

Lanthanide complexes of 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol: evidence for heterotrinnuclear species in aqueous solution †

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1,3,5-Triamino-1,3,5-trideoxy-*cis*-inositol (L) gives trinuclear complexes of trivalent lanthanide cations, $[\text{Ln}_3\text{L}_2\text{H}_{-6}]^{3+}$. In this contribution, we demonstrate the capability of this cyclohexanic ligand to form heterotrinnuclear complexes of 4f cations in aqueous solutions containing mixtures of rare-earths. Electrospray ionization mass spectra clearly show the presence of heterometallic complexes together with the corresponding homonuclear species. Moreover, these compounds have very characteristic ^1H and ^{13}C NMR parameters; paramagnetic chemical shifts and longitudinal relaxation times are typical of the lanthanide cations inserted in the complexes. Potentiometric analysis of solutions containing two different lanthanide salts affords the stability constants of the heterotrimetallic $[\text{Ln}_2\text{Ln}'\text{L}_2\text{H}_{-6}]^{3+}$ complexes. Furthermore, ^1H NMR titrations show the appearance of the complexes in order of stability as the pH is increased and confirm the potentiometry results. The order of trinuclear complex stabilities deduced from these experiments is: $\text{Nd}_3 < \text{Nd}_2\text{Sm} < \text{Nd}_2\text{Eu} < \text{NdSm}_2 < \text{NdSmEu} \sim \text{NdEu}_2 < \text{Sm}_3 < \text{Sm}_2\text{Eu} < \text{Eu}_3 < \text{SmEu}_2$. These constants are compared to the statistical introduction of the three lanthanide cations in $[\text{Ln}_3\text{Ln}'\text{L}_2\text{H}_{-6}]^{3+}$ complexes and the deviations suggest that the ionic recognition between the metallic sites is quite limited when the lanthanide cations are close in the 4f series.

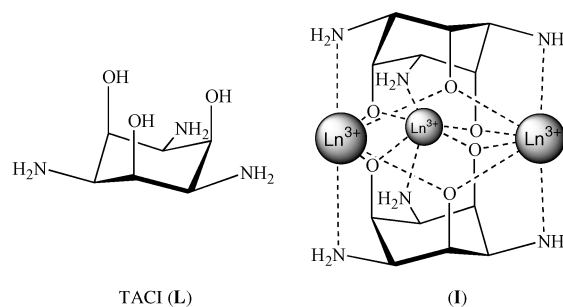
Introduction

Trivalent lanthanide coordination chemistry has received increasing attention in the few past decades because of the characteristic magnetic and photophysical properties of their compounds.¹ Practical applications soon emerged in the field of shift reagents in analytical chemistry² and in separation science.^{3,4} More recently, research on the chemistry of rare-earth metal ions has focused on their potential uses in biomedical applications, taking advantage of the electronic and magnetic properties of complexes of these elements. For example, paramagnetic gadolinium(III) complexes find utility as contrast agents for magnetic resonance imaging (MRI),⁵⁻⁷ luminescent probes such as fluoroimmunoassays,⁸ and catalysts for the cleavage of RNA and DNA.^{9,10}

The physico-chemical properties of metallic compounds can be extended by the introduction of several different ions into chemical architectures. Numerous 3d–4f heterometallic systems have been investigated, mainly to rationalize the weak magnetic exchange interactions between d- and f-block ions.¹¹⁻¹⁸ Less research has been devoted to 4f polymetallic systems.¹⁹ Homodi- and trinuclear lanthanide(III) complexes have been described with macrocyclic ligands,²⁰⁻²² calix[8]arene,²³ and an iminophenolate cryptand.^{24,25} Some flexible tripodal²⁶ and tetrapodal²⁷ ligands give M_3L_2 homotrimetallic compounds. Self-assembled dinuclear lanthanide(III) helicates have been the subject of extensive studies in the solid state and in solution.²⁸⁻³¹ In contrast to 3d–4f heterometallic systems, only a few reports describe heterodimetallic f–f complexes. The preparation of such species requires the recognition of each lanthanide ion in a specific coordination site and represents a real challenge

because lanthanide(III) cations are very similar. Statistical mixtures of homo- and heterodimetallic 4f complexes have been spectroscopically analysed^{20,29,32-34} and the energy-transfer processes between the two lanthanide ions have been studied by luminescence. But, to our knowledge, only one heterodimetallic complex has been characterized in the solid state.³⁵

In the course of our investigations of lanthanide(III) complexation by some cyclohexane-based ligands,^{36,37} the molecule 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (TACI)^{38,39} attracted our attention because it gives some trinuclear lanthanoid complexes with an unusual sandwich-type structure I (Scheme 1).⁴⁰



Scheme 1

The $[\text{Gd}_3(\text{TACIH}_{-3})_2(\text{H}_2\text{O})_6]^{3+}$ complex has been especially studied as a model compound from the point of view of MRI.⁴¹ Recently, an extensive study of lanthanide(III) complexation by TACI (L) has shown that the $[\text{Ln}_3\text{L}_2\text{H}_{-6}]^{3+}$ complex was the only metallic complex present in solution over the entire 4f series, and that the thermodynamic stability constants for complex formation (see equilibrium 1) were very dependent on



† Electronic supplementary information (ESI) available: ES-MS spectra of samples containing $\text{M}(\text{OTf})_3$ ($\text{M} = \text{Pr}$ or Nd), $\text{Eu}(\text{OTf})_3$ and TACI. See <http://www.rsc.org/suppdata/dt/b1/b105173n/>

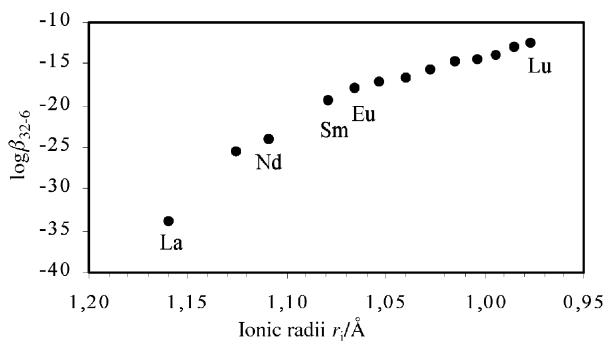


Fig. 1 $[\text{Ln}_3\text{L}_2\text{H}_{-6}]^{3+}$ complex formation constants ($\log \beta_{32-6}$) according to equilibrium 1 as a function of lanthanide(III) ionic radii.

the cation radius,⁴² as evidenced in Fig. 1.⁴³ Furthermore, the isostructurality of these complexes from praseodymium to ytterbium has been demonstrated by the analysis of the proton paramagnetic NMR chemical shifts.

