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Thermodynamics of Core Metal Replacement and Self-Assembly of Ca^{2+} 15-Metallacrown-5[†]

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The equilibria for *core* Ca^{2+} replacement by Ln^{3+} in copper(II) 15-MC-5 complexes have been investigated using a series of visible spectrophotometric titrations of calcium(II) metallacrowns ($\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$) with Ln^{3+} ions (H_2L = pheha, (*S*)-α-phenylalaninehydroxamic acid, or trpha, (*S*)-α-tryptophanhydroxamic acid). These studies allowed the determination of the equilibrium constants for the reaction $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + Ln^{3+} \rightarrow \{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+} + Ca^{2+}$ in methanol/water 9:1 ($Ln^{3+} = La^{3+}$, Gd^{3+}, Dy^{3+}, Er^{3+}) or 99:1 ($Ln^{3+} = La^{3+}$, Nd^{3+}, Gd^{3+}, Dy^{3+}, Er^{3+}, Yb^{3+}), respectively. The log *K* for these reactions decreases with increasing atomic number of the lanthanide(III), ranging from 6.1 to 3.91 in methanol/water 9:1. The same behavior is observed in methanol/water 99:1, although the constants are uniformly lower (log $K = 4.09-2.52$). A significant thermodynamic selectivity was observed for the later lanthanides ($Gd^{3+}-Yb^{3+}$) while a smaller selectivity is present throughout the beginning of the series ($La^{3+}-Gd^{3+}$). This observation has been interpreted on the basis of the size correspondence between the metal ions and the metallacrown cavity. The overall stability of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ in methanol/water 9:1 has been determined by pH-spectrophotometric titrations with HCl. The resulting log *K* values are 63.46(12) and 65.05(13) for pheha and trpha, respectively ($Ca^{2+} + 5Cu^{2+} + 5HL^{-} = \{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + 5H^{+}$). The stability of both the La^{3+} and Ca^{2+} 15-metallacrown-5 complexes in the presence of high Na^{+} concentrations has also been demonstrated by spectophotometric studies. Based upon these observations, the preference of the 15-MC-5 for Ca^{2+} complexation compared to crown ethers has been quantitatively demonstrated for the first time.

Introduction

The application of the lanthanides for a variety of commercial applications ranging from hard magnets to luminescent sensors has dramatically increased over the past 20 years. One issue influencing the cost of such systems is the difficulty of separating the different lanthanides because of their extremely similar chemistry. Thus, it has been desirable to develop new chelation regiments that could lead to discrimination and, ultimately, facile separation of these ions.

Metallamacrocycles represent alternative potential platforms for achieving lanthanide ion discrimination. Since the isolation of the first planar 15-metallacrown-5 in 1996,[1,2] there has been a growing interest in the capability of these compounds to encapsulate, with various degrees of selectivity, appropriate core metal ions. Metallacrowns (MC, Scheme 1), which are self-assembled metallamacrocycles and the inorganic analogues of crown ethers, encapsulate in their cavity mono-, di-, and trivalent metal ions as a function of the metal coordination and cavity geometries.[3] Investigations on copper(II) metallacrowns (i.e., MCs with Cu^{2+} as the *ring metal*) showed that Cu^{2+}, which may adopt distorted octahedral, square pyramidal, or square planar coordination geometries, can be encapsulated in the cavity of $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+}$ (Scheme 1).[4−8] On the

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[†] This paper is dedicated to Professor Francesco Dallavalle in recognition of his many contributions to the field of solution thermodynamics.

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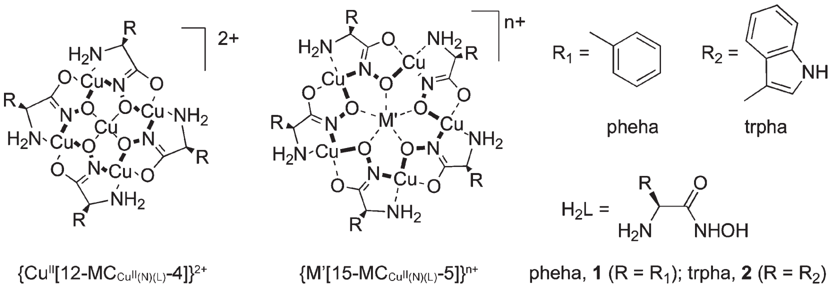
Scheme 1. Schematic Representations of the $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+}$ (left) and $\{M'[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{n+}$ (center) Complexes of pheha (R = R_1, **1**) and trpha (R = R_2, **2**)[a]



[a] The species $\{M'[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{n+}$ corresponds to the metallacrown complexes in compounds **3** ($M'^{n+} = Ca^{2+}$, R = R_1), **4** ($M'^{n+} = Ca^{2+}$, R = R_2) or **5** ($M'^{n+} = La^{3+}$, R = R_1). *Core metal*: Cu^{2+} (left), M'^{n+} (center); *ring metal*: Cu^{2+}. For notation and nomenclature, see ref 9.

contrary $\{M'[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{n+}$, which possess a planar cavity formed by 5 hydroxymato oxygens, are more versatile ligands toward those cations (M'^{n+}) with dimensions that require an expanded coordination sphere (Scheme 1).[1−3]

Previous investigations have shown that, for α-aminohydroxamic acids, $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+}$ is the only metallacrown present in solution.[9] In the excess of ligand, this species is formed only in the pH range 4−6 but, for Cu:L ratios close to 1, the 12-metallacrown-4 is the predominant species in a wide range of pH from 4 to 11 (in water and methanol/water 9:1 v/v).[10−12] The most remarkable result of the thermodynamic studies on these complexes is that a vacant $[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]$ has never been observed in solution, and the 15-MC-5 scaffold has not yet been isolated in the absence of a suitable core metal ion capable of accepting an in-plane, 5-oxygen atom coordination geometry. On the other hand, a series of copper(II) 15-MC-5 with encapsulated monovalent alkali metals (Na^+),[13] divalent alkaline earth metals (Ca^{2+}),[1,14] lanthanide and actinide ions (Ln^{3+}, UO_2^{2+}),[1−3,15] and large transition metals (Ag^+, Pb^{2+}, Hg^{2+}, Y^{3+})[13] were isolated and structurally characterized in the past decade.

