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# Lanthanide Identity Governs Guest-Induced Dimerization in Ln<sup>III</sup>[15-MC<sub>Cu</sub><sup>II</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> Metallacrowns

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Abstract: [SB1] Series of lanthanide-containing metallic coordination complexes are frequently presented as structurally analogous, due to the similar chemical and coordinative properties of the lanthanides. In the case of chiral (Ln<sup>III</sup>[15-MC<sub>Cu</sub><sup>II</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> metallacrowns (MCs), which are well established supramolecular hosts, the formation of dimers templated by a dicarboxylate guest (muconate) in solution of neutral pH is herein shown to have a unique dependence on the identity of the MC's central lanthanide. Calorimetric data and nuclear magnetic resonance diffusion studies demonstrate that MCs containing larger or smaller lanthanides as the central metal only form monomeric host-guest complexes whereas analogues with intermediate lanthanides (e.g., Eu, Gd, Dy) participate in formation of dimeric host-guest-host compartments. The driving force for the dimerization event across the series is thought to be sensitive to the size of the lanthanidea competition between formation of highly stable MCs (larger lanthanides) and optimally linked bridging guests (smaller lanthanides).

## Introduction

Synthetic supramolecular complexes with a hydrophobic cavity are attractive for their likeness to the hydrophobic active sites of some enzymes, which are highly substrate-selective via a combination of appropriate chemical interactions balanced with suitable shape and size. Along this vein, supramolecular complexes may take the approach of utilizing the steric and chemical conditions of such a hydrophobic compartment to enhance host-guest selectivity, including several examples of metal-based supramolecular catalysts.<sup>[11]</sup> Understanding the noncovalent interactions that drive formation of molecular nanocompartments in solution is critical for development of the function and applications of such systems.

Metallacrowns (MCs), a class of metallamacrocycles that are structurally analogous to crown ethers, self-assemble typically from hydroximate ligands and transition metal ions to form an IM-N-O] repeating unit in place of the more familiar [C-C-O] repeat of crown ethers.<sup>[2]</sup> Within the subgroup known as 15-metallacrown-(15-MC-5), the incorporation of chiral L-phenylalanine 5 hydroximate (pheHA) ligands with Cu(II) and a central lanthanide coordinated by the oxime oxygens creates a "hand-like" amphipathic metallacrown with a hydrophilic face and an opposing hydrophobic face, which is capable of selectively recognizing various moieties, such as nitrates, carboxylates, and chiral amino acids.<sup>[3]</sup> Crystallographically, we observed these MCguest complexes were capable of selectively sequestering dicarboxylate guests of appropriate size within the hydrophobic interior cavity of an MC dimer (Scheme 1) [4] Our recent investigation of the behavior of metallacrown-dicarboxylate systems in aqueous solution demonstrated that (Gd<sup>ill</sup>[15- $MC_{Cu}^{II}_{N(L-pheHA)}$ -5])<sup>3+</sup> (**Gd-MC**) could form a dimeric 2:1 MC<sub>2</sub>-guest complex at neutral pH that remained in equilibrium with a 1:1 MCguest complex.<sup>[5]</sup> Further evaluation of the solution behavior of this system when different lanthanides occupy the central MC cavity is warranted.



Scheme 1: Illustrations of (Ln<sup>III</sup>[15-MC<sub>Cu</sub><sup>II</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> (A and B),<sup>[4a]</sup> dicarboxylate guest (C), and host-guest-host dimeric compartment (D).<sup>[4c]</sup>

Structurally, lanthanides frequently are treated as interchangeable - often existing as 3<sup>+</sup> cations (at neutral pH and ambient temperatures) with similar coordination geometries that lead to the ability to synthesize a series of structurally analogous compounds varying only by identity of the lanthanide. However, the trivalent lanthanides decrease in radius by almost 0.2 Å across the series (1.16 Å (La<sup>III</sup>) to 0.98 Å (Lu<sup>III</sup>) for eight-coordinate ions) and increase in radius with greater coordination number (for La<sup>III</sup>, radius increases from 1.10 Å to 1.27 Å for coordination number 7 to 10)<sup>[6]</sup> which can lead to slight differences in structure and stability. Within the series of isostructural 15-MC-5 pheHAbased metallacrowns, as the lanthanide ion radius increases. the diameter of the MC ring cavity expands to accommodate the larger ions, with a corresponding increase in planarity of the MC ring<sup>[7]</sup> and reduced thermodynamic stability of the complex with respect to Ln coordination in the central cavity.<sup>[8]</sup> Therefore, we wished to examine implications of different lanthanides for the solution-state formation of the MC<sub>2</sub> dimer, expecting small to moderate differences in the thermodynamic parameters, when compared to the previously published Gd-MC. Much to our surprise, we observed that with certain lanthanides, the 15-MC-5 metallacrowns were completely unable to participate in guestinduced dimerization. We present our results examining this effect by two complementary techniques: calorimetry and NMR.

