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Isomerization kinetics of lanthanide(III) complexes with the pendant-arm macrocyclic ligand 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane†

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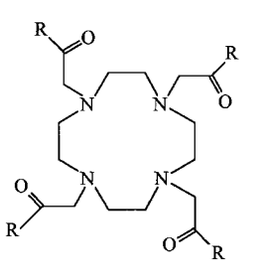
The ^{13}C and ^{1}H NMR spectra of the complexes of La^{III}, Eu^{III} and Lu^{III} with 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane (L^1) in acetonitrile or methanol indicated the presence of two enantiomers the interconversion of which proceeds through both a ring inversion and a rearrangement of the pendant arms. The following kinetic parameters were extracted from temperature-dependent ^{13}C NMR spectra for the ring inversion in $[LaL^1]^{3+}$, $[EuL^1]^{3+}$, $[LuL^1]^{3+}$ in CD_3OD and $[EuL^1]^{3+}$ in CD_3CN: k(298 K) = 1396, 1055, 1288 and 880 s^{-1}; $\Delta H^{\ddagger}$ = 37.6, 41.1, 48.2 and 47.7 kJ mol^{-1}; $\Delta S^{\ddagger}$ = −58.5, −49.2, −23.8 and −28.4 J K^{-1} mol^{-1}, respectively. The lanthanide(III) substitution induces a continuous variation of the kinetic parameters, implying the same pathway for the enantiomerization. The behaviour of $[LnL^1]^{3+}$ in solution is compared with that of complexes with similar 12-membered tetraaza macrocycles bearing pendant arms.

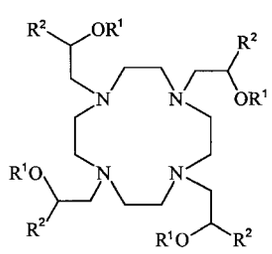
Important applications of trivalent lanthanide ions in biology and medicine[1] include (*i*) the design of luminescent chelates for immunoassays, (*ii*) the analysis of NMR spectra with the help of Eu-containing shift reagents, (*iii*) the use of Gd-containing contrast agents in diagnostic medicine and (*iv*) the labelling and specific cleavage of DNA and RNA.[2] In the last two cases, efficient lanthanide species proved to be complexes with 12-membered tetraaza macrocyclic ligands featuring pendant arms: $[Gd(dota)]^-$ (H_4dota = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) for NMR imaging[3] and $[LnL^1]^{3+}$,[4–6] $[LnL^2]^{3+}$,[5–7] or $[LaL^3]^{3+}$[8,9] for the cleavage of RNA oligomers. These octadentate ligands efficiently encapsulate the lanthanide ions, forming stable and inert complexes while leaving the possibility for one further interaction with a solvent molecule, an essential feature for contrast agents.

The first lanthanide complexes with L^1, $[LnL^1][CF_3SO_3]_3$ (Ln = La or Eu), were isolated by Morrow and Chin[4] who showed that the ethylenic groups of the pendant arms were rigid on the NMR time-scale at low temperature in methanol, and adopt the same conformation. At elevated temperature the macrocycle loses its rigidity and a dynamic process takes place which involves the ethylenic groups. In water the ligand L^1 remains strongly bonded to the lanthanide ions and the complexes are inert towards metal-ion dissociation.[4] It was later demonstrated that the lanthanum complex promotes transesterification of the 4-nitrophenyl phosphate ester of polyethylene glycol and cleavage of RNA oligomers.[5,6] With respect to the unsubstituted tetraaza macrocycle, the pendant arms of L^1 and related ligands increase the ability of metal ions to reside in the macrocyclic cavity and generates possibilities for intramolecular dynamic processes. Complexes of L^1 with alkali-metal ions have been investigated[10] and ^{13}C NMR spectra point to an enantiomerization of square-antiprismatic $[ML^1]^+$ and $[ML^4]^+$ complexes in methanol with M = Li, Na or K.[11] A similar isomerization has been evidenced for L^1 and L^4 complexes with divalent transition metals, Pb, Cd and Hg.[12,13]

Understanding the biochemical effects of lanthanide complexes requires a precise knowledge of the co-ordination properties of the lanthanide ions and of all the dynamic processes taking place within the complexes. In this paper we investigate the intramolecular exchange involving the ring inversion in lanthanide complexes of L^1 by means of variable-temperature ^{13}C and ^{1}H NMR spectroscopy. Our purpose is to unravel the influence of the lanthanide ion radius (La, Eu, Lu) and of the solvent (CD_3CN *versus* CD_3OD).



	R
H_4dota	OH
L^3	NH_2



	R^1	R^2
L^1	H	H
L^2	H	CH_3
L^4	CH_3	H

Results and Discussion

Preparation of 1,4,7,10-tetraazacyclododecane

We have improved the general procedure of Richman and Atkins[14] for the synthesis of unsubstituted tetraazacyclododecane by skipping the isolation of the disodium salt of *N*,*N*′,*N*″-tris(*p*-tolylsulfonyl)diethylenetriamine. Its preparation *in situ* leads to a quantitative yield in 1,4,7,10-tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraazacyclododecane and to a worthwhile improvement of the overall synthesis of 1,4,7,10-tetraazacyclododecane.