In this contribution, the formation of 4f heterotrinnuclear complexes of TACI in aqueous solution will be discussed. The characterization of these trinuclear species relies on the combination of electrospray ionization mass spectrometry and paramagnetic solution NMR. Moreover, for the neodymium–samarium–europium triplet, potentiometric titrations have been performed in the presence of different lanthanide salts in order to get a precise knowledge of heterometallic complex stabilities in aqueous solution. Their thermodynamic formation constants have then been determined and are compared to those of the corresponding homotrinnuclear species, as well as to the expected statistical values calculated in a simple model.

Results and discussion

Mass spectrometry studies

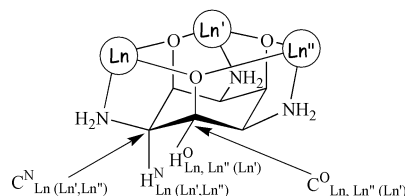
Electrospray ionization mass spectrometry (ES-MS) has been shown to be a suitable technique to characterize qualitatively preformed ions in solution⁴⁴ and, moreover, has been used for the identification of supramolecular coordination complexes.^{45–47} It is a gentle ionization method that minimizes the fragmentation of the analyte molecules. Many lanthanides possess several isotopes and the MS peak patterns are therefore characteristic of the nature and the number of cations present in the compounds. This allows easy identification of polymetallic species.⁴⁸ Mass spectrometry has previously been used to demonstrate the exclusive formation of trinuclear complexes of trivalent lanthanide cations with TACI. Whatever the metal to ligand ratio and the pH are, the ES-MS spectra show three major peak envelopes which correspond to the monocharged ions $[\text{Ln}_3\text{L}_2\text{H}_{-6}(\text{OTf})_2]^+$, $[\text{Ln}_3\text{L}_2\text{H}_{-6}(\text{OTf})(\text{OH})]^+$, and $[\text{Ln}_3\text{L}_2\text{H}_{-6}(\text{OH})_2]^+$. For polyisotopic lanthanides, each envelope has the isotopic pattern characteristic of a trimetallic complex.

ES-MS was used here to investigate the formation of heterotrinnuclear complexes of ligand TACI, including different lanthanides in the same structure. Solutions of two lanthanide triflates and ligand TACI (L) in presence of triethylamine at constant pH were analysed for the following stoichiometric conditions: Ln_3L_2 , $\text{Ln}_2\text{Ln}'\text{L}_2$, $\text{Ln}_{1.5}\text{Ln}'_{1.5}\text{L}_2$, $\text{LnLn}'_2\text{L}_2$, and $\text{Ln}'_3\text{L}_2$. The ES-MS spectra of samples containing Eu^{3+} and Tm^{3+} reveal the presence of heterotrinnuclear complexes together with the previously identified homotrinnuclear species, as evidenced in Fig. 2. Europium has 2 isotopes (^{151}Eu , 47.80; ^{153}Eu , 52.20%), whereas thulium has only one (^{169}Tm , 100%). $[\text{Eu}_3\text{L}_2\text{H}_{-6}]^{3+}$ peak patterns thus look roughly like quartets, $[\text{Eu}_2\text{TmL}_2\text{H}_{-6}]^{3+}$ like triplets, $[\text{EuTm}_2\text{L}_2\text{H}_{-6}]^{3+}$ like doublets and $[\text{Tm}_3\text{L}_2\text{H}_{-6}]^{3+}$ like singlets. Although ES-MS does not allow any quantitative analysis, it can be seen in Fig. 2 that the peak intensities are dependent on the initial ratio between the 2

metals. When the Eu : Tm ratio is 1 : 2 [Fig. 2(b)], the peak corresponding to the homotrinnuclear complex of thulium is much more intense than the other signals, whereas when the Eu : Tm ratio is 2 : 1 [Fig. 2(c)], the signals of species containing europium are more intense. The spectra are much more dense in the case of the Nd–Eu couple. Neodymium has several isotopes (^{142}Nd , 27.13; ^{143}Nd , 12.18; ^{144}Nd , 23.80; ^{145}Nd , 8.30; ^{146}Nd , 17.19; ^{148}Nd , 5.76; ^{150}Nd , 5.64%) and the peak patterns of the homo- and heterotrinnuclear complexes containing this metal are therefore much more complicated. Careful analysis of the ES-MS spectrum shows nevertheless the overlapping peak envelopes of the polymetallic species containing Nd and Eu. Relevant data are reported in Table 1 for different lanthanide couples. In every case, the ES-MS spectra indicate the presence of the four expected homo- and heterotrinnuclear complexes, $[\text{Ln}_3\text{L}_2\text{H}_{-6}(\text{X})(\text{Y})]^+$, $[\text{Ln}_2\text{Ln}'\text{L}_2\text{H}_{-6}(\text{X})(\text{Y})]^+$, $[\text{LnLn}'_2\text{L}_2\text{H}_{-6}(\text{X})(\text{Y})]^+$, and $[\text{Ln}'_3\text{L}_2\text{H}_{-6}(\text{X})(\text{Y})]^+$, where X and Y are either OTf or OH.

