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# Metal-Mediated Interactions in Homo- and Heterobimetallic Edifices with Lanthanides: A Study in Solution

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† This work is dedicated to the memory of Anne-Marie Albrecht-Gary, deceased.

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Dr M. Elhabiri, Dr Boris Le Guennic, Prof. A. Shanzer, Dr A.-M. Albrecht-Gary

## Abstract

We report here on the coordination properties of a series of lanthanide cations (Ln = La, Nd, Eu, Tb, Er) with a tripodal homoditopic ligand **L**, which is bearing three diamido-dihydroxamate arms anchored on a tertiary amine. The complexes of **L** with lanthanides were studied in a MeOH/H<sub>2</sub>O (80/20 by weight) solvent and a marked size-discriminating effect depending on the intramolecular interactions was observed in the tripodal dinuclear lanthanide edifice. Positive cooperative effects favour the formation of the bimetallic **LLn<sub>2</sub>** complexes compared with the monometallic analogues for the heavier lanthanide cations (Eu, Tb, Er), while the lighter ones (La, Nd) show a decrease of cooperative interactions in the corresponding bimetallic species. Moreover, increased levels of heterobimetallic complexes are detected for Ln(III) pairs containing a lighter Ln(III) ion and a heavier one. In contrast with the adjunctive ligand exchange reported for **LFe<sub>2</sub>** and CDTA, the corresponding substitution reaction for **LLn<sub>2</sub>** occurs according to a disjunctive mechanism. Our work thus highlights the importance of the balance between the rigidity of a tripodal structure and the flexibility of the side arms to accommodate two trivalent cations in a supramolecular ensemble.

## Introduction

Metal recognition processes have generated novel nanodevices with predetermined magnetic, photophysical and/or physico-chemical properties.<sup>1-3</sup> Helical arrangements containing *d*-metal cations such as Cu(I),<sup>4-9</sup> Ag(I),<sup>10</sup> Co(II),<sup>11</sup> Ni(II),<sup>12,13</sup> Ru(II)<sup>14</sup> or Fe(II)<sup>15,16</sup> received a special attention as testified by the considerable amount of studies dedicated to double- or triple-stranded helicates<sup>17-19</sup> with bipyridine, terpyridine and benzimidazolylpyridine- or catechol-containing ligands. In addition, other examples of metallofoldamers and supramolecular systems were previously discussed.<sup>20,21</sup>

Numerous supramolecular complexes were also prepared with trivalent lanthanides(III).<sup>22-31</sup> The specific magnetic and luminescent properties of these devices were implemented in biochemical and analytical applications such as time-resolved fluoroimmunoassays,<sup>32</sup> MRI contrast agents<sup>33</sup> or efficient luminescent sensors with novel supramolecular topographies, including triple-stranded helicates.<sup>34-36</sup> A considerable effort also resulted in the preparation and characterisation of several heterometallic f-f complexes, where two different functional centres are combined within a single probe.<sup>37-39</sup> Interestingly, a selective binding of lanthanides can be also achieved by designing suitable bio-sourced scaffolds.<sup>40</sup> Over the decade, several discrete heterometallic systems have been designed for light up-conversion purposes. Starting from bi- and trinuclear helicates,<sup>41</sup> nona-nuclear lanthanide molecular complexes with very promising up-conversion efficiencies have been recently reported in this context.<sup>42</sup>

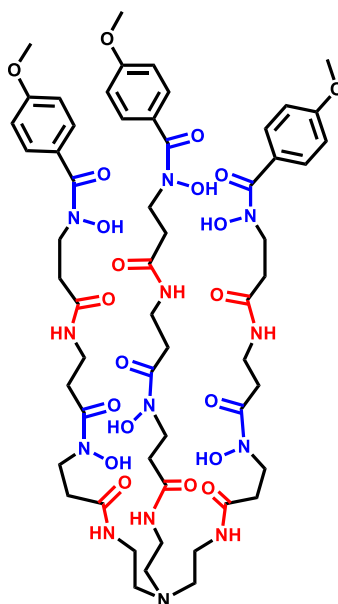
Lanthanide complexes with tripodal ligands were lately reviewed in terms of structural and thermodynamic properties.<sup>43</sup> In addition to a number of monometallic podands,<sup>43,44</sup> there are few preorganized tripodal ligands designed for complexing two lanthanide cations in a helical C<sub>3</sub>-symmetrical fashion. Indeed, homo- and heterometallic dinuclear podates with a benzimidazolylpyridine binding site were obtained and characterized by Piguet et al.<sup>45</sup> An

analogous  $C_3$ -symmetrical ligand was also prepared by some of us.<sup>46</sup> However, a short anchor does not allow the formation of the targeted dinuclear podand and an tetrahedral octanuclear complex with four helical portions was isolated instead. In several cases, Ln(III) complexes with tripodal ligands exhibit also different thermodynamic stabilities along the series that potentially allows to fine-tune the binding selectivity.<sup>47</sup> While flexible tripodal ligands will stabilize different Ln(III) complexes through “induced fit”, more rigid macrocyclic ligands may provide higher specificity for a particular cation.<sup>48</sup>

Previously, tripodal diferric helicates with a fine-tuning of the intramolecular interactions between the two trivalent cations were reported.<sup>49-51</sup> These ligands are based on hydroxamate coordination sites and form helical diferric complexes. In this context, we have decided to examine the ability of these hydroxamate ligands for binding lanthanide(III) cations instead iron(III). To satisfy the coordination preferences of lanthanide(III) cations, the coordination by hydroxamate moieties can be indeed completed by the neighbouring amide carbonyls on each strand. Despite a more demanding initial synthetic effort to access such tripodal ligands where the ligating chains are covalently linked to a common anchor, the number of possible complex species is drastically reduced.<sup>43</sup> Moreover, it is expected that this ligand preorganization will increase the stability and inertness of resulting  $C_3$ -symmetrical edifices. Comparing with the Piguet’s tripodal ligand, the charge of trivalent lanthanide(III) cations is here compensated by the negatively charged and “hard” hydroxamate moieties, which allows the investigation of resulting complexes in aqueous solvents.

In this contribution, a fruitful combination of analytical methods (ESI-MS, UV-visible absorption spectrophotometry) and kinetic techniques (stopped-flow) has been used to investigate the interactions between two lanthanide(III) cations with **L** (Figure 1) along the lanthanide series (La, Nd, Eu, Tb, Er). Thorough analysis of the thermodynamic data is performed to reveal cooperativity effects along the Ln(III) series as the result of the

preorganization of the binding sites within ligand **L**. These effects are particularly interesting to rationalize the formation of the heterobimetallic complexes, where a spontaneous distribution of metal ions within these edifices deviate from statistics. We also carefully investigated the reactivity of the tripodal bimetallic complexes  $\text{LLn}_2$  (i) in the presence of a competing ligand (CDTA) and (ii) in large excess of metallic cations leading to the less organized trimetallic lanthanide(III) "clover-leaf" complexes.



**Figure 1.** Chemical formula of the tripodal hydroxamate ligand **L**.

## Results

**Electrospray mass spectra.** ESI-MS measurements were first carried out at various  $[\text{Ln}]_{\text{tot}}/[\text{L}]_{\text{tot}}$  ratios. For the whole range of Ln(III) cations used in this study (Ln = La, Nd, Eu, Tb, Er), three complexes  $\text{LLn}$ ,  $\text{LLn}_2$  and  $\text{LLn}_3$  have been clearly evidenced. As a typical example, the electrospray mass spectra measured for three different  $[\text{Eu}]_{\text{tot}}/[\text{L}]_{\text{tot}}$  ratios are shown in

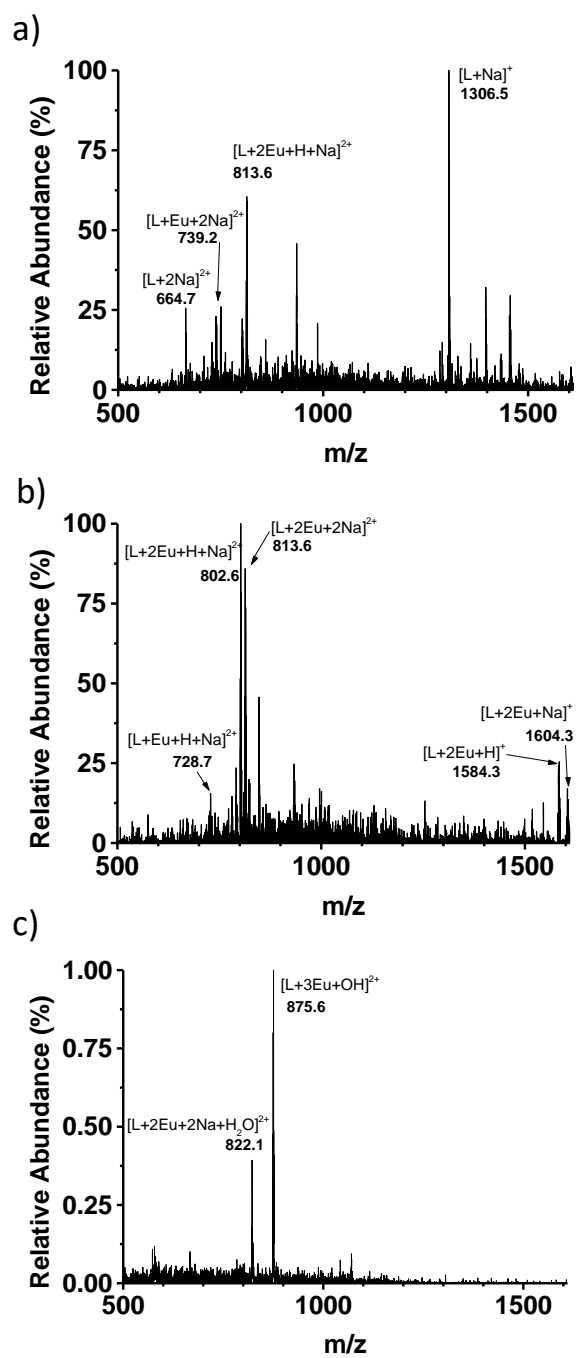
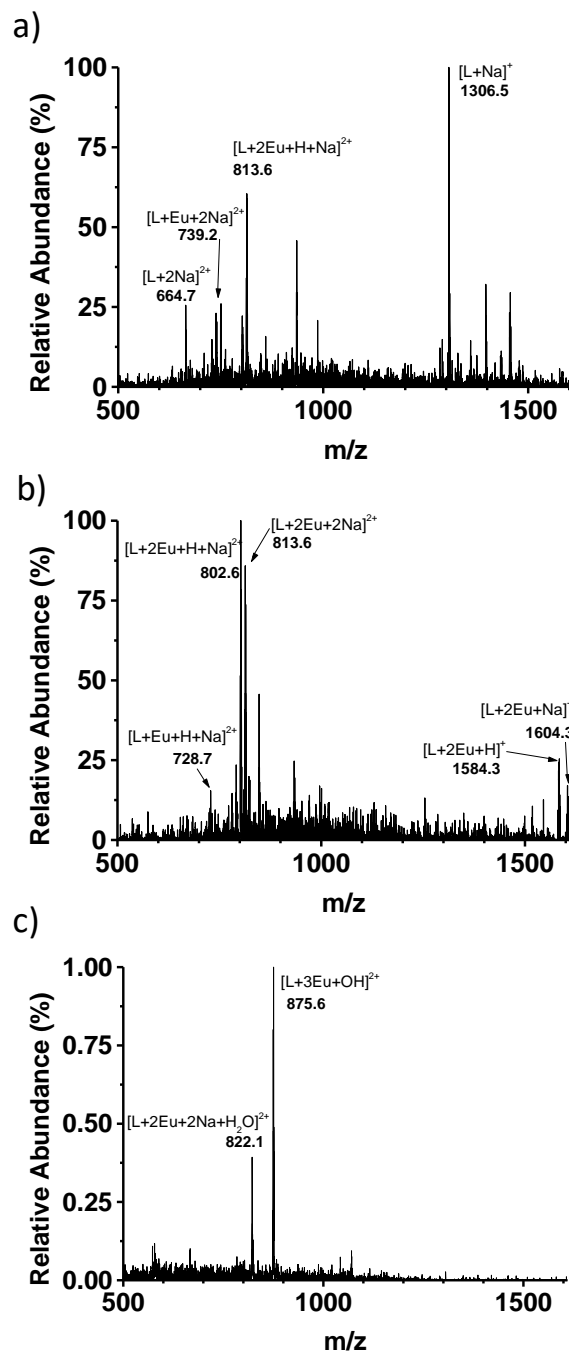


Figure 2, the spectra of other Ln(III) are given in the Supporting Information (Figure S1).





