 H 2.40 N 10.85%.

Methods

The NMR spectra were taken on Bruker Avance 500 and AMX 300 spectrometers. The chemical shifts were referenced to the residual solvent signal. The COSY, NOESY and HMQC spectra were acquired using 256 × 1 K data points and zero filled to 1 K × 1 K matrix. The NOESY spectra were recorded with mixing times of 50–800 ms. Electrospray mass spectra were obtained using Finnigan TSQ-700 instrument equipped with EST ion source. The elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer.

X-ray structure determination of L2

X-ray measurements were made on a KUMA KM4CCD diffractometer with graphite monochromatised MoK α radiation. The data was collected at 100 K using the Oxford Cryosystem cooler. Structure was solved by direct methods using the SHELXS97 program [10], and refined by a full-matrix least-squares technique using SHELXL97 [11]. All H atoms were fixed on the distance 0.99 Å. The non-hydrogen atoms were refined with anisotropic thermal parameters. Crystal data for L2*2THF: C₆₂H₅₄N₂O₆, *M* = 923.07, colourless, parallelepiped crystal (0.4 × 0.25 × 0.03), monoclinic, P2₁, *a* = 8.900(3), *b* = 16.215(4) *c* = 16.211(4) Å, β = 95.48(3)°, *V* = 2328.8(11) Å³, *Z* = 2, *T* = 100(2) K, *D*_c = 1.316 g cm⁻³, number of reflections measured = 10447, number of observed reflections [*I* ≥ 3 σ(*I*)] *R*(*F*) = 0.0645, *R*_w(*F*²) = 0.0937.

Results and discussion

The [LnL]³⁺ complexes were obtained in a templated 2+2 condensation of (R)-2,2′-diamino-1,1′-binaphthyl and 2,6-diformylpyridine. The identity of the complexes is confirmed by positive mode ESI MS spectra of methanol solutions which show signals of [LnL](NO₃)⁺ and [LnL](NO₃)₂⁺ species (see experimental part). In the case of the methanol/acetic acid solution of the [LaL](NO₃)₃ complex the ESI MS spectra show peaks at *m/e* 482, 1024 and 1027 corresponding to ions [LaL](AcO)²⁺, [LaL](AcO)₂⁺ and [LaL](AcO)(NO₃)⁺, respectively. The observation of acetate complexes in the spectra indicate easy exchange of nitrate anions that occupy axial positions. The formation of the macrocyclic ligand L is also confirmed by the NMR

spectra of the complexes. The spectra of the diamagnetic La(III) derivative show that signals of the formyl and amine groups of the substrates disappear and new compound containing binaphthyl fragment, pyridine fragment and azomethine group is formed. The nine ^1H NMR signals and fourteen ^{13}C NMR signals observed for the obtained complexes can be explained only by assuming the formation of macrocycle L of effective D_2 symmetry. In the case of La(III) and Eu(III) complexes it was possible to fully assign the spectra on the basis of COSY, NOESY and HMQC measurements. The COSY spectra (Figure 1) identifies the two pairs of coupled protons **a**, **b** and **d**, **e** and set of four coupled naphthyl signals **e**, **f**, **g**, **h** (see Scheme 1 for labelling). The signal of proton **a** can be easily identified by integration as triplet of intensity 2H. Its COSY-correlated partner has to correspond to signal **b**. The assignment is completed by analysis of the NOESY spectra (Figure 2) that show cross-peaks corresponding to pairs of neighbouring protons **ab**, **bc**, **cd**, **de**, **ef**, **fg**, and **gh**, in accord with the structure of macrocycle L. In turn, the identification of proton signals enables assignment of signals of respective carbon atoms on the basis of HMQC correlations (Figure 3).

