

Structure and dynamics of all of the stereoisomers of europium complexes of tetra(carboxyethyl) derivatives of dota: ring inversion is decoupled from cooperative arm rotation in the *RRRR* and *RRRS* isomers

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The absolute configuration of the four stereoisomeric α -substituted derivatives of dota has been defined; in their Eu complexes, 2D-NMR methods have revealed that in solution ring inversion is independent of pendant arm rotation and the (*RRRR*)-[EuL^{1a}] complex which in the solid state crystallises as a square antiprismatic structure.

The octadentate ligands derived from 1,4,7,10-tetraazacyclododecane (cyclen) by tetra-*N*-substitution define an important subgroup of modern lanthanide complexation chemistry.¹ Eight-coordinate tetraacetate ('dota'), phosphinate and carboxamide derivatives form kinetically robust complexes in aqueous solution, permitting their use in targeted radiotherapy,² as contrast agents in magnetic resonance imaging (MRI)³ and as single-component luminescent probes in biochemical analyses.⁴ In the lanthanide complexes of dota, or its achiral carboxamide derivatives, there are two independent elements of chirality, associated with the ring N–C–C–N and side-arm N–C–C–O torsion angles (*i.e.* each five-ring chelate is δ or λ). Accordingly there are four stereoisomers, related as two pairs of enantiomers, which may interconvert in solution *via* ring inversion ($\delta\delta\delta\delta \rightarrow \lambda\lambda\lambda\lambda$) or concerted arm rotation ($\Delta \rightarrow \Lambda$). Either motion, in isolation, will exchange the coordination geometry between a square-antiprismatic arrangement, [$\Delta(\lambda\lambda\lambda\lambda)/\Lambda(\delta\delta\delta\delta)$], with an N_4/O_4 twist angle of *ca.* 40°, and a more open twisted square antiprism [$\Delta(\delta\delta\delta\delta)/\Lambda(\lambda\lambda\lambda\lambda)$] with a twist angle of *ca.* 29°. Introduction of a stereogenic centre β or γ to the ring nitrogen has been shown to impart considerable rigidity into the complex, inhibiting arm rotation in particular, as shown with the tetraphosphinoxymethyl complexes, and leading to preferential formation of one major stereoisomer in solution.^{1,5,6} The effect of introducing a substituent α to each ring nitrogen on the structure and solution dynamics of the derived europium complexes is now described.^{5b} Such a substitution gives rise to 6 ligand stereoisomers L¹ defined by the absolute configuration at carbon: *RRRR* (*SSSS*), *RSSS* (*SRRR*), *RSRS* and *RRSS*. In the corresponding lanthanide complexes, for a given ligand configuration, there are theoretically four stereoisomeric complexes (Fig. 1), which in principle may exchange by sequential arm rotation and/or ring inversion.

Alkylation of cyclen with racemic dimethyl-2-bromoglutarate (K₂CO₃–MeCN) led to formation of a mixture[‡] of the expected diastereoisomeric esters. Base hydrolysis (6 M NaOH, 80 °C) afforded a mixture of ligands L^{1a}–L^{1d} which was separated by fractional crystallisation and analysed by reverse-phase HPLC. The absolute configuration of each ligand was established by an X-ray structural analysis. Europium complexes of each ligand were formed by heating with Eu(NO₃)₃ at pH 5.5 (18 h, 90 °C). The complexes were purified by crystallisation from water. Proton NMR spectra for each complex were recorded (Fig. 2), highlighting the symmetry of the complex in solution. Thus in the high frequency region of the shifted spectrum, the C₄-symmetric complex [EuL^{1a}] gave

rise to only two signals (δ_{H} 24.2 and 44.0) in ratio 4 : 1. ¹H–¹H COSY NMR showed that these resonances correspond to an axial ring proton in each of the isomeric species, consistent with earlier NMR analyses of such systems.^{7,8} With the 'C₂-symmetric' complex [EuL^{1c}], two pairs of axial ring protons were observed also in a ratio of 4 : 1; with both [EuL^{1b}] and [EuL^{1d}] which lack any rotational symmetry, each of the four 'axial' ring hydrogens gave rise to a separate resonance and the observed ratio of stereoisomers was *ca.* 2 : 1 and $\geq 12 : 1$ respectively.