## **Results and Discussion**

#### **Calorimetry**

Since calorimetry has been shown to be an accurate and reliable technique to determine both the species and their binding constants in solution<sup>[3b, 5, 9]</sup> we resorted to Isothermal Titration Calorimetry (ITC), as done previously with Gd-MC.<sup>[5]</sup> Also, since it was proved that the chain length is the crucial parameter for the formation of the compartment in solution, we focused our attention on the interaction of muconate (Muc) with a series of (Ln<sup>III</sup>[15-MC<sub>Cu</sub><sup>II</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> (Ln = La, Nd, Sm, Eu, Dy, Ho) metallacrowns to assess whether the central ion of the cavity affected the formation of the complex species in solution. The power curves for the Eu-MC/, Sm-MC/ and Nd-MC/Muc systems are reported in Fig. S1-S3 as an example. As we titrate the guest into the Ln-MC, the formation of the 2:1 (MC-guest-MC) compartment is more favored in the earliest region at very low guest/host ratio. To analyze this region, we had to expand the very initial region of the full scan titration since the initial points of a power curve unfortunately suffer from the so called 'first injection anomaly';[10] thus, if we were to exclude the first one-two points from a full scan titration, we would neglect the entire set of points collected with an 'expanded' titration. On the other hand, such a procedure, while permitting collection of a sufficient number of points in the region of interest, poses a problem since the software provided by ITC manufacturers does not provide capability for the combined refinement of different titrations. The inset of Fig. S1, S2 or S3 shows a titration that expands the very first region of the full scan curve. To refine full scan and expanded titrations together we used HypCal,<sup>[11]</sup> a software, set up *ad hoc* in our research group, that allows for the simultaneous refinement of calorimetric data collected from different titrations. Experiments were designed so that full scan and expanded titrations would have comparable power values; this avoids weighting data points (or titrations) which might introduce artifacts. 1:1 and 2:1 species were tested both separately and in combination and led to the results summarized in Fig. 1 as well as in Table S1.

Despite numerous attempts (change of Muc/Ln-MC ratios and concentrations), some Ln-MCs unvaryingly failed to show the formation of the MC-guest-MC species (Fig. 1). Ho-MC represents a case of its own. Although there were indications of formation of the 2:1 (Ho-MC)<sub>2</sub>-Muc species, its percentage was so low as to hamper a satisfactory determination; in other words, its exclusion did not alter significantly the statistical parameters, that are used as a criterion to accept/reject a model.

The first inclusion step is entropically favored and driven for all Ln-MCs, regardless of whether or not the process goes any further to yield the (Ln-MC)<sub>2</sub>-Muc species, and this indicates that the inclusion of muconate into the MC cavity involves a significant desolvation. A (Ln-MC)2-Muc species is detected for Eu, Gd, and Dy only. Unlike for the formation of MC-Muc, for this second step (i.e. the formation of a compartment), the enthalpic contribution is always favorable whilst the entropic contribution is significantly lower than that determined for the first step. This indicates that (i) the entropy gained when desolvation of an MC is induced by a system (Ln-MC-Muc) that has already desolvated is sizably smaller than when induced by a free guest (Muc) and (ii) the compartment involves additional intramolecular (favorable) interactions that are not present in the 1:1 species. This may be explained by assuming that in solution the (Ln-MC)<sub>2</sub>-Muc species maintains the arrangement found in the solid state in which the phenyl substituents of the metallacrown contact one another like two folded hands forming a compartment that incorporates the dicarboxylate allowing the phenyl groups from the two metallacrown units to give rise to a favorable  $\pi$ - $\pi$  interaction<sup>[4]</sup> (Fig. S16). In summary, the lower entropic contribution of the second step would result from a lesser desolvation as well as from the formation of a more rigidified ensemble.