In the case of $[\text{CeL}]^{3+}$ and $[\text{EuL}]^{3+}$ complexes the proton signals are affected by the paramagnetic contribution, that proves coordination of lanthanide(III) ion within macrocycle core. In particular, the value of chemical shift observed for the azomethine proton **c** of

the $[\text{EuL}]^{3+}$ complex, equal to -11.23 ppm, falls in the range characteristic for this position in other Eu(III) macrocyclic complexes [4, 5, 12]. The paramagnetic shifts of binaphthyl protons, in particular the large shift of proton **i**, suggest sizeable contact contribution to the paramagnetic shift and spin delocalisation via the network of π bonds.

The NOESY spectra that show cross-peaks between the signals of neighbouring protons, exhibit additional correlation between position **c** and **i** (Figure 2), while correlation between positions **c** and **f** is not observed. It means that the naphthyl fragment, which for the “flat” macrocyclic structure depicted in Scheme 1 should be far away from the azomethine group, is in fact positioned very close in space to this group. This observation points to a sizeable wrapping of the macrocycle around the lanthanide(III) ion, that results in short distance between protons **c** and **i**. Indeed the MM+ models of the $[\text{LaL}]^{+3}$ and $[\text{EuL}]^{+3}$ complexes (Figure 4) show that the macrocycle L is wrapped around the metal ion in a helical fashion. Such a wrapping of the macrocycle is accompanied by formation of a loop by the binaphthyl fragment, that results in close proximity of the protons **c** and **i** (with the distances in the order of 3.6 Å). These structures show that coordination of nitrogen atoms on one hand, and the steric requirements of binaphthyl fragments on the other hand, force the macrocycle L to adopt highly twisted conformation [13]. Metal complexes of the hexaaza and crown ether macrocycles

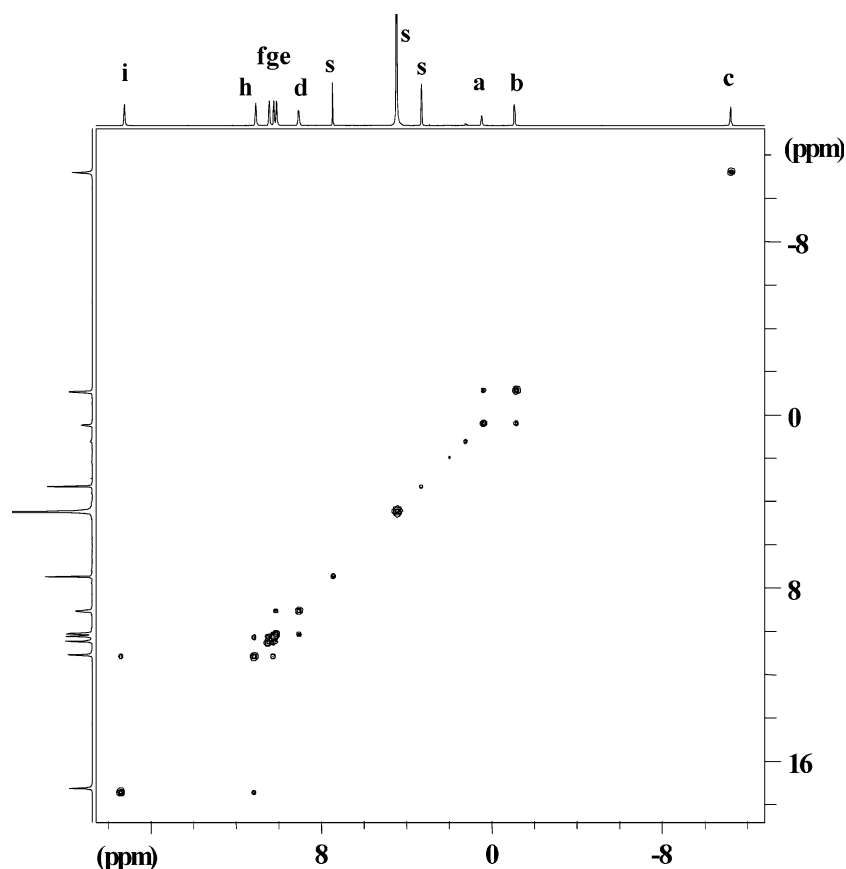


Figure 1. COSY spectrum of the $[\text{EuL}(\text{NO}_3)_2]_3[\text{Eu}(\text{NO}_3)_6] \cdot 3\text{CHCl}_3 \cdot 3\text{H}_2\text{O}$ complex (298 K, $\text{CD}_3\text{OD}/\text{CDCl}_3$ 1:2 vv, s – residual solvent signal).