Solution behaviour of $[LnL^1][CF_3SO_3]_3$ and assignment of the NMR signals

The molar conductivity of 10^{-3} mol dm^{-3} solutions of $[LnL^1][CF_3SO_3]_3$ in acetonitrile was Λ_m = 303 (La^{III}), 313 (Eu^{III}) and 313 S cm^2 mol^{-1} (Lu^{III}). These values are in between the ranges

† *Supplementary data available* (No. SUP 57210, 2 pp.): ^{13}C NMR chemical shifts. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1.
Non-SI unit employed: bar = 10^5 Pa.

Table 1 Chemical shifts, in ppm referred to internal $SiMe_4$, of the ^{13}C NMR signals arising from L^1 and $[LnL^1][CF_3SO_3]_3$ solutions (0.025 mol dm^{-3}) in deuteriated methanol or acetonitrile

Compound, solvent	*T*/K	NCH_2 (ring)	NCH_2 (arms)	CH_2OH	Ref.
L^1, CD_3OD	298	51.4	56.0	58.5	*a*
L^1, CD_3CN	298	52.6	57.5	59.7	*a*
$[LaL^1][CF_3SO_3]_3$, CD_3OD	298	50.80[b]	53.80	60.75	4
CD_3CN	243.7	49.1, 51.6	53.8	60.5	*a*
	329.9	50.9	54.2	60.7	*a*
$[EuL^1][CF_3SO_3]_3$, CD_3OD	290	84.2[b]	(76.4)[c]	(88.6)[c]	4
CD_3OD	241.2	85.5, 88.6	(76.9)[c]	(93.8)[c]	*a*
	326.1	83.4	(75.4)[c]	(88.5)[c]	*a*
CD_3CN	241.2	89.8, 95.6	(73.5)[c]	(91.1)[c]	*a*
	326.1	86.0	(73.7)[c]	(87.1)[c]	*a*
$[LuL^1][CF_3SO_3]_3$, CD_3CN	243.7	49.2, 51.1	51.4	60.0	*a*
	329.9	50.6	51.9	60.3	*a*

[a] This work. [b] Broad. [c] For Eu^{III} the paramagnetism of the cation prevents the assignment of the NCH_2 and the CH_2OH signals of the arms on the sole basis of the chemical shifts.

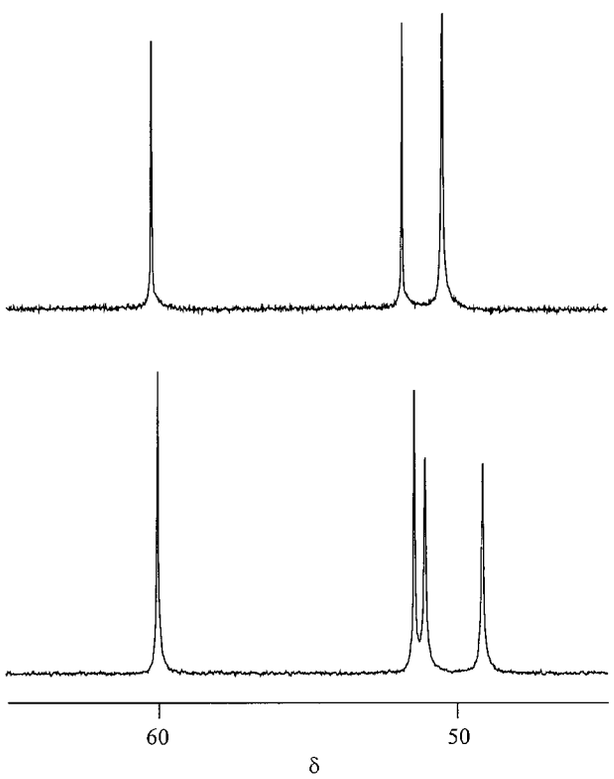


Fig. 1 The 100.614 MHz ^{13}C-{^1H} NMR spectra of $[LuL^1]^{3+}$ (0.025 mol dm^{-3}) in CD_3CN; at 329.9 (top) and 243.7 K (bottom)

expected for 1:2 (220–300) and 1:3 electrolytes (340–420 S cm^2 mol^{-1})[15] and indicate a partial association of one $CF_3SO_3^-$ anion (triflate) to the lanthanide cation. Whether this interaction is inner or outer sphere cannot be decided on the basis of conductivity measurements alone. Co-ordination of triflate has been observed in the solid state, the crystal structure of $[LaL^3(EtOH)(CF_3SO_3)][CF_3SO_3]_2$ featuring ten-co-ordinate[8] La^{III} with one oxygen atom of the anion bonded to the metal. On the other hand, the crystal structure of $[EuL^3(H_2O)][CF_3SO_3]_3 \cdot 2MeOH$ has revealed a nine-co-ordinate Eu^{III}, without evidence of anion co-ordination.[9] The molar conductivity is lower for La^{III} than for Eu^{III} or Lu^{III}, which may reflect a greater tendency to anion association in the case of the lighter lanthanide complex.