Heteronuclear complex characterization by solution NMR

ES-MS gives information about species in the mass spectrometer source, and thus in the gas phase. The presence of these compounds in solution has therefore to be confirmed by other characterization techniques, such as solution NMR. A detailed NMR analysis was thus undertaken with three well-chosen lanthanide cations. Neodymium, samarium, and europium are good candidates: although they are paramagnetic, they induce reasonable paramagnetic relaxation times, allowing 2D-NMR experiments to be performed. The proton NMR spectra of samples containing two lanthanide salts together with the ligand TACI at pH 8, displays twelve well-resolved resonances characteristic of a mixture of paramagnetic complexes, as shown in Fig. 3 for the Nd–Eu couple. The homotrinnuclear species, having D_{3h} symmetry give rise to two proton NMR signals, one corresponding to the nucleus H^{N} (Nd: 21.8; Sm: 5.5; Eu: –21.5 ppm) and the other to H^{O} (Nd: 19.1; Sm: 6.4; Eu: –14.4 ppm). The heterometallic complexes incorporating two different lanthanide cations, $[\text{Ln}_2\text{Ln}'\text{L}_2\text{H}_{-6}]^{3+}$, have a lower symmetry, C_{2v} , and show four proton NMR signals: $\text{H}^{\text{N}}_{\text{Ln}(\text{Ln},\text{Ln}')} (intensity\ 2)$, $\text{H}^{\text{N}}_{\text{Ln}'(\text{Ln},\text{Ln}')} (intensity\ 1)$, $\text{H}^{\text{O}}_{\text{Ln},\text{Ln}(\text{Ln}')} (intensity\ 1)$, and $\text{H}^{\text{O}}_{\text{Ln},\text{Ln}'(\text{Ln}')} (intensity\ 2)$, according to the nucleus nomenclature described in Scheme 2. These protons possess very



Scheme 2 ^1H and ^{13}C labelling scheme in NMR spectra.

characteristic paramagnetic chemical shifts and longitudinal relaxation times, both depending on the metals present in the complex. Proton chemical shifts were assigned by ^1H – ^1H COSY experiments and longitudinal relaxation time measurements, whereas carbon chemical shifts were obtained by performing ^1H – ^{13}C HMQC (heteronuclear multiple quantum coherence) experiments. The typical paramagnetic NMR properties of these six heterotrinnuclear complexes are given in Table 2. These solution NMR studies show that the two heterotrinnuclear complexes are present in aqueous solution together with the two corresponding homotrinnuclear species, confirming that the four trimetallic compounds detected in the ES-MS spectra are preformed in aqueous solution.

The complex simultaneously incorporating the three different cations, $[\text{NdSmEuL}_2\text{H}_{-6}]^{3+}$, was identified by its six proton and six carbon resonances due to its C_s symmetry in solution. The proton NMR spectra of samples containing the 3 triflate salts

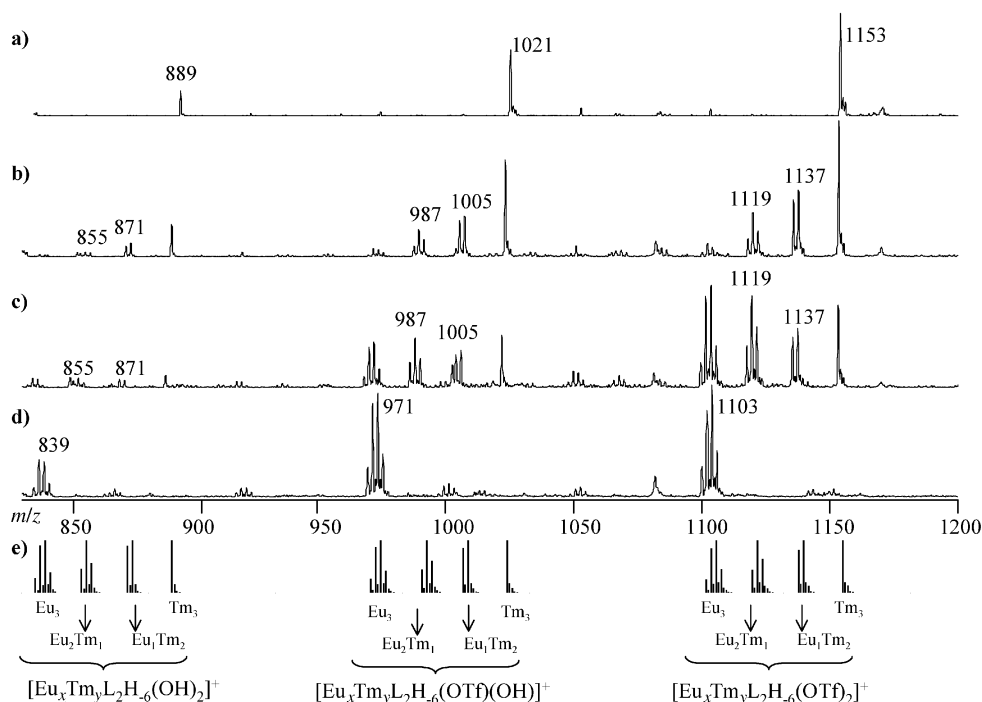
Table 1 Electrospray mass spectrometric data (m/z) for Ln(OTf)₃-Ln'(OTf)₃-TACl samples at pH 8 in water^a

Complex	Ln-Ln' couple						
	Nd-Eu	Pr-Eu	Eu-Tb	Eu-Ho	Eu-Tm	Eu-Lu	Tm-Lu
[Ln ₃ L ₂ H ₋₆ (OTf) ₂] ⁺	1078	1069	1103	1103	1103	1103	1153
[Ln ₃ L ₂ H ₋₆ (OTf)(OH)] ⁺	946	937	971	971	971	971	1021
[Ln ₃ L ₂ H ₋₆ (OH) ₂] ⁺	814	805	839	839	839	839	889
[Ln ₂ Ln'L ₂ H ₋₆ (OTf) ₂] ⁺	1085	1081	1109	1115	1119	1125	1159
[Ln ₂ Ln'L ₂ H ₋₆ (OTf)(OH)] ⁺	953	949	977	983	987	993	1027
[Ln ₂ Ln'L ₂ H ₋₆ (OH) ₂] ⁺	821	817	845	851	855	861	895
[LnLn' ₂ L ₂ H ₋₆ (OTf) ₂] ⁺	1094	1091	1117	1129	1137	1149	1165
[LnLn' ₂ L ₂ H ₋₆ (OTf)(OH)] ⁺	962	959	985	997	1005	1017	1033
[LnLn' ₂ L ₂ H ₋₆ (OH) ₂] ⁺	830	827	853	865	873	885	901
[Ln' ₃ L ₂ H ₋₆ (OTf) ₂] ⁺	1103	1103	1123	1141	1153	1171	1171
[Ln' ₃ L ₂ H ₋₆ (OTf)(OH)] ⁺	971	971	991	1009	1021	1039	1039
[Ln' ₃ L ₂ H ₋₆ (OH) ₂] ⁺	839	839	859	877	889	907	907

^a Only the m/z peaks corresponding to the most abundant isotopic mass are reported.