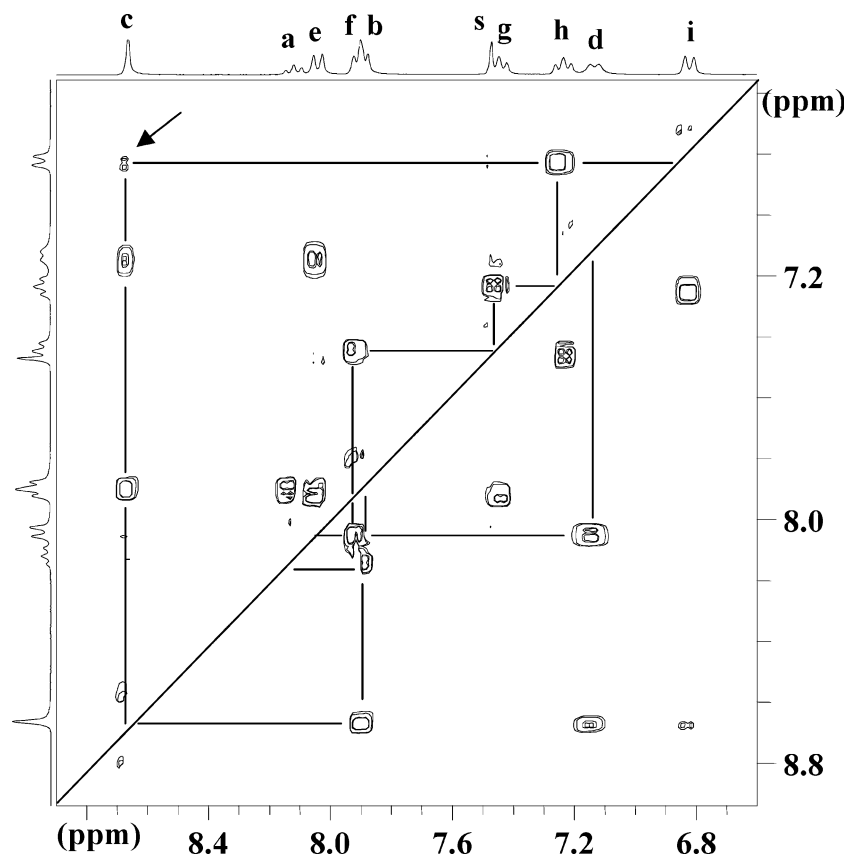


Figure 2. NOESY spectrum of the $[\text{LaL}(\text{NO}_3)] \cdot 4\text{H}_2\text{O}$ complex (298 K, $\text{CD}_3\text{OD}/\text{CDCl}_3$ 1:2 v/v, s – residual solvent signal). Arrow indicate correlation between protons c and i.