At 329.9 K the ^{13}C-{^1H} NMR spectrum of 0.025 mol dm^{-3} $[LuL^1][CF_3SO_3]_3$ in acetonitrile exhibits three peaks at δ 50.9, 54.2 and 60.7, in a 2:1:1 ratio (Fig. 1, Table 1), as observed for the free macrocycle in solution. The first one is assigned to the NCH_2 of the ring while the last two are ascribed to the NCH_2 and CH_2OH carbon atoms of the arms, respectively. Upon lowering the temperature the first signal broadens and splits into two resonances so that four peaks of equal intensity are observed at 243.7 K (Fig. 1), indicating that a ring-inversion process takes place. The same observation was made for the complexes of La and Eu in acetonitrile and has also been reported by Morrow and Chin[4] for solutions of these two complexes in methanol. The full process is however not totally observable for the methanolic solutions of $[LaL^1][CF_3SO_3]_3$ and $[LuL^1][CF_3SO_3]_3$: the broadening of the NCH_2 ring signal occurs with a decrease of the chemical shift difference between this signal and the multiplet arising from CD_3OD at about δ 47, leading to their superposition in the temperature range 270–290 K. Below 260 K the NCH_2 ring signal appears to resolve into two peaks, but that at higher field interferes with the solvent multiplet. As a consequence the determination of the rate constants for the ring inversion by a line-shape analysis of the ^{13}C-{^1H} NMR spectra was performed in acetronitrile for La, Eu and Lu, the solvent signals[16] at δ 118.2 and 1.3 being well separated from the NCH_2 ring resonances, and also in methanol for the europium complex. In the latter case the NCH_2 ring resonances appear at higher frequencies compared to those of the diamagnetic complexes of La^{III} and Lu^{III} and the paramagnetic effect of Eu^{III} removes the interference with the solvent signals in the temperature range studied.

The ^{13}C NMR spectra of the deuteriated acetonitrile solutions of $[LnL^1][CF_3SO_3]_3$ show that the solvent signals experience a decrease in their chemical shift when switching from Ln = La or Lu to Eu (SUP 57210). This effect is almost imperceptible for the CD_3 moiety (<0.1 ppm) but a significant decrease of 0.3 ppm is observed for the CN group. This change in chemical shift indicates that the solvent experiences the paramagnetism of Eu^{III}, implying some binding of the solvent, through the nitrogen atom, to the lanthanide. In the solid state the crystal structures of $[\{LaL^2(H_2O)\}_2][CF_3SO_3]_6 \cdot 2EtOH \cdot H_2O$,[7] $[LaL^3(EtOH)(CF_3SO_3)][CF_3SO_3]_2$[8] and $[EuL^3(H_2O)][CF_3SO_3]_3 \cdot 2MeOH$[9] are examples where a solvent molecule can be co-ordinated to the lanthanide cation. In solution the conductivity measurements and the ^{13}C NMR observations point to interaction of the lanthanide, either inner or outer sphere, with anion and/or solvent molecules. The octadentate nature of L^1 and the common co-ordination number of nine for Ln^{III} in solution provide support for the penetration of an additional molecule in the inner sphere, most probably a solvent molecule as the concentration of the latter is about 200 times higher than that of $CF_3SO_3^-$. The number of co-ordinating sites is expected to decrease with the ionic radius of the Ln^{III}, due to steric hindrance, as observed in the solid state for the $[LaL^3]^{3+}$ and $[EuL^3]^{3+}$ species.[8,9] The co-ordinating power of the solvent is also expected to be crucial in determining the occupancy of the first co-ordination sphere.

The ^{13}C NMR resonances of $[EuL^1][CF_3SO_3]_3$ appear at different frequencies, depending upon the nature of the solvent, acetonitrile or methanol. The significant differences observed (Table 1) reveal substantial changes in the local paramagnetism encountered by the carbon atoms. They are due to modifications of the spatial position of the carbon atoms relative to Eu^{III}. Slight distortions of the complex can lead to a new conformation, with the same symmetry, but giving a spectrum exhibiting different chemical shifts. These distortions may be induced by changes in the nature or in the number of molecules completing the co-ordination sphere.

The ^{1}H NMR spectrum of $[LuL^1][CF_3SO_3]_3$ in acetonitrile at 233 K shows four resonances exhibiting complex couplings, consistent with an ABCD pattern for the NCH_2CH_2O in the *gauche* form and an AA′BB′ pattern for NCH_2CH_2N also in the *gauche* form, the rotation of both ethylenic groups being slow on the NMR time-scale.[17] At 345 K the spectrum is much simpler and features a triplet for the CH_2O and a singlet for NCH_2, in an 1:3 intensity ratio. At this higher temperature the rapid rotation of both the NCH_2CH_2O and NCH_2CH_2N results respectively in A_2B_2 and A_4 patterns. Similar observations have been made for $[LaL^1][CF_3SO_3]_3$ in acetonitrile and have also been reported for that complex in methanol.[4] The nature of the solvent affects the chemical shifts, changing the general aspect of the spectra at low temperature. This is attributed to slight distortions of the complex induced by the nature of the solvent, as discussed above in the case of the ^{13}C-{^{1}H} NMR spectra of $[EuL^1][CF_3SO_3]_3$. For the latter the broadness of the ^{1}H NMR pattern obscures any coupling at low temperatures.

Kinetic analysis of the ring-inversion process and mechanism

For the three complexes studied the exchange between the two magnetic environments of the NCH_2 ring carbon atoms may be characterized by a two-site line-shape analysis. Typical experimental and calculated ^{13}C NMR spectra for Lu are displayed in Fig. 2. The dependence of the rate constants on temperature (Fig. 3) was fitted by the Eyring equation, yielding the parameters k^{298}, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ reported in Table 2.