Table 2 Proton chemical shifts (δ^H), longitudinal relaxation times (T_1^H), and carbon chemical shifts (δ^C) of the heterotrinnuclear complexes [Ln₂Ln'L₂H₋₆]³⁺, where Ln and Ln' are Nd, Sm, or Eu, in D₂O at 400 MHz and 298 K

Ln ₂ Ln'	$X^N_{Ln(Ln, Ln')}$			$X^N_{Ln'(Ln, Ln')}$			$X^O_{Ln, Ln(Ln')}$			$X^O_{Ln, Ln'(Ln)}$		
	δ^H/ppm	T_1^H/ms	δ^C/ppm	δ^H/ppm	T_1^H/ms	δ^C/ppm	δ^H/ppm	T_1^H/ms	δ^C/ppm	δ^H/ppm	T_1^H/ms	δ^C/ppm
Nd ₂ Sm	19.0	24	60	10.4	4.9	86	18.2	11	31	13.0	18	57
Sm ₂ Nd	7.9	87	75	16.3	32	49	7.1	87	84	12.1	20	58
Nd ₂ Eu	14.9	21	42	-10.4	31	103	18.2	11	35	1.6	14	97
Eu ₂ Nd	-16.2	37	74	9.0	24	13	-15	24	162	1.5	15	102
Sm ₂ Eu	2.0	148	46	-14.9	79	81	6.6	116	89	-4.4	50	124
Eu ₂ Sm	-18.3	59	64	-1.4	94	29	-15.1	32	163	-3.9	40	129

**Fig. 2** Theoretical and experimental ES-MS spectra of samples containing Eu(OTf)₃, Tm(OTf)₃, and TACl at pH 8 in water for different Eu : Tm : L ratios: (a) 0 : 3 : 2; (b) 1 : 2 : 2; (c) 2 : 1 : 2; (d) 3 : 0 : 2. (e) Theoretical isotope distributions.

and the ligand in the Nd : Sm : Eu : L ratio 1 : 1 : 1 : 2 show signals due to the previously identified complexes, [Ln₃L₂H₋₆]³⁺ and [Ln₂Ln'L₂H₋₆]³⁺, described above. In addition to these resonances, the six proton signals of [NdSmEuL₂H₋₆]³⁺ were detected and assigned *via* a ¹H-¹H COSY experiment. A ¹H-¹³C HMQC experiment gave the assignment of the six carbons (see Table 3 and Scheme 2 for nucleus labelling).

Heteronuclear complexes have lower symmetry (C_{2v} or C_s) than the homotrinnuclear species (D_{3h}), and intramolecular

dynamic processes in solution could therefore be investigated by using two-dimensional exchange spectroscopy (EXSY). At 400 MHz and 298 K, no exchange correlations are detected in the EXSY spectra. The proton paramagnetic relaxation times for the trinuclear complexes containing neodymium, samarium, and europium are quite small ($10 < T_1 < 150$ ms), and therefore the mixing time (τ_m) used in the EXSY sequence cannot exceed 20 ms. During that short mixing time, no magnetization exchange could be evidenced because the characteristic time

Table 3 Proton (δ^H) and carbon (δ^C) chemical shifts of the heterotrinnuclear complex $[\text{NdSmEuL}_2\text{H}_{-6}]^{3+}$ in D_2O at 298 K

	δ^H/ppm	δ^C/ppm
$\chi_{\text{Eu(Nd,Sm)}}^{\text{N}}$	-12.8	92
$\chi_{\text{Sm(Nd,Eu)}}^{\text{N}}$	4.2	57
$\chi_{\text{Nd(Sm,Eu)}}^{\text{N}}$	12.7	31
$\chi_{\text{Nd,Sm(Eu)}}^{\text{O}}$	12.4	62
$\chi_{\text{Nd,Eu(Sm)}}^{\text{O}}$	1.1	98
$\chi_{\text{Sm,Eu(Nd)}}^{\text{O}}$	-4.0	123

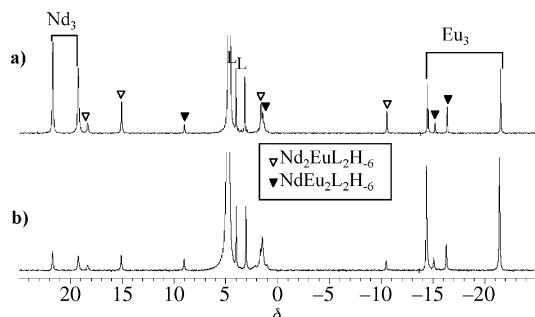


Fig. 3 400 MHz ^1H NMR spectra of Nd–Eu–TACl samples in D_2O at pD 8 and 298 K for Nd : Eu : TACl ratios: (a) 2 : 1 : 2; (b) 1 : 2 : 2.

constant of exchange ($\tau_{\text{ex}} = 1/k_{\text{ex}}$, k_{ex} being the pseudo-first-order rate constant for exchange) is too long in comparison to the mixing time τ_{m} . By working at higher temperature, two effects which favour the observation of exchange correlations combine. Firstly, τ_{ex} becomes shorter because the kinetics of exchange are speeded up. Secondly, the paramagnetic relaxation times are longer, essentially due to the T^2 dependence of the Curie contribution⁴⁹ and the mixing time could thus be lengthened to 70 ms, allowing the detection of exchange correlation at 363 K. The EXSY spectrum registered at 400 MHz and 363 K on a sample containing the three salts and TACl in the ratio 1 : 1 : 1 : 3 is presented in Fig. 4. Some nuclear