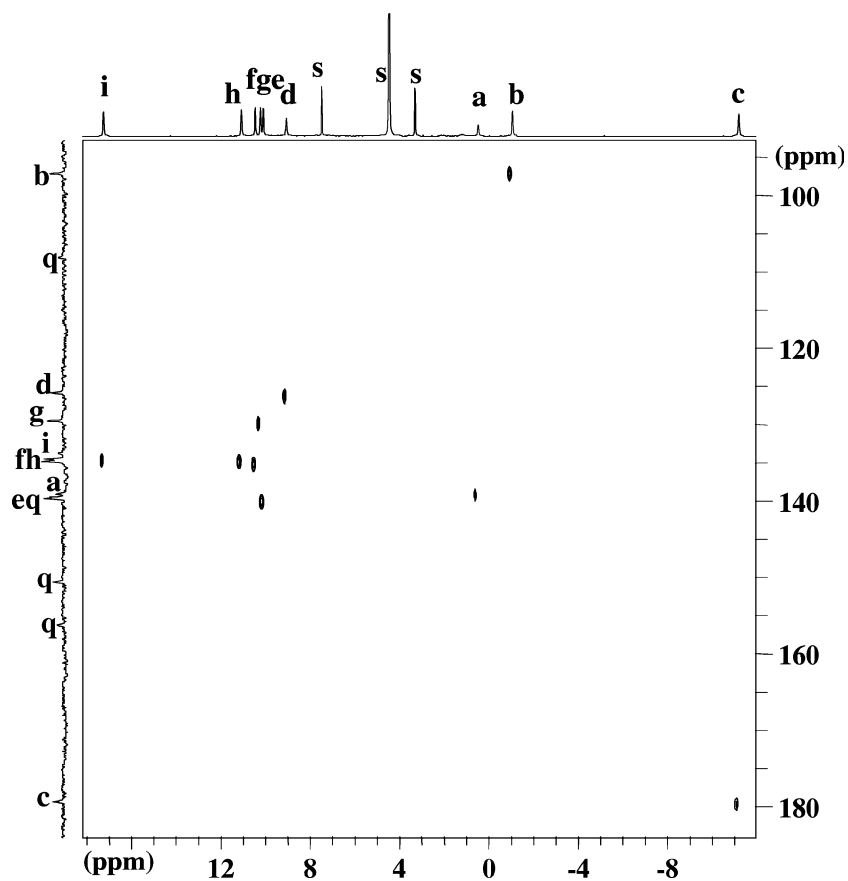


Figure 3. HMQC spectrum of the $[\text{EuL}(\text{NO}_3)_2]_3[\text{Eu}(\text{NO}_3)_6] \cdot 3\text{CHCl}_3 \cdot 3\text{H}_2\text{O}$ complex (298 K, $\text{CD}_3\text{OD}/\text{CDCl}_3$ 1:2 v/v, s – residual solvent signal).

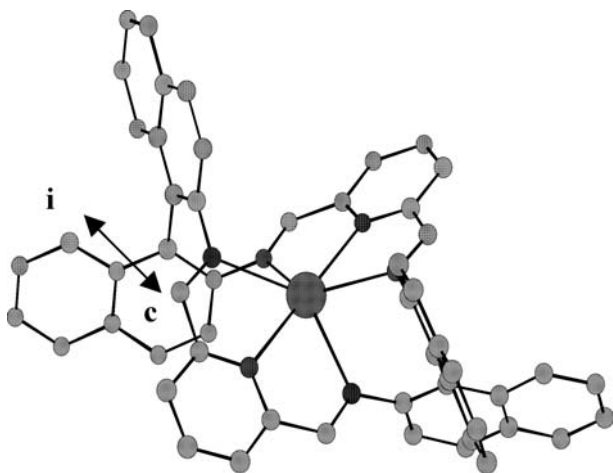


Figure 4. Molecular model of the $[\text{EuL}]^{+3}$ complex indicating close proximity of positions **c** and **i** illustrated in Scheme 1.

containing two 2,6-substituted pyridine rings usually exhibit helical twist of the macrocycle (often accompanied by substantial fold). This twist, that can be measured by the angle determined by the two pyridine rings or, better, by the *cis* torsion angle determined by C–N bonds of two pyridine rings, is moderate for lanthanide complexes with values in the range of $0.44\text{--}51.92^\circ$, while it can be much larger for transition metal ions [14]. The above C–N–N–C torsion angle range from 60.7° to 69.2° for modelled structures of $[\text{LnL}]^{3+}$ complexes. These values correspond to the largest helical twist for this class of complexes.