A ring-inversion process has been described by Lincoln and co-workers for complexes of Pb^{II}, Cd^{II} and Hg^{II} with L^1 (ref. 12) and L^4 (ref. 13) and of Na, Li and K with L^1 or L^4 (ref. 11) in methanol. It was concluded that $[PbL^1]^{2+}$ undergoes an intramolecular exchange between two square-antiprismatic enantiomers with C_4 symmetry, in which Pb^{II} is co-ordinated by the four nitrogen atoms of the macrocycle and the four oxygen atoms of the arms (Scheme 1). In this complex the arms wrapping the metal ion have a helical arrangement. Support for this mechanism has been provided by the observation of enantiomeric pseudo-square-antiprismatic structures for $[KL^1]^+$ in the solid state[18] and by the absence of changes in the magnetic environments of the pendant-arm carbon atoms during the isomerization.[12] Lincoln and co-workers[12] have concluded that this intramolecular exchange between two enantiomers Δ and Λ also applies for the other L^1 or L^4 complexes they have studied. The enantiomerization can be seen by the simultaneous occurrence of two intramolecular exchanges: (*a*) ring inversion and (*b*) rotation of the arms around the N–CH_2 bond. The line-shape analysis of the ^{13}C NMR peaks arising from the macrocyclic carbon atoms provides kinetic information on the ring inversion only, whatever the rate of rotation of the arms. However, our ^{1}H NMR spectra show that both processes (*a*) and (*b*) do occur simultaneously in the temperature range studied, as indicated by the loss of rigidity of both the NCH_2CH_2N and NCH_2CH_2O moieties upon increasing the temperature from 233 to 345 K. The measurement of the rate constants for processes (*a*) and (*b*) from the ^{1}H NMR spectra has nevertheless not been attempted due to the complexity of the exchanging system. However, the occurrence of both processes in the temperature range studied indicates that the order of magnitude of

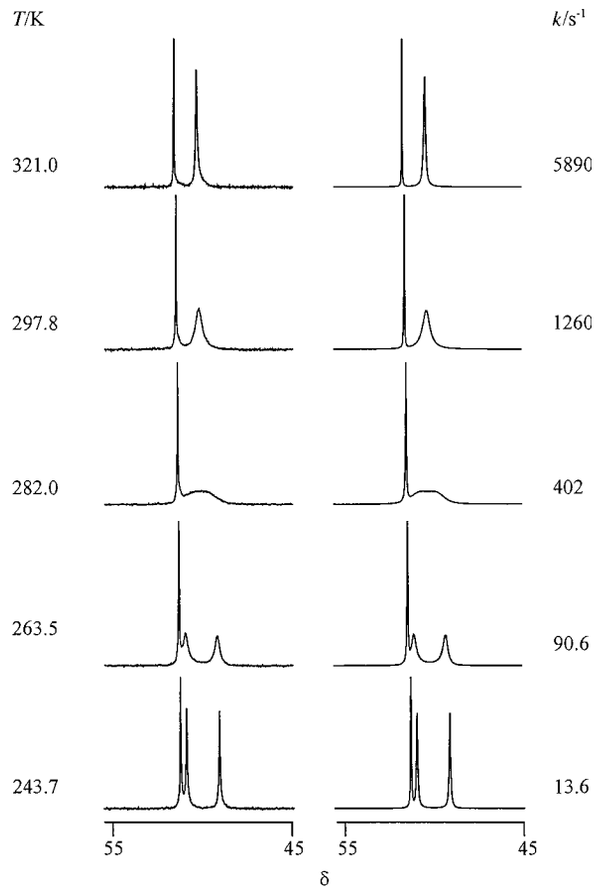


Fig. 2 Typical exchange 100.614 MHz ^{13}C-{^{1}H} NMR spectra of $[LuL^1]^{3+}$ (0.025 mol dm^{-3}) in CD_3CN. Experimental temperatures and spectra appear on the left, and the best-fit calculated line shapes and corresponding *k* values appear to the right

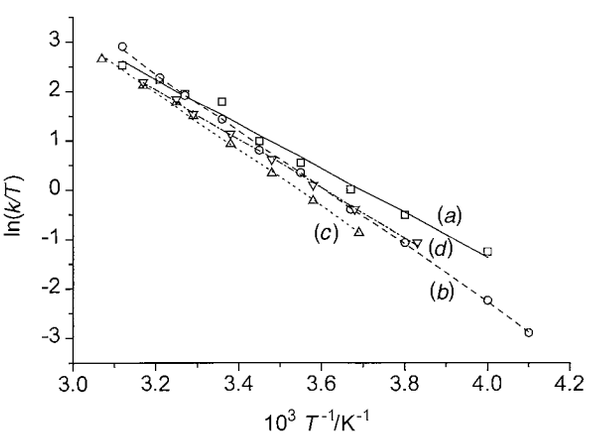


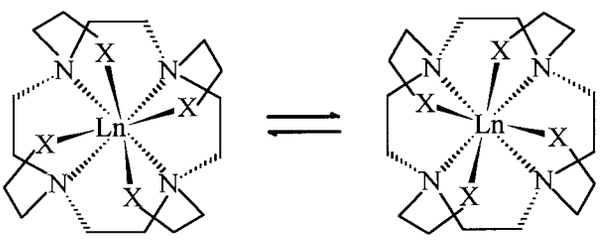
Fig. 3 Eyring plots for the enantiomerization of $[LnL^1]^{3+}$: (*a*) $[LaL^1]^{3+}$ in CD_3CN, (*b*) $[LuL^1]^{3+}$ in CD_3CN, (*c*) $[EuL^1]^{3+}$ in CD_3OD and (*d*) $[EuL^1]^{3+}$ in CD_3CN

their rate constants should not be very different and is further evidence for the interconversion between two enantiomers as depicted in Scheme 1.