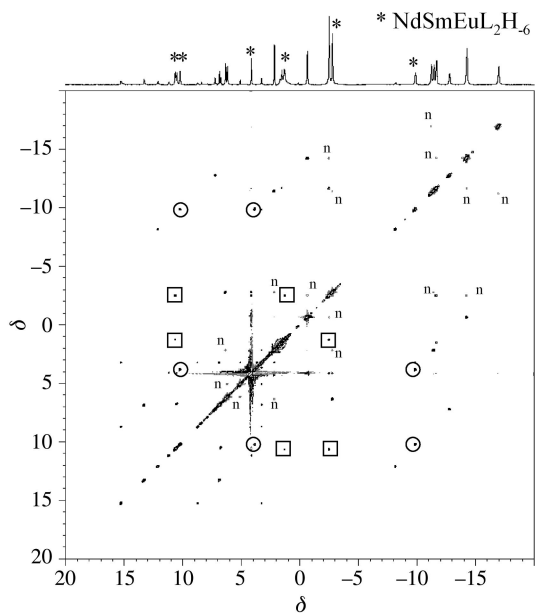


Fig. 4 400 MHz EXSY spectrum of a Nd–Sm–Eu–TACl (1 : 1 : 1 : 3) sample in D_2O at pD 8 and 363 K ($\tau_{\text{m}} = 70$ ms). \circ : H^{N} exchange correlations in the $\text{NdSmEuL}_2\text{H}_{-6}$ complex; \square : H^{O} exchange correlations in the $\text{NdSmEuL}_2\text{H}_{-6}$ complex; n: nOe effects.

Overhauser effects (nOe) are detected in the complexes whose protons don't relax too fast, that is complexes that don't contain the neodymium cation. Weak exchange correlations are detected between the free ligand and the complexes, corresponding to complexation decomplexation processes. No

exchange correlations are seen between protons belonging to two different complexes, whereas strong ones are detected between protons belonging to the same complex. They are symbolized by squares and circles in Fig. 4 for H^{O} and H^{N} , respectively in the $[\text{NdSmEuL}_2\text{H}_{-6}]^{3+}$ complex. These latter correlations are indicative of an intramolecular rotation of the ligand with respect to the lanthanide ions that moves, for instance, a proton H^{N} , which is close to a europium cation, to a position close to a neodymium ion. Similar 2D-EXSY spectra have been obtained with samples containing the ligand and only two salts.

The evolution of the proton NMR spectra as a function of pD allows estimation of the relative stabilities of the trinuclear complexes, since the more stable a complex is, the lower its formation pH. Samples containing Nd, Sm, Eu, and TACl(HCl)₃ in the ratio 1 : 1 : 1 : 3 have been titrated with sodium deuteroxide and some of the spectra registered are shown in Fig. 5. The formation of the complexes can be clearly seen when

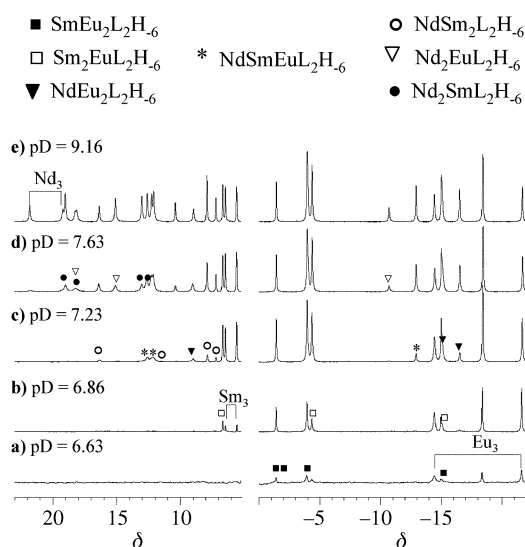


Fig. 5 500 MHz ^1H NMR spectra of a sample containing Nd, Sm, Eu, and TACl(HCl)₃ in the ratio 1 : 1 : 1 : 3, in D_2O as a function of pD.

the pD is increased. Initially, when no sodium deuteroxide is added, only 2 signals at 3.68 and 4.41 ppm due to the protonated ligand are detected. Then, when base is added, the signals from the paramagnetic complexes start to grow. The most stable species, containing europium and samarium, are detected at the lowest pD. $\text{Eu}_3\text{L}_2\text{H}_{-6}$ and $\text{Eu}_2\text{SmL}_2\text{H}_{-6}$ appear first at pD = 6.63 [Fig. 5(a)], then $\text{EuSm}_2\text{L}_2\text{H}_{-6}$ and $\text{Sm}_3\text{L}_2\text{H}_{-6}$ are detected at pD = 6.86 [Fig. 5(b)]. Signals due to $\text{NdEu}_2\text{L}_2\text{H}_{-6}$ and $\text{NdSmEuL}_2\text{H}_{-6}$ begin to appear at pD = 7.09 closely followed by $\text{NdSm}_2\text{L}_2\text{H}_{-6}$ at pD = 7.23 [Fig. 5(c)]. The last complexes to be detected are those containing two or three neodymium cations; $\text{Nd}_2\text{SmL}_2\text{H}_{-6}$ and $\text{Nd}_2\text{EuL}_2\text{H}_{-6}$ at pD = 7.63 [Fig. 5(d)], and finally the least stable $\text{Nd}_3\text{L}_2\text{H}_{-6}$ complex at pD = 8.20. The order of appearance of the homotrinnuclear species as the pD increases is consistent with their formation constants, β_{32-6} ($\text{Nd}_3 < \text{Sm}_3 < \text{Eu}_3$).⁴³ From these experiments, it is possible to roughly classify the trinuclear complexes according to their thermodynamic stabilities in the order $\text{Nd}_3 < \text{Nd}_2\text{Sm} \sim \text{Nd}_2\text{Eu} < \text{NdSm}_2 < \text{NdSmEu} \sim \text{NdEu}_2 < \text{Sm}_3 \sim \text{Sm}_2\text{Eu} < \text{Eu}_3 \sim \text{SmEu}_2$.

Thermodynamic constant determination

The formation constants of the homotrinnuclear complexes have previously been determined by potentiometric titrations; $\log\beta_{32-6}$, according to equilibrium 1, is -24.1, -19.3, and -17.9 for $\text{Nd}_3\text{L}_2\text{H}_{-6}$, $\text{Sm}_3\text{L}_2\text{H}_{-6}$, and $\text{Eu}_3\text{L}_2\text{H}_{-6}$, respectively.⁴³ Similar experiments were run with a mixture of two lanthanide ions in order to calculate the stability constants of the heterotrinnuclear species identified by ES-MS and solution NMR.