A concerted arm rotation will interconvert the axial protons of the major isomer with the axial protons of the minor isomer. However, a ring inversion interconverts the axial protons of the major isomer with equatorial protons of the minor (Fig. 1). Such processes have been observed with [Eu(dota)][–] at room temperature.^{8,9} Two-dimensional exchange spectroscopy (¹H

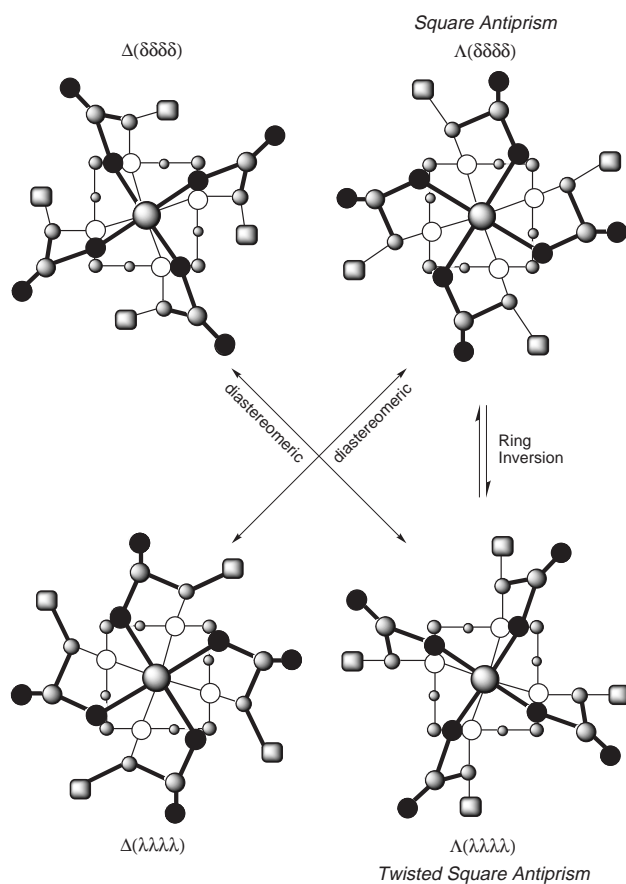


Fig. 1 Stereoisomerism in chiral eight- or nine-coordinate lanthanide complexes of α -alkylated derivatives of dota: ring inversion interconverts ($\delta\delta\delta\delta$) and ($\lambda\lambda\lambda\lambda$) isomers, and concerted arm rotation allows Δ and Λ isomers to exchange. The shaded square represents an alkyl group.

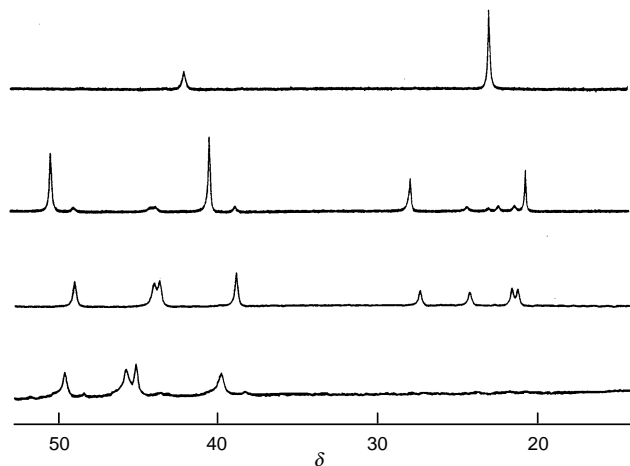


Fig. 2 ^1H NMR spectra (pD 6, D_2O , 293 K) of the europium complexes of (from top to bottom), (a) L^{1a} , (b) L^{1c} , (c) L^{1b} , (d) L^{1d} showing the shifted axial ring proton resonances which define the nature and relative proportion of complex stereoisomers

EXSY) was used to probe these processes in the complexes $[\text{EuL}^{1a}]$, $[\text{EuL}^{1b}]$ and $[\text{EuL}^{1c}]$ (293 K, pD 6). The 2-D EXSY spectra of $[\text{EuL}^{1a}]$ and $[\text{EuL}^{1b}]$ showed cross-correlations between related axial and equatorial protons, indicating that ring inversion is occurring at room temperature. No cross-peaks were observed arising from the interconversion of axial protons in the major and minor isomers. This is consistent with fast ring inversion but slow arm rotation, on the NMR timescale. Thus, major/minor isomer interconversion occurs primarily through ring inversion, rendering two of the four possible diastereoisomeric structures less accessible. This accounts for the observation of just two species in solution in the ^1H NMR spectrum (Fig. 2). On warming the sample, the two high frequency axial protons began to broaden and the minor resonance moved towards the major, with coalescence not observed but likely to be not much above 60 °C. The rate of exchange between the two isomers through ring inversion ($\lambda\lambda\lambda\lambda$ to $\delta\delta\delta\delta$), was measured by selective pulse inversion methods, examining the axial proton (H_{ax} , δ 44) to equatorial (H_{eq} , δ -8) exchange process. The measured rate was $45 \pm 15 \text{ s}^{-1}$, very similar to that found for $[\text{Eu}(\text{dota})]^-$,⁸ indicating clearly that the process of ring inversion is independent of arm rotation. The situation with $[\text{EuL}^{1c}]$ was quite different: at room temperature, cross-peaks associated with both arm rotation and ring inversion were observed indicating that both processes were occurring at comparable rates. Indeed the EXSY spectra were very similar to those defined for $[\text{Eu}(\text{dota})]^-$.⁸