Figure 1. Thermodynamic parameters for the species obtained by titrating muconate solution into a solution of the proper Ln-MC host, for each of the Ln-MCs examined, at 25 °C in buffered aqueous solution (pH 7.2, 50 mM MOPS). [SB3]Conditions and procedure are reported in SI.

In any case the  $\Delta G^{\circ}$  value of the second step for the three **Ln-MC** systems in which the formation of a compartment is detected is always larger than that of the first step. Interestingly, such a trend had already been found for compartments formed by **Gd-MC** with a series of dicarboxylates, including muconate, in a previous work<sup>[5]</sup> and is here observed again for both the Eu and Dy (**Ln-MC**)<sub>2</sub>-Muc species. This further corroborates the interpretation of the thermodynamic data as it shows that in this step there is a degree of cooperativity (*i.e.*<sub>a</sub> an extra-stabilization with respect to the first step) that ranges from 3-4 kJ mol<sup>-1</sup> for the Eu and Dy species to about 6 kJ mol<sup>-1</sup> for the Gd system.

#### Paramagnetic NMR

Despite line broadening of NMR signals due to the presence of Cull in the metallacrown ring and LnIII in the central cavity, we are able to collect paramagnetic <sup>1</sup>H NMR spectra for several species of the (Ln<sup>III</sup>[15-MC<sub>Cu</sub>II<sup>I</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> series (La, Nd, Sm, Eu, Tb, Dy, Ho, Er) and Y<sup>III</sup> (Fig. S10). Inversion recovery experiments determined the T<sub>1</sub> (longitudinal) relaxation time for each proton in the complex (Table S2). When subjected to the gradient sequence of the diffusion ordered spectroscopy experiment (DOSY), proton relaxation in Y and La complexes (although these have diamagnetic central metals) was too attenuated for collection of PGSE NMR. Based on experience with other paramagnetic MC systems,<sup>[12]</sup> we attribute the sharpening of spectral lines for certain Ln-MCs (i.e., with paramagnetic central metals such as Nd or Sm) to additional coupling between the central paramagnetic lanthanide and the copper(II) coupled system. According to relaxation rate principles,<sup>[13]</sup> the coupling between a fast relaxing and a slow relaxing metal results in the increase of the electron relaxation rate of the slowest, which in

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turn slows down the relaxation of the nearby <sup>1</sup>H nuclei.<sup>[12]</sup>[SB4] We determined that three of the species with the longest relaxation times (Nd, Sm, Eu) were suitable for study with a pulsed gradient spin echo (PGSE) NMR sequence. We were only able to collect data for one species (**Eu-MC**) that was shown by ITC to participate in formation of the (**Ln-MC**)<sub>2</sub>-Muc species, since the very fast relaxation times of **Dy-MC** and **Gd-MC** species proved unsuitable for analysis using our pulsed gradient sequence.

In the host-guest equilibrium of the **Ln-MC**-carboxylate system, the observed value of D depends on the coefficients  $D_{MC}$ ,  $D_{1:1}$  and  $D_{2:1}$ , where MC, 1:1 and 2:1 refer to free MC, 1:1 (**Ln-MC**)-Muc (or MC-corbate) adduct, and 2:1 the dimeric (**Ln-MC**)<sub>2</sub>-Muc capsule, respectively. The observed D depends also on the relative amount of each species in solution, in turn depending on the formation constants and molar fractions ( $\chi$ ) of the different species (eq. 1):

$$D_{obs} = D_{MC}\chi_{MC} + D_{1:1}\chi_{1:1} + D_{2:1}\chi_{2:1}$$
(1)

