

Inclusion complexes of trivalent lutetium cations with an acidic derivative of per(3,6-anhydro)- α -cyclodextrin†

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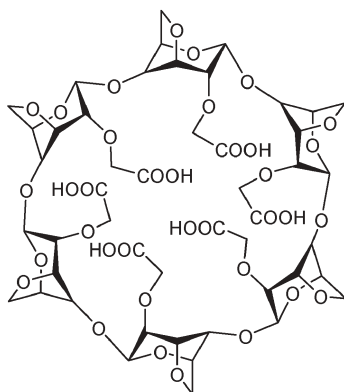
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The cyclodextrin derivative (hexakis (2-*O*-carboxymethyl-3,6-anhydro)- α -cyclodextrin) forms mono- and bimetallic complexes with lutetium(III) in aqueous solution; the X-ray structure of the binuclear complex $[\text{Lu}_2(\text{ACX})(\text{H}_2\text{O})_2]$ is the first example of a lanthanide–cyclodextrin inclusion complex.

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six (α), seven (β), or eight (γ) D-glucose rings bonded through α (1–4) linkages. They are biocompatible, have moderate solubility in water and are known to host organic compounds or fragments in their hydrophobic cavity.¹ In recent years, examples of lanthanide complexes with CD derivatives have been described in the field of luminescence,² discrimination of enantiomeric substrates,³ DNA hydrolysis,⁴ and MRI.⁵ The cation coordination is most often achieved with an appended lanthanide chelating group based on edta, dota or nitrogen-donor aromatics. The interaction of the lanthanide cation with the cyclodextrin itself is seldom reported due to the fact that the hydrophobic cavity of the CD is not suited for cations.^{6,7}

The chemical modification of native CDs, leading to per-3,6-anhydro derivatives,⁸ drastically affects the structure of the host providing an hydrophilic cavity capable of metal binding.⁹ To reinforce the affinity of these hosts for hard metal cations, the residual hydroxyl groups have been substituted by carboxymethyl groups to obtain hexakis(2-*O*-carboxymethyl-3,6-anhydro)- α -cyclodextrin named ACX (Scheme 1),¹⁰ which is highly soluble in water.



Scheme 1 ACXH₆ structure.

In this Communication, we report on solid state and solution studies of trivalent lutetium complexes with this α -CD derivative that combines an hydrophilic cavity with six carboxylate arms to coordinate hard lanthanide ions.

The $[\text{Lu}_2(\text{ACX})(\text{H}_2\text{O})_2]$ complex was obtained as colourless crystals suitable for X-ray diffraction analysis, by slow solvent evaporation of an aqueous 2 : 1 solution of $\text{Lu}(\text{OTf})_3$ and ACXNa_6 . Fig. 1 shows the structure of this neutral complex in