Samples containing the protonated ligand $L(HCl)_3$ and two lanthanide chloride salts in the $Ln : Ln' : L$ ratios, 2 : 1 : 2 and 1 : 2 : 2 were titrated with potassium hydroxide at 298 K and in 0.1 mol L^{-1} KCl for the three couples Nd–Eu, Nd–Sm, and Sm–Eu. The experimental curves for the Nd–Eu system are shown in Fig. 6; the formation of the complexes is character-

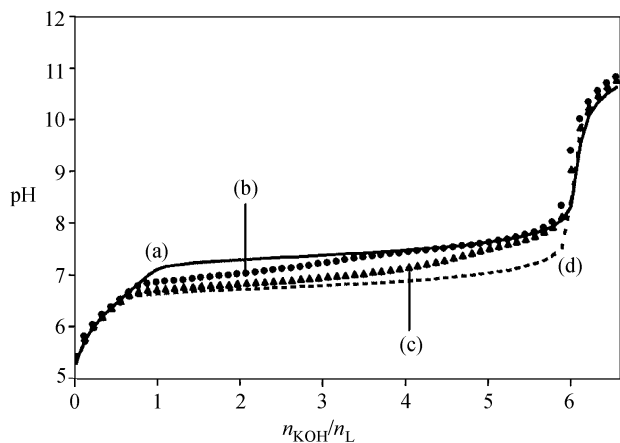


Fig. 6 Alkalimetric titrations of aqueous solutions containing 10^{-3} mol L^{-1} $L(HCl)_3$ and different Nd : Eu ratios at 298 K and 0.1 mol L^{-1} KCl. Nd : Eu : L ratios: (a) 3 : 0 : 2, (b) 2 : 1 : 2, (c) 1 : 2 : 2, (d) 0 : 3 : 2.

ized by the low slope of the curve in the pH range 6 to 8, which is very sensitive to the nature of the trinuclear species formed. The experimental data were analysed using the program Hyperquad 2000.⁵⁰ The ligand protonation constants and the homotrimeric complex formation constants ($\log\beta_{32-6}$) were fixed to the values previously calculated, and the stability constants of the 2 heterotrimeric complexes, β_{212-6} according to equilibrium 2, were refined in the pH range 5 to 8.

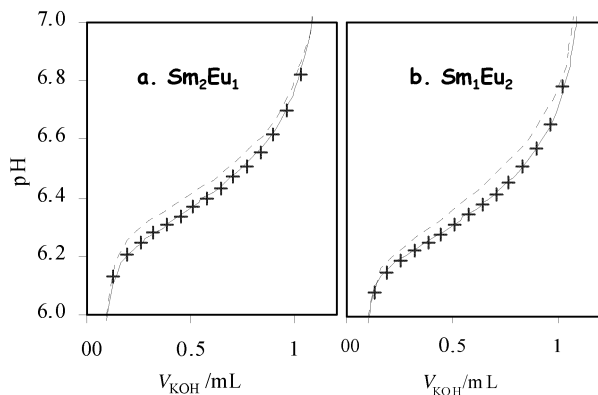
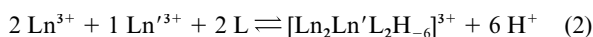


Fig. 7 Experimental and calculated titration curves for Sm–Eu–L samples: (a) 2 : 1 : 2; (b) 1 : 2 : 2. Crosses are experimental points. Broken lines are calculated data⁵⁰ considering only homotrimeric complex stability constants. Full lines are calculated data⁵⁰ considering homo- and heterotrimeric complex stability constants.

Fig. 7 shows the comparison between experimental points and simulated titrations in the program HYSS⁵⁰ in the significant pH range for the Sm–Eu system. The simulated curves obtained considering only the homotrimeric complex formation constants (broken lines) show a large deviation from the experimental points. Even for these two cations, which are very similar (europium is next to samarium in the periodic table) and whose homotrimeric complex stability constants are very close, it is obvious that the heteronuclear complexes have to be considered to simulate the experimental data. The heterotrimeric complex stability constants have been determined for the six heterometallic species and are given in Table 4. Except

Table 4 Stability constants of trinuclear lanthanide complexes of TACl in water at 298 K and $I = 0.1$ mol L^{-1} (KCl): $[Ln_3L_2H_{-6}]^{3+}$, $\log\beta_{32-6} = [Ln_3L_2H_{-6}^{3+}][H^+]^6/[Ln^{3+}]^3[L]^2$; $[Ln_2Ln'L_2H_{-6}]^{3+}$, $\log\beta_{212-6} = [Ln_2Ln'L_2H_{-6}^{3+}][H^+]^6/[Ln^{3+}]^2[Ln'^{3+}][L]^2$; $E = -RT(\ln\beta - \ln\beta_{stat})$

Complex	$\log\beta_{212-6}$	$\log\beta^{stat}$	$E/kJ mol^{-1}$
$Nd_3L_2H_{-6}$	-24.09 ± 0.01		
$Sm_3L_2H_{-6}$	-19.29 ± 0.02		
$Eu_3L_2H_{-6}$	-17.93 ± 0.01		
$Nd_2SmL_2H_{-6}$	-22.4 ± 0.3	-22.0	$+2.3$
$Nd_2EuL_2H_{-6}$	-21.7 ± 0.2	-21.5	—
$NdSm_2L_2H_{-6}$	-20.5 ± 0.1	-20.4	—
$NdEu_2L_2H_{-6}$	-20.1 ± 0.5	-19.5	$+3.4$
$Sm_2EuL_2H_{-6}$	-18.8 ± 0.3	-18.4	$+2.3$
$SmEu_2L_2H_{-6}$	-17.68 ± 0.06	-17.91	-1.3
$NdSmEuL_2H_{-6}$	-20.1 ± 0.5	-19.7	—

for the $SmEu_2L_2H_{-6}$ complex, the heavier the three lanthanide cations inserted in the structure are, the more stable the species is. These thermodynamic stability constants measured by potentiometry are totally in accordance with the stability scale determined by 1H NMR titration. Since the $NdSmEuL_2H_{-6}$ complex is formed in the same pH range as $NdEu_2L_2H_{-6}$, as shown by NMR, the logarithm of its stability constant can therefore be expected to be close to -20.1 .