The structure of the neutral complex $[\text{Eu}(\text{H}_5\text{L}^{1a})]$ was determined by X-ray crystallography[§] and both the (*RRRR*) and (*SSSS*) complexes crystallised together (in $P\bar{1}$) (Fig. 3). The Eu ion is nine-coordinate with Eu–O and Eu–N distances averaging 2.38 and 2.68 Å and the Eu–water oxygen bond distance was 2.445(7) Å. For the (*RRRR*)-enantiomer, the ring adopted a square [3333] conformation with each five-ring (N–C–C–N) chelate in a δ configuration (N–C–C–N torsion angle averaging +59.4°) and the N–C–C–O torsion angles were all negative (averaging -34.1°) consistent with a Λ configuration. For the (*SSSS*)-enantiomer, both sets of torsion angles were of opposite sign. Thus the configuration of the stereogenic centre at carbon in the ligand determines both the overall helicity of the complex and its ‘macrocylic’ ring configuration, in the solid-state structures. In solution (Fig. 2), comparison of the ^1H NMR spectrum of $[\text{EuL}^{1a}]$ with those of its three diastereoisomers and $[\text{Eu}(\text{dota})]^-$,⁹ suggests that the minor isomer also possesses the

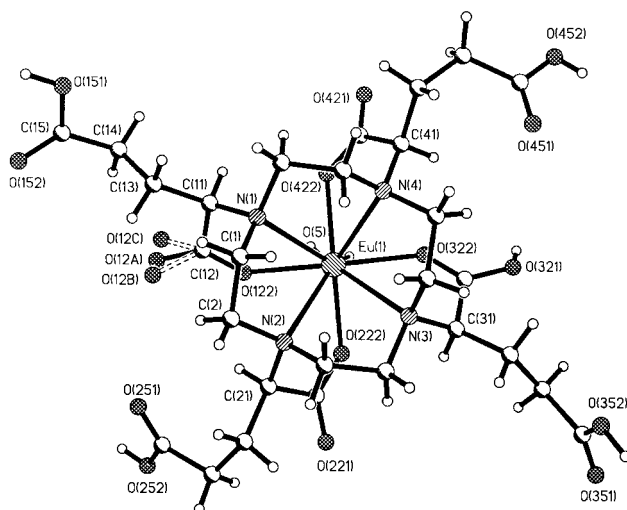


Fig. 3 Structure of (*RRRR*)- $[\text{Eu}(\text{H}_5\text{L}^{1a})(\text{H}_2\text{O})]$ in the crystal showing the mono-capped square antiprismatic geometry about the Eu ion, and the left-handed lay-out of the pendant arms

$\Lambda(\delta\delta\delta\delta)$ configuration (specifying *R* configuration). The major isomer in solution must then adopt the $\Lambda(\lambda\lambda\lambda\lambda)$ configuration. In the complexes of $[\text{EuL}^{1b}]$, $[\text{EuL}^{1c}]$ and $[\text{EuL}^{1d}]$, it follows that the major isomer must adopt a square antiprismatic geometry. Thus it is the minor isomer of $[\text{EuL}^{1a}]$ that has crystallised preferentially.

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Notes and References

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‡ Statistically, this reaction leads to 50% of the *RRRS/SSSR* L^{1b} , 25% of the *RRSS* L^{1d} and 12.5% of each of L^{1a} and L^{1c} .

§ *Crystal data* for $\text{C}_{28}\text{H}_{49}\text{EuN}_4\text{O}_{20.25}$, $M = 917.67$, triclinic, space group $P\bar{1}$, $a = 9.637(2)$, $b = 12.690(4)$, $c = 16.186(5)$, $\alpha = 102.47(2)$, $\beta = 101.28(3)$, $\gamma = 110.42(3)^\circ$, $U = 1729.8(1) \text{ \AA}^3$, $D_c = 1.762 \text{ g cm}^{-3}$, $\lambda(\text{Mo-K}\alpha) 0.71073 \text{ \AA}$, $Z = 2$, $\mu = 1.906 \text{ mm}^{-1}$. Data were collected on a SMART at 150(2) K. Refinement of 627 parameters by full matrix least squares on F^2 (SHELX 93) converged at $R = 0.031$, $wR_2 = 0.067$ for 7242 reflections with $I > 2\sigma(I)$. CCDC 182/875.

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