**Figure 2.** Electro spray mass spectra.  $[\mathbf{L}]_{\text{tot}} = 1.85 \times 10^{-5} \text{ M}$ ; (a)  $[\text{Eu}]_{\text{tot}}/[\mathbf{L}]_{\text{tot}} = 1.0$ ; (b)  $[\text{Eu}]_{\text{tot}}/[\mathbf{L}]_{\text{tot}} = 2.0$  and (c)  $[\text{Eu}]_{\text{tot}}/[\mathbf{L}]_{\text{tot}} = 5.0$ . Solvent: methanol/water (80/20 by weight); positive mode; Skimmer = 40 V.

Pseudomolecular ions of the different species observed with  $\mathbf{L}$  and Ln(III) ions (Ln(III) = La, Nd, Tb or Er) in the electro spray mass spectra are collected in Table 1. In contrast to ferric

complexes<sup>51</sup> formed with **L**, fragmentation processes did not occur under our experimental conditions.



**Table 1.** Intensity Maxima of the Major L-Ln(III) Complexes and Adduct Ions Observed by ESI-MS.<sup>a</sup>

Lanthanides	La		Nd		Eu		Tb		Er	
Molecular ions	m/z observed	m/z calculated	m/z observed	m/z calculated	m/z observed	m/z calculated	m/z observed	m/z calculated	m/z observed	m/z calculated
[LH <sub>6</sub> + H + Na] <sup>2+</sup>	<b>653.7</b>	653.8								
[LH <sub>6</sub> + 2Na] <sup>2+</sup>	<b>664.7</b>	664.8	<b>664.7</b>	664.8	<b>664.8</b>	664.8	<b>664.7</b>	664.8		
[LH <sub>6</sub> + Na] <sup>+</sup>	<b>1306.5</b>	1306.6	<b>1306.5</b>	1306.6	<b>1306.5</b>	1306.6	<b>1306.4</b>	1306.6		
[LH <sub>3</sub> Ln + 2H] <sup>2+</sup>	<b>710.2</b>	710.7			<b>717.9</b>	717.7	<b>720.9</b>	721.2		
[LH <sub>3</sub> Ln + H + Na] <sup>2+</sup>	<b>722.2</b>	721.7	<b>724.4</b>	724.2	<b>728.7</b>	728.7	<b>731.7</b>	731.7		
[LH <sub>3</sub> Ln + 2Na] <sup>2+</sup>	<b>732.7</b>	732.7			<b>739.2</b>	739.7	<b>742.7</b>	742.7		
[LH <sub>3</sub> Ln + H] <sup>+</sup>	<b>1420.5</b>	1420.5								
[LH <sub>3</sub> Ln + Na] <sup>+</sup>	<b>1442.5</b>	1442.4			<b>1456.4</b>	1456.5	<b>1462.3</b>	1462.5		
[LLn <sub>2</sub> + 2H] <sup>2+</sup>	<b>778.6</b>	778.7	<b>783.8</b>	783.7	<b>791.6</b>	791.7	<b>799.1</b>	798.7	<b>806.8</b>	806.7
[LLn <sub>2</sub> + H + Na] <sup>2+</sup>	<b>789.7</b>	789.7	<b>794.7</b>	794.7	<b>802.6</b>	802.7	<b>809.6</b>	809.7	<b>818.2</b>	817.7
[LLn <sub>2</sub> + 2Na] <sup>2+</sup>	<b>800.6</b>	800.7	<b>805.7</b>	805.7	<b>813.6</b>	813.7	<b>820.6</b>	820.7	<b>828.7</b>	828.7
[LLn <sub>2</sub> + 2Na + H <sub>2</sub> O] <sup>2+</sup>	<b>809.1</b>	809.7	<b>814.7</b>	814.7	<b>822.1</b>	822.7				
[LLn <sub>2</sub> + H] <sup>+</sup>	<b>1556.4</b>	1556.3	<b>1566.5</b>	1566.3	<b>1584.3</b>	1584.4	<b>1596.4</b>	1596.4	<b>1612.5</b>	1612.4
[LLn <sub>2</sub> + Na] <sup>+</sup>	<b>1578.4</b>	1578.3	<b>1588.4</b>	1588.3	<b>1604.3</b>	1604.4	<b>1618.3</b>	1618.4	<b>1634.4</b>	1634.4

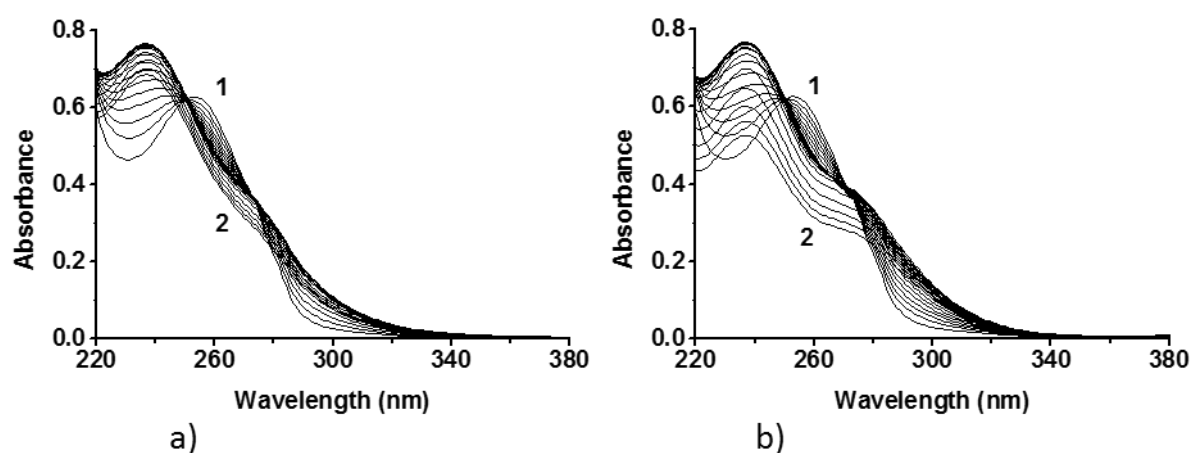
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$[\text{LLn}_3]^{3+}$	<b>564.7</b>	564.7	<b>569.8</b>	569.8						
$[\text{LLn}_3 - \text{H}]^{2+}$									<b>889.2</b>	889.2
$[\text{LLn}_3 + \text{OH}]^{2+}$	<b>855.6</b>	855.6	<b>863.7</b>	863.7	<b>875.6</b>	875.6	<b>885.6</b>	885.6	<b>898.2</b>	898.2
$[\text{LLn}_3 + \text{ClO}_4]^{2+}$	<b>896.6</b>	896.6	<b>905.2</b>	905.1						
$[\text{LLn}_3 + \text{OH} + \text{ClO}_4]^+$							<b>1870.3</b>	1870.2	<b>1895.2</b>	1895.3

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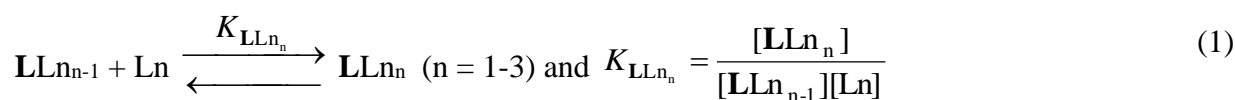
(a) Solvent: methanol/water (80/20 by weight); positive mode; skimmer = 40 V; major signals in bold.

**Thermodynamics and spectrophotometry.** Thermodynamic studies were then performed in methanol/water (80/20 by weight) at pH = 6.35.<sup>51</sup> In order to determine the stability constants of Ln(III) (Ln = La, Nd, Eu, Tb, Er) complexes with **L**, absorption spectrophotometric titrations of the polytopic ligand **L** were carried out for Ln/**L** ratios in the range 0-50. The corresponding variations of the absorption spectra are given for Ln = Eu and Er in Figure 3 and for La, Nd and Tb in Figure S2.



**Figure 3.** Spectrophotometric titrations of **L** ( $9.01 \times 10^{-6}$  M) with Ln(III). (a) Ln = Eu; (1)  $[\text{Eu}]_{\text{tot}}/[\text{L}]_{\text{tot}} = 0$ ; (2)  $[\text{Eu}]_{\text{tot}}/[\text{L}]_{\text{tot}} = 50.3$ ; (b) Ln = Er; (1)  $[\text{Er}]_{\text{tot}}/[\text{L}]_{\text{tot}} = 0$ ; (2)  $[\text{Er}]_{\text{tot}}/[\text{L}]_{\text{tot}} = 53.5$ . Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01$  M;  $T = 25.0 \pm 0.2$  °C. Absorption spectra not corrected for dilution.

The analysis of the spectrophotometric data suggested the formation of three Ln(III) species, a mono-, a bi- and a trimetallic complex, which was qualitatively confirmed with mass spectrometry. The respective successive stability constants (equation (1)) were calculated using a least-squares method (Table 2).<sup>86</sup>

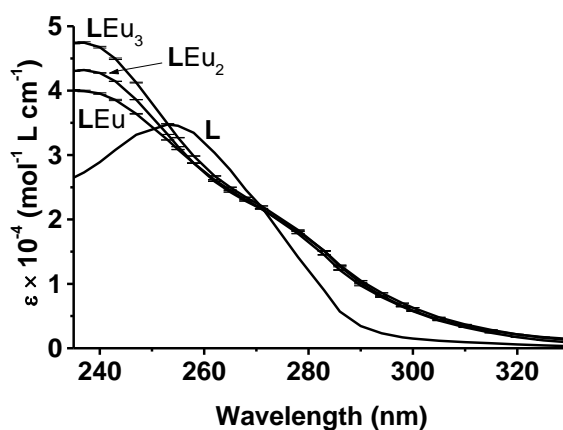


**Table 2.** Successive Stability Constants for Complexes of Ln(III).<sup>a</sup>

Metal	$\log K_{LLn} (3\sigma)$	$\log K_{LLn_2} (3\sigma)$	$\log K_{LLn_3} (3\sigma)$	$\log K_{Ln(OH)}$
La(III)	6.25(5)	5.50(6)	3.92(6)	-8.81
Nd(III)	7.4(2)	6.8(3)	4.5(2)	-8.18
Eu(III)	7.77(8)	7.67(9)	3.98(8)	-7.76
Tb(III)	7.45(1)	7.48(6)	4.13(7)	-7.64
Er(III)	6.5(2)	7.0(2)	4.81(9)	-7.52

(a) Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01$  M;  $T = 25.0 \pm 0.2$  °C.  $\sigma$  = standard deviation. Hydrolysis constants of Ln(III) in water from ref. 52.

The electronic spectra of the mono-, bi- and trimetallic complexes with **L** were calculated<sup>52-89</sup> for all lanthanide complexes and a typical example is presented in Figure 4 for Eu(III). The corresponding electronic spectra for Ln = La, Nd, Tb and Er are given in Figure S3.



**Figure 4.** Electronic spectra of Eu(III) complexes with **L**. Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01$  M;  $T = 25.0 \pm 0.2$  °C.

Upon complexation, the main absorption band of **L** centred at 253 nm undergoes a split on either side with a hypsochromic shift of about 16 nm of the maximum of the absorption band and the formation of a shoulder at longer wavelengths. The absorption changes suggest the

meridional coordination of Ln(III) ions by the hydroxamate binding units, in agreement with similar variations observed for *N*-methylacetohydroxamic acid.<sup>53</sup> The formation of the successive mono-, bi- and trimetallic complexes is therefore characterized by the hyperchromic changes at 236 nm for all Ln(III) cations (Ln = La, Nd, Eu, Tb, Er). For the spectrophotometric titration with Tb(III) and Er(III) at pH = 6.35 ± 0.05, the formation of the trimetallic species was also characterized by significant absorption variations at about 280 nm. This could be explained by the dissociation and subsequent conversion of dinuclear complex to less saturated<sup>54</sup> "clover-leaf" structures of **LL**<sub>3</sub> complexes, where each metal is coordinated by one strand completed with solvent molecules. The unsaturated character of **Ln**<sub>3</sub>**L** is also suggested by ESI-MS analyses, where the trinuclear complexes are detected as adducts with OH<sup>-</sup> (Table 1,



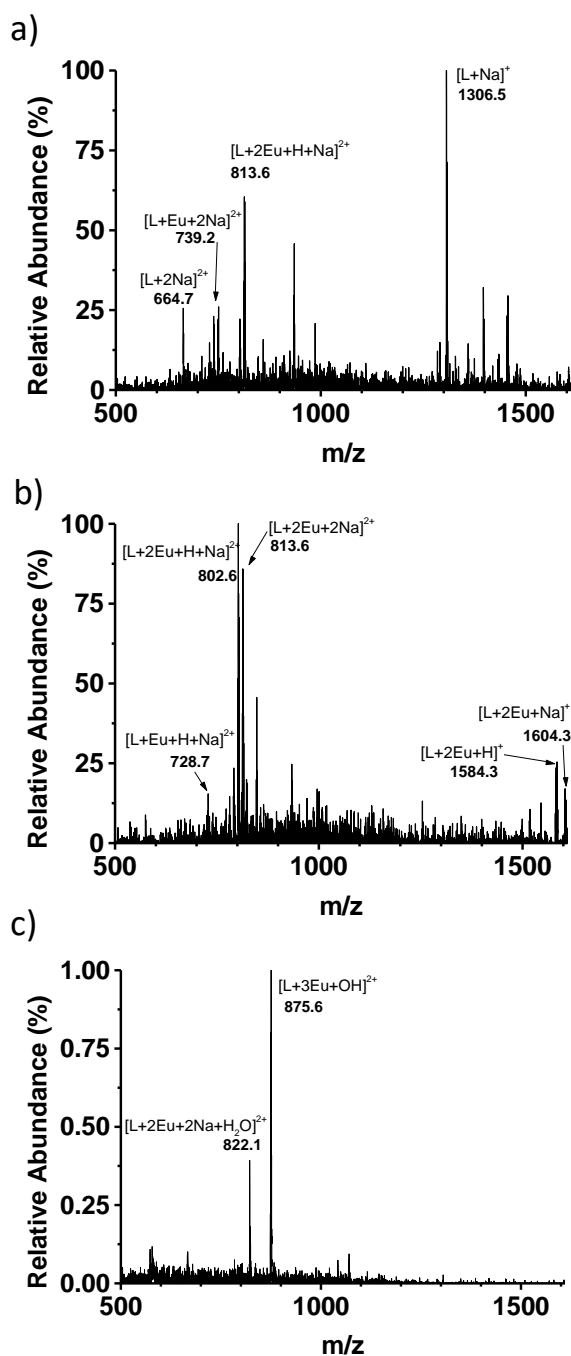


Figure 2).