The knowledge of every stability constant affords a predictive quantitative model for the formation of heterotrimeric lanthanide complexes of TACl. Fig. 8 and 9 show the speciation

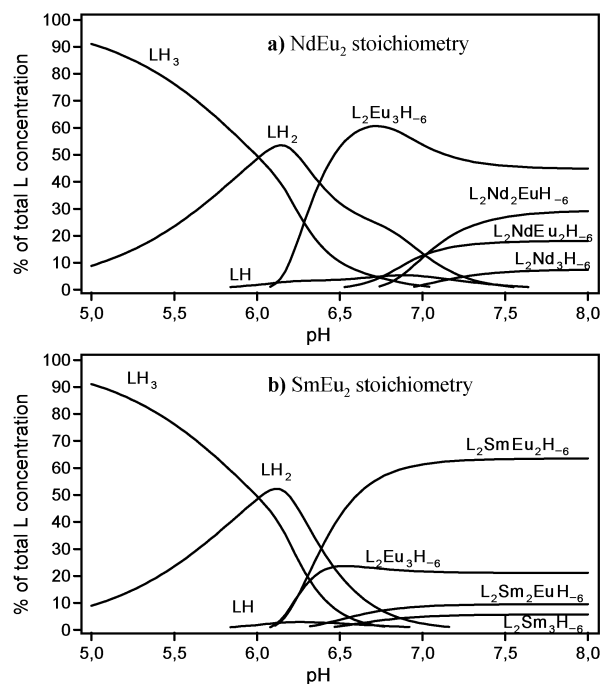


Fig. 8 Species distribution in equilibrated aqueous solutions with $[L]_0 = 0.001$ mol L^{-1} , $[Eu]_0 = 0.001$ mol L^{-1} , and $[Ln]_0 = 0.0005$ mol L^{-1} : (a) $Ln = Nd$, (b) $Ln = Sm$. The stability constants listed in Table 4 were used for the calculations.

of the different trinuclear complexes present in aqueous solution, deduced from potentiometry measurements, with respect to external conditions such as stoichiometry, concentrations, and pH. As evidenced in Fig. 8, the evolution of the complex distributions as a function of pH is very dependent on the lanthanide couple studied. For the Nd–Eu system, the most stable Eu_3 complex is formed at pH 6.1 and is consumed at higher pH to allow the formation of the two heterotrimeric species, $NdEu_2$ and Nd_2Eu . In the second case, for the Sm–Eu couple [Fig. 8(b)], the $SmEu_2$ heterometallic complex, which is slightly more stable than Eu_3 , is formed first and remains preponderant during the whole titration. The distributions can

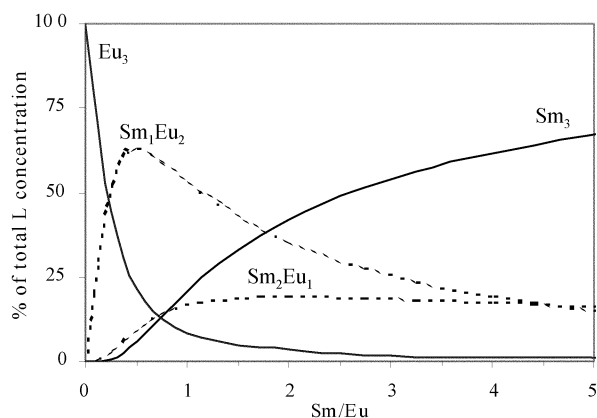


Fig. 9 Species distribution in an equilibrated aqueous solution at pH = 8 with $[L]_0 = 0.001 \text{ mol L}^{-1}$ and $[Eu]_0 + [Sm]_0 = 0.0015 \text{ mol L}^{-1}$.

also be predicted as a function of the ratio of the two metals, as shown in Fig. 9 for the Sm–Eu couple at pH 8. It appears that SmEu_2 complex formation is particularly favoured, it represents more than 60% of the ligand in solution when $\text{Sm} : \text{Eu} = 1 : 2$.

In order to selectively produce heterotrimetallic complexes, it is essential to detect species whose distributions deviate from the statistics. The thermodynamic stability constants obtained under statistical conditions may be predicted according to a very simple model if the two ligands are considered as a ‘cluster’, see eqn. 3. The term $\log(s)$ comes from statistical entropic considerations that take into account the number of different arrangements allowed in heterotrimetallic complexes compared to homotrimetallic species.

$$\log(\beta_{\text{LnLnLnLnLnLn}}^{\text{stat}}) = \frac{1}{3}[\log(\beta_{\text{Ln}}^{\text{Ln}}) + \log(\beta_{\text{Ln'}}^{\text{Ln'}}) + \log(\beta_{\text{Ln''}}^{\text{Ln''}})] + \log(s) \quad (3)$$

$$s = 3 \text{ if } \text{Ln} = \text{Ln}' \neq \text{Ln}'' \quad (4)$$

$$s = 6 \text{ if } \text{Ln} \neq \text{Ln}' \neq \text{Ln}'' \quad (5)$$

The stability constants calculated according to this simple model are given in Table 4 and the deviations from the expected statistics are expressed in kJ mol^{-1} when the difference between the calculated and the measured stability constants were significant (see Table 4). These deviations are small, between -1 and $+3 \text{ kJ mol}^{-1}$, signifying that the distributions are close to the statistical ones. The formation of heterotrimetallic complexes of TACI incorporating the very similar Nd, Sm, and Eu trivalent cations is globally unfavourable, except for the SmEu_2 species, which is stabilized by 1 kJ mol^{-1} in comparison to the statistics. These results indicate that there is only little ionic recognition between the metallic sites, when the lanthanide cations are close in the 4f series.

Conclusion

The 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol gives uncommon trinuclear complexes of trivalent lanthanide cations, $[\text{Ln}_3\text{L}_2\text{H}_6]^{3+}$. In this work, the capability of this cyclohexanic ligand to form rare-earth heterotrimetallic complexes in solution has been demonstrated. In aqueous solutions containing different 4f cations, a mixture of homo- and heterotrimetallic complexes is indeed evidenced by electrospray ionization mass spectrometry and paramagnetic solution NMR. The potentiometric analysis of the Nd–Sm–Eu–TACI system has shown that the heteronuclear complex stabilities are in between those of the corresponding homotrimetallic complexes. Globally, the heavier the three metals are, the more stable the trinuclear complex is. The complex simultaneously incorporating three different cations, $[\text{NdSmEuL}_2\text{H}_6]^{3+}$, is also formed in solution, as

evidenced by its typical ^1H and ^{13}C NMR chemical shifts. Its stability is close to that of the $[\text{NdEu}_2\text{L}_2\text{H}_6]^{3+}$ species, as evidenced by ^1H NMR titrations as a function of pH.