In the presence of the internal standard DMSO, however, it is convenient to use the following (eq. 2):

$$D'_{obs} = (D'_{MC} \cdot \mathscr{M}_{MC} + D'_{1;1} \cdot \mathscr{M}_{1:1} + D'_{2:1} \cdot \mathscr{M}_{2:1}) \cdot \frac{1}{100}$$
(2)

where the D' values of MC, 1:1 and 2:1 species correspond to  $\frac{D_{species}}{D_{DMSO}}$ . D'<sub>obs</sub> is  $\frac{D_{abs}}{D_{DMSO}}$  which equals the ratio of the exponential decay parameters of the MC and DMSO in the PGSE experiment at the titration point at which the % values of the species are calculated, *i.e.*, from the formation constants of the MC/muconate adducts obtained using speciation information obtained by calorimetry (see SI; speciation diagrams shown as Figs. S6-S9). As described by Stokes-Einstein theory, the decrease of D<sub>obs</sub> (and consequently of  $\frac{D_{obs}}{D_{DMSO}}$ ) can be attributed to an increase in the size of the MC over the course of the titration.<sup>[14]</sup>

The D'obs values for the Eu-MC, Nd-MC, and Sm-MC over the course of titration with potassium muconate as dicarboxylate guest as well as titration of Eu-MC with potassium sorbate, as monocarboxylate, are presented in Figure 2 as an average of 3 titrations. [SB5] Minimal change in diffusion is observed for titrations (Figure 2) of Sm-MC and Nd-MC with Muc (~2%), but a more significant decrease is observed for the Eu-MC/Muc system (~8%). Precipitation of the complex occurred at titration points beyond those shown. A control titration with potassium sorbate as guest with Eu-MC indicates that a monocarboxylate does not induce a change in the diffusion and that the observed decrease with the dicarboxylate is a valid effect. Simple <sup>1</sup>H NMR for this titration shows changes in chemical shift for both the MC and sorbate, implying an interaction between the two species is maintained (Fig. S11). As compared to the NMR spectra of Sm-MC and Nd-MC, the observed signal for the Eu-MC was less intense due to its shorter T1. This decreased sensitivity required more concentrated samples (6 mM, as opposed to 2 mM) as well as adjustment of experimental parameters, in which a very short relaxation delay parameter was employed (see SI).

To evaluate reliability of the NMR and test whether ITC and NMR data reinforce one another, equation 2 was used to determine  $D'_{MC}$ ,  $D'_{1:1}$  and  $D'_{2:1}$  coefficients by least square fit of the  $D'_{obs}$  values obtained from the muconate titrations with % values from ITC used as fixed parameters in the least square analysis. Regression analysis showed Nd and Sm titrations fit very well to a 2 species model (free MC and 1:1 adduct (**Ln-MC**)-Muc), indeed consistent with calorimetric data which excluded the formation of 2:1 (**Ln-MC**)<sub>2</sub>-Muc adducts. On the other hand, a very good fit of data for the titration of Eu was obtained by considering the presence of all three MC species: free metallacrown, 1:1 and 2:1

species. The exclusion of the 2:1 species did not provide a good fit to the experimental data (details in SI; Fig. S12-S14).

The dimerization of a spherical species that results in a sphere of twice the original volume is expected to decrease D (increase radius) and therefore decrease D' by a factor of 1.26. [SB6]Our least squares analysis of the Eu-MC system indicated that  $D'_{2:1}$  is lower than  $D'_{MC}$  by a factor of 1.14. The difference from the theoretical value is, therefore, a factor of just 0.12 corresponding to a difference in radius of ca. 0.7 Å, which is less than a solvation shell around the MC dimer. The deviation from theoretical behavior may be accounted for by structural aspects, such as solvent effects (NMR was performed in 50% MeOD solution), which may alter the side chain interactions, or deviation from sphericity of MC particles. If the latter explanation is considered, measurements from crystal structures<sup>[4a, 4c]</sup> show that the monomer could be considered more oblate (Scheme 1B), which could lead to more resistance to diffusion, and that the dimer is more spherical (Scheme 1D), with the effect that the dimer would diffuse faster than anticipated.