**Heterobimetallic lanthanide complexes.** We have undertaken ESI-MS measurements in order to probe the distribution of the lanthanide complexes for solutions containing **L** and two different Ln(III). As expected from the stability constants reported in Table 2, the spectra clearly evidence the prominent formation of bimetallic complexes, with cationization resulting from adducts with H<sup>+</sup> and/or Na<sup>+</sup>. For each pair of lanthanide(III) cations considered in this work,

$LLn_2$ ,  $LLn'_2$  and  $LLnLn'$  complexes were characterized and identified from their isotopic distribution and the relative concentrations of the homo- and heterobimetallic complexes were estimated on the basis of the intensities of the maximum of the peaks within the same spectrum

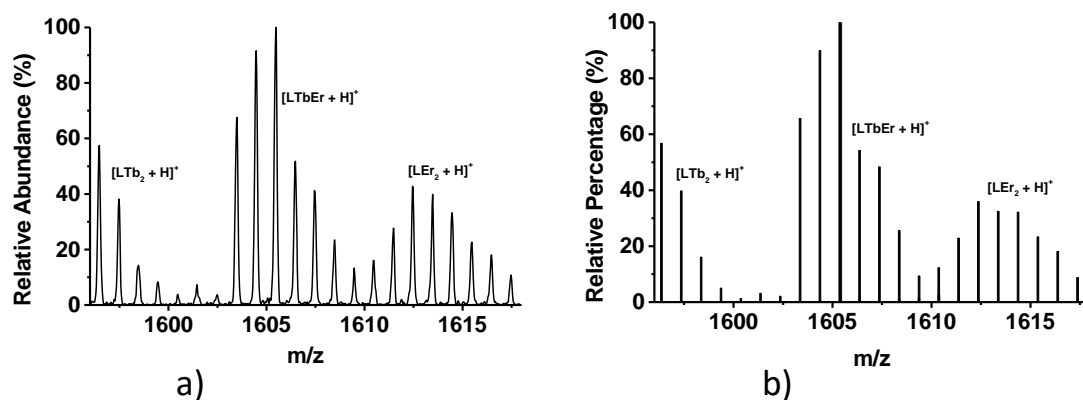
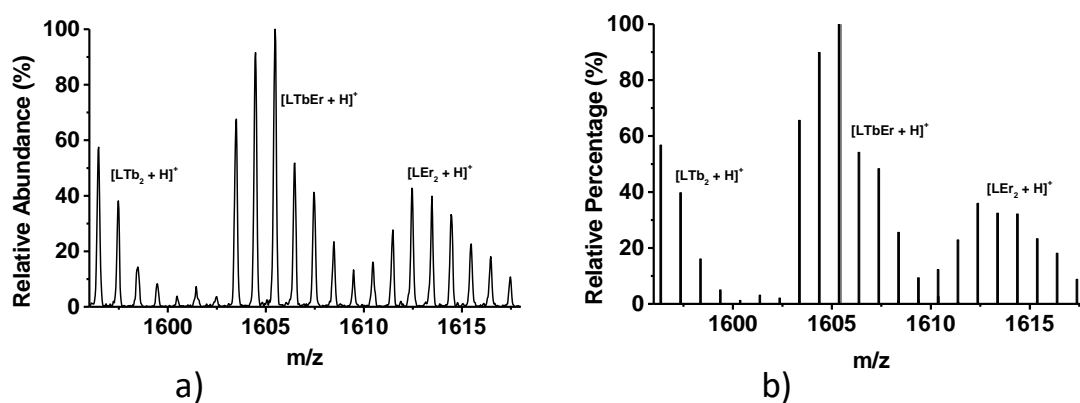


Figure 5 and Figures S6-S10).<sup>38</sup> The distribution of homo- and heterobimetallic species is summarized in Table 3. Under these experimental conditions, it is expected that the solvation effects are the same for a series of related species having the same total charge and stoichiometries.<sup>38</sup>



**Figure 5.** (a) Isotopic distribution of the ESI-MS peaks of  $[LTbErH]^+$ ,  $[LTbTbH]^+$ ,  $[LErErH]^+$ .  $[L]_{tot} = 1.80 \times 10^{-5}$  M,  $[Tb]_{tot}/[Er]_{tot}/[L]_{tot} = 1:1:1$ . (b) Simulated spectrum.

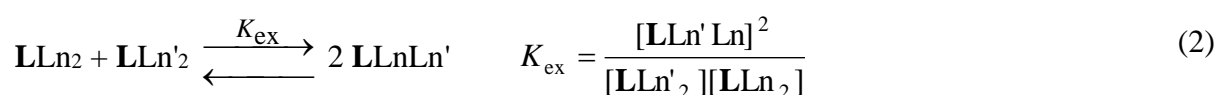
**Table 3.** Percentages of Homo- and Heterobimetallic complexes with **L** with Respect to the Total Amount of complexes Determined by ESI-MS Spectrometry.

$Ln/Ln'$	% $LnLn$	% $Ln'Ln'$	% $LnLn'$	$K_{ex}$	$\log \beta_{LLnLn'}^a$	$u^{LnLn'}$	$\Delta E^{LnLn'}$ (kJ/mol)
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La/Nd	11	38	51	6.0(6)	13.4(1)	1.1(4)	-0.1(9)
La/Eu	2	53	45	14(1)	14.2(1)	2.8(5)	-2.6(4)
La/Tb	5	39	56	16(2)	14.0(1)	3.5(4)	-3.1(3)
La/Er	3	24	73	90(9)	13.6(1)	14(6)	-6.5(9)
Eu/Er	10	27	63	15(2)	15.1(1)	12(4)	-6.2(9)
Tb/Er	16	31	53	5.9(6)	14.6(1)	9(3)	-5.4(9)

(a) Formal stability constants estimated from the ESI-MS intensities of  $[\text{LLnLn}'\text{H}]^+$ ,  $[\text{LLn}_2\text{H}]^+$  and  $[\text{LLn}'_2\text{H}]^+$  adducts (see eqs 9 and 10 and Table 2). Estimated errors on ESI-MS percentages = 10 %. The quoted errors correspond to  $3\sigma$  ( $\sigma$  = standard deviation).

The exchange process in bimetallic complexes is defined by equilibrium (2), where  $K_{\text{ex}}$  can be estimated from relative intensities of the ESI-MS peaks (eq 3). The cumulative stability constants of heterobimetallic complexes  $\beta_{\text{LLnLn}'}$  (Table 3) are then calculated with eq (4) using the stability constants of homobimetallic complexes determined above by spectrophotometric titrations ( $\beta_{\text{LLn}_2}$  and  $\beta_{\text{LLn}'_2}$ , Table 2).

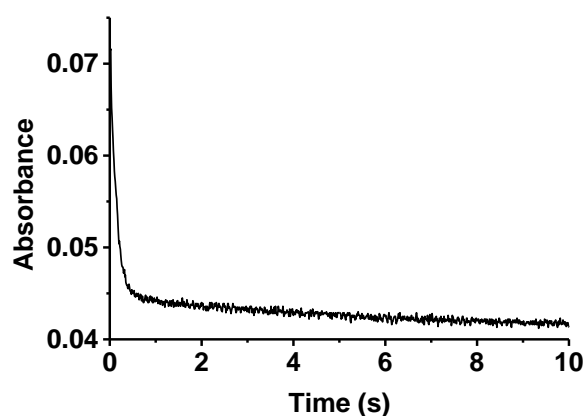


$$K_{\text{ex}} = \frac{(I^{\text{LLnLn}'})^2}{I^{\text{LLn}_2} I^{\text{LLn}'_2}} \quad (3)$$

$$K_{\text{ex}} = \frac{(\beta_{\text{LLnLn}'})^2}{\beta_{\text{LLn}_2} \beta_{\text{LLn}'_2}} \Rightarrow \beta_{\text{LLnLn}'} = \sqrt{K_{\text{ex}} \beta_{\text{LLn}_2} \beta_{\text{LLn}'_2}} \quad (4)$$

**Exchange kinetics.** The lanthanide exchange process of the tris(hydroxamato)-Ln(III) complexes  $\text{LEu}_2$  and  $\text{LEr}_2$  complexes (i.e., prepared *in situ* by mixing 2 equivalents of the Ln(III) salt with 1 equivalent of **L**;  $[\text{LnL}]$  and  $[\text{Ln}_3\text{L}]$  are estimated to be below 10% under these experimental conditions) with CDTA as competing ligand was elucidated with the help of a fast

mixing technique (stopped-flow apparatus). CDTA (*trans*-1,2-diaminocyclohexane-*N,N,N',N'*-tetraacetic acid), a well known strong chelator of Ln(III) cations,<sup>55</sup> was preferred to EDTA as a scavenger for solubility reasons in our solvent. In excess of CDTA, the spectrophotometric signal recorded at 288 nm undergoes a decrease in absorbance with two exponential signals in the second time range (Figure 6 and Figure S4).



**Figure 6.** Variation of the absorption at 288 nm versus time for LEu<sub>2</sub>. [LEu<sub>2</sub>]<sub>tot</sub> = 6.21 × 10<sup>-6</sup> M; [CDTA]<sub>tot</sub> = 1.94 × 10<sup>-4</sup> M. Solvent: methanol/water (80/20 by weight); pH = 6.35 ± 0.05; acetic acid/acetate buffer (0.01 M); *I* = 0.01 M; *T* = 25.0 ± 0.2 °C.

The variation of the two corresponding pseudo-first-order rate constants  $k_{1,obs}^{Ln}$  and  $k_{2,obs}^{Ln}$  versus [CDTA]<sub>tot</sub> (Tables S1 and S2) is presented in

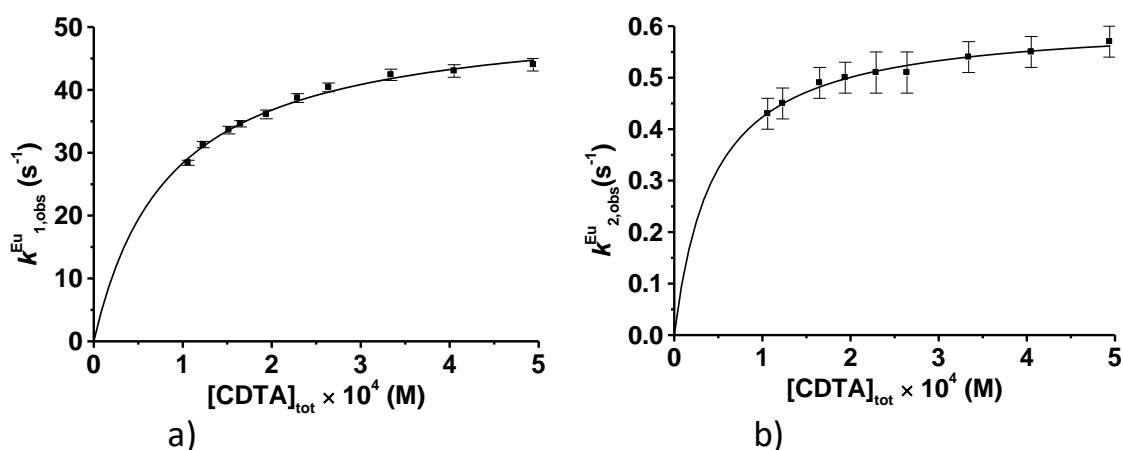
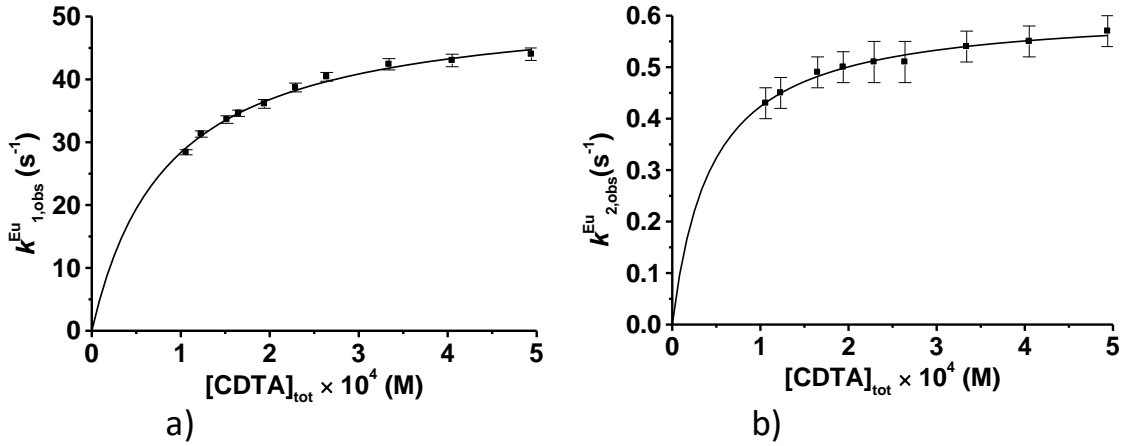


Figure 7 for LEu<sub>2</sub>. The dependences obtained for LEr<sub>2</sub> are given in Figure S5.