$\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{3+}$ complexes (pheha = (*S*)-α-phenylalalninehydroxamic acid, Scheme 1) have been investigated in recent years for their ability to bind anions on both the *core* and *ring metals*,[3,16] and they have shown an extraordinary capability to act as selective hosts for carboxylates.[17−19] The structural features of chiral and face-differentiated 15-metallacrown-5 complexes allowed preferential host discrimination of carboxylates containing unsaturation over aliphatic carboxylates into the MC hydrophobic pocket, with a thermodynamic selectivity that has been recently investigated by means of several techniques.[17,18,20,21] It has also been demonstrated that $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{3+}$ are capable of forming dimers, helicates, and larger compartments,[22−24] and that their formation can be controlled through an appropriate choice of the solvent and the core Ln^{3+} employed in the synthesis.[23] Finally, Ln^{3+}/Cu^{2+} metallacrowns showed interesting properties as single-molecule magnets,[25,26] as potential MRI contrast agents,[26,27] and as building blocks for the synthesis of supramolecular nanochannels.[24]

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(9) In several previous papers treating the formation equilibria of metallacrowns and aminohydroxamic acid, the ligands pheha and trpha were defined as HL, instead of H_2L (see for instance ref 11 and 12, and references therein). In general, this notation was adopted for all aminohydroxamic acids with non-ionizable side chains since pheha and trpha are monoprotic acids and, in absence of metal ions, can be deprotonated only once under normal solution conditions. Thus, in those papers the L^- form of the ligand corresponds, following the notation of the present paper, to the HL^- species. The following correspondences apply between the two notations (this manuscript vs previous notation): $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} = \{Ca[Cu_5L_5H_{-5}]\}^{2+}$; $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+} = \{Ln[Cu_5L_5H_{-5}]\}^{3+}$; $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+} = [Cu_5L_4H_{-4}]^{2+}$. Moreover, for binary Cu^{2+}/ligand species, the following correspondences apply: $[Cu(HL)]^+ = [CuL]^+$; $[Cu(HL)_2] = [CuL_2]$; $[Cu(HL)L]^- = [CuL_2H_{-1}]^-$. On the basis of these notations, the equilibrium $Ca^{2+} + 5Cu^{2+} + 5HL^- = \{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + 5H^+$ (this paper) corresponds to the equilibrium $Ca^{2+} + 5Cu^{2+} + 5L^- - 5H^+ = \{Ca[Cu_5L_5H_{-5}]\}^{2+}$ (previous notation). The log *K* of the former equilibrium is numerically equal to the log β of the latter. As the pK_a of the HL^- species is not known, the log β for the $Ca^{2+} + 5Cu^{2+} + 5\,L^{2-} = \{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ equilibrium cannot be calculated by pH-metric data, but as log *K* for the proton displacement equilibrium as stated above.

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Since 2004, the stability of copper(II) 15-metallacrown-5 as a function of the nature of core metal has been investigated.[8,13,28,29] It has been shown that for $\{M'[15\text{-}MC_{Cu^{II}(N)\text{-}picha}\text{-}5]\}^{n+}$ (picha = picolinehydroxamic acid), the order of stability is Na^+, $Ag^+ < Ln^{3+}$, $Hg^{2+} < Pb^{2+}$.[13] It has also been shown that among lanthanides, lighter ones (namely, La^{3+}, Ce^{3+}, and Nd^{3+}) are more stable than those of Sm^{3+} and heavier rare earth metals.[8] This result is also supported by the observation that $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{n+}$ with Er^{3+} or heavier lanthanides of α-aminohydroxamates are difficult to isolate.[23] Finally, it has also been shown that $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+}$ complexes of pheha and leuha (α-leucinehydroxamic acids) can be converted into $\{M'[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{n+}$ by the addition of Ln^{3+} ions or UO_2^{2+} ions.[29] These studies have also demonstrated that Ln^{3+} ions are replaced by UO_2^{2+}, while the latter is not replaced by Ca^{2+}.[28] Despite the extensive investigations into the solution stability of metallacrowns and the ability to replace core metal ions, there have appeared only qualitative descriptions of these processes. Neither complete thermodynamic nor mechanistic studies have been reported to date; however, designing agents that are capable of lanthanide (and possibly actinide) separations in good yield requires a quantitative evaluation of the relative ion affinities for the hosts.

In this paper, we present the thermodynamic study of the Ca^{2+} substitution reaction by Ln^{3+} ions in the cavity of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{2+}$ (**3**) and $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$ (**4**, trpha = (*S*)-α-tryptophanhydroxamic acid). These equilibria have been investigated in methanol/water 9:1 v/v by visible spectrophotometric titrations, using La^{3+}, Gd^{3+}, Dy^{3+}, and Er^{3+}. Moreover, a wider Ln^{3+} series (La^{3+}, Nd^{3+}, Gd^{3+}, Dy^{3+}, Er^{3+}, and Yb^{3+}) was studied in methanol/water 99:1 v/v to correlate the thermodynamic equilibrium constants with the kinetic rates of $Ca^{2+}-Ln^{3+}$ substitution in methanol obtained for the same lanthanide(III) ions.[14,30] In this paper we also present the determination of the complex formation constants of the Ca^{2+}/Cu^{2+} 15-metallacrown-5 complexes of both pheha and trpha in methanol/water 9:1 v/v. The role of Na^+ present in the buffered solutions employed for the spectrophotometric studies and the complexation capabilities of 15-MC-5 compared to those of the crown ethers is also discussed.

Results

$Ca^{2+}-Ln^{3+}$ Substitution Equilibria. The equilibrium constants for the reaction $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + Ln^{3+} \rightarrow \{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+} + Ca^{2+}$ (H_2L = pheha, trpha) have been determined by visible spectrophotometric titrations of solutions of the calcium(II) metallacrowns (**3** and **4**) in methanol/water 9:1 v/v with solutions of Ln^{3+} nitrates ($Ln^{3+} = La^{3+}$, Gd^{3+}, Dy^{3+}, Er^{3+}). All the titrations have been carried out in methanol/water buffered mixtures (pH 6.5, buffer MES 50 mM).

Previous investigations on the reaction rates for the same processes showed that the substitution of the core Ca^{2+} cation is kinetically slow (ca. 2 days in methanol).[14,30] For this reason, the titrations were carried out using a batch (out of cell) strategy as fixed time assays: a series of vials, each containing the same $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ concentration, were added with increasing Ln^{3+} quantities (up to Ln/Ca ca. 1.4−2.0). The solutions were left to equilibrate for 72 h, and the visible (400−800 nm) spectra were recorded. The respective Ca(II) or Ln(III) metallacrowns were indefinitely stable under these conditions so one need not correct for complex decomposition. The spectra of the samples did not change within the subsequent 24−48 h. An analogous procedure was applied for the determination of the equilibrium constants for the same reaction in methanol/water solution 99:1 v/v, with trpha using a wider Ln^{3+} series (La^{3+}, Nd^{3+}, Gd^{3+}, Dy^{3+}, Er^{3+}, Yb^{3+}). The 1% water was used to ensure the dissolution of MES at 50 mM concentration and pH 6.5.