From the observation that the enantiomerization of $[KL^1]^+$ is slower than the L^1 exchange reaction, with similar activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the two processes, Lincoln and co-workers[11a] attributed an intermolecular mechanism for the enantiomerization of $[KL^1]^+$, occurring through the dissociation of the complex. Since for both $[LiL^1]^+$ and $[NaL^1]^+$ the rates of L^1 exchange are substantially slower than those of enantiomerization, these authors concluded that an intramolecular mechanism occurs which, however, may imply either

Table 2 Kinetic parameters for the ring inversion of 0.025 mol dm^{-3} $[LnL^1][CF_3SO_3]_3$ solutions in deuteriated acetonitrile or methanol

Ln, solvent	k^{298}/s^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ J K^{-1} mol^{-1}	$\Delta G^{\ddagger}$/ kJ mol^{-1}
La, CD_3OD	1396 ± 78	37.6 ± 2	−58.5 ± 5	55.1 ± 0.1
Eu, CD_3OD	1055 ± 19	41.1 ± 1	−49.2 ± 2	55.8 ± 0.1
Lu, CD_3OD	1288 ± 22	48.2 ± 1	−23.8 ± 1	55.3 ± 0.1
Eu, CD_3CN	880 ± 21	47.7 ± 1	−28.4 ± 3	56.2 ± 0.1



Scheme 1

a concerted twisting process or the detachment of one or more arms. The variation in the kinetic parameters for both enantiomerization and ligand exchange does not display a clear trend, which has been considered as consistent with a variation with M^+ of the bonding and ligand strain generating different transition-state enthalpies and entropies for the three $[ML^1]^+$ complexes. The kinetic parameters for the enantiomerization of $[LnL^1]^{3+}$ continuously change in going from La^{III} to Eu^{III} and to Lu^{III} (Table 2). Moreover, the tendency of $[LnL^1]^{3+}$ towards decomplexation is small as indicated by the low dissociation rates[4] of $[LaL^1]^{3+}$ ($<10^{-5}$ s^{-1}) and $[EuL^1]^{3+}$ ($<10^{-6}$ s^{-1}) in aqueous solution at pH 6.0 and $T = 310$ K, and by the absence of any free L^1 resonance in both the ^1H and ^{13}C NMR spectra of $[LnL^1][CF_3SO_3]_3$ in acetronitrile or methanol. Therefore, we conclude that the enantiomerization of $[LnL^1]^{3+}$ is occurring through an intramolecular mechanism implying either a concerted twisting process or the detachment of one or more arms.

In acetonitrile the comparable rate constants obtained for the three lanthanide complexes studied are indicative of the similarity of the ring-inversion mechanism. Nevertheless, going from La^{III} to Lu^{III} results in an increase in $\Delta H^{\ddagger}$ and less negative values of $\Delta S^{\ddagger}$ (Table 2). For the three lanthanide complexes the transition state will be very similar and changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ will reflect differences in the conformation of the enantiomer induced by the nature of the central ion. A tighter wrapping of the arms is expected with the smaller Lu^{III} compared to the situation with the larger La^{III}. Therefore, the energy needed for raising the arms at the transition state will be larger for the smaller ions. This metal-size effect is even larger for the enantiomerization of the L^1 complexes of alkali-metal ions in methanol,[11a,b] with $\Delta H^{\ddagger} = 24.6$ kJ mol^{-1} for Na and 41.3 kJ mol^{-1} for the smaller Li. For these complexes the increase in $\Delta H^{\ddagger}$ parallels less negative $\Delta S^{\ddagger}$ values. Similar observations have been made for the complexes of Na and Li[11b,c] with L^4. Reactions where bond elongation or breaking predominates induce positive values of $\Delta S^{\ddagger}$, as observed for the dissociative enantiomerization of $[KL^1]^+$ in methanol, $\Delta S^{\ddagger} = +8.8$ J K^{-1} mol^{-1}; on the other hand, an increase in the symmetry at the transition state will have the opposite effect. Therefore, the negative $\Delta S^{\ddagger}$ values obtained for the enantiomerization of $[LnL^1][CF_3SO_3]_3$ in acetonitrile indicate that the gain in symmetry at the transition state is the major term affecting $\Delta S^{\ddagger}$. If the amplitude of this term is the same for all complexes, the less negative values of $\Delta S^{\ddagger}$ may reflect a higher tendency to bond elongation when Lu^{III} is complexed. Such a predominance would not be surprising, given the expected tighter wrapping of the arms around smaller ions.

The results obtained for the enantiomerization of $[EuL^1][CF_3SO_3]_3$ in methanol differ from those collected in acetonitrile (Table 2). The small decrease in the rate constant observed on going from acetonitrile to methanol is, however, larger than the changes measured in acetonitrile when the size of the Ln^{III} is varied. The value of $\Delta H^{\ddagger}$ increases while $\Delta S^{\ddagger}$ decreases, as observed in acetonitrile solutions when the size of the Ln^{III} becomes smaller. The alterations of the ^{13}C NMR chemical shifts induced by the solvent have been taken as representative of distortions of the complex. According to the intramolecular mechanism depicted in Scheme 1, a concerted twisting process produces a complex of C_{4v} symmetry at the transition state, implying planarity of the ring carbon atoms and loss of the helical arrangement of the arms which become perpendicular to the ring plane. The C_{4v} symmetry will not be affected by the nature of the solvent and significant changes in the activation parameters will arise only if the ligand arrangement characteristic of one pair of enantiomers is solvent dependent.