**Figure 2:** Change in diffusion coefficient of the Ln<sup>III</sup>[15-MC<sub>Cu</sub><sup>II</sup><sub>N(L-pheHA)</sub>-5])<sup>3+</sup> species, characterized by D<sup>\*</sup><sub>0bs</sub> = D<sub>obs</sub>/D<sub>DMS0</sub> as it is titrated with muconate or sorbate guest as determined by NMR. Dark gray squares: Nd-MC (2 mM) with 40 mM Muc; gray triangles: Sm-MC (2 mM) with 40 mM Muc; open diamonds: Eu-MC (6 mM) with 60 mM Muc; Black circles Eu-MC (6 mM) with 60 mM sorbate. Each point was calculated as the ratio of the exponential decay parameters determined by fit of combined data of multiple PGSE <sup>1</sup>H NMR experiments. Eu-MC/Muc titration at 6 mM resulted in significant precipitation after 0.5 eq muconate added.

#### Analysis of Lanthanide Trend[SB7]

Plotting the present work's log *K* stability constants against lanthanide radius (Fig. 3A) for Sm<sup>3+</sup> through Ho<sup>3+</sup> (Fig. S5, all examined **Ln-MCs**), we notice a correlation between the first and second complexation events. If the binding constant of the first step ( $K_1$ , referring to **MC** + Muc  $\rightleftharpoons$  (**MC**)Muc) is weak, the binding constant of the second step ( $K_2$ , indicating **MC** + (**MC**)Muc  $\rightleftharpoons$  (**MC**)<sub>2</sub>Muc) is stronger and compartment formation is observed.

However, in those cases where  $K_1$  is large, such as that of Sm and Nd, the second step was not detected. Furthermore, we notice the plot of the binding constants exhibits a pattern of two opposing V shapes, with Gd as the apex and nadir of each. If we continue the trend down from the  $K_2$  of Gd and Dy, Ho's second binding constant would be quite close to its first, such that the second binding event may be disfavored due to the high stability of the 1:1 (**Ln-MC**)-Muc complex. A similar observation can be

made for Sm³+, where the theoretical  $K_2$  point would be notably close to its  $K_1$ .

Unfortunately Decidedly, we cannot determine whether this thermodynamic observation is a cause or an effect of compartment formation, nor can we determine what physical aspect could be causing the trend. With respect to the However, to explain the larger observed lanthanide trends, we first considered the crystallographic structures and thermodynamic data in the literature. The larger lanthanides are known to have greater affinity for the 15-MC-5 macrocycle (Figure 3B)<sup>[8a]</sup> and are thus highly stable structures in their monomeric form. In crystal structures structures, La<sup>3+</sup> and Nd<sup>3+</sup> both have been found, in general, to favor lying out of the MC plane towards the hydrophilic face\_in the absence of carboxylate guests, (although there are examples where La<sup>3+</sup> was drawn toward the hydrophobic face by a quest molecule, such as isonicotinate<sup>[4b]</sup>), whereas smaller lanthanides have more frequently been found to lie toward the hydrophobic face or fit into the plane of the MC ring.<sup>[7]</sup> When a guest molecule is introduced, crystal structures with La3+ have often been shown to bind guests on the hydrophilic face in addition to examples with binding on the hydrophobic face with significant variation in binding modes (e.g., bidentate to La<sup>3+</sup>, bridging La<sup>3+</sup> and ring Cu<sup>2+</sup>).<sup>[3b, 3e, 4a, 4b]</sup> As a consequence of the protrusion of the larger lanthanides, we believe it is more difficult for guest binding to achieve the appropriate orientation to bridge the hydrophobic faces of two MCs to form the (Ln-MC)<sub>2</sub>-Muc structure. While calorimetric data cannot determine whether or not La<sup>3+</sup> and Nd<sup>3+</sup> lie toward the hydrophilic face in solution, if we assume this preference, we may conclude that an Lphenylalanine hydroxamic acid complex with a larger central metal will not dimerize easily across the hydrophobic faces. This structural tendency is a reasonable explanation for why the larger lanthanides do not form the (Ln-MC)2-Muc structure.