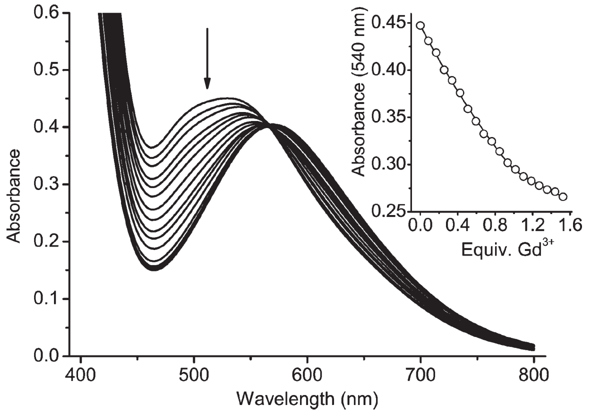

Figure 1. Corrected spectra for the titration of **4** ($\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$) with Gd^{3+} in methanol/water 9:1 v/v solution ($C_{15\text{-}MC\text{-}5} = 1.01 \times 10^{-3}$ M, Gd/Ca = 0−1.53, buffer MES 50 mM, pH 6.5). (Experimental spectra were multiplied for the dilution factor V_{sample}/V_0). Inset: experimental (o) and calculated (line) values of the absorbance values at 540 nm.

The spectral data (400−800 nm) for the titrations of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ complexes carried out in methanol/water 9:1 v/v showed, for all lanthanides(III), a shift of the absorption band from about 530 nm to about 575 nm and a decrease in the overall absorbance of the spectrum (Supporting Information). The spectral set for the titration of compound **4** with Gd^{3+} (corrected for dilution) is reported in Figure 1. The corrected absorption spectra showed that for all the titrations an isosbestic point can be observed in the range 560−575 nm, depending on the Ln^{3+} ion involved. The logarithms of the equilibrium constants (log *K*) for the $Ca^{2+}-Ln^{3+}$ replacement reaction in methanol/water 9:1 are reported in Table 1. The calculated visible spectral parameters for the $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+}$ complexes are also reported, together with the ionic radii and the most common coordination numbers of the Ln^{3+} ions in 15-MC-5 complexes.[3]

The relative binding affinities (log *K*, Table 1) of Ln^{3+} versus Ca^{2+} of the 15-MC-5 are similar for pheha and trpha and decrease along the lanthanide series. In particular these constants are not different for La^{3+} and Gd^{3+} (the latter corresponding to the central lanthanide in the rare earth metals series), while a decrease is shown going from Gd^{3+} to Er^{3+} (2−2.2 log units).

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Table 1. Logarithms of the Equilibrium Constant of the Replacement Reaction $\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{2+} + \mathrm{Ln}^{3+} \rightarrow \{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{3+} + \mathrm{Ca}^{2+}$ in Methanol/Water 9:1 or 99:1 v/v Solutions for Compounds **3** or **4**[a]

	log *K*		$\lambda_{\max}$, ε [b]		log *K*	$\lambda_{\max}$, ε [b]		
	methanol/water 9:1 (v/v)				methanol/water 99:1 (v/v)			
	3	**4**	**3**	**4**	**4**		ionic radius (Å)[c]	C. N.[d]
La^{3+}	6.2(1)	6.2(1)	570, 384	568, 377	4.09(1)	572, 388	1.216	9
Nd^{3+}					4.05(3)	572, 417	1.109	8
Gd^{3+}	6.1(1)	6.13(6)	571, 409	571, 401	3.79(3)	571, 420	1.053	8
Dy^{3+}	4.85(2)	4.62(2)	572, 411	572, 413	3.42(5)	576, 412	1.027	8
Er^{3+}	4.13(4)	3.91(3)	576, 424	576, 427	3.07(3)	582, 404	1.004	8
Yb^{3+}					2.52(6)	596, 463	0.985	8

[a] Standard deviations are reported in parentheses. $\lambda_{\max}$ and ε values are those of the calculated spectra of the $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{3+}$ species. Ionic radii and common coordination numbers (C.N.) of the Ln^{3+} ions in 15-MC-5 complexes are also reported. [b] $\lambda_{\max}$ (nm), ε ($\mathrm{M^{-1}\ cm^{-1}}$). [c] Effective ionic radii as reported in ref 31. Ionic radii are reported for C.N. = 8 except for La^{3+} (C.N. = 9). [d] Coordination numbers refer to the most common coordination numbers presented by these cations in 15-MC-5 complexes with Cu^{2+} and α-aminohydroxamates, see ref 3.

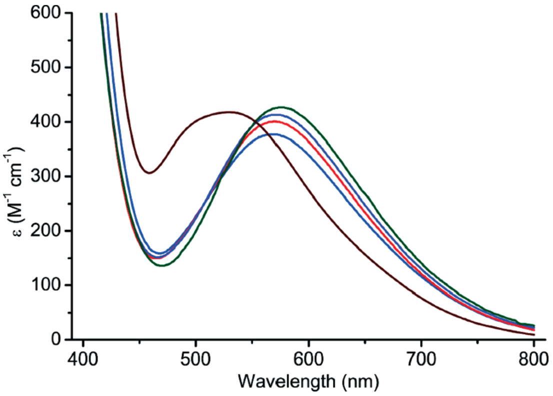

Figure 2. Calculated molar absorption spectra for the $\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{2+}$ and $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{3+}$ complexes (methanol/water 9:1 v/v, buffer MES 50 mM, pH 6.5). Ca^{2+} (brown), La^{3+} (blue), Gd^{3+} (red), Dy^{3+} (purple), Er^{3+} (green).

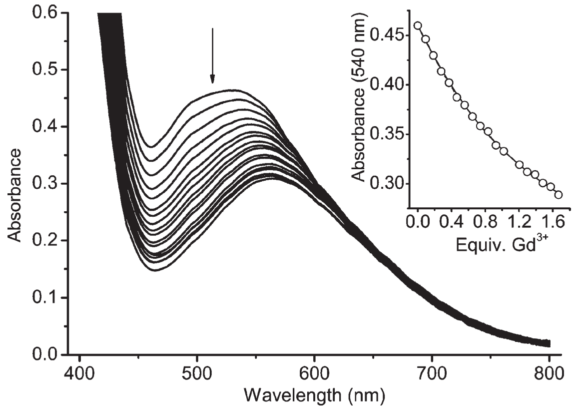

Figure 3. Experimental spectra for the titration of **4** ($\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{2+}$) with Gd^{3+} in methanol/water 99:1 v/v solution ($C_{15\text{-}\mathrm{MC}\text{-}5} = 1.01 \times 10^{-3}$ M, Gd/Ca = 0−1.74, buffer MES 50 mM, pH 6.5). Inset: experimental (o) and calculated (line) values of the absorbance values at 540 nm.

The $\lambda_{\max}$ and ε values for the calculated molar absorption spectra for the $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{3+}$ species with both ligands are also very similar. For all the Ln^{3+} 15-MC-5 complexes the visible absorption band is centered at about 570 nm, with molar absorption values of about 380−430 $\mathrm{M^{-1}\ cm^{-1}}$. This band is well separated from the absorption band of the $\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{2+}$ species which has a maximum at 529 nm and an unsymmetrical shape, with a shoulder just below 500 nm. Along the lanthanide series, a small *red shift* of the $\lambda_{\max}$ values and a simultaneous hypercromic shift of the spectra of the $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(L)}}\text{-}5]\}^{3+}$ species is observed. The calculated molar absorption spectra for the $\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{2+}$ and $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{3+}$ complexes are reported in Figure 2.