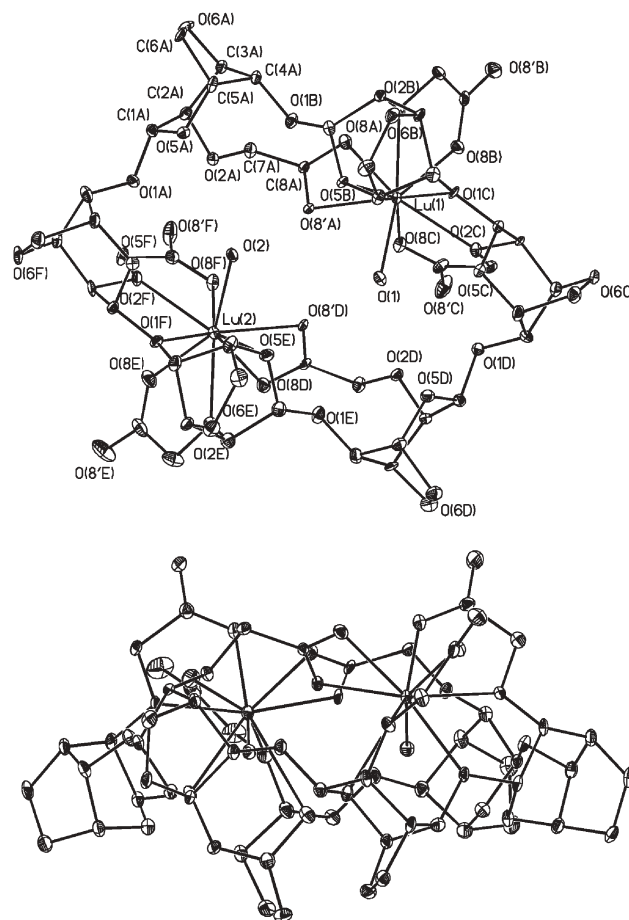


Fig. 1 Crystal structure of $[\text{Lu}_2(\text{ACX})(\text{H}_2\text{O})_2]$; hydrogen atoms are omitted for simplicity. Selected bond lengths (in Å) : Lu(1)–O(8C) 2.245(5), Lu(1)–O(8B) 2.245(4), Lu(1)–O(8'A) 2.272(4), Lu(1)–O(1) 2.318(4), Lu(1)–O(1C) 2.392(4), Lu(1)–O(2C) 2.394(5), Lu(1)–O(8A) 2.403(5), Lu(1)–O(2B) 2.420(4), Lu(1)–O(5B) 2.728(4), Lu(2)–O(8E) 2.232(4), Lu(2)–O(8F) 2.236(5), Lu(2)–O(8'D) 2.283(4), Lu(2)–O(2) 2.325(4), Lu(2)–O(2F) 2.384(5), Lu(2)–O(1F) 2.390(4), Lu(2)–O(8D) 2.391(5), Lu(2)–O(2E) 2.433(5), Lu(2)–O(5E) 2.825(5).

† Electronic supplementary information (ESI) available: synthesis and characterization of ACXNa_6 , crystallographic data in .cif format. See <http://www.rsc.org/suppdata/cc/b4/b414870c/>
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which two lutetium cations are encapsulated inside the modified CD cavity. Both Lu(III) ions have crystallographically identical coordination environments; they are nine-coordinated by oxygen atoms. Each cation is bound to four oxygen atoms of carboxylate groups (two are monodentate and one is bidentate), to a glycosidic oxygen atom O(1), to two oxygens O(2) of the OCH₂ groups, and to one O(5) of the D-glucopyranoside heterocycle. A ninth coordination site is occupied by one water molecule and the coordination polyhedron can be best described as a distorted capped-square antiprism. The distance between the two Lu ions is 5.74 Å and is longer than the ones found in other macrocyclic binuclear lutetium complexes.¹¹ Therefore, the complex can be seen as two independent subunits. The average distances Lu–O(monodentate carboxylate) and Lu–OH₂ are respectively 2.24 and 2.32 Å. They are slightly shorter than similar Lu–O distances reported in the literature.¹² Lu–O(2) and Lu–O(1) distances fall in the range 2.384–2.433 Å and are also slightly shorter than Ln–O(ether) distances reported for crown-ether or linear polyether adducts with lanthanides.¹³ Lu–O(5) distances are the longest, probably due to steric constraints imposed by the intracyclic position of these oxygen atoms. These data show that the two lutetium cations are embedded in the cavity and have strong interactions with the carboxylate functions as well as with neutral oxygen atoms of the CD framework.

Solution studies were carried out in order to determine whether this structure is retained in water. First, the protonation constants of the ligand ACX were determined by potentiometry at 298 K in 0.1 mol L⁻¹ KCl [$pK_{a1} = 3.1(2)$, $pK_{a2} = 3.5(1)$, $pK_{a3} = 4.18(8)$, $pK_{a4} = 4.40(6)$, $pK_{a5} = 5.02(7)$, $pK_{a6} = 5.40(7)$]. The stability constants of lutetium complexes were then obtained from potentiometric titrations of LuCl₃ : ACX mixtures for different metal to ligand ratios ($\rho = \text{metal/ligand}$). When $\rho = 1$, only mononuclear complexes are necessary to analyze the experimental data, whereas for $\rho > 1$ the formation of the binuclear complex is clearly evidenced. The stability constants are summarized in Table 1.

The formation of mono- and binuclear lutetium complexes is confirmed by electrospray ionization mass spectrometry (ESI-MS). The stability constant of the mononuclear lutetium complex is $\log \beta = 7.4$ and is close to those obtained with tripodal ligands bearing three carboxylates as coordinating groups ($\log \beta_{R-TOTA-Gd} = 7.0(2)$).¹⁴ This suggests that only three carboxylates are coordinated to the lutetium in the mononuclear complex, leading to a structure similar to the one obtained in the solid state for the binuclear complex but with only one compartment occupied by a lutetium cation. Accordingly, the three protonation constants of

Table 1 Stability constants of Lu–ACX complexes in water at 298 K in 0.1 mol L⁻¹ KCl. $\beta_{mnp} = [\text{Lu}_m(\text{ACX})_n\text{H}_p]/[\text{Lu}]^m[\text{ACX}]^n[\text{H}]^p$