On the other hand, the weak propensity for Ho to yield the (Ln-MC)<sub>2</sub>-Muc species indicates that an opposing trend takes over for the latter end of the lanthanide seriesthe ionic radius cannot be the sole constraint driving the formation of the molecular container in solution. The size mismatch of the heavier Ln's within the 15-MC-5 ring is reflected in their lower stability constants (Figure 3B). The smaller lanthanides do not accommodate as well the Ln-O distance required to bind effectively to the five metallacrown ring oxygen atoms. Therefore, ions such as Ho<sup>3+</sup> must stay nearly within the plane of the oxygen atoms to form a stable host complex. At the same time, crystal structures with smaller Ln's typically are consistent with quest binding in the orientation to bridge the hydrophobic faces of two MCs.<sup>[3b, 3e, 4a, 4c]</sup> However, bridging a dicarboxylate to form (MC)<sub>2</sub>Muc from (MC)Muc and another MC would strainforces the lanthanide ion to be more displaced from the 15-MC-5 ring, which weakens the stability of the host.'s position within the second MC ring. Therefore, the system favors the 1:1 complex for the later Ln's due to the low binding constant of the Ln within the ring, despite the presumably favorable orientation of the guest and high Lewis acidity of the central lanthanide.





Figure 3. A) Summary of Stability constants for 1st and 2nd complexation events of muconate quest with MC host Log K according to lanthanide species ionic radius, <sup>[6]</sup> Seelected lanthanides Sm<sup>3+</sup> through Ho<sup>3+</sup> with ionic radii of 8coordinate species. Black squares:  $K_1$  values to describe the equilibrium MC + Muc  $\neq$  (MC)Muc; Open circles:  $K_2$  values for MC + (MC)Muc  $\Rightarrow$  (MC)<sub>2</sub>Muc B) Previously published stability constants of Ln<sup>3+</sup> substitution for Ca<sup>2+</sup> in the 15-MC-5 motif (99:1 MeOH:H<sub>2</sub>O; ligand is tryptophan hydroxamic acid)[SB8]<sup>[8a]</sup>

Decidedly, we cannot determine whether thic thormodynamicobservation is or offoct 2 causo 20 compartment formation, norcan dotormino what physical MO aspect could be causing the trend. Regarding a physical rationale. although the calorimetry indicates that a (Ln-MC)-Muc complex is favored, it does not tell us how the guest binds, e.g., monodentate or bidentate to the Ln<sup>3+</sup>. The smallest lanthanides may not be able to bind a guest in a bidentate fashion that geometrically would allow bridging of the guest across the hydrophobic faces which could, in turn, lead the system to favor exclusion of the dimeric (Ln-MC)2-Muc.[SB9]

Size dependency of rare earth-complex formation has been well-documented, especially in rare earth element separations, with examples ranging from tripodal ligands with a size-sensitive lanthanide binding aperture and monomer/dimer equilibrium<sup>[15]</sup> to lanthanide-dependent self-assembly of varied polyhedra.<sup>[16]</sup>

bioinorganic examples of lanthanide-containing bacterial proteins,<sup>[17]</sup> derive selectivity primarily from size and steric based considerations discriminating best between early and late lanthanides -with systematic increasing or decreasing trends in binding constant. Much less common are compounds that exhibit their highest selectivity for intermediate lanthanides, including Ln<sup>3+</sup>(OBETA) reported by Platas-Iglesias and Botta,<sup>[18]</sup> and Ln<sup>3+</sup>(TCMC) described by Morrow.<sup>[19]</sup> whereas Notably, while the stability of Ln<sup>3+</sup> complexation within the 15-MC-5 macrocycle has previously been shown to follow a systematic decrease across the lanthanide series (Figure 3B),<sup>[8a]</sup> the phenomenon we have described with respect to the host-guest chemistry for the compartment formation se of MCs complexes with a dicarboxylate guest is only observed for for-intermediate lanthanides. Neither does our reported trend reflect the curves of the rare earth element "tetrad" effect<sup>[20]</sup> reportedly observed in partitioning trends with some organic extractants, which typically group Eu in a separate trend than Dy. The narrow range of lanthanides involved in the MC dimerization phenomenon must be achieved through a balance of Ln size and favorable molecular interactions to bind a second MC.