From rate constants estimated at four temperatures, Morrow and Chin[4] have calculated an energy of activation $E_a = 52$ kJ mol^{-1} for the enantiomerization of $[LaL^1]^{3+}$ in methanol. Using our kinetic data we obtain $E_a = 50$ kJ mol^{-1} for the enantiomerization of $[EuL^1]^{3+}$ in methanol. The similarity of these values suggests that the mechanism of the enantiomerization of $[LnL^1]^{3+}$ in methanol does not differ markedly in the first half of the lanthanide series, as observed in acetonitrile.

Comparison with similar complexes

The ^{13}C and ^1H NMR spectra of methanolic solutions of $[Ln(S\text{-}L^2)]^{3+}$ (Ln = La, Eu or Lu; L^2 in the *S* configuration at all α-carbons)[7] indicate that only one diastereomer is present in the temperature range 291–373 K while the process depicted in Scheme 1 leads to a pair of diastereomers. This behaviour suggests that one diastereomer is energetically preferred. Thus, the presence of the methyl group dictates the arrangement of the pendant arms and favours a more rigid conformation of the ring leading to a higher stability of $[Ln(S\text{-}L^2)]^{3+}$ towards dissociation, compared to $[LnL^1]^{3+}$. The absence of fluxionality has also been reported[13] for $[M(S\text{-}L^2)]^{2+}$ complexes, with $M = Cd^{II}$, Hg^{II} or Pb^{II}, while the rate of diastereomerization of $[Na(S\text{-}L^2)]^+$ at 298 K is markedly lower ($k = 125$ s^{-1}) than the rate of enantiomerization of $[NaL^1]^+$ ($k = 7100$ s^{-1}).[11b]

Desreux[19] has observed one pair of interconverting enantiomers in aqueous solutions of $[Ln(dota)]^-$ and postulated that the process is due to the ring inversion, with $k = 23$ s^{-1} at 278 K for $[La(dota)]^-$. More recently, several groups have revised this conclusion, their ^1H and/or ^{13}C NMR spectra providing evidence for the presence of two isomeric forms the relative abundance of which changes markedly along the lanthanide series.[20–22] Aime *et al.*[20] deduced that the two isomers differ in the layout of the acetate arms, the ring conformation being identical in both species. The interconversion between the two isomers occurs at high temperature and this process may be independent of the ring inversion, as shown by ^{13}C NMR spectra of $[Nd(dota)]^-$ and by two-dimensional exchange spectroscopy (EXSY) experiments on $[Yb(dota)]^-$. Hoeft and Roth[21] also detected two independent intramolecular isomerizations by use of EXSY experiments and showed for $[Eu(dota)]^-$ that the faster process is the rotation of the four acetate arms around the C–N bonds [$\Delta(\lambda\lambda\lambda\lambda) \leftrightarrow \Lambda(\lambda\lambda\lambda\lambda)$, $k^{278} = 78$ s^{-1}], while the ring inversion is slower [$\Delta(\lambda\lambda\lambda\lambda) \leftrightarrow \Delta(\delta\delta\delta\delta)$, $k^{278} = 35$ s^{-1}]. The intramolecular racemization of the $\Delta(\lambda\lambda\lambda\lambda)$ main isomer into its $\Lambda(\delta\delta\delta\delta)$ enantiomer includes two successive isomerizations in a $\Delta(\lambda\lambda\lambda\lambda) \longrightarrow \Lambda(\lambda\lambda\lambda\lambda) \longrightarrow \Lambda(\delta\delta\delta\delta)$ sequence and is the slower process, with $k = 23$ s^{-1}. Marques *et al.*[22] have analysed the dipolar contributions to the paramagnetic shifts of $[Ln(dota)]^-$ aqueous solutions to show that the two isomers

have identical ring conformations and differ only in the co-ordination or orientation of the acetate arms.

The enantiomerization of $[LnL^1]^{3+}$ (k = 200–500 s^{-1} at 278 K) is faster than for $[Ln(dota)]^-$. Experimentally, the higher apparent rigidity of the dota complexes parallels the larger stability of the $[Ln(dota)]^-$ species, induced by the strong co-ordinating ability of the acetate arms. The hydroxyethyl arms of L^1 are more apt to rearrange, contributing to the decreased rigidity of $[LnL^1]^{3+}$. However, the main difference between these two series of complexes is that only one pair of enantiomers is detected by ^{13}C or ^1H NMR spectroscopy for $[LnL^1]^{3+}$. We explain this difference either by similar rate constants for processes (*a*) and (*b*) in the case of $[LnL^1]^{3+}$, or by a sequence of fast metal–oxygen bond-breaking and -making processes in which short-lived intermediates with one or several non-bonding arms are present. Both phenomena preclude the observation of intermediates similar to those present in $[Ln(dota)]^-$ solutions. No direct evidence for decomplexation of the arms has been found for lanthanide(III) complexes; however, evidence for such phenomenon in the case of alkali-metal complexes is given by the dissociative enantiomerization[11a] of $[KL^1]^+$ in methanol and by the crystal structure of $[NaL^1]^+$ where one arm is non-co-ordinating.[18]

Finally, ^{13}C and ^1H NMR spectra[8] demonstrate that $[LaL^3]^{3+}$ sustains a dynamic process involving a change in conformation of the ethylenic units in concert with movement of the pendant arms. The activation energy E_a = 56.1 kJ mol^{-1} is intermediate between the values obtained for $[LaL^1]^{3+}$ in methanol (52 kJ mol^{-1})[4] and $[La(dota)]^-$ in water (61.9 kJ mol^{-1}),[19] reflecting the stronger co-ordination ability of acetate and amide over hydroxyethyl arms. The crystal structure[8] of $[EuL^3(H_2O)][CF_3SO_3]_3 \cdot 2MeOH$ reveals the presence of two diastereomers differing in the helicity of their arms, in a similar way to $[Ln(dota)]^-$. In aqueous solution luminescence data suggest that the two species are in rapid exchange.

