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Discriminating between lanthanide ions: self-assembly of heterodimetallic triple-stranded helicates

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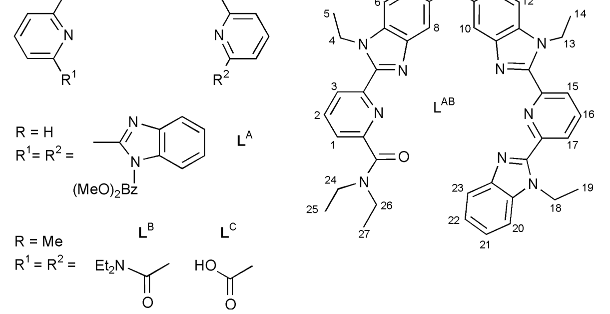
A bis-terdentate segmental ligand has been designed which self-assembles with lanthanide ions of different size to yield heterodimetallic triple-stranded helicates

Luminescent lanthanide complexes are increasingly used as diagnostic tools in biomedical analysis, as responsive analytical systems,[1] as luminescent labels for enhanced imaging of cancer[2] or for fluoroimmunoassays,[3] and in colour-tailored fluorophores for simultaneous detection of multiple targets on DNA strands.[4] In this context, heterodimetallic molecules are potentially interesting because they would combine two luminescent or one magnetic and one luminescent centres in one probe. The recognition of one specific lanthanide ion in the presence of others is, however, a very difficult challenge, in view of the limited difference in the size of these ions and of their similar chemical properties.[5] We have previously shown that planar tridentate ligands based on the bis(benzimidazole)-pyridine framework display a size-discriminating effect, resulting in an unusual selectivity for the mid-range Ln^{III} ions.[6] On the other hand, the stability of complexes with the diethylamide derivative of 2,6-pyridine dicarboxylic acid smoothly increases along the Ln^{III} series.[7] In parallel, we have designed symmetric ditopic ligands (Scheme 1) which self-assemble with Ln^{III} ions to yield thermodynamically stable triple-stranded homodimetallic helicates in organic solvents (L^A, L^B)[8,9] or in water (L^C).[10] Combining the two approaches, we present here the synthesis of the unsymmetrical ditopic ligand L^{AB}, bearing one benzimidazole–pyridine–carboxamide unit programmed to complex preferentially the smaller lanthanide ions and one, less strongly coordinating, bis(benzimidazole)pyridine moiety which interacts preferentially with the larger Ln^{III} ions. We demonstrate that this molecular engineering indeed leads to the simultaneous recognition of two different lanthanide ions provided their size difference is large enough.

Ligand L^{AB} has been synthesized using the strategies developed earlier[8,9] and has been fully characterised.† Its interaction with Ln^{III} ions in acetonitrile was initially monitored by ^1H NMR spectroscopy, titrating L^{AB} by La^{III} in the range $R = [La]_t/[L^{AB}]_t = 0.3–1.0$. When the metal ion is added to the ligand, the signals of the latter broaden and diminish, while bands attributable to two different species appear. Analysis of these spectra and comparison with the data previously reported for the complexes with L^A and L^B [8,9] lead us to conclude that these species correspond to the expected isomers (HHH)-$[La_2(L^{AB})_3]^{6+}$ and (HHT)-$[La_2(L^{AB})_3]^{6+}$.‡ All the signals for the (HHH)[11] species are observed: five triplets for methyl groups 5, 14, 19, 25 and 27; ten doublets of quartets for the diastereotopic methylene protons 4, 13, 18, 24 and 26; two doublets for protons 9 and two singlets for protons 8 and 10. For the (HHT) species, some of the signals overlap so that all the resonances cannot be identified, but the predicted six singlets are observed for protons 8 and 10. At the stoichiometric ratio $R = 2/3$ the proportion of the (HHH) and (HHT) species amounts to 85 and 15%, respectively, which significantly deviates from the statistics (25, 75%) and suggests a preference for the coordination of each lanthanide to three identical terdentate segments of the ligands. A similar titration of L^{AB} with Lu^{III} reveals (i) a less important proportion of the (HHH) 2:3 complex (65% for $R = 2/3$) and (ii) the presence of other species with $Lu:L^{AB}$ stoichiometry 2:2, 1:2 and, possibly, 1:3, pointing to (HHH)-$[Lu_2(L^{AB})_3]^{6+}$ being less stable than its La^{III} counterpart. The spectrum of a solution containing a $La:Lu:L^{AB}$ ratio equal to 1:1:3 is comprised of a relatively small number of signals (Fig. 1) revealing the presence of a single major species (*ca.* 90%) corresponding to (HHH)-$[LaLu(L^{AB})_3]^{6+}$. Weak interstrand NOE effects between H^4/H^{11}, H^7/H^{13}, and H^{13}/H^{18} confirm the helical wrapping of the ligands[12] and detailed analyses of the multiplicities and chemical shifts unambiguously points to Lu^{III} being coordinated to the amide groups of the three ligand strands, as planned in the ligand design.