## Conclusion

The calorimetric results in combination with the NMR data detailed above converge to provide compelling evidence from two experimentally distinct and independent techniques that the identity of the lanthanide affects the dimerization phenomenon. Ln-MCs with Eu, Gd, and Dy are able to dimerize in the presence of a dicarboxylate guest to form 2:1 (Ln-MC)<sub>2</sub>-Muc species in equilibrium with 1:1 (Ln-MC)-Muc species and free MC monomer, whereas larger lanthanides such as La, Nd, Sm, and smaller ones like Ho can only form the (Ln-MC)-Muc species in equilibrium with the monomer. Based on the  $\Delta H$  values, that to some extent quantitate the favorable intramolecular interactions determining the formation of the molecular container, the Gd-based metallacrown is the one in which the  $\pi$ - $\pi$  interaction between the phenyl substituents of the two converging halves of the compartment is maximized. While most Ln-containing systems follow systematic increasing or decreasing trends in the equilibrium constant K according to the size of the Ln, there are relatively few examples where the stability peaks half-way through the lanthanide series. Furthermore, to our knowledge this is the first example where the identity of the lanthanide has consequences for host-guest supramolecular assembly.

In the MC supramolecular system, the size of the lanthanide was proven to play a critical role, which has implications for the development of lanthanide-containing catalytic systems and informs our basic understanding of the complex characteristics of lanthanides in coordination complexes.

## **Experimental Section**

#### **Materials**

All reagents were obtained from commercial sources and used as received unless specified. Ln<sup>III</sup>(15-MC-<sub>Cull(N)beHA</sub>-5)<sup>3+</sup> complexes were prepared based on literature procedure as previously described.<sup>[7]</sup>

Example synthesis of  $Ln^{III}(15-MC-_{Cull(M)pheHA}-5)^{3+}$ : L-phenylalanine hydromaic acid (L-pheHA) (1.0 mmol),  $Cu(OAc)_2 \cdot H_2O$  (1.0 mmol) and  $Ln(NO_3)_3 \cdot 6H_2O$  (0.20 mmol) were stirred in 20 mL of  $H_2O$  plus 2 mL MeOH for 2 hours. The solution was gravity filtered to remove green precipitate and left for slow evaporation (~1 month) to yield deep blue-purple crystals.

Additional reagents for Calorimetry: Muconate (Muc) was of the highest purity commercially available (Sigma Aldrich) and was used as received. KOH solutions (Merck, Titrisol Normex), used to have Muc in its full deprotonated form, were standardized by titration with potassium hydrogen phthalate. High purity water (Millipore, Milli-Q Element A 10 ultrapure water) and grade A glassware were employed throughout.

Additional reagents for NMR: Trans-trans muconic acid (Acros) used for NMR studies was recrystallized from hot THF. Dipotassium muconate (Muc) was prepared by neutralizing the recrystallized muconic acid in water with potassium hydroxide and precipitating the solid with acetone. The solid was collected by vacuum filtration, rinsed with ether, and dried under vacuum.

#### **Isothermal Titration Calorimetry**

Preliminarily solubility tests were carried out to define the optimal experimental conditions for ITC measurements. All **Ln-MC**s are soluble (~ 1mM) in water at pH 7.2, the pH value selected to have Muc in the dianionc form. However, potentiometric measurements indicated that pH slightly changes over 3-4 hours; thus a suitable buffer (50mM MOPS) was used in all ITC experiments.

ITC titrations were carried out at 25 °C using two isothermal titration calorimeters (Nano-ITC, TA Instruments) equipped with a 100 μL injection syringe. The reaction mixture in the sample cell was stirred at 250 rpm during the titrations. All solutions were softly degassed under vacuum for about 15 min before each experiment. The calorimeters were calibrated chemically by a test HCI/TRIS reaction according to the procedure previously described.<sup>[106]</sup> The instruments were also double checked through an electrical calibration.

ITC measurements were carried out by titrating aqueous solution of Muc into a Ln-MC solution; both Ln-MC and Muc were dissolved in 50 mM MOPS buffer (pH 7.2) to minimize any contribution from the interaction of either the guest or the MCs with the proton.

The equilibrium between the 1:1 (Ln-MC-Muc) and 2:1 ((Ln-MC)<sub>2</sub>-Muc) species is shifted towards the compartment in the first region of the calorimetric curve, that is in the presence of excess Ln-MC, and consequently two sets of experiments were specifically designed for this purpose. Full scan titrations ( $C_{Muc} = 38 - 42 \text{ mM}, C_{Ln-MC} = 0.4 - 0.5 \text{ mM}, Muc/MC$  ratio up to 8) were run to define the 1:1 species, whereas expanded titrations ( $C_{Muc} = 4 - 6 \text{ mM}, C_{Ln-MC} = 0.9 - 1.1 \text{ mM}, Muc/MC$  ratio up to 0.4) were run to better detect the 2:1 ((Ln-MC)<sub>2</sub>-Muc) complex that, when existing, is fully formed in the very first points of the full scan experiment.