**Figure 7.** Variation versus  $[\text{CDTA}]_{\text{tot}}$  of the pseudo-first order rate constants  $k_{1,\text{obs}}^{\text{Eu}}$  (a) and  $k_{2,\text{obs}}^{\text{Eu}}$  (b) for  $\text{LEu}_2$ . Solvent: methanol/water (80/20 by weight);  $\text{pH} = 6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01 \text{ M}$ ;  $T = 25.0 \pm 0.2 \text{ }^\circ\text{C}$ .

The variation of  $k_{n,\text{obs}}^{\text{Ln}}$  with  $[\text{CDTA}]_{\text{tot}}$  revealed a hyperbolic curvature, which could be in agreement with a saturation behaviour. Therefore, we suggest that the Ln(III) removal from the bimetallic complex  $\text{LLn}_2$  ( $\text{Ln} = \text{Eu}$  and  $\text{Er}$ ) involves the formation of a ternary intermediate complex in fast pre-equilibrium (eq 5) followed by its disjunctive<sup>56</sup> rate limiting step (eq 6). Therefore, the absorbance at the beginning of the rate-limiting step corresponds to the kinetic intermediate (Figure 6).<sup>57</sup>



The rate law corresponding to eq (6) is expressed by the following expression:

$d[\text{LLn}_2]/dt = k_1^{\text{Ln}} \times [\text{LLn}_2\text{CDTA}]$  and leads to:

$$k_{1,\text{obs}}^{\text{Ln}} = \frac{k_1^{\text{Ln}} K_1^{\text{Ln}} [\text{CDTA}]_{\text{tot}}}{1 + K_1^{\text{Ln}} [\text{CDTA}]_{\text{tot}}} \quad \text{with} \quad K_1^{\text{Ln}} = \frac{[\text{LLn}_2\text{CDTA}]}{[\text{LLn}_2][\text{CDTA}]} \quad (7)$$

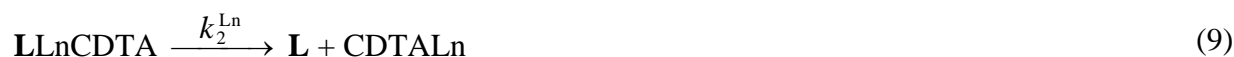
The rate constants  $k_1^{\text{Eu}}$  and  $k_1^{\text{Er}}$  as well as the stability constants  $K_1^{\text{Eu}}$  and  $K_1^{\text{Er}}$ , which were determined using a non-linear least squares method<sup>58</sup>, are listed in Table 4.

**Table 4.** Ligand Exchange Kinetic Parameters.<sup>a</sup>

Metal	$K_1^{\text{Ln}}$ ( $\text{M}^{-1}$ )	$k_1^{\text{Ln}}$ ( $\text{s}^{-1}$ )	$K_2^{\text{Ln}}$ ( $\text{M}^{-1}$ )	$k_2^{\text{Ln}}$ ( $\text{s}^{-1}$ )
Eu(III)	$1.2(2) \times 10^4$	52(2)	$2.2(5) \times 10^4$	0.61(2)
Er(III)	$1.1(2) \times 10^3$	20(2)	$7(3) \times 10^2$	3.1(9)

(a) Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01$  M;  $T = 25.0 \pm 0.2^\circ\text{C}$ . Calculated standard errors.

The second rate-limiting step shows an identical behaviour as the previous one. It could be easily attributed to the removal of the second lanthanide cation via an intermediate species:



The corresponding rate law can be written:

$d[\text{LLn}]/dt = k_2^{\text{Ln}} \times [\text{LLn}] \times [\text{CDTA}]$  and leads to:

$$k_{2,\text{obs}}^{\text{Ln}} = \frac{k_2^{\text{Ln}} K_2^{\text{Ln}} [\text{CDTA}]_{\text{tot}}}{1 + K_2^{\text{Ln}} [\text{CDTA}]_{\text{tot}}} \quad (10)$$

with  $K_2^{\text{Ln}} = \frac{[\text{LLn}_2\text{CDTA}]}{[\text{LLn}_2][\text{CDTA}]}$ . The processing<sup>58</sup> of our kinetic data allows the determination of

$k_2^{\text{Ln}}$  and  $K_2^{\text{Ln}}$  (Table 4).

## Discussion

The tripodal ditopic ligand **L** is based on a  $C_3$ -symetric trisamine anchor and is constituted by two binding cavities coded for metals with octahedral stereochemical preferences. It has been shown that the amide-containing spacers induce interstrand H-bonds such as to minimize random coiling and to stabilize specific conformations.<sup>59</sup> This feature results in strong pre-organization

of the two trihydroxamate binding sites. Our previous study on the coordination properties of **L** with iron(III) also showed strong allosteric effects. The observation of positive cooperativity to produce diferric **LFe<sub>2</sub>** helicate encourages us to examine the metal-mediated interactions in this tripodal structure with lanthanides(III). As part of our investigations of supramolecular edifices with various polytopic ligands,<sup>34,35,60</sup> the focus of this work is a better understanding of the key structural features, which are of great importance to positively drive the efficient formation of bimetallic complexes.

**Monometallic and homobimetallic lanthanide complexes.** We have clearly characterized three Ln(III) complexes (**LL<sub>n</sub>**, **LL<sub>n2</sub>** and **LL<sub>n3</sub>**) for the series of Ln(III) cations examined here by a combination of absorption spectrophotometry and electrospray mass spectrometry. For analogous chiral tripods,<sup>22</sup> it has been shown by CD measurements that the binding of two iron(III) cations produces a diferric helicate. In these bimetallic complexes, the control of helical versus "side-by-side" configuration results from the particular stereochemistry and the length of the alkyl chains connecting the binding units. Therefore, in the presence of lanthanide(III) cations, we anticipate that **L** could be able to form tripodal bimetallic complexes. In each binding sites, the bidentate hydroxamates and the amide groups could participate to the coordination of Ln(III) ions to fulfil their high coordination numbers (CN = 8-9). To consolidate these expectations, we have used DFT calculations (see computational details) to optimize the structures of the Ln(III) complexes with **L** (

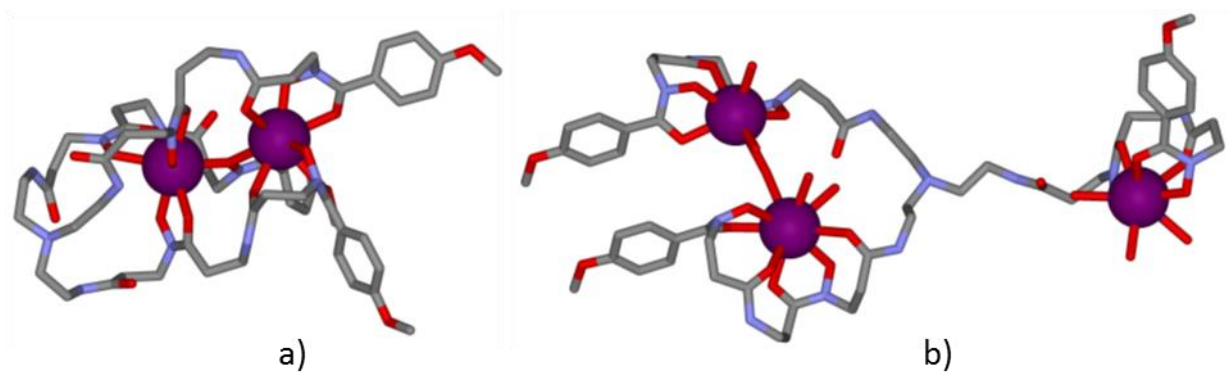


Figure 8, Figure S11). In the monometallic complex, the first Ln(III) cation is proposed to occupy

the lower hydroxamate-cavity close to the amine anchor as it was already reported for iron(III).<sup>51</sup> Moreover, the calculated energies show that this configuration is also more stable (by ~ 30 kcal/mol) compared to the alternative binding in the “upper” site (Figure S11). Consequently, the binding of a second Ln(III) cation takes place in the upper coordination cavity and leads to the formation of the bimetallic complex  $LLn_2$ . Its optimized structure in

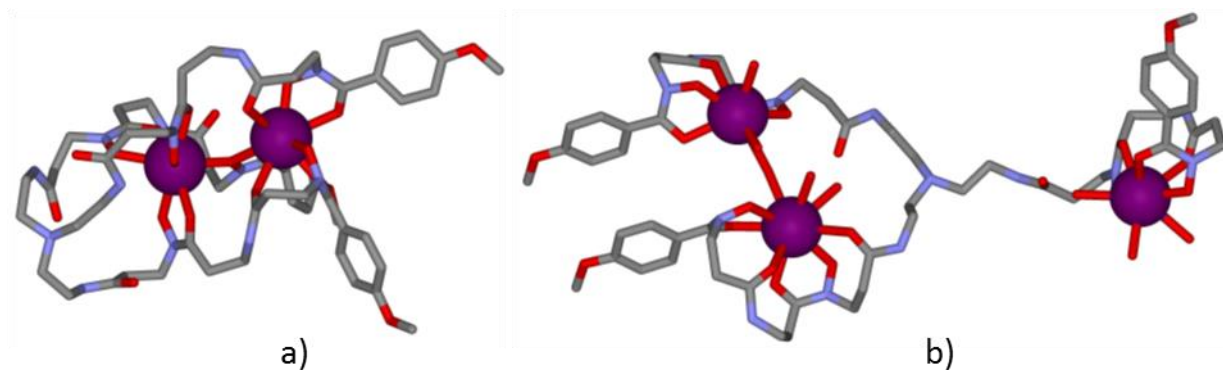
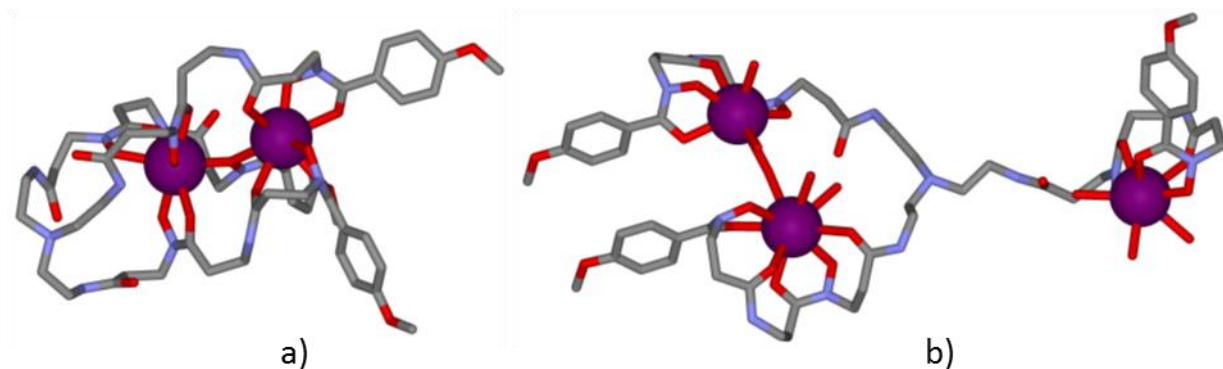


Figure 8 is indeed compatible with a side-by-side tripodal arrangement. All the hydroxamate groups are tightly coordinated to the metal ions, while the carbonyl oxygens are not bound systematically for steric reasons. Therefore, lanthanide cations seem to be coordinated by only 7-8 atoms of **L**, but the overall assembly can be additionally stabilised by hydrogen bonding.