Complex	<i>m</i>	<i>n</i>	<i>p</i>	log β_{mnp}
Lu(ACX)	1	1	0	7.4(1)
Lu(ACX)H	1	1	1	12.0(1)
Lu(ACX)H ₂	1	1	2	15.7(1)
Lu(ACX)H ₃	1	1	3	19.3(2)
Lu(ACX)(OH)	1	1	-1	1.3(1)
Lu ₂ (ACX)	2	1	0	10.8(3)
Lu ₂ (ACX)(OH)	2	1	-1	6.4(1)
Lu ₂ (ACX)(OH) ₂	2	1	-2	1.5(1)

Lu(ACX) would correspond to the protonations of the three non-coordinated carboxylate functions. The stepwise formation constant of the binuclear complex ($K_2 = [\text{Lu}_2(\text{ACX})]/([\text{Lu}][\text{Lu}(\text{ACX})])$) is $\log K_2 = 3.4$ and is lower than $\log \beta_{110}$. It is thus more difficult to introduce the second lutetium in the cavity, probably due to electrostatic repulsion between the two metals. Soluble hydroxocomplexes are formed at low pH (~5). The water molecule coordinated to the metal is more acidic in ACX complexes than in the aqua ion. Indeed, the hydrolysis constant of the mononuclear complex is -6.1 compared to -7.94 for the aqua ion $[\text{Lu}(\text{H}_2\text{O})_8]^{3+}$.

¹H NMR spectra are also characteristic of an evolution in complex species as the lutetium concentration increases. Indeed, when the metal to ligand ratio is less than 1.5, the signals of free ACX are highly broadened, which is a typical feature of a dynamic process (either an equilibrium between several species or an intramolecular move of the cation into the ligand cavity). When more Lu is added, the spectrum changes dramatically and lots of sharp resonances appear, which have been assigned, by 2D-NMR classical experiments, to a C₂-symmetry complex compatible with Lu₂(ACX) characterized in the solid state. The same experiment carried out with the paramagnetic ytterbium cation, also shows the formation of an Yb(ACX)₂ complex of C₂-symmetry in excess of metal. The mononuclear complex (detected for $\rho < 1.3$) is totally dissymmetric. Indeed, each sugar cycle gives different resonances (C₁ symmetry) confirming that the lanthanide ion is not at the centre of the CD cavity and thus not coordinated to every carboxylate functions.

In summary, we have described the first example of a lanthanide cyclodextrin inclusion complex. Indeed, the crystal structure of the $[\text{Lu}_2(\text{ACX})(\text{H}_2\text{O})_2]$ complex reveals that each lutetium cation interacts with three carboxylate arms as well as with four neutral oxygen atoms of the cyclodextrin framework, demonstrating the important role of the cavity in the lanthanide ion coordination. Solution studies have confirmed the formation of this bimetallic species in water, together with the monometallic complex, and afford a predictive speciation model that allows the control of the number of encapsulated cations in the cyclodextrin. The complexes of other lanthanide cations are currently under investigation. Furthermore, preliminary studies with biological metal ions, like Ca^{II} and Cu^{II}, show an interesting selectivity of ACX towards Ln^{III}.[‡]

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Notes and references

[‡] Crystal data: $[\text{Lu}_2\text{C}_{48}\text{H}_{54}\text{O}_{36}(\text{H}_2\text{O})_2](\text{H}_2\text{O})_{22.37}$, $\text{Lu}_2\text{C}_{48}\text{H}_{102.73}\text{O}_{60.37}$; $M = 1995.81$, crystal size $0.1 \times 0.1 \times 0.5$ mm; monoclinic, space group $P2(1)$, $a = 14.241(2)$ Å, $b = 13.931(2)$ Å, $c = 20.098(2)$ Å, $\alpha = 90^\circ$, $\beta = 109.17(1)^\circ$, $\gamma = 90^\circ$, $V = 3766.3(6)$ Å³, $Z = 2$, $D_c = 1.760$ mg m⁻³, $\mu = 2.728$ mm⁻¹. 10716 independent reflections ($\theta_{\text{max}} = 28.9^\circ$) were collected at 223 K. Refinement using the SHELXTL 5.05 package on all

data converged at $R_1 = 0.0316$, $wR_2 = 0.0852$. Data were collected using a Bruker SMART CCD area detector three-circle diffractometer (Mo- $K\alpha$ radiation, $\lambda = 0.71073$ Å, graphite monochromator). CCDC reference number 251891. See <http://www.rsc.org/suppdata/cc/b4/b414870c/> for crystallographic data in .cif or other electronic format.

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