The enantiomeric purity of the discussed complexes is verified by the exchange reaction of the axial nitrate anion for chiral carboxylate. Thus, only one diastereomer is observed when the $[\text{EuL}](\text{NO}_3)_3$ complex is reacted with 1 equivalent of L-lithium lactate. ^1H NMR spectrum indicates formation of mixed nitrate/carboxylate complex of C_2 symmetry, what is accompanied by doubling of the number of resonances, e.g. now 2 signals of positions **i** at 15.96 and 16.39 ppm are observed. When 1 equivalent of racemic DL-lithium lactate is used, apart from the above signals, additional set of signals is observed, corresponding to diastereomer containing bound D-lactate, e.g. two additional signals of protons **i** are observed at 16.83 and 16.97 ppm. As expected, the chiral $[\text{LnL}](\text{NO}_3)_3$ complexes exhibit intense CD signals of the ligand chromophore.

The ligand L is related to the chiral crown ether L2 [8], and we expected the latter ligand to form complexes of similar geometry to that of $[\text{LnL}](\text{NO}_3)_3$. However, all our attempts to insert lanthanide(III) ions into the free macrocycle L2 were unsuccessful – macrocycle L2 remained unreacted. For instance, reaction of L2 with Yb(III) or Eu(III) salts (nitrates, chlorides or trifluoromethanesulfonates) in various solvents (methanol, chloroform, water, isopropanol, DMSO) did not lead to any metal complexes that can be detected on the basis of mass spectrometry or observation of paramagnetic signals in NMR spectra. On the other hand, modification

of synthesis of crown ether L2, based on the addition of Pr(III) isopropanolate as a template, suppressed formation of the macrocycle. It should be noted that other N_2O_4 crown ethers related to L2, containing two pyridine fragments (macrocycle L4, Scheme 1) easily coordinate lanthanide(III) ions [2b, c].

To explain the apparent incompatibility of ligand L2 with the lanthanide(III) ions we have determined its molecular structure (Figure 5). The conformation of free ligand L2 is very different to that of complexed ligand L, in particular the aromatic protons **i** are now much farther away from the methylene protons **c** ($4.87\text{--}5.71 \text{ \AA}$). The macrocycle L2 is “squeezed” by $\pi\text{--}\pi$ stacking interaction between the two pyridine fragments; the distance between pyridine planes is equal to 3.77 \AA . The pyridine ring, methylene bridge, oxygen atom and one of the naphthyl fragments form almost planar parts of the molecule that are approximately parallel. The remaining naphthyl fragments together with oxygen atoms are also almost parallel. These planar parts viewed from the top of the molecule form parallelogram arrangement (Figure 5), with binaphthyl hinges and remaining two methylene bridges corresponding to corners of the figure. The macrocycle L2 is of C_2 symmetry, in contrast to complexed macrocycle L, which is of D_2 symmetry. The binaphthyl dihedral angle is equal to 81.91° and is larger than that obtained for modelled conformation of complexed L (64.4°).

Although the models show that the macrocycle L2 can adopt helical conformation very similar to that discussed above for macrocycle L, the rearrangement of the “squeezed” conformation to helically twisted conformation would require major structural changes. The crystal structure of L2 indicates that the arrangement of the two arms of the pyridine rings correspond to anti and gauche conformations of the two N–C–C–O fragments. In order to obtain helical conformation of L2 these fragments have to convert into syn–syn conformation. At the same time the two parallel pyridine fragments have to be stretched away, placed in one plane and subsequently the macrocycle should be considerably twisted.

The squeezed conformation of L2 is different to the more open conformations of other crown ethers containing binaphthyl fragments [15]. In fact the X-ray crystal structure of the inclusion complex of the related crown ether L5 [16] show conformation of the macrocycle that is more similar to the above described conformation of hexaazamacrocycle L.