**Figure 8.** DFT optimized structure of the dinuclear (a) and trinuclear (b) La(III) complexes formed with **L** (apical tertiary amine is protonated at our experimental conditions). Protons were removed from the structures for the sake of simplicity.

In order to quantify the metal-mediated intramolecular interactions between the two tris(hydroxamato) cores, we present the successive stability constants in Table 2. Contrary to a monotonous increase of hydrolysis constants along the series (Table 2), an interesting and



significant size-discriminating effect is observed for complexes with **L** for which  $\log K_{LLn}$  and  $\log K_{LLn_2}$  values increase from La to Eu and then strongly and then sparingly decrease from Eu to Er respectively (

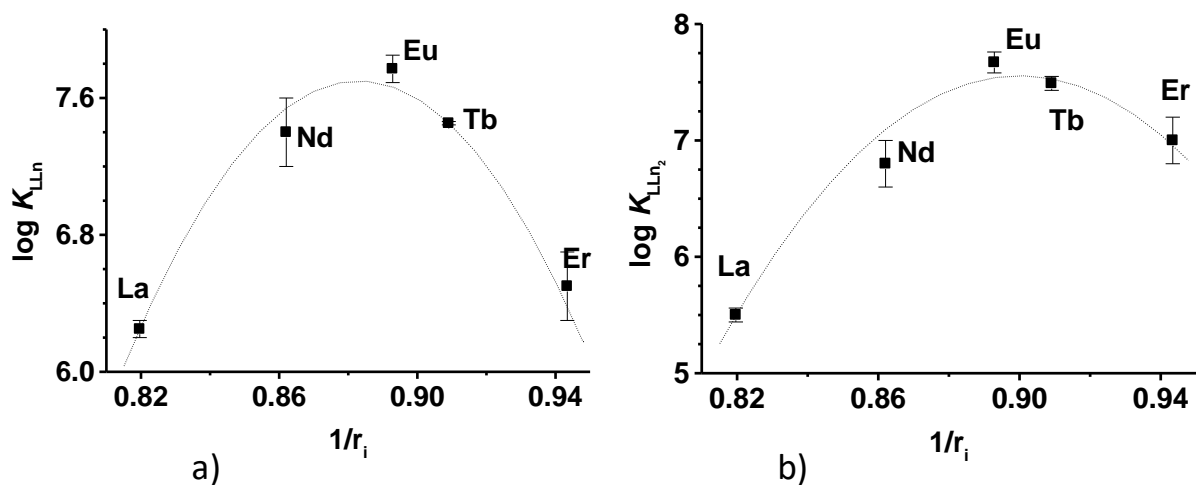
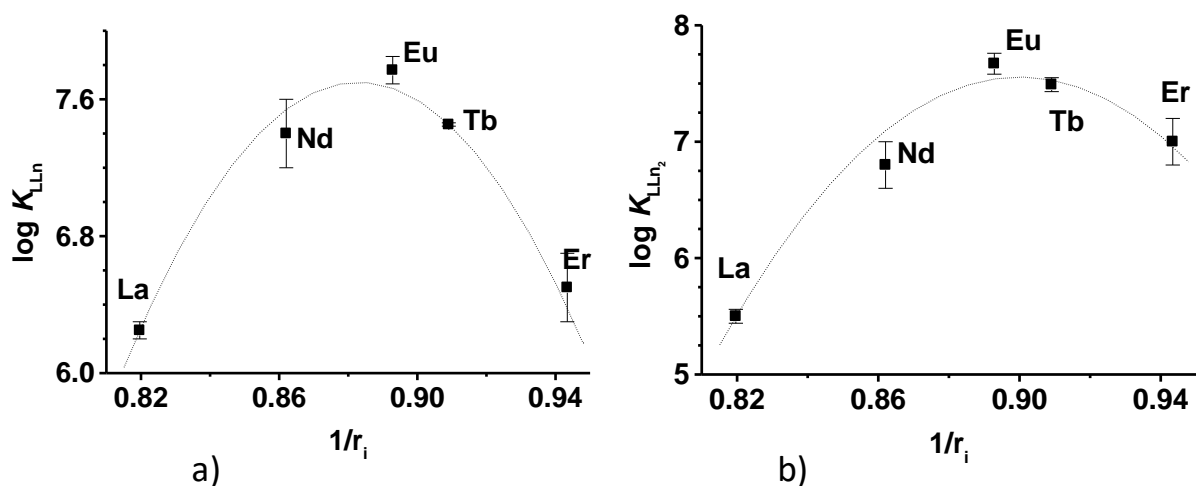
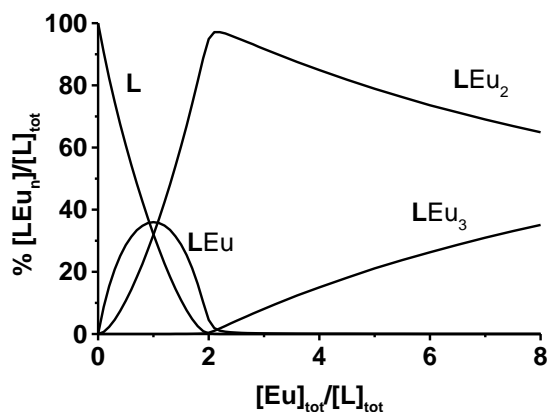


Figure 9). Only peculiar supramolecular arrangements for **LLn** and **LLn<sub>2</sub>** could explain this size-discriminating effect as partially observed for mononuclear lanthanide podands.<sup>47</sup> Decreased thermodynamic stability of smaller lanthanides may also be associated with further dissociation of carbonyl moieties due to steric constraints within these complexes.



**Figure 9.** Variation of  $\log K_{LLn}$  (a) and  $K_{LLn_2}$  (b) versus the reciprocal of the ionic radii for a coordination number of 9. The trend lines are only guides for the eyes.

The distribution diagrams<sup>61</sup> presented in Figure 10 and Figure S12 show that the bimetallic complexes  $LLn_2$  ( $Ln = Eu, Tb$  and  $Er$ ) are the predominant complexes under our experimental conditions over a large range of  $[Ln]_{tot}/[L]_{tot}$  ratios.



**Figure 10.** Distribution diagram of Eu(III) complexes formed with **L**.  $[L]_{tot} = 1.00 \times 10^{-5}$  M. Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $I = 0.01$  M;  $T = 25.0 \pm 0.2^\circ\text{C}$ .

This result strongly indicates a positive cooperativity of the assembly process leading to the bimetallic complex as already observed for diferric triple-stranded helicates formed with **L**.<sup>51</sup> Assuming that its two binding sites are equivalent, the  $K_{LLn_2}/K_{LLn}$  ratio (Table 5) of successive stability constants defined by eq (1) ( $n = 1, 2$ ) enables us to determine qualitatively the metal-mediated intramolecular interactions between the metal centres in these tripodal structures (Figure S13). This ratio for  $Ln = Eu, Tb$  and  $Er$  is larger than the statistical value  $\frac{K_{LLn_2}}{K_{LLn}} = 0.25$  being the value expected for a statistical model of two identical binding sites.<sup>62</sup> Statistical effects within the experimental errors are measured for  $Ln = La$  and  $Nd$  (Table 5).

Classical plots of  $r/[Ln]_{eq}$  as a function of  $r$  (Scatchard plots)<sup>63</sup> and of  $\ln(r/(2-r))$  as a function of  $\ln[Ln]_{eq}$  (Hill plots),<sup>64</sup> for which  $r$  is the occupancy factor, also constitute usual tests

for cooperativity (

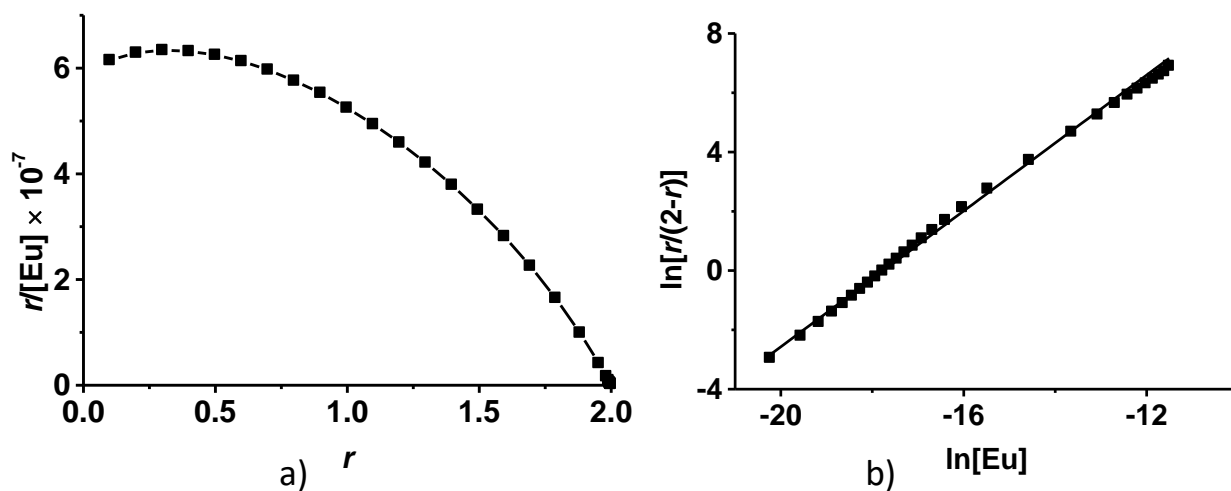
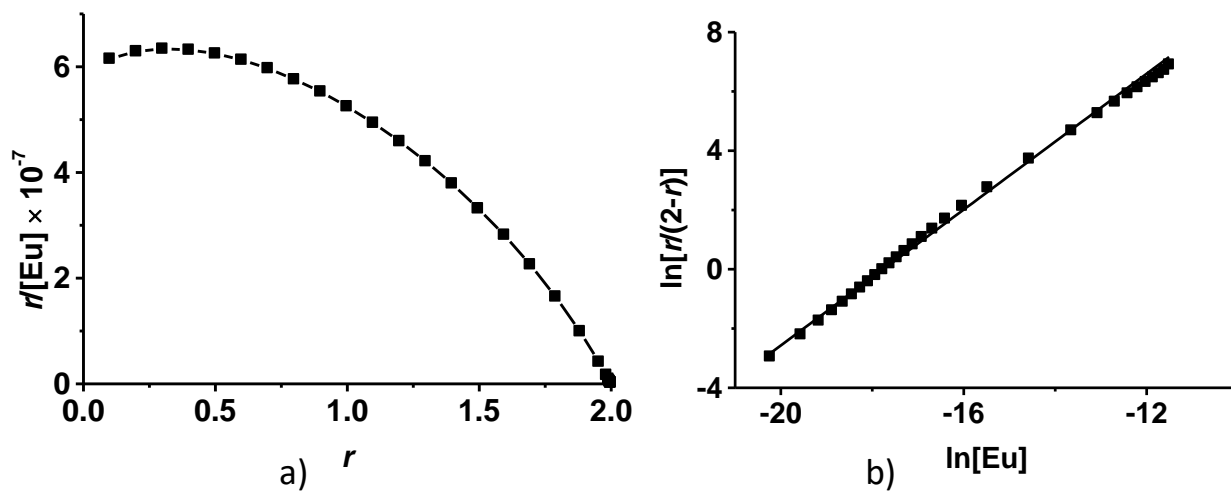


Figure and Table 5) with the same qualitative results.



**Figure 11.** Intramolecular interactions in bimetallic europium(III) complexes with **L** versus  $1/r_i$ . (a) Scatchard plot and (b) Hill plot.

**Table 5.** Intramolecular Interactions in Bimetallic Lanthanide Complexes with **L**.<sup>a</sup>

Metal	$r_i$	$K_{\text{LLn}_2}/K_{\text{LLn}}$ ( $3\sigma$ )	$r_{\text{max}}$	$n_{\text{H}}$
La(III)	1.22	0.18(3)	-	0.94
Nd(III)	1.16	0.3(2)	-	1.01
Eu(III)	1.12	0.8(2)	0.31	1.15
Tb(III)	1.10	1.1(1)	0.50	1.17

Er(III)	1.06	3.1(2.1)	0.69	1.49
Fe(III) <sup>b</sup>	0.65	3.2(4)	0.74	1.46

(a) Solvent: methanol/water (80/20 by weight); pH = 6.35 ± 0.05; acetic acid/acetate buffer (0.01 M);  $T = 25.0 \pm 0.2$  °C. (b) Solvent: methanol; pH = 6.5 ± 0.1;  $I = 0.05$ ;  $T = 25.0 \pm 0.2$  °C.<sup>49</sup>  $n_H$  - Hill coefficient;  $r_{\max}$  - maximum at Scatchard plot;  $I = 0.01$  M;  $r_i$  = ionic radius.  $\sigma$  = standard deviation.