Conclusion

Complexes with 12-membered tetraaza macrocyclic ligands featuring achiral pendant arms are present in solution as interconverting isomers. For $[LnL^1]^{3+}$, where the co-ordinating power of the pendant arm is weak, only one pair of enantiomers is observed in solution. The kinetic parameters for the enantiomerization show a continuous variation on passing from La^{III} to Eu^{III}, then to Lu^{III}. The isomerization proceeds through simultaneous ring inversion and change in helicity of the arms. It can be hindered by the presence of chiral arms, the dynamic process producing diastereomers of different stability, as observed for $[Ln(S\text{-}L^2)]^{3+}$ being present as a single form. For $[Ln(dota)]^-$, which exhibit the highest stability amongst these ligands, two diastereomeric pairs are present, due to different rates for the ring inversion and helicity change. Complexes of ligands with pendant arms of intermediate co-ordinating power show a behaviour in between those of $[Ln(dota)]^-$ and $[LnL^1]^{3+}$. For all these complexes the octadentate nature of the ligand makes possible the interaction of one or more molecules of solvent or anions with the central Ln^{III}.

Experimental

Syntheses

1,4,7,10-Tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraazacyclododecane. The entire synthesis was conducted under a dry N_2 atmosphere. *N*,*N*′,*N*″-Tris(*p*-tolylsulfonyl)diethylenetriamine[23] (28.0 g, 0.05 mol) was dissolved in dimethylformamide (dmf) (400 cm^3) (Fluka, puriss p.a.) and NaH (55–65% in paraffin oil, Fluka, purum; 10 g, 0.23–0.27 mol) was added in small portions with stirring to produce the disodium salt of the amine. The solution was stirred during 2 h and the excess of NaH filtered off. The filtrate was heated to 110–120 °C, a solution of *N*,*O*,*O*′-tris(*p*-tolylsulfonyl)diethanolamine[24] (28.0 g, 0.05 mol) in dmf (200 cm^3) was added dropwise, the resulting mixture stirred 2 h, then allowed to cool at room temperature and transferred to a flask (3 dm^3) equipped with a mechanical stirrer. The addition of water (1 dm^3) with vigorous stirring produced a white solid, which was filtered off, washed with water (500 cm^3) and dried (overnight, 1 mbar, 60 °C). Yield: 39.3 g, 100%. TLC: R_f = 0.5 (1% MeOH in $CHCl_3$). M.p. 266–268 °C. $\delta_H(CDCl_3)$ 2.42 (s, 12 H, aryl CH_3), 3.41 (s br, 16 H, NCH_2), 7.31 (d, 8 H, J = 8, aryl H) and 7.67 (d, 8 H, J = 8 Hz, aryl H).

1,4,7,10-Tetraazacyclododecane. 1,4,7,10-Tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraazacyclododecane (39.3 g, 0.05 mol) was detosylated in 96% H_2SO_4 (100 cm^3) during 48 h at 100 °C. The resulting black mixture was cooled in an ice-bath and 6 mol dm^{-3} HCl (50 cm^3) was very slowly added with stirring. **CAUTION**: HCl is evolved. The addition of 25% HCl (50 cm^3) produced a greyish solid, which was filtered off, washed with 25% HCl (2 × 10 cm^3) and dried over KOH [12 h, 1 mbar, room temperature (r.t.)]. It was divided into three portions, each of which was dissolved in 1 mol dm^{-3} NaOH (100 cm^3) and extracted five times with $CHCl_3$ (200 cm^3). The chloroform extracts were evaporated and the resulting solid was purified by sublimation (1 mbar, 95 °C), then dried (overnight, 1 mbar, 30 °C) giving 1,4,7,10-tetraazacyclododecane as a white solid (5.1 g, 59%). TLC: 1 spot, R_f = 0.35 (BuOH–pyridine–$MeCO_2H$–water 17:12:6:15). M.p. 115–116 °C. $\delta_H(CDCl_3)$ 2.66 (s, NCH_2).

1,4,7,10-Tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane (L^1). This compound was prepared as previously described.[25] $\delta_H(CDCl_3)$ 2.47 (t, 8 H, J = 5, NCH_2 arms), 2.57 (s, 16 H, NCH_2 ring), 3.60 (t, 8 H, J = 5 Hz, CH_2O) and 5.10 (s br, 4 H, OH).