The spectra of the titrations of $\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{2+}$ (**4**) with Ln^{3+} in methanol/water 99:1 (v/v) are similar to those observed for the analogous experiment in methanol/water 9:1. In Figure 3 the experimental spectra for the titration of **4** with Gd^{3+} are reported. The *red shift* of the visible band from about 530 nm to about 570 nm has been observed also in these experiments. The treatment of the spectral data allowed for the determination of the logarithm of the equilibrium constants for the Ca^{2+}−Ln^{3+} replacement reaction, which are reported in Table 1 together with the $\{\mathrm{Ln^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{3+}$ visible spectral parameters.

15-MC-5−18-C-6 Competition Equilibria. The competition between the 15-MC-5 scaffold and the 18-crown-6 toward Ca^{2+} complexation has been evaluated by two different experiments. In the first experiment, an unbuffered solution containing compound **4** ($\{\mathrm{Ca^{II}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}trpha}}\text{-}5]\}^{2+}$) in methanol/water 9:1 has been titrated with the 18-C-6 ligand up to 8 equiv of crown ether. The visible spectra have been collected 5 min after each addition of the colorless 18-C-6 solution to the brick red 15-MC-5 solution (1.6 equiv of 18-C-6 each addition, Figure 4). The shape of the spectrum does not change upon addition of the 18-C-6 up to 8 equiv. The spectrum of the final solution (8-fold excess of 18-C-6 vs 15-MC-5) has been collected 5 min and 24 h after ligand addition, showing no change in the absorption spectrum. A similar experiment was performed by adding 8 equiv of 18-crown-6 ether to metallacrown **5** ($\{\mathrm{La^{III}}[15\text{-}\mathrm{MC_{Cu^{II}(N)(\mathit{S})\text{-}pheha}}\text{-}5]\}^{3+}$), and yet the spectrum did not show any change in its shape (see Supporting Information).

In the second experiment, two solutions were prepared each containing Cu^{2+} and pheha in a 1:1.24 molar ratio in methanol/water 9:1 (green solution). One fifth of an equivalent (vs Cu^{2+}) of calcium nitrate or compound **6** ($[\mathrm{Ca}\subset(18\text{-}\mathrm{C}\text{-}6)](\mathrm{NO_3})_2$,) was added to the two solutions, respectively. The solutions became brick red within 1 h, and the spectra of the two solutions were collected 2 weeks after sample preparation. The intensity and shape

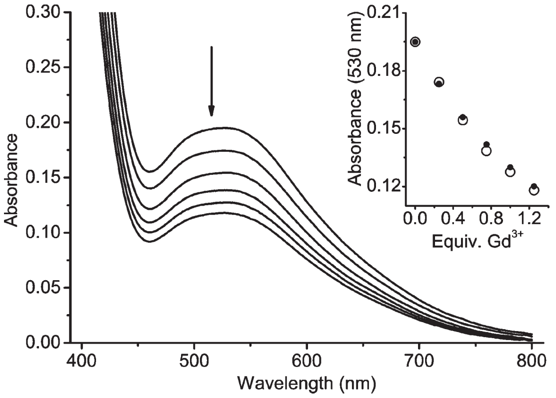

Figure 4. Experimental spectra of the titration of **4** (4.23×10^{-4} M) with the 18-crown-6 ether. Each spectrum corresponds to 1.6 equiv of crown ether added versus **4**. Inset: o = Experimental absorbance at 530 nm; ● = calculated absorbance obtained by correcting the first spectrum for the dilution factor (V_0 = 2 mL).

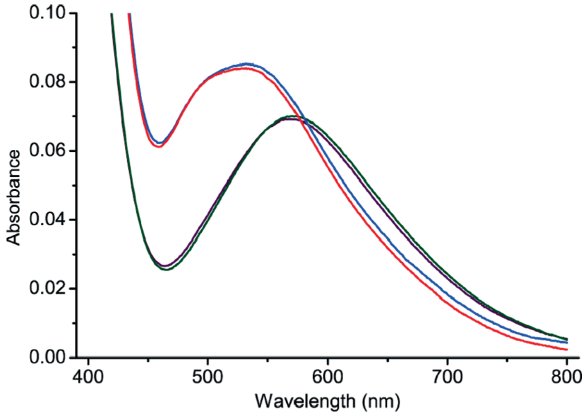

Figure 5. Spectra of solutions of compounds **3** and **5** (0.2 mM) either in presence or in the absence of 50 mM NaCl in methanol/water 9:1 (v/v). Compound **3**, red line; **3**+NaCl, blue line; Compound **5**, purple line; **5**+NaCl, green line.

of the two spectra is the same, and they both correspond to the spectrum of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{2+}$ species dissolved in methanol/water with the same Cu^{2+} concentration (see Supporting Information).

Interaction of 15-MC-5 Complexes with Na^+. A series of experiments aimed to assess the absence of a competing role of the Na^+ ion of the MES buffered solutions. The visible spectra of solutions of **3** and **5** ($\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{2+}$ and $\{La^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{3+}$ at 0.2 mM concentration) in methanol/water 9:1, added with solid NaCl to obtain a 50 mM Na^+ solution were collected. All spectra were collected 72 h after samples preparation. The spectra of the 15-MC-5 complexes alone and those of the solutions added with NaCl are very similar (Figure 5). Only a slight increase of the absorbances above 505 to 800 nm are observed for **3**, while the spectrum of **5** containing Na^+ does not differ significantly from that of a solution of the 15-MC-5 alone, and no change in the maximum wavelength was observed (568−570 nm).

Determination of the Ca^{2+} 15-MC-5 Formation Constant. To obtain information on the stability of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ species, a spectrophotometric analysis of samples of compounds **3** and **4** in methanol/water 9:1 at different pH conditions was performed. Batch titrations were carried out by addition of different aliquots of standard HCl in methanol/water 9:1 v/v to a series of vials containing the same concentration of the Ca^{2+} 15-MC-5 complexes. For increasing HCl concentrations a change of color from brick red to green was observed in a few hours. Moreover, a drift of the pH reading was observed for the first 24 h after samples preparation, and the spectra were thus collected after 72 h. These studies were performed without the addition of supporting electrolytes to avoid the formation of the green insoluble material that precipitated from the green solutions at pH about 4−6 with higher ionic strength (see Discussion section). The spectra for the titration of **4** are reported in Figure 6 (spectra of **3** are reported as Supporting Information). The spectra for the titrations of both compounds **3** and **4** are very similar, and they both show two isosbestic points at about 475 and 585 nm from pH 4 to 7.4. In this pH range, the intensity of the visible band at 530 nm decreases, with a corresponding increase of the band at 645 nm. At pH lower than 4, the isosbestic point is lost and a progressive *red shift* of the d-d band is observed. The elaboration of the spectrophotometric data at different pH was performed taking into account the speciation models for the binary Cu^{2+}/pheha or trpha systems and the calculated visible spectra of the binary species reported in the literature as fixed parameters (namely, those of $[Cu(HL)]^+$, $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(L)}\text{-}4]\}^{2+}$, $[Cu(HL)_2]$, and $[Cu(HL)L]^-$).[9] A good fitting of the experimental spectra was obtained by introducing the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ species together with the four before mentioned species (Figure 6 and Supporting Information).[10] As the pK_a values for the HL^- species cannot be determined in water, the formation constants of the Ca^{2+} 15-MC-5 complexes could be calculated as log K for the $Ca^{2+}+5Cu^{2+}+5HL^- = \{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + 5H^+$ equilibria. The log K values resulted 63.46(12) and 65.05(13) for H_2L = pheha or trpha, respectively.[9]