The heats of dilution were determined in separate blank experiments by titrating solutions of Muc (in MOPS) into a solution containing MOPS only. 6-7 independent experiments were usually run for each system to collect a proper number of data points to satisfactorily analyse both the first and last portion of the calorimetric curve.<sup>[10a]</sup> The net heats of reaction, obtained by subtracting the heat from the blank experiments, were handled by HypCal, a software able to refine both stability constant and enthalpy change values and to simultaneously treat data from multiple titrations.<sup>[11]</sup> The two sets of experiments (full scan and expanded titrations) were refined together to obtain the final parameters.

#### **NMR Experiments**

One and two dimensional <sup>1</sup>H NMR were performed on a 400 MHz spectrometer (Varian MR400) equipped with Varian 5 mm PFG AutoX Dual Broadband probe ( $T_1$  inversion recovery) or a 500 MHz spectrometer (Varian VNMRS) equipped with a Varian 5 mm PFG OneNMR Probe (PGSE DOSY experiments).

One dimensional <sup>1</sup>H NMR spectra of the Ln-MCs (Figure S10) were taken for samples of 2 mM Ln-MC (excepting Gd-MC, which was 6 mM) in 100 mM MOPS buffer in  $D_2O$  (pD 7.2 ± 0.1, pD corrected from pH reading for  $D_2O$ <sup>[21]</sup>). Using these samples for the  $T_1$  inversion recovery experiments, a standard two-pulse sequence was used using 15 delay time values (r) ranging from 0.001 s to 0.3 s between the 180° and 90° pulses and a relaxation delay of 1.2 s, except in the case of Gd in which case *r* values range from 0.0001 s to 0.3 s.

The pulsed gradient spin echo (PGSE) experiment used a standard double stimulated echo pulse sequence with a convection compensation and a duration of rectangular gradient pulses,  $\delta$ , of 2.2 ms (Sm, Nd) or 3.2 ms (Eu), a delay between gradient pulses,  $\Delta$ , of 45 ms (Eu), 50 or 70 ms (Sm),

or 90 ms (Nd), and constant temperature ( $25 \pm 0.3^{\circ}$ C). For the PGSE, fifteen spectra were collected with varying gradient strength, *G*, from 2.4 to 59.6 G/cm with relaxation delay, d<sub>1</sub>, of 0.5 s (Sm, Nd) or 0.2 s (Eu) and acquisition time of 3.5 s (Sm) or 2.0 s (Nd, Eu).

NMR titrations were performed in triplicate and carried out in 1:1 MeOD:D\_2O buffer (100 mM MOPS, pD 7.2 ± 0.15, pD corrected from pH reading for D\_2O<sup>[21]</sup>, prior to dilution with MeOD) with DMSO used as an internal standard. Deuterated methanol was used to avoid precipitation at the mM level concentrations that were necessary for NMR. An exception is for 6 mM Eu – sorbate titration: only two PGSE experiments were performed for the points at 0.58 eq and 1 eq; only 10 G<sup>2</sup> values were used for one of the experiments at 0.83 eq. NMR Spectra processing and analysis, including fit of T<sub>4</sub>, was performed using MestReNova 11.0.2 software. All other least square regression analyses were performed using SPSS Statistics 26.0 software.

A detailed account of the mathematical treatment for analyzing the NMR titrations is included in the SI, including a new treatment for translating the error of the measured diffusion coefficient into corresponding error for hydrodynamic radius.

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**Keywords:** calorimetry • host-guest systems • lanthanides • metallacrowns • paramagnetic NMR

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The formation of metallacrown compartments in neutral aqueous solution can be templated by an anionic guest, *e.g.*, muconate. As demonstrated by calorimetric and NMR techniques, metallacrowns containing larger or smaller central lanthanides only form monomeric host-guest complexes, whereas intermediate lanthanides uniquely form dimeric host<sub>2</sub>-guest compartments.[SB10]

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