As mentioned above, the donor set of L2 is sufficient for strong binding of the lanthanide(III) ions and this ligand has the same carbon skeleton as the hexaazamacrocycle L that forms stable complexes with these ions. It cannot be excluded that the apparent inability of the chiral crown ether L2 to bind lanthanide(III) ions results from slight modification of the steric requirements and donating properties of L2 in comparison to L. However it is more likely that its inability to bind Ln(III) ions is due to kinetic reasons related to

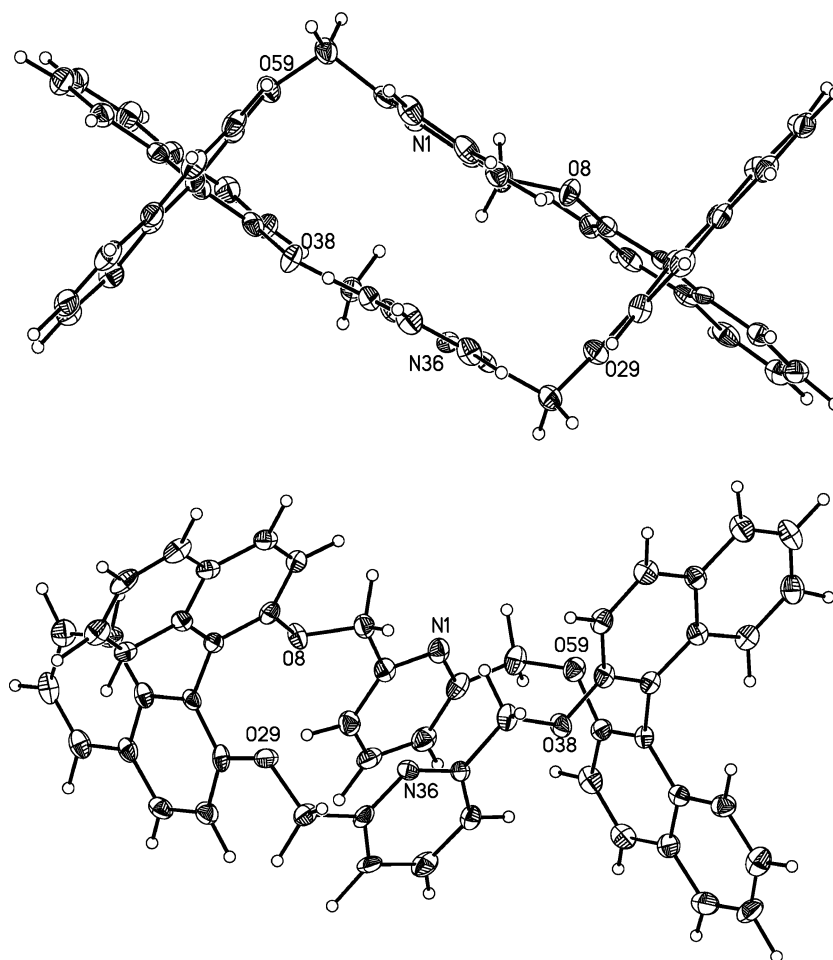


Figure 5. Top and side view of macrocycle L2.

unfavourable conformation of the free L2 macrocycle. The crown ether L2 is “squeezed” and the two parallel pyridine rings form narrow cleft that is not suitable for the coordination of the large Ln(III) ions. Additionally the spatial arrangement of coordinating atoms does not predispose them to simultaneous coordination of metal ion. The initial coordination of lanthanide(III) ion only by 1 or 2 donor atoms is not sufficient to overcome the π - π interaction between pyridine rings and “opening” of the macrocycle core. On the other hand, the Schiff base macrocycle L is formed from the very beginning in the suitable helical conformation on the metal template.

In conclusion we have synthesised enantiopure lanthanide complexes of new chiral macrocycle, that exhibit exceptionally large helical twist of the macrocyclic ligand. The closely related N₂O₄ crown ether adopts bent structure and is not predisposed for coordination of lanthanide(III) ions.

Supplementary data

Supplementary data for L2 structure are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) on request, quoting the deposition number CCDC 243859.

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