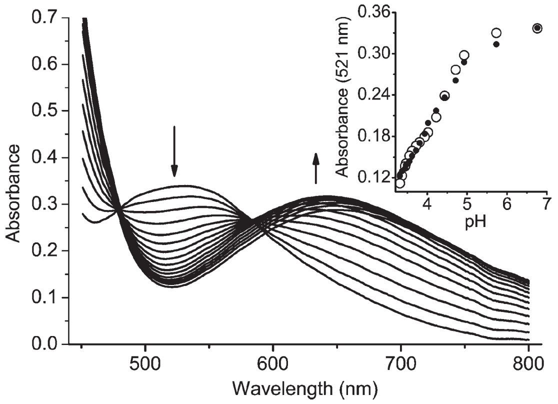

Figure 6. Experimental spectra for the pH-spectrophotometric titration of **4** with HCl in methanol/water 9:1 (v/v) ($C_{15\text{-}MC\text{-}5} = 7.64 \times 10^{-4}$ M). The pH range is 3.3−6.8. Inset: Observed (o) and calculated (●) absorbance values measured at 521 nm at different pH.

Discussion

Ca^{2+}−Ln^{3+} Substitution Equilibria. Table 1 reports the calculated equilibrium constants for the reaction $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + Ln^{3+} \rightarrow \{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+} + Ca^{2+}$ in methanol/water 9:1 or 99:1 (v/v) for

H_2L = pheha and trpha. These equilibrium constants are the relative binding affinities of the MC scaffold for the core metal ions Ln^{3+} versus Ca^{2+}, and the difference between the log *K* values for two lanthanides is also the difference between the overall formation constants of their 15-MC-5 complexes. All the titrations have been carried out in methanol/water buffered mixtures (pH 6.5, buffer MES 50 mM).

The log *K* values reported in Table 1 show that the stability of the $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+}$ species in methanol/water 9:1 is very similar for pheha and trpha metallacrowns with the same lanthanide. The different nature of the ligand residues does not affect the binding affinity of the MC scaffold for the same Ln^{3+} ions. The log *K* values reported in Table 1 show also that the stability of the Ln^{3+} 15-MC-5 diminishes along the lanthanide series. For compound **4** in methanol/water 9:1, for instance, the difference in stability from La^{3+} to Er^{3+} is 2.3 log units, while in methanol/water 99:1 the difference is slightly less marked (1.6 log units). Table 1 also shows that the decrease of the log *K* values is smooth from La^{3+} to Gd^{3+}, while it becomes steeper from Gd^{3+} to Yb^{3+}. The log *K* values from La^{3+} to Gd^{3+} are the same in methanol/water 9:1, while they are slightly different (0.3 log units) in methanol/water 99:1. On the contrary, the Δlog *K* from Gd^{3+} to Er^{3+} is greater in methanol/water 9:1 (2−2.2 log units) than in methanol/water 99:1 (0.8 log units).

Although a number of studies on Ln^{3+} complexes with simple crown ethers and their derivatives in different solvents have been reported, direct comparison of the values is difficult as a number of different ligands or conditions (solvent, etc.) have been used and the results are sometimes contradictory.[32−40] In particular, there are many data in poorly coordinating solvents such as propylene carbonate (PC) or acetonitrile, while there are few data for 15-crown-15/Ln^{3+} complexation equilibria in methanol. Table 2 reports the log β values for the complexation of Ln^{3+} ions by different 15-crown-5 ligands in different solvents. These data show, with the exception of the data reported by Bünzli and co-workers for 15-C-5 in propylene carbonate,[38] that the stability constants decrease with increasing atomic number along the lanthanide series. These conclusions have been reported also for the Ln^{3+} complexes with 18-C-6.[34,37−39,41] It is worthy of note that Bünzli and co-workers have observed the formation of M/L 1:2 complexes, and that their formation log β_2 diminish as the lanthanide size decreases. It is, however, worth noting that a monotonic decrease of log β values has not been reported for all crown ethers, and the stability/Ln^{3+} relationships for the derivatives of these macrocycles is often very complex.[34,40]

Table 2. Logarithms of Complex Stability Constants (log β) for the Complexation of Lanthanide(III) Cations by 15-Crown-5 Derivatives (M/L 1:1 species). [a]

	solvent							
	H_2O	CH_3CN				PC^g		
	ligand							
	SB15-C-5[b]	15-C-5[c]	B15−C-5[c]	S15−C-5[c]	15-C-5[d]	15-C-5[e]	15-C-5[f]	4tBuB15-C-5[f]
La	2.04	5.17	4.07	2.22	6.38	6.27	6.49	3.26
Ce	1.98	4.62	3.41	2.21				3.62
Pr	1.91	4.45	2.41	3.04	6.97	6.22		3.6
Nd	1.81	3.93	2.48	2.35			6.55	3.75
Pm								
Sm	1.77	2.81	2.48	2.13	7.34	6.11		3.45
Eu	1.66	2.26	2.49	2.1				
Gd	1.63	2.03	2.49					3.02
Tb					7.1		5.96	2.85
Dy	1.21					5.66		2.9
Ho								2.8
Er	1.00				7.5	5.53		2.82
Tm								2.81
Yb	0.50				7.25	5.53		2.8
Lu					7.50		5.83	2.8

[a] See list of abbreviations at the end of the text. [b] Ref 36. [c] Ref 34. [d] Ref 38. [e] Ref 37. [f] Ref 40. [g] PC = Propylene carbonate.

The cation selectivity of a macrocycle is the result of a balance of several factors. Since Pedersen's pioneering work on the synthesis of crown ethers and their binding ability toward metal ions, the host−guest size-fit (or size correspondence) and the cation desolvation energy were recognized as two effects with a great influence on the stability constants of the metal-macrocycle adducts.[42,43] Ligand-cation binding energy (size-fit) is lower for cations that are not properly accommodated into the macrocycle (i.e., an ionic radius either smaller or larger compared to the cavity size).[35,43] Large cations may form side-on or ML_2 sandwich complexes although for alkali and alkali-earth metals such species are not favored in strongly solvating media such as water, methanol, and dimethylformamide.[43,43,44] Alternatively, desolvation energies (especially in polar solvents) are larger for cations with smaller ionic radii, and their high enthalpic change for the release of the water molecules is one of the reasons of the lower stability of complexes with later lanthanides.[34,39,45,46] These factors are shown when evaluating the complexation of the lighter lanthanides with the 15-C-5 and 18-C-6. The radius of the cavities of these two macrocycles are equal to 0.85−0.9 Å and 1.30−1.43 Å,[43,44] respectively. Therefore, solely on the basis of the size correspondence it is expected that 15-C-5 should bind Gd^{3+} (I.R. = 1.053 Å) better than La^{3+} (I.R. = 1.216 Å),[31] while the opposite is expected for

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18-C-6. Despite the relative dimensions, La^{3+} gives the highest stability constants with both ligands as the result of a higher desolvation energy for Gd^{3+}, which is not compensated by the energy gain due to complexation.[34] Izatt and co-workers have observed that the size correspondence can be a predominant factor in determining the binding selectivity only for cations that can fit into the cavity of the macrocycle (i.e., cations with an ionic radius equal or smaller than the cavity radius).[44] For cations smaller than the cavity, the stability is low as both the increase of desolvation energy and the poor host−guest fit conspire against metal−ligand complex formation. For cations larger than the cavity, the selectivity or stability trend is the result of the delicate balance of all factors including solvation energies of the free ligand and products, and the presence of particular counterions. Thermodynamic investigations on several complexes of X-crown-5 and X-crown-6 derivatives with lighter Ln^{3+} have actually shown that a very complex dimensions-stability relationship often exists, as the result of the balance of all these factors which is difficult to predict.[34]

To establish a possible role of the size correspondence in determining the selectivity of the 15-MC-5 for the cations examined we have evaluated the structural features of the cavity occupied by Ln^{3+} ions in $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{3+}$ using the available X-ray crystal structures.[3,47] Besides a common 5 in-plane oxygen coordination, the lanthanide ions in these structures present very different coordination environments because of the presence of carboxylates as coligands coordinated to the *core metal* ions, which mostly influences the Ln-oxygen plane distance.

For all these structures, the internuclear centroid-oxygen distances range between 2.45 and 2.39 Å, corresponding to the internuclear cavity radii. These values show a contraction along the lanthanide series. Taking into account an ionic radius of 1.36 Å for the tricoordinated oxygen,[31] the cavity radius falls between 1.03−1.09 Å, ranging from La^{3+} to Dy^{3+}, respectively. Noteworthy, this value is intermediate between the cavity radii of the 15-C-5 and 18-C-6. It is then clear that La^{3+} (I.R. = 1.216 Å) is too large to properly fit into the 15-MC-5 cavity, and this forces this cation to adopt a higher coordination number and to present a side on coordination to the 5 hydroximato oxygens, with a deviation from the oxygen mean plane of 0.5−0.6 Å. From these cavity radii, all the lanthanides from Sm to Dy are expected to fit into the cavity, and indeed they present a small deviation from the oxygen plane, in many cases of about 0.2 Å.

The effect of the size correspondence on the capability of 15-MC-5 to encapsulate the lanthanide ions can be seen as follows: La^{3+} and Nd^{3+}, which are larger or on the upper edge of the proper ionic radius to fit into the 15-MC-5 cavity (1.216 and 1.109 Å, respectively), behave as large cations and, thus, no marked selectivity is observed among them. This trend appears to hold through the smaller, lower coordination number Gd^{3+}. The latter ion, which actually possess an ionic radius of about 1.053 Å, represents the cation (among those taken into account in this study), which is expected to best fit into the 5 oxygen cavity. All the other cations (Dy^{3+}, Er^{3+}, and Yb^{3+}) can be treated as small cations. A steep decrease of stability of the 15-MC-5 for lanthanides heavier than Gd^{3+} (Table 1) leads to a marked selectivity away from their complexation. Figure 7 reports the correlation between the log K values for the $Ca^{2+}-Ln^{3+}$ substitution equilibria for $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$ in methanol/water 99:1 (Table 1) and the log β values of the Ln^{3+} complexation equilibria for the sulfobenzo-15-crown-5 ligand (SB15-C-5) in water (Table 2).[36] The correlation parameter between the values is $R = 0.98$. The log K values as a function of the ionic radius of the Ln^{3+} ions is also reported in Figure 7. As occurs for simple crown ethers, the size fit factor has no significant role in determining metallacrown stabilities with the lighter lanthanides, while it does apply for the heavier ones. Unfortunately, the data presented herein only allow a discussion of the overall metal replacement free energy change, and cannot allow a discrimination between the enthalpic and entropic contributions so they do not provide any information on desolvation processes.

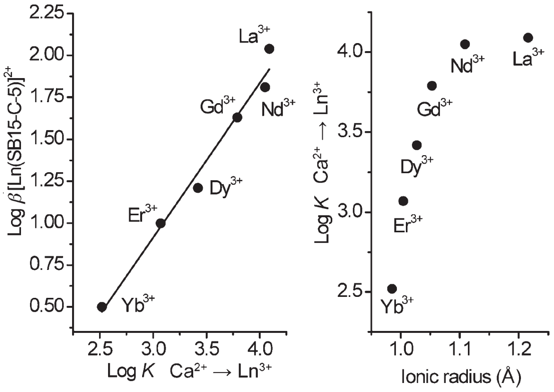

Figure 7. Plot of the log K values of Table 1 (compound **4** in methanol/water 99:1) and the log β values for the sulfobenzo-15-crown-5 ligand (SB15-C-5, ref 36 and Table 2) in water (left), and plot of the log K values as a function of the Ln^{3+} ionic radius (right).

The different Lewis acidities of the Ln^{3+} ions examined lead to the *red shift* of the visible band for the 15-MC-5 complexes from La^{3+} to Er^{3+} (Figure 2, and Table 1). This *red shift* is present in methanol/water 9:1 and, for Gd^{3+} to heavier lanthanides, also in methanol/water 99:1. The electron density on the hydroximato oxygens of the MC cavity is more effectively polarized by the Ln^{3+} as the charge/radius ratio of the ion increases. As these oxygens are also involved in Cu^{2+} coordination, the polarization reduces the ligand field on the copper(II) ions, which correspondingly produces a *red shift* in the Cu^{2+} d-d band at 570 nm.

Ln^{3+} versus Ca^{2+} Selectivity. The stabilities of $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+}$ are 6.2 to 2.5 orders of magnitude higher than those of Ca^{2+} depending on the Ln^{3+} and solvent (Table 1). As regards the parent 15-crown-5 ether, the thermodynamic data on the complexation of both Ca^{2+} and Ln^{3+} ions by 15-crown-5 in homogeneous conditions are unfortunately limited to acetonitrile or propylene carbonate. In these solvents the stability of Ca^{2+} complexes is higher or at least equal to those of Ln^{3+} ions. For instance, in acetonitrile the ML complex with

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(47) A detailed structural analysis can be found in: A. D. Cutland Van Noord, Ph.D. Dissertation, University of Michigan, Ann Arbor, MI, **2003**.

Ca^{2+} has log β = 5.41,[33,48] while the same species with Ln^{3+} range from 5.17 (La^{3+}) to 2.03 (Gd^{3+}).[34] A similar relationship has been found for the 4-*tert*-butylbenzo-15-crown-5 complexes in propylene carbonate, where the log β of the Ca^{2+} complex is 6.05,[35,49] and those of Ln^{3+} range from 3.75 for Nd^{3+} to 2.80 for Yb^{3+} and Lu^{3+} (Table 2).[40] This more favorable Ca^{2+} complexation cannot be accounted simply with the size correspondence effect. In fact, Ca^{2+} has an ionic radius of about 1.12 Å (C.N. = 8)[31] which is very similar to that of Nd^{3+} and significantly larger than the cavity radius of the 15-C-5, yet Ca^{2+} is preferentially encapsulated by 15-crown-5.

The data in Table 1 reveal that $\{Ln^{III}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{3+}$ are more stable in methanol/water than the corresponding Ca^{2+} metallacrowns. Because the log β values for the complexation of lanthanides and calcium by 15-C-5 in methanol and for homogeneous conditions are unavailable, we will refer to those values reported for 18-C-6 to explain this selectivity. The $\log \beta_{Ca} > \log \beta_{Ln}$ relationship described for 15-C-5 in aprotic solvents has also been observed in pure methanol for 18-C-6, as the log β values for the $M\subset(18\text{-}C\text{-}6)^{z+}$ species are 3.86−4.0 for Ca^{2+} and 3.29−1.84 for La^{3+}-Eu^{3+}.[39,43]

Izatt and co-workers first observed that the complexation of Ln^{3+} by 18-C-6 in methanol has an unfavorable positive enthalpy and is essentially entropic in nature.[39] In contrast, the complexation of Ca^{2+} by 18-C-6 has both favorable enthalpic and entropic contributions (−11.3 kJ mol^{-1} and +38.6 J mol^{-1} K^{-1}, respectively).[44] The substitution of Ca^{2+} by Ln^{3+} is unfavored in methanol for enthalpic reasons, as the ΔH of the replacement process is positive and not compensated by the positive, though small, entropic change. What is different for 15-MC-5 is the presence of oxygen atoms in the cavity that carry a partial negative charge. We may expect that the electrostatic interactions between a 3+ *core metal* and the five partial negative charges of the cavity is energetically more favorable compared to that with a 2+ cation. The negative charged cavity in 15-MC-5 may then play a major role in the stabilization of the Ln^{3+} complexes, which in turn accounts for their enhanced encapsulation ability.

As regards 18-C-6 complexes, the log β for Ca^{2+} drops from 4.0 to 0.5 from pure methanol to pure water, while the log β value for Ln^{3+} ions (La^{3+}, Ce^{3+}) increases from pure methanol to 30% methanol in water (3.09−3.57 to 4.29−4.70).[39,50] The increase of water content tends thus to favor the Ln^{3+} over Ca^{2+} complexation for 18-C-6 in methanol. This behavior is consistent with that observed for metallacrowns, where a more favorable Ca^{2+} replacement by Ln^{3+} exists as the water content increases (e.g., 4.09 to 6.2 for La^{3+} in methanol/water 99:1 to 9:1, respectively, Table 1).

Interaction of 15-MC-5 Complexes with Na^+. The medium used for the study of the Ca^{2+}−Ln^{3+} replacement equilibria also contained high Na^+ concentration. This high sodium concentration comes from the MES buffer after pH correction to 6.5 by addition of NaOH. As the pK_a of MES is about 6.2−6.3 (in water),[33] it is expected that at pH 6.5 the Na^+ concentration is in the 25−50 mM range. We then performed a series of experiments assessing the integrity of the 15-MC-5 species in the presence of high concentrations of this cation which may itself act as a *core metal* upon replacement of either Ca^{2+} or Ln^{3+} ions. The need for these investigations was suggested by the evaluation of the formation constants of Na^+ and Ca^{2+} with crown ethers. The log β value for the ML complexes of Na^+ and Ca^{2+} of the 15-C-5 ligand in methanol are 3.32 and 2.2, respectively,[43] demonstrating that the addition of 1 equiv of Na^+ to the Ca^{2+} complex of 15-C-5 displaces the latter cation from the crown ether cavity.

The spectrum of the solution containing compound **3** (0.2 mM) in presence of 50 mM NaCl (250 equiv excess) does not present a marked difference if compared to the spectrum in the absence of Na^+ and suggests that Ca^{2+} is not displaced from the MC cavity (Figure 5). The effect of the addition of Na^+ to a solution of $\{La^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{3+}$ (compound **5**) is even lower, and the spectrum in the absence and in the presence of the alkali metal is not significantly altered. The differences between the two spectra at their absorption maxima are of the order 2.5% for Ca^{2+} MC and 1% for La^{3+} MC, and the differences are limited to a small *red shift* of the d-d absorption bands.

The complete integrity of the La^{3+} 15-MC-5 species in the presence of Na^+ is consistent with the data reported in the literature for the analogous metallacrowns of picolinehydroxamic acid for which the order of stability as a function of the core metal is $Na^+ < Ln^{3+}$, while no similar data are available for Ca^{2+} metallacrowns.[13] The observation that Na^+ forms the weakest adduct is consistent with our explanation for the added stability of Ln^{3+} compared to Ca^{2+} which invokes the enhanced affinity of trivalent ions to the MC cavity because of the partial negative charge of the ring oxygen donors.

Previous investigations excluded the formation in solution of K^+ 15-MC-5 complexes with Cu^{2+} and pheha or trpha even at in a 0.1 M KCl solution.[10] With the aim to assess the presence of Na^+ 15-MC-5 complexes, we added NaCl to a Cu^{2+}/pheha 1:1 green solution ($C_{Cu} = 10^{-3}$ M, pH 5.9) to obtain a 50 mM Na^+ solution. A green gelatinous precipitate appeared after 6−12 h, which could not be isolated as a powder. Part of the material (isolated by centrifugation) was dissolved in methanol and analyzed by ESI-MS. The spectrum revealed that it contained $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)\text{-}pheha}\text{-}4]\}^{2+}$ as the most abundant ion, which is the predominant species expected for a Cu^{2+}/pheha 1:1 solution at pH about 5.9. The visible spectrum is also very similar to that of the latter solution. Similar, very insoluble green precipitates were obtained with NaCl, $NaNO_3$, KNO_3, KPF_6, NEt_4PF_6, MES buffer corrected to pH 6.2, and even KCl, suggesting that the high anion concentrations leads to a product containing the $\{Cu^{II}[12\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}4]\}^{2+}$ species. This solid was not detected during previous potentiometric titrations in the presence of KCl probably because the time required for each titration run is too short (ca. 2 h) for the precipitate to appear.[10] All these data show, however, that the Cu^{2+}/pheha system forms a green precipitate in the presence of NaCl, while solutions of $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ are brick red and they do not

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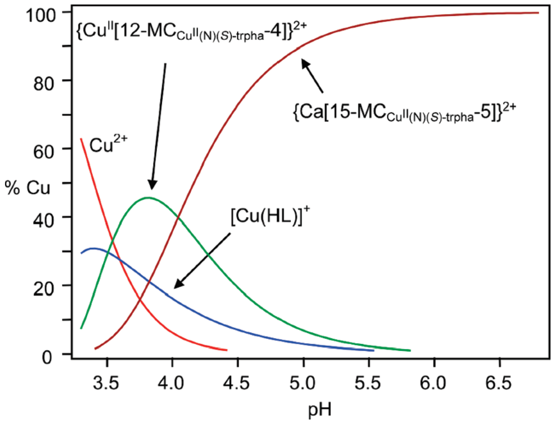

Figure 8. Representative Cu^{2+} distribution diagram for the Ca^{2+}/Cu^{2+}/trpha (H_2L, **2**) system in methanol/water 9:1 (v/v, Ca/Cu/L 1:5:5, $C_{Ca} = 7.6 \times 10^{-4}$ M).

change appreciably upon addition of 250 equiv of Na^+. On the basis of these observations, it is clear that the replacement of Ca^{2+} or Ln^{3+} by Na^+ in 15-MC-5 species is thermodynamically unfavored.

Ca^{2+} 15-MC-5 Formation Constants. The vacant 15-MC-5 scaffold cannot be isolated or assembled in solution; thus the log β value for the process $[15\text{-MC}_{Cu^{II}(N)(L)}\text{-5}] + Ca^{2+} \rightarrow \{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(L)}\text{-5}]\}^{2+}$ cannot be directly determined. To assess the formation constants of the Ca^{2+} 15-MC-5, pH-spectrophotometric titrations of solutions of **3** or **4** with HCl was performed (Figure 6 and Supporting Information). Data treatment allowed the determination of the formation constants for the $Ca^{2+} + 5Cu^{2+} + 5HL^- = \{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(L)}\text{-5}]\}^{2+} + 5H^+$ equilibria with log K values of 63.46(12) and 65.05(13) for H_2L = pheha or trpha, respectively.[9]

The similarity between these two values suggests that there are no relevant hydrophobic interactions or steric hindrance effects between the 15-MC-5 residues to affect the overall stability of the 15-MC-5 in solution. The experimental spectra for the titration of **4** with HCl are reported in Figure 6, and the Cu^{2+} distribution diagram as a function of pH is reported in Figure 8. The possible formation of Ca^{2+}/aminohydroximate species has been taken into account including in the calculations log K = 2.45 for Ca^{2+} binding to the hydroximate moiety in water;[51] however, the calculations proved that Ca^{2+} is not coordinated to the ligand, with the latter either being bound to Cu^{2+} or in the protonated H_3L^+ form. A similar result was obtained in previous investigations of Ln^{3+} 15-MC-5 complexes in water where no Ln^{3+}/ligand binary species were detected in presence of Cu^{2+} which promotes the complete incapsulation of the core metal into a MC scaffold.[52]

The most relevant reaction that occurs during the titration of **3** or **4** with HCl is the 15-MC-5 disassembly process described as $\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(L)}\text{-5}]\}^{2+} + 3H^+ = Ca^{2+} + \{Cu^{II}[12\text{-MC}_{Cu^{II}(N)(L)}\text{-4}]\}^{2+} + H_3L^+$. The direct conversion between the Ca^{2+} 15-MC-5 into the Cu^{2+} 12-MC-4 species is supported by the presence of the two isosbestic points and by the disappearance of the 15-MC-5 band (ca. 550 nm) with the appearance of a band at about 640 nm typical of $\{Cu^{II}[12\text{-MC}_{Cu^{II}(N)(L)}\text{-4}]\}^{2+}$.[10,52] For the titration of **4** with HCl, the isosbestic points are present for the first nine spectra (pH 6.8 to 3.9) while the distribution diagram shows, in the same pH range, the simultaneous presence of both the $\{Cu^{II}[12\text{-MC}_{Cu^{II}(N)(L)}\text{-4}]\}^{2+}$ and $[Cu(HL)]^+$ species. The species distribution is, however, consistent with the presence of the isosbestic points as the molar absorption of the latter species is much lower than that of the 12-MC-4, and the amount of $[Cu(HL)]^+$ is low above pH 4.5 (see Supporting Information).[10]

Integrity of Ca^{2+} 15-MC-5 in Presence of Crown Ethers. The low capability of the crown ethers to remove Ca^{2+} from the 15-MC-5 cavity has also been demonstrated experimentally by a spectrophotometric titration of compound **4** in methanol/water 9:1 using the 18-C-6 macrocycle. The latter crown ether, rather than 15-C-5, was chosen as it shows a higher affinity for Ca^{2+} (log β = 4.0 in methanol, compared to 2.2 for 15-C-5 and 2.80 for 21-C-7, respectively).[43,53] The addition of 18-C-6 to compound **4** up to an excess of 8 equiv of the crown ether did not affect the integrity of the $\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(\mathit{S})\text{-trpha}}\text{-5}]\}^{2+}$ complex (Figure 4). The reduction of absorbance is fully accounted for by dilution (Figure 4). Similar results were obtained using compound **5** ($\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(\mathit{S})\text{-trpha}}\text{-5}]\}^{2+}$ 48 h after 18-C-6 has been added (see Supporting Information). These results prove the superior Ca^{2+} and La^{3+} complexation capabilities of the 15-MC-5 scaffold compared to 18-C-6.

The speciation calculations are consistent with the experimental results: the amount of Ca^{2+} sequestered by the 18-C-6 is expected to be 1.1% (log β = 2.97 for $[Ca\subset(18\text{-C-}6)]^{2+}$ in methanol/water 90% wt.).[43] Moreover, even in the presence of a 100-fold excess of 18-C-6, the amount of $[Ca\subset(18\text{-C-}6)]^{2+}$ is expected to be only 2.7% total calcium (see Supporting Information). A similar calculation using a value of 2.2 for the log β of the $[Ca\subset(15\text{-C-}5)]^{2+}$ showed that in presence of a 100-fold excess of the less coordinating 15-C-5 the amount of $[Ca\subset(15\text{-C-}5)]^{2+}$ complex is only about 1% total calcium (at pH 7, see Supporting Information).[43]

A reverse experiment was carried out, and the assembly of the $\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(\mathit{S})\text{-pheha}}\text{-5}]\}^{2+}$ species was obtained quantitatively adding either Ca^{2+} or $[Ca\subset(18\text{-C-}6)]^{2+}$ to a Cu^{2+} acetate and pheha solution (almost equimolar concentration in methanol/water 9:1). This assembly of $\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(\mathit{S})\text{-pheha}}\text{-5}]\}^{2+}$ through the extraction of Ca^{2+} from the crown ether cavity and the integrity of compound **5** (La^{3+} 15-MC-5) in presence of an excess of 18-C-6 is a direct consequence of the better Ca^{2+} and