Moreover, reliable quantification of intermetallic interactions can be advantageously obtained with the *site binding* model, which was previously developed by Piguet and coworkers.<sup>65</sup> This thermodynamic model applies for Ln(III) complexes with **L** and allows the evaluation of (i) specific binding affinity of a metal ion to a preorganized binding site and (ii) intermetallic interaction parameter, which quantify the deviations from the statistical binding. The treatment of experimental data was demonstrated for closely related complexes of **L** with Fe(III)<sup>66</sup> and the application to the lanthanide analogues is straightforward. We may assume that both nine-coordinated cavities along the strands are equivalent. Experimental cumulative stability constants for Ln**L** and Ln<sub>2</sub>**L** (Table 2) are thus modelled as following:

$$\beta_{\text{LLn}} = 2 \cdot k^{\text{Ln}} \quad (11)$$

$$\beta_{\text{LLn}_2} = (k^{\text{Ln}})^2 \cdot u^{\text{LnLn}} \quad (12)$$

where  $k^{\text{Ln}}$  is the specific binding affinity of Ln(III) to the binding site of **L** and  $u^{\text{LnLn}}$  reflects the interaction energy  $\Delta E^{\text{LnLn}}$  expressed as the Boltzman factor  $u^{\text{LnLn}} = e^{-\frac{\Delta E^{\text{LnLn}}}{RT}}$ . The latter parameter can be modelled as the electrostatic work required for complexing two Ln(III) considered as triply charged dots.<sup>65</sup> With these two equations (11-12), both thermodynamic parameters  $k^{\text{Ln}}$  and  $u^{\text{LnLn}}$  can be calculated for each Ln(III) cation (Table 6). It is evident, that the binding affinities  $k^{\text{Ln}}$  follow the same trend as the stability constants  $K_{\text{LLn}}$  showing the size–discriminating effect (Figure 8a). A criterion for cooperative binding was clearly defined in term of free energy of

interactions. Statistical binding (i.e., no influence on the coordination of another metal) is detected for Nd(III), since  $\Delta E^{\text{LnLn}} = 0$ . When  $\Delta E^{\text{LnLn}} > 0$ , negative cooperativity occurs (i.e. La), when  $\Delta E^{\text{LnLn}} < 0$ , positive cooperativity operates, as shown for Eu, Tb and Er.

**Table 6.** Intramolecular Intermetallic Interactions in Bimetallic Lanthanide Complexes with **L**.<sup>a</sup>

Metal	$r_i$	$\log k^{\text{Ln}}$	$u^{\text{LnLn}}$	$\Delta E^{\text{LnLn}}$ (kJ/mol)
La(III)	1.22	5.95(5)	0.7(1)	0.9(5)
Nd(III)	1.16	7.1(2)	1.0(7)	0(2)
Eu(III)	1.12	7.47(8)	3.2(9)	-2.9(7)
Tb(III)	1.10	7.15(1)	4.4(6)	-3.7(4)
Er(III)	1.06	6.2(2)	12(8)	-6(2)
Fe(III) <sup>b</sup>	0.65	5.52 <sup>c</sup>	3.0 <sup>c</sup>	-2.7 <sup>c</sup>

(a) Solvent: methanol/water (80/20 by weight); pH =  $6.35 \pm 0.05$ ; acetic acid/acetate buffer (0.01 M);  $T = 25.0 \pm 0.2$  °C. (b) Solvent: methanol; pH =  $6.5 \pm 0.1$ ;  $I = 0.05$ ;  $T = 25.0 \pm 0.2$  °C.<sup>49</sup>  $I = 0.01$  M;  $r_i$  = ionic radius. (c) The values reported in reference 66. Errors are given as  $3\sigma$ .

It clearly demonstrates that cooperativity effects linearly increase with decreasing of the ionic radii and the formation of the bimetallic complexes **LLn<sub>2</sub>** is thermodynamically favoured. In addition, this is supported by the accumulation of **LLn<sub>2</sub>** complexes along the lanthanides series in the ESI-MS spectra for Ln/**L** ratios 1:1 (

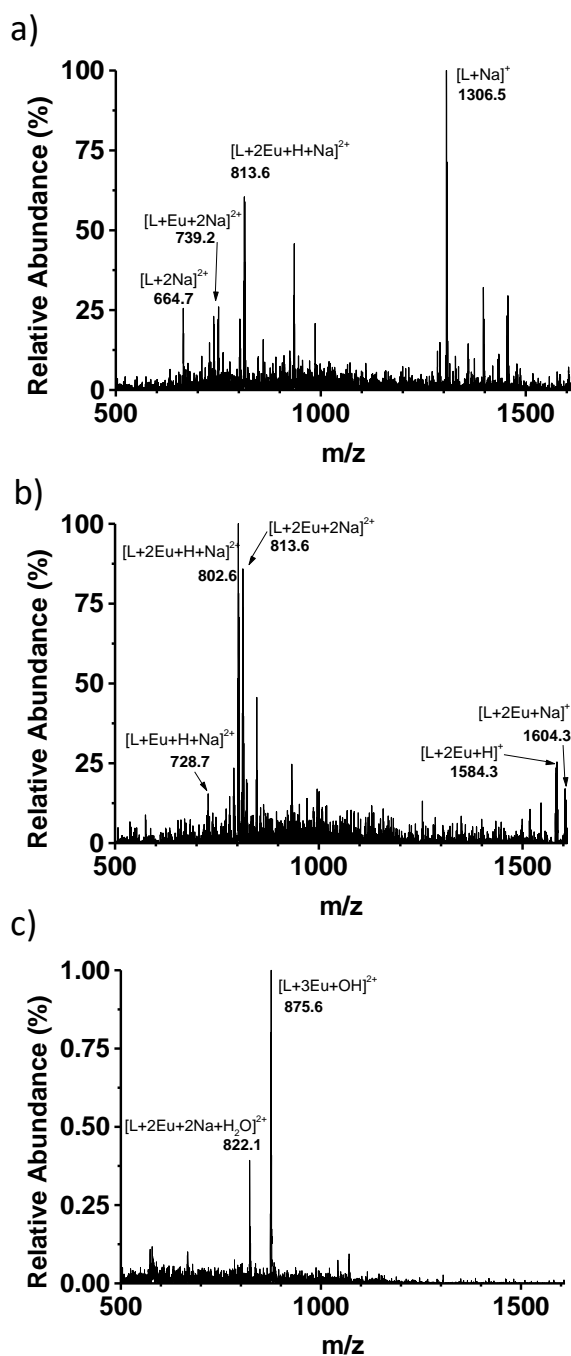


Figure 2, Table 1 and Figure S1). Pre-organization of the monometallic receptor  $LL_n$  with the efficient charge compensation by the deprotonated hydroxamate groups is indeed able to compensate the electrostatic repulsions between the two cations. Moreover, it is noteworthy, that these metal-mediated effects are tuned by the size of the entering cations along the lanthanide series. Despite the small difference in ionic radii between La(III) and Lu(III) (i.e.,  $\sim 0.2 \text{ \AA}$ : "lanthanide contraction"),<sup>19</sup> the decrease of ionic radius on going from lighter to heavier

lanthanide(III) ions induces stronger Ln-O<sub>(hydroxamate)</sub> interactions and shorter Ln-O<sub>(hydroxamate)</sub> distances. As a possible consequence, it causes the shortening of Ln-Ln distances.<sup>34</sup> Alternatively, a more twisted structure may also provide a better protection of Ln(III) centres by organic chains that will weaken their electrostatic repulsions. Moreover, it leads to the formation of the second coordination cavity, which is better adapted for the binding of a heavier lanthanide, as evidenced by a strong positive cooperativity observed for Tb(III) or Er(III). Therefore, it appears that, in spite of the constraint introduced by the tripodal nature of **L**, the flexibility of the three ditopic arms allows to significantly reduce the intramolecular interactions between a wide range of trivalent cations.

**Heterobimetallic lanthanide complexes.** Homo- and heterobimetallic complexes (**LLn**<sub>2</sub>, **LLn'**<sub>2</sub>, **LLnLn'**) dominate the ESI-MS spectra of solutions containing two different Ln(III) and **L** in equimolar concentrations (

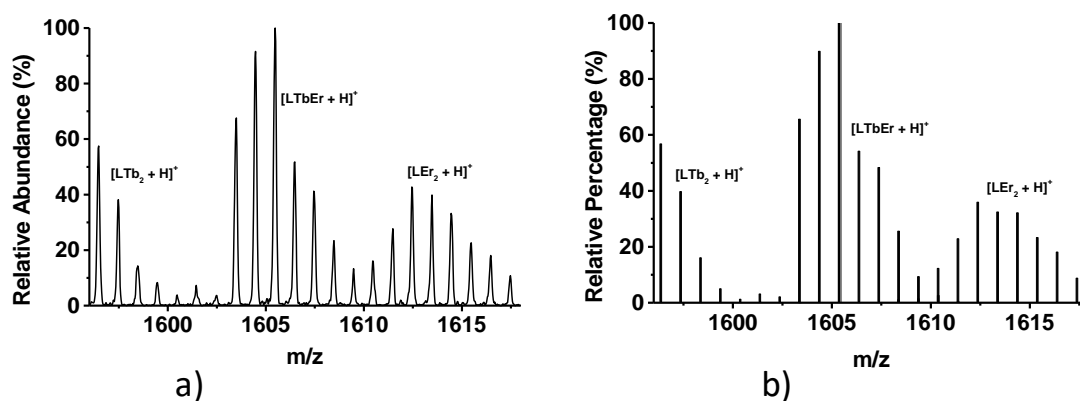


Figure 5 and Table 3, ratio Ln:Ln':**L** = 1:1:1). The signals of mono- and trimetallic complexes were not observed in significant intensities. Therefore, the equilibrium can be defined as the exchange reaction between two homobimetallic complexes to provide heterobimetallic species (equilibrium 2). The exchange constant is calculated by using the relative intensities of homo- and heterobimetallic complexes in ESI-MS spectra (eq 3).

Cooperativity in heterobimetallic complexes can be tested with the site-binding model.<sup>65,66</sup> Similarly to homobimetallic complexes, its application to heterobimetallic complexes allows the

determination of average intermetallic interactions between two different lanthanides. The stability constants of heterobimetallic complexes are modelled with equation  $\beta_{\text{LnLn}'} = \beta_{\text{LnLn}} = s \cdot k^{\text{Ln}} \cdot k^{\text{Ln}'} \cdot u^{\text{LnLn}'}$ , where the factor  $s = 2$  accounts for the degeneracy of the microspecies. Therefore, the interaction parameter  $u^{\text{LnLn}'}$  can be extracted using affinities  $k^{\text{Ln}}$  and  $k^{\text{Ln}'}$ , which were determined for the homometallic complexes (Table 6). In our case,  $u^{\text{LnLn}'}$  is advantageously calculated using the exchange constant  $K_{\text{ex}}$  according to eqs (13) and (14). Numerical values for  $u^{\text{LnLn}'}$  and  $\Delta E^{\text{LnLn}'}$  are summarized in Table 4.

$$K_{\text{ex}} = \frac{(\beta_{\text{LnLnLn}})^2}{\beta_{\text{LnLn}_2} \cdot \beta_{\text{LnLn}'_2}} = \frac{(2 \cdot k^{\text{Ln}} \cdot k^{\text{Ln}'} \cdot u^{\text{LnLn}'})^2}{(k^{\text{Ln}})^2 \cdot u^{\text{LnLn}} \cdot (k^{\text{Ln}'})^2 \cdot u^{\text{LnLn}'}} = 4 \cdot \frac{(u^{\text{LnLn}'})^2}{u^{\text{LnLn}} \cdot u^{\text{LnLn}'}} \quad (13)$$

$$u^{\text{LnLn}'} = 0.5 \cdot \sqrt{K_{\text{ex}} \cdot u^{\text{LnLn}} \cdot u^{\text{LnLn}'}} \quad (14)$$

The parameter  $u^{\text{LnLn}'}$  and the corresponding interaction energy  $\Delta E^{\text{LnLn}'}$  quantify the intermetallic interactions between two different lanthanides. Statistical interactions are observed for the La/Nd pair, where  $u^{\text{LnLn}'}$  is close to 1 ( $\Delta E^{\text{LnLn}'} \sim 0$ ). Interestingly, other investigated heterobimetallic complexes exhibit positive intermetallic interactions ( $u^{\text{LnLn}'} > 1$ ) with interaction energies  $\Delta E^{\text{LnLn}'}$  about (-2)-(-7) kJ/mol.

Under statistical conditions, the interaction parameters  $u^{\text{LnLn}}$ ,  $u^{\text{LnLn}'}$  and  $u^{\text{LnLn}'}$  are identical and eq (13) is reduced to  $K_{\text{ex}} = 4$ , which corresponds to a statistical distribution of 25% of each homobimetallic species and 50% of the heterobimetallic complex. In that case,  $\beta_{\text{LnLn}_2} = \beta_{\text{LnLn}'_2}$ ,  $K_{\text{LnLn}} = K_{\text{LnLn}'}$  and the stability constants of heterobimetallic complexes can be expressed with eq (15),

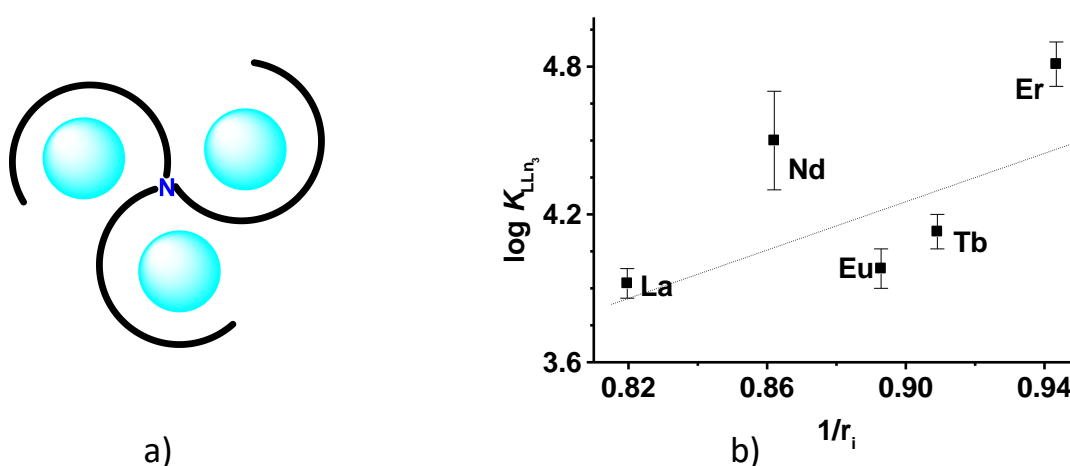
$$\log \beta_{\text{LnLn}'} = \frac{\log \beta_{\text{LnLn}_2} + \log \beta_{\text{LnLn}'_2}}{2} + \log(s) \quad (15)$$

where  $s$  holds for a degeneracy  $s = 2$  reflecting the number of different arrangements allowed in heterobimetallic complexes compared to the homobimetallic species.<sup>67</sup> However, accumulation of the heterobimetallic complexes is observed for the whole range of Ln/Ln' pairs ( $K_{\text{ex}} > 4$ ) except the La/Nd pair.



Our results show that cooperative effects in heterobimetallic lanthanide complexes could occur and emphasize the structural keys of this ditopic ligand relevant to the size discrimination of homo- and heteropairs of lanthanide(III) cations. The tripodal structure of **L** results in strong pre-organization of the two binding sites, which leads to minimization of the intramolecular interactions in  $LLn_2$  and  $LLnLn'$  complexes for heavier lanthanide(III) cations. Our system stands a significant deviation from the statistical behaviour with allosteric effects in bimetallic complexes (eq 14),<sup>51</sup> but a differentiation resulting from the non-equivalent binding affinity of both coordination sites cannot be excluded. Enhancements of the concentrations of heterometallic complexes over the statistical distribution deduced with stability constants of homobimetallic complexes roughly correlates with increasing difference in ionic radii of lanthanide(III) heteropairs. Similar trends were observed for bimetallic<sup>38,45</sup> and trimetallic<sup>37</sup> helicates with different binding sites. Our data show only 73 % of the formation of the heterobimetallic La/Er complexes comparing to 90 % obtained by Bünzli et al. for La/Lu system.<sup>38</sup> Improvement of the selective formation of heterometallic complexes can be possibly achieved by playing with different Ln:Ln' ratios, as it was demonstrated by Chapon et al.<sup>67</sup>

**Trimetallic lanthanide complexes.** In large excess of Ln(III) ions, a third complex  $LLn_3$  is formed, and probably results from the opening of the podate to produce a "clover-leaf" structure (Figure 12a) as already evidenced for iron(III) complexes.<sup>51</sup> This is suggested by a slight monotonous increase of  $\log K_{LLn_3}$  with the reciprocal of the ionic radius (



**Figure b)** along the lanthanide(III) series obtained for **L**, which corresponds to the usually expected increase of electrostatic interactions when going from La(III) to Lu(III) in non-organized structures that are flexible. The continuous increase in the stability constants from La(III) to Lu(III) measured for polyaminocarboxylate ligands such as EDTA,<sup>55</sup> NTA, ODA, IDA<sup>68</sup>, CDTA<sup>69</sup>, i.e. in the absence of well-organized structures, is indeed in line with our observations and strongly suggests flexible non-organized structures as evidenced by DFT calculations

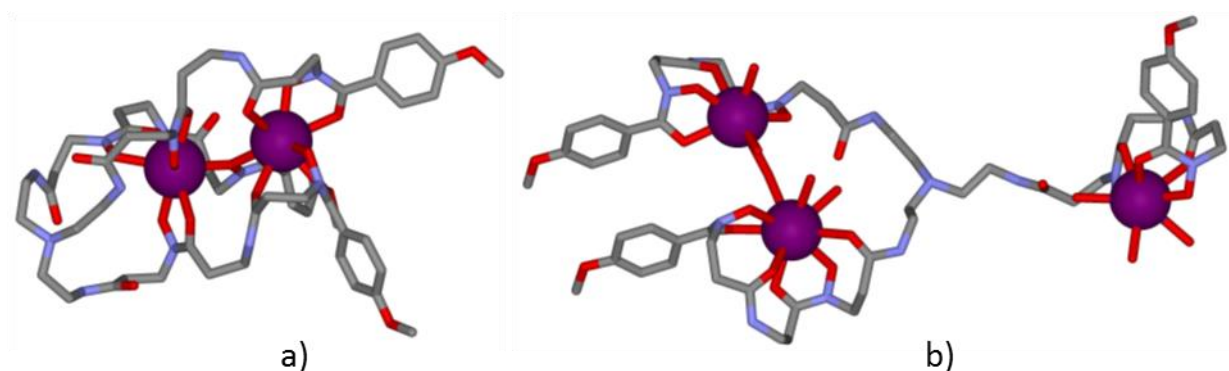
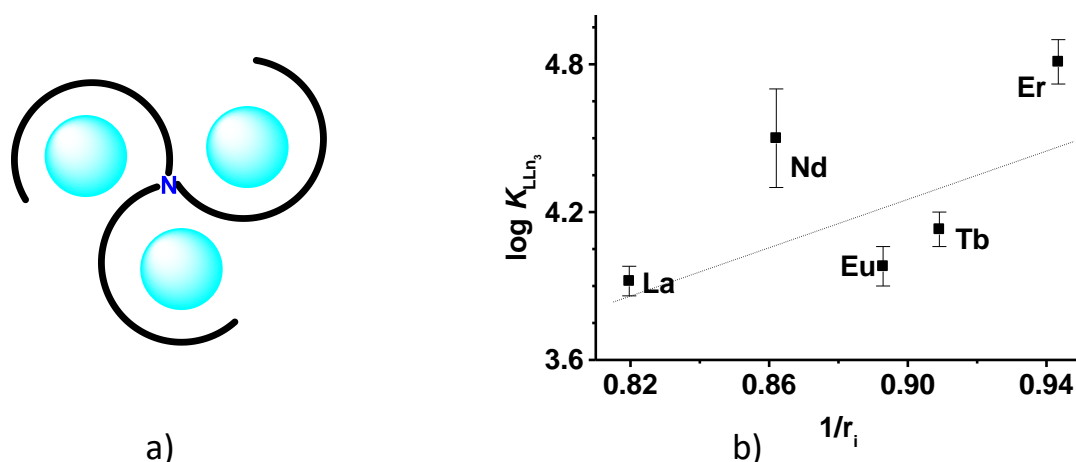


Figure 8). For other acyclic polyaminocarboxylate chelators such as DTPA,<sup>70</sup> while the stability constants increased monotonously with the inverse of the ionic radius of the Ln(III) cations, a maximum was, however, reached for Tb(III)-Ho(III), a consequence of a less flexible ligand unable to wrap successfully around the smaller Ln(III) ions. Another recent report<sup>71</sup> suggested that the shift from increasing stability to its flattening for the second half of the Ln(III) cations with DTPA might coincide with the primary hydration sphere of these ions decreasing from 9 to 8. The flattening of the curve could thus be related to a decrease of the entropic stabilization (less water molecules released by the hydrated cation during the formation of the complex) combined with an increase of the steric repulsion between the acetate units of the bound ligand for the heavy Ln(III). It has been shown that for a same ligand denticity a (semi-)rigid structure (pre-organization) is related to a significant stabilization of the complexes over the Ln(III) series (e.g., CDTA *versus* EDTA). The  $\Delta \log K_{(Lu-La)}$  has been measured to be about  $> 5$  for CDTA and related compounds.<sup>72</sup> The  $\Delta \log K_{(Lu-Er)}$  measured for **LLn<sub>3</sub>** ( $\sim 1$  log unit) displaying a "clover-leaf"

structure is in the magnitude of order than those measured for hydroxamic acid derivatives,<sup>73</sup> thus in line with lack of pre-organization and lower denticity.



**Figure 12.** a) "Clover-leaf" structure of LLn<sub>3</sub>. b) Variation of  $\log K_{LLn_3}$  versus the reciprocal of the ionic radii for a coordination number of 9. The trend lines are only guides for the eyes.

**Exchange processes in homobimetallic lanthanide complexes with CDTA.** The Ln(III)-exchange reaction between the bimetallic complex and CDTA proceeds along two rate-limiting steps under our experimental conditions for both, L<sub>Eu</sub><sub>2</sub> and L<sub>Er</sub><sub>2</sub> complexes. The hyperbolic dependence of the pseudo-first-order rate constants  $k_{1,obs}^{Ln}$  and  $k_{2,obs}^{Ln}$  (

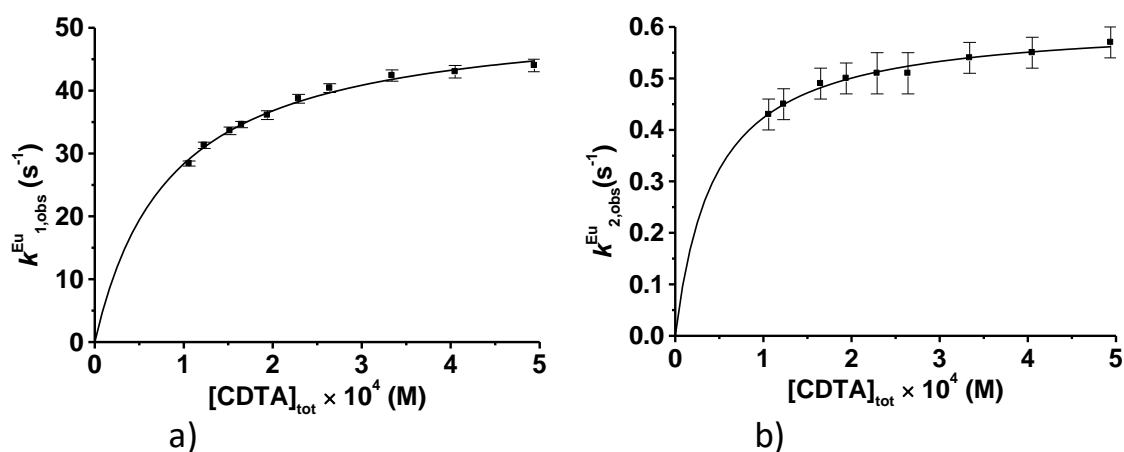


Figure 7 and Figure S5, Tables S1 and S2) indicates a ligand exchange mechanism, which is limited by the successive release of the cations. This mechanism stands for an interesting contrast with the exchange process of the diferric complex with CDTA<sup>74</sup> which displays two successive

iron(III)-withholding rate limiting steps without formation of preliminary ternary intermediates.<sup>74</sup> Indeed, the poor stereochemical preferences and the variable coordination numbers of lanthanide(III) cations<sup>19</sup> allow the fast formation of stable ternary intermediates. Moreover, numerous studies dealing with exchange kinetics of helical monoferric tris(hydroxamato) complexes with EDTA have evidenced the fast formation of ternary intermediates prior to the iron(III) exchange<sup>75</sup> between the two ligands, and emphasized the differences in reactivity between EDTA and CDTA. The stability of the ternary  $LLn_2(CDTA)$  and  $LLn(CDTA)$  ranging from  $2.2 \times 10^4 M^{-1}$  to  $7 \times 10^2 M^{-1}$  are comparable to values reported for tetrakis(*N*-methyl-4-pyridyl)-porphyrin-Gd-EDTA complex ( $K = 7.6 \times 10^3 M^{-1}$ )<sup>76</sup>, Ln-S-CDTA (Ln = La, Nd, Pr and S = malic, glycolic, lactic, salicylic, sulfosalicylic acids and 8-quinolinol;  $K$  ranging from  $4.16 \times 10^2$  to  $7.4 \times 10^5 M^{-1}$ )<sup>77</sup> and Ln-HA-CDTA (Ln = La, Nd, Dy, Gd and  $H_2A$  = maleic or citraconic acids;  $K$  ranging from  $6.16 \times 10^5$  to  $9.55 \times 10^5 M^{-1}$ ),<sup>78</sup> but are larger than those measured for tris(hydroxamato)-iron(III)-EDTA complexes.<sup>79,80</sup> The exchange rate constant  $k_{1,obs}^{Eu}$  is 85 times higher than  $k_{2,obs}^{Eu}$  whereas  $k_{1,obs}^{Er}$  is only about 6 times higher than  $k_{2,obs}^{Er}$ . These results could reflect structural effects induced by the size of the lanthanide cations, as already suggested by the significant differences observed for  $K_{LLn}$  and  $K_{LLn_2}$  with Eu(III) and Er(III) respectively.

## Conclusion

In this work, we examined the lanthanide coordination properties of a ditopic tripodal ligand **L**, which is made up of three diamido-dihydroxamate arms anchored on a tertiary amine. Interestingly, **L** is a rare ligand of tripodal nature that was reported in the literature to be able forming diferric helicates.<sup>28,49</sup> The presence of two amide groups in each arm of **L** offers the possibility of two nonadentate binding sites suitable for lanthanides(III) coordination. However,

DFT calculations revealed that not all carbonyl groups can participate in the coordination of lanthanides.

We examined the complexation of **L** with a series of lanthanide cations (La, Nd, Eu, Tb, Er). Three lanthanide complexes (**LL<sub>n</sub>**, **LL<sub>n2</sub>** and **LL<sub>n3</sub>**) were identified by absorption spectrophotometry and ESI-MS. Our results supported by DFT calculations strongly suggest, that both **LL<sub>n</sub>** and **LL<sub>n2</sub>** are tripodal non-helical complexes, while **LL<sub>n3</sub>** species correspond to a less organized arrangement, which results from an opening of the podates to "clover-leaf"-type trimetallic structures in excess of cations. An unexpected and significant size-discriminating effect on the intramolecular interactions in the bimetallic complexes has been observed. A positive cooperative effect favours the formation of the bimetallic podates compared to the monometallic analogues for the heavier lanthanide cations (Eu, Tb, Er), while the lighter ones (La, Nd) induce a statistical or negatively cooperative binding of a second Ln(III). These intramolecular interactions in homo- and heterobimetallic complexes are advantageously quantified with the site-binding model and positive deviations from the statistics are observed for Ln/Ln' differing significantly in their ionic radii (lighter + heavier lanthanide). The CDTA-mediated dissociation of the Eu(III) and Er(III) podates processes in two rate-limiting steps corresponding to the release of each lanthanide cations via prior formation of stable ternary intermediates. In contrast with the adjunctive ligand exchange reported for **LFe<sub>2</sub>** and CDTA, the corresponding substitution reaction for **LL<sub>n2</sub>** occurs according to a disjunctive mechanism. Our work points out the importance of the balance between the rigidity of a tripodal structure and the flexibility of the arms in order to accommodate two trivalent cations in a stable supramolecular edifice.

## Experimental Section

**Starting materials and solvents.** Distilled water was further purified by passing through a mixed bed of ion-exchanger (Bioblock Scientific R3-83002, M3-83006) and activated carbon (Bioblock Scientific ORC-83005). A methanol/water mixture (80/20 by weight) was prepared using a spectroscopic grade methanol (Merck, dried, p.a.) and used as a solvent, since it solubilizes the reactants and products. Acetic acid/acetate buffer (0.01 M,  $pK_a = 6.8$  in methanol/water 80/20 by weight) was prepared by dissolution of sodium acetate trihydrate (Fluka, p.a.) in methanol/water mixture (80/20 by weight) and adjusted to  $pH = 6.35 \pm 0.05$  with  $HClO_4$  (Fluka, p.a., 70%). The ionic force is thus kept constant (0.01 M) along the experiments.

The free hydrogen ion concentrations were measured with a combined glass electrode (Metrohm 6.0234.500, Long Life). The Ag/AgCl reference electrode was filled with 0.1 M NaCl (Fluka, p.a.) in MeOH/H<sub>2</sub>O (80/20 by weight).<sup>81-83</sup> Potential differences were given by a Tacussel Isis 20.000 millivoltmeter. Standardisation of the millivoltmeter and verification of the linearity ( $2.00 < pH < 13.60$ ) of the electrode were performed using buffers according to classical methods. **L** was synthesized according to previously published procedure.<sup>51</sup>  $La(ClO_4)_3 \cdot nH_2O$ ,  $Eu(ClO_4)_3 \cdot nH_2O$  and  $Tb(ClO_4)_3 \cdot nH_2O$  were prepared from the corresponding oxides (Rhône-Poulenc, 99.99%) in the usual way. *Caution! Perchlorate salts combined with organic ligands are potentially explosive and should be handled in small quantities and with the adequate precautions.*<sup>84</sup>  $Nd(ClO_4)_3$  and  $Er(ClO_4)_3$  (50% in water) were bought from Strem Chemicals. All solutions were prepared using an AG 245 Mettler Toledo analytical balance (precision 0.01 mg) and kept under argon atmosphere.

**Electrospray mass spectrometric measurements.** Electrospray mass spectra of Ln(III) complexes formed with **L** were carried out with ion-trap instrument (Bruker Esquire 3000plus, Bruker Daltonic, Bremen, Germany) equipped with an Agilent electrospray (ESI) ion source (Agilent Headquarters, Palo Alto, USA). The solutions containing ligand **L** ( $1.85 \times 10^{-5}$  M) and 1.0, 2.0, 5.0 and/or 10.0 equivalents of Ln(III), prepared in MeOH/H<sub>2</sub>O solvent (80/20 by

weight), were continuously introduced into the mass spectrometer source with a syringe pump (Cole-Parmer Instrument Company, Illinois, USA) at a flow rate of 2.5  $\mu\text{L}/\text{min}$ . For electrospray ionization, the drying gas was heated to 250  $^{\circ}\text{C}$  (flow rate 5  $\text{L}/\text{min}$ ), with 18 p.s.i. nebulizer pressure. The capillary voltage, capillary exit and *Skimmer* were set at 4000 V, 140-205 V and 40 V respectively. Scanning was performed from  $m/z = 200$  to 2000 and no fragmentation process was observed. In order to examine the formation of heterobimetallic complexes  $\text{L}\text{Ln}\text{Ln}'$ , solutions were prepared by adding various equivalents of each  $\text{Ln}(\text{III})$  and  $\text{Ln}(\text{III})'$  cations to a solution of **L** ( $1.80 \times 10^{-5}$  M). These samples were introduced into the mass spectrometer source with the same experimental conditions as previously described (capillary exit at 144.7 V, *Skimmer* at 40 V, positive mode).

**Spectrophotometric measurements.** A stock solution of ligand **L** ( $[\text{L}]_{\text{tot}} = 9.01 \times 10^{-6}$  M) was prepared by quantitative dissolution of a solid sample in acetic acid/acetate buffer ( $\text{pH} = 6.35 \pm 0.05$ ;  $I = 0.01$  M). Concentration of  $\text{Ln}(\text{III})$  stock solutions in methanol/water (80/20 by weight) was ascertained by complexometric titration. The solutions were acidified to below  $\text{pH} < 4$  with  $\text{H}_2\text{SO}_4$  (Carlo Erba Reagenti, 96%) before complexometric titration to avoid hydroxide precipitation. Standardized  $\text{Na}_2\text{H}_2\text{EDTA}$  solution (Fluka, p.a.) and ammonium acetate (Prolabo, rechapur) buffered medium were used with xylenol orange as indicator.<sup>85</sup> The spectrophotometric titrations of **L** with  $\text{Ln}(\text{III})$  were carried out in a Hellma quartz optical cell (2 cm). Microvolumes of a concentrated solution of  $\text{Ln}(\text{III})$  in methanol/water (80/20 by weight) buffered at  $\text{pH} = 6.35 \pm 0.05$  (acetic acid/acetate buffer) were added to 4 mL of the ligand **L** solution with an Eppendorf multipette<sup>®</sup> plus microburette. The  $[\text{Ln}]_{\text{tot}}/[\text{L}]_{\text{tot}}$  ratio was varied from 0 to about 50. Special care was taken to ensure that complete equilibration was attained. The temperature was maintained constant at  $25.0 \pm 0.2$   $^{\circ}\text{C}$  with a Haake NB 22 thermostat. UV-visible absorption spectra (220-400 nm) were recorded with a Kontron Uvikon 941 spectrophotometer.

**Analysis and refinement of spectrophotometric data.** The spectrophotometric data were processed with both the Letagrop-Spefo and Specfit programs, which adjust the absorptivities and the stability constants of the species formed at equilibrium. Letagrop-Spefo<sup>86,87</sup> uses the Newton-Raphson algorithm to solve mass balance equation and a pit-mapping method to minimize the errors and determine the best values of parameters. Specfit<sup>88,89</sup> uses factor analysis to reduce the absorbance matrix and to extract the eigenvalues prior to the multiwavelength fit of the reduced data set according to the Marquart algorithm.<sup>90,91</sup> Conditional stability constants in methanol/water (80/20 by weight) at pH = 6.35 ± 0.05 (*I* = 0.01 M) are given in this work. For the sake of simplicity, charges and protons are omitted in all the chemical equilibria given here.

**Kinetic measurements.** All kinetic measurements were performed using an Applied Photophysic stopped-flow spectrophotometer SX-18MV. The Ln(III)-exchange process was studied in methanol/water (80/20 by weight) at pH = 6.35 ± 0.05 (*I* = 0.01 M). The reactants were thermostated at 25.0 ± 0.2 °C (Lauda M12 thermostat) and mixed in a 1 cm optical cell. The data sets, averaged out of at least three replicates, were recorded and analysed with the commercial software Biokine.<sup>92</sup> This program fits up to three exponential functions to the experimental curves with the Simplex algorithm<sup>93</sup> after initialization with the Padé-Laplace method.<sup>94</sup> The exchange process of Ln(III)/L complexes (Ln = Eu and Er) with cyclohexylene-1,2-dinitrilotetraacetate (CDTA, Titriplex<sup>®</sup> IV, MERCK, p.a.) in excess was monitored at 288 nm. Eu(III) and Er(III) complexes were prepared by mixing a solution of L (6.6 × 10<sup>-6</sup> M for Eu(III); 1.24 × 10<sup>-5</sup> M for Er(III)) with 2.0 equivalents of Eu(III) and Er(III) respectively. Under these experimental conditions and using the stability constants determined in this work, [LEu<sub>2</sub>]<sub>tot</sub> and [LEr<sub>2</sub>]<sub>tot</sub> are equal to 6.21 × 10<sup>-6</sup> M and 1.04 × 10<sup>-5</sup> M, respectively. The concentration of mono- or trinuclear species is thus lower than 8% with respect to L. CDTA concentrations were varied from 1.06 × 10<sup>-4</sup> M to 4.94 × 10<sup>-4</sup> M for Eu(III) and from 3.10 × 10<sup>-4</sup> M to 1.43 × 10<sup>-3</sup> M for Er(III).



**Computational details.** The theoretical calculations were performed with Gaussian16.A03 using default algorithms, procedures, and convergence thresholds.<sup>95</sup> The ground-state geometries were optimized with the PBE0 hybrid functional<sup>96</sup> and we checked that the minimal structures were true minima (absence of an imaginary frequency) at the very same level of theory. Lanthanum atoms were described with the LANL2DZ basis set and the corresponding ECP,<sup>97</sup> while light atoms were described with SVP basis sets.<sup>98</sup>

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## Keywords

Cooperativity, heterobimetallic, homobimetallic, hydroxamate, lanthanide, supramolecular edifice, tripodal structure.

**Supporting Information Available:** Figures showing additional mass spectra (S1), spectrophotometric titrations (S2), electronic spectra (S3), variation of the absorbance for  $\text{L}Er_2$  (S4), variation of  $k_{\text{obs}}^{\text{Er}}$  (S5), isotopic distribution of the ESI-MS peaks and simulation (S6-S10), calculated structures of monometallic complexes (S11), distribution diagrams (S12), intramolecular interactions (S13), Tables (S1 and S2) with  $k_{\text{obs}}^{\text{Ln}}$  data are given. This material is available free of charge via the Internet at <http://chemistry-europe.onlinelibrary.wiley.com>.

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