The combination of complementary experimental methods, like electrospray ionization mass spectrometry, solution NMR, and potentiometry, affords a predictive quantitative model. It is now possible to anticipate appropriate conditions, for instance initial stoichiometries and pH, that will favour formation of one specific trinuclear complex. Comparison of the stability constants measured by potentiometry with the statistical introduction of different lanthanide cations in the heterotrimetallic complexes allows the detection of species whose distributions deviate from the statistics. For the trio studied in this work, Nd–Sm–Eu, only small significant deviations are observed. The ionic recognition between the metallic sites is thus very limited, probably because these three lanthanide cations are close in the 4f series, and hence very similar. We are presently studying other Ln–Ln'–TACI systems to see if the results obtained with the Nd–Sm–Eu trio can be generalized. The effects of lanthanide position in the series on heteronuclear complex stabilities and structures are currently under investigation.

Experimental

Materials

Lanthanide chlorides and triflates were commercially available materials of highest possible quality. 1,3,5-Triamino-1,3,5-trideoxy-*cis*-inositol (TACI) and 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol trihydrochloride $[\text{TACI}(\text{HCl})_3]$ were synthesized according to published procedures.⁵¹

Mass spectrometry

The mass spectra were acquired on an LCQ-ion trap (Finnigan-Thermoquest, San Jose, CA, USA) equipped with an electrospray source. Electrospray full scan spectra in the range m/z 100–1300 were obtained by infusion through fused silica tubing at $2\text{--}10 \mu\text{L min}^{-1}$. The solutions were analysed in the positive mode. The LCQ calibration (m/z 50–2000) was achieved according to the standard calibration procedure from the manufacturer (mixture of caffeine, MRFA and Ultramark 1621). The temperature of the heated capillary of the LCQ was set to $170 \text{ }^\circ\text{C}$, the ion-spray voltage was in the range of 1–6 kV with an injection time of 5–200 ms. Samples for ES-MS were prepared by dissolving the ligand ($10^{-3} \text{ mol L}^{-1}$) and the lanthanide triflate salts in water. pH was then adjusted with triethylamine (pH = 8).

Potentiometry

All titrant solutions were prepared using water purified by passage through a Millipore Milli-Q reverse-osmosis cartridge system (resistivity $18 \text{ M}\Omega \text{ cm}$). Carbonate-free 0.1 mol L^{-1} KOH and 0.1 M HCl were prepared from Fisher Chemicals concentrates. Potentiometric titrations were performed in 0.1 mol L^{-1} aqueous KCl under an argon atmosphere, the temperature was controlled to $\pm 0.1 \text{ }^\circ\text{C}$ with a circulating water bath. The p[H] ($\text{p[H]} = -\log[\text{H}^+]$, concentration in molarity) was measured in each titration with a combined pH glass electrode (Metrohm) filled with 3 M KCl and the titrant addition was automated by use of a 751 GPD titrino (Metrohm). The electrode was calibrated in hydrogen ion concentration by titration of HCl with KOH in 0.1 mol L^{-1} KCl.⁵² A plot of meter reading versus p[H] allows the determination of the electrode standard potential (E°) and the slope factor (f). Continuous potentiometric titrations with KOH 0.1 mol L^{-1} were conducted on 20 mL of aqueous solutions containing $10^{-3} \text{ mol L}^{-1}$ $\text{TACI}(\text{HCl})_3$, $10^{-3} \text{ mol L}^{-1}$ LnCl_3 , $0.5 \times 10^{-3} \text{ mol L}^{-1}$ $\text{Ln}'\text{Cl}_3$ and 0.1 mol L^{-1} KCl. Ligand concentrations were determined by potentiometric titration, and the metal concentrations by EDTA titrations

using xylenol orange indicator. Back titration with 0.1 mol L⁻¹ HCl was performed after each experiment to check whether equilibration had been achieved. 100 points were measured, with a 5 min delay between the measurement of each point.

Experimental data were refined using the computer program Hyperquad 2000.^{50,53} All equilibrium constants are concentration quotients rather than activities. The ionic product of water at 25 °C and 0.1 mol L⁻¹ ionic strength is $pK_w = 13.78$.⁵⁴ For the determination of heteronuclear complex stability constants, $\beta_{wxyz} = [\text{Ln}_w \text{Ln}'_x \text{L}_y \text{H}_z] / [\text{Ln}]^w [\text{Ln}']^x [\text{L}]^y [\text{H}]^z$, fixed values were used for pK_w , ligand acidity constants ($pK_{a_1} = 6.01$, $pK_{a_2} = 7.43$, $pK_{a_3} = 8.84$), homotriconuclear complex stability constants,⁴³ and total concentrations of metal, ligand, and acid. All values and errors (one standard deviation) reported represent the average of at least three independent experiments.

NMR spectroscopy

Samples for NMR spectroscopy were prepared by dissolving the ligand (10^{-2} to 10^{-3} mol L⁻¹) and the lanthanide triflate salt in 700 μ L of deuterium oxide (Euriso-top, 99.9 atom% D). pD was then adjusted with a sodium deuterioxide solution ($pD = pH_{\text{read}} + 0.41$).⁵⁵ NMR spectra were recorded either on AVANCE 400, 500 Bruker, or MERCURY 400 Varian spectrometers. The methyl protons of DSS [3-(trimethylsilyl)-1-propanesulfonic acid] were used as an external reference for the ¹H and ¹³C spectra recorded in D₂O. Longitudinal relaxation rates were measured using a non-selective inversion recovery pulse sequence, and T_1 values were obtained from a three-parameter fit of the data to an exponential recovery function. ¹H–¹H COSY and ¹H–¹³C HMQC spectra were recorded in magnitude mode using 256 increments and recycle delays optimized for fast-relaxing species. ¹H–¹H EXSY spectra were registered in phase sensitive mode, using a mixing time of 70 ms at 363 K and 256 increments.

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