Lanthanide trifluoromethanesulfonates (Ln = La, Eu or Lu). A solution of water (8 g) and CF_3SO_3H (5 g, 33.6 mmol) was added dropwise to a suspension of Ln_2O_3 (5 mmol, Nucor, 99.99%) in water (2 g). The mixture was heated to 80 °C for 4 h. After cooling, the solution was filtered on sintered glass and the water evaporated. The resulting solid was suspended in diethyl ether (70 cm^3), then refluxed for 10 min, cooled and the lanthanide salt was filtered off and dried under vacuum over KOH (1 mbar, 1 h at r.t. and overnight at 45 °C). The exact lanthanide(III) content of the salts was determined by titration with 0.01 mol dm^{-3} ethylenedinitrilotetraacetate.

Complexes $[LnL^1][CF_3SO_3]_3$ (Ln = La, Eu or Lu). The macrocycle (0.6 mmol) and $Ln(CF_3SO_3)_3 \cdot xH_2O$ (x = 1.4–2.2) (0.6 mmol) were heated under reflux in dry MeCN (60 cm^3) for 16 h. After cooling, the solution was filtered on sintered glass; part of the solvent was evaporated to a final volume of 5–10 cm^3 and dry CH_2Cl_2 (40 cm^3) was added. The resulting solution was kept overnight at 4 °C and the deposited solid was filtered off in a dry-box, washed with dry CH_2Cl_2 and dried (60 h, 1 mbar, 40 °C). The salts $[LnL^1][CF_3SO_3]_3$ were obtained in yields of 70 (La^{III}), 68 (Eu^{III}) and 66% (Lu^{III}) Found: C, 24.3; H, 3.95; N, 6.0. Calc. for $C_{19}H_{36}F_9LaN_4O_{13}S_3$: C, 24.4; H, 3.9; N, 6.0. Found: C, 23.85; H, 3.75; N, 5.85. Calc. for $C_{19}H_{36}EuF_9N_4O_{13}S_3$: C, 24.1; H, 3.85; N, 5.9. Found: C, 23.3; H, 3.95; N, 5.7. Calc. for $C_{19}H_{36}F_9LuN_4O_{13}S_3$: C, 23.5; H, 3.75; N, 5.75%). The ^1H and ^{13}C NMR spectra of $[LaL^1][CF_3SO_3]_3$ and $[EuL^1][CF_3SO_3]_3$ in CD_3OD agreed well with those previously reported.[4] For $[LuL^1][CF_3SO_3]_3$, $\delta_H(CD_3OD$, 250 K) 2.62 (2 H, t, NCH_2), 2.72 (1 H, d, NCH_2), 3.7 (3 H, m, NCH_2), 4.14 (1 H, t, CH_2O) and 4.47 (1 H, t, CH_2O); (CD_3CN, 234 K) 2.5 (3 H, m, NCH_2), 3.4 (3 H, m, NCH_2), 4.09 (1 H, m, CH_2O) and 4.28 (1 H, m, CH_2O), (345 K) 3.08 (6 H, s, NCH_2) and 4.29 (2 H, t, J = 6.5 Hz, CH_2O).

Physicochemical measurements

The TLC checks were performed on silica gel 60 F_{254} plates, with UV quenching detection at 254 nm. Elemental analyses were performed by Dr H. Eder at the Laboratoire de chimie pharmaceutique of the University of Geneva. Melting points are uncorrected. Conductivity measurements of millimolar solutions of $[LnL^1][CF_3SO_3]_3$ in dry acetonitrile were performed at 25.0 °C, under Ar, with a Metrohm 712 conductimeter and a conductivity cell equipped with a Pt-100 resistor for temperature monitoring. The solvents CD_3OD and CD_3CN (Armar, 99.8 atom% D) were used as received. Proton NMR spectra were recorded at 360 MHz on a Bruker AM-360 spectrometer. For complex characterization solutions contained a known amount of $CHCl_3$ and the ^1H NMR signal integration ratios agreed within 5% of the calculated ones. For variable-temperature ^{13}C-{^1H} NMR measurements, solutions of 0.025 mol dm^{-3} $[LnL^1][CF_3SO_3]_3 \cdot xH_2O$ in CD_3OD or CD_3CN, with 0.025 mol dm^{-3} $SiMe_4$, were prepared by weight in a dry-box and transferred to sealed tubes (outside diameter 10 mm). The ^{13}C-{^1H} NMR spectra were recorded at 100.614 MHz with a Bruker AM-400 spectrometer. The tubes were thermostatted with a flux of nitrogen and the temperature was measured by a substitution technique.[26] The field was locked using the deuterium signal of the solvent. The sweep width ranged from 10 to 20 kHz, the number of data points from 16 to 32 K and the number of scans from 5000 to 20 000 with a pulse length of 10 μs. Chemical shifts were referred to the signal of $SiMe_4$, which was also used to estimate inhomogeneity corrections. The calculated spectra were least-squares fitted to the observed spectra by using a program derived from EXCHNG.[27] When a resonance of a non-exchanging carbon appeared in the spectral range used for the calculation a third site was included in the exchange matrix, without modifying the calculation of the rate constant. The chemical shifts of all the non-exchanging peaks and of the two exchanging peaks (mean) varied linearly with temperature, even for the complex, both in acetonitrile and methanol. These data show that the paramagnetic europium(III) complex adopts a pseudo-Curie behaviour in the temperature range studied. The relationships were used to evaluate the chemical shifts needed in the line-shape calculations. The widths at half-height of the non-exchanging peaks were constant over the temperature range considered, within experimental errors. Those used in the line-shape analysis were measured at the lowest temperatures, corrected to take account of variations in inhomogeneity. The changes in the calculated rate constant induced by an increase or decrease in 50% of the half-height width were smaller than the calculated error.

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