Scheme 1

The speciation in solutions 10^{-3} mol dm^{-3} in acetonitrile featuring a stoichiometric ratio $Ln:Ln':L^{AB}$ equal to 1:1:3 was further investigated by ES-MS spectroscopy. The spectra mainly display signals arising from the homo- and heterodimetallic species, which are easily identified by their perchlorate adducts: $\{[Ln_2(L^{AB})_3](ClO_4)_n\}^{(6-n)+}$, $\{[Ln'_2(L^{AB})_3](ClO_4)_n\}^{(6-n)+}$ and $\{[LnLn'(L^{AB})_3](ClO_4)_n\}^{(6-n)+}$ (n =

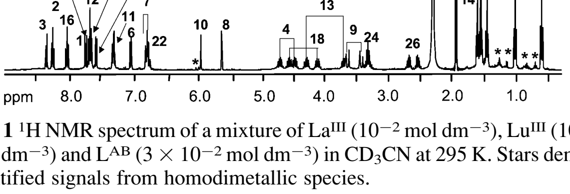


Fig. 1 ^1H NMR spectrum of a mixture of La^{III} (10^{-2} mol dm^{-3}), Lu^{III} (10^{-2} mol dm^{-3}) and L^{AB} (3×10^{-2} mol dm^{-3}) in CD_3CN at 295 K. Stars denote identified signals from homodimetallic species.

Table 1 Percentage of heterodimetallic species in acetonitrile as determined by ES-MS (left) in 10^{-3} mol dm^{-3} solutions and ^{1}H NMR (right) in 10^{-2} mol dm^{-3} solutions

Ln	Ln′	ES-MS	^{1}H NMR
La	Lu	89	90
La	Yb	—[a]	87
La	Er	79	81
La	Eu	65	—[a]
Pr	Er	70	—[a]
Eu	Lu	57	65
Eu	Er	55	—[a]
Eu	Tb	51	—[a]

[a] Not determined.

0–3). The percentages of the heterodimetallic species are reported in Table 1 for several LnLn′ couples, along with those determined by ^{1}H NMR spectroscopy on 10^{-2} mol dm^{-3} solutions in CD_3CN. The two sets of data are in good agreement, pointing to stable helicates, since the speciation does not change in the range 10^{-2}–10^{-3} M. For several systems, the proportion of heterodimetallic species deviates substantially from the statistical distribution (50%; $\Delta G(298) = -3.4$ kJ mol^{-1} for the equilibrium $Ln_2 + Ln'_2 \rightleftharpoons 2LnLn'$) pointing to an enrichment in the heterodimetallic complexes, which is largest for LaLu ($\approx$90%; $\Delta(\Delta G) = -7.4$ kJ mol^{-1}). In fact, this enrichment is a relatively smooth function of the difference between the ionic radii of the two lanthanide ions as shown on Fig. 2,[13] in line with the stability data reported for the monometallic compounds.[6,7] A substantial proportion of heterodimetallic helicate ($>$70%; $\Delta(\Delta G) < -0.8$ kJ mol^{-1}) is obtained when Δr_i is larger than 0.1 Å.

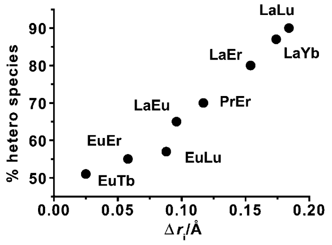


Fig. 2 Percentage of heterodimetallic species as a function of the ionic radius difference for nine-coordinate Ln^{3+}.[14]

Finally, we were able to obtain single crystals suitable for X-ray diffraction for the LaEu heterodimetallic helicate.§ Its molecular structure presented in Fig. 3 fully confirms the structural data obtained in solution, the three ligand strands being helically wrapped around the two metal ions and the three amide functions being coordinated to the heaviest metal ion, Eu^{III}. Bond lengths and angles of the coordination polyhedron are standard for the two ions and compare well, after correction for ionic radius differences, with those found in the previously reported homodimetallic structures of $[Eu_2(L^A)_3]^{6+}$,[8] $[Tb_2(L^B)_3]^{6+}$,[9] and $[Ln_2(L^C\text{-}2H)_3]$ (Ln = Eu, Tb, Yb).[10]

In conclusion, we have presented here the first design of an unsymmetrical ditopic ligand coded for the supramolecular recognition of two different lanthanide ions. A recent paper reported on the first structurally characterized example of a heterodimetallic LaYb complex obtained with a potentially decadentate Schiff base.[14] However, the corresponding crystals were isolated from a mixture of homo- and hetero-dimetallic complexes, that is, this ligand displays unspecific binding to any lanthanide ion. Since synthetic strategies for the substitution of the ditopic symmetrical receptors at the pyridine 4-position are at hand,[15,16] we are working toward achieving a better fine-tuning of the selectivity of unsymmetrical receptors, allowing the recognition of pairs of lanthanide ions with a difference in their ionic radius smaller than 0.1 Å.

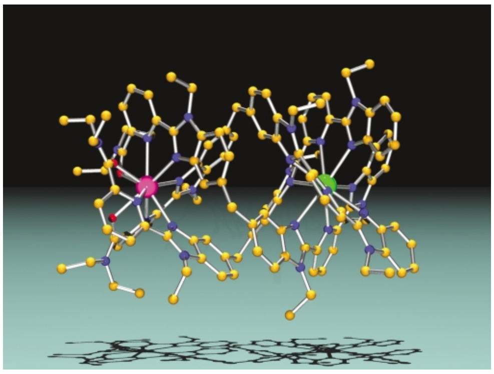


Fig. 3 Molecular structure of $[LaEu(L^{AB})_3](ClO_4)_6\cdot 3MeCN\cdot 3EtCN$.

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Notes and references

† Calc. for $C_{43}H_{43}N_9O\cdot 0.5H_2O$: C, 72.65; H, 6.24; N, 17.73. Found: C, 72.51; H, 6.28; N,17.60%.

‡ HHH stands for *head-head-head* and means that the three ligand strands bind each La(III) ion through the same functional end; HHT stands for *head-head-tail* and indicates that two ligand strands bind one La(III) ion through the same functional end whereas the third ligand binds through the other functional end. These two isomers have different symmetry and they may be readily recognised in the NMR spectra.

§ *Crystal data*: $C_{144}H_{153}N_{33}O_{27}Cl_6EuLa$, $M = 3281.56$, monoclinic, space group $P2_1/c$, $a = 14.759(3)$, $b = 26.369(5)$, $c = 37.217(7)$ Å, $\beta = 90.12(3)°$, $V = 14\,484(5)$ Å^3, $Z = 4$, $\mu = 0.915$ mm^{-1}, $T = 143(2)$ K, $F(000) = 6744$, 46327 reflections collected, 17176 independent reflections, 1805 parameters, $R1\ [I > 2\sigma(I)] = 0.0669$, $wR2$ (all data) = 0.1981. Mean distances: Eu–N 2.603(7), Eu–O 2.395(6), La–N, 2.648(7) Å. Due to the large number of parameters, the structure has been refined using the full-matrix-block on F^2 method with fixed anisotropic displacement parameters. Solvent molecules occupy what would have been voids in the crystal lattice and are not well defined.

CCDC reference number 172173. See http://www.rsc.org/suppdata/cc/b1/b109065h/ for crystallographic data in CIF or other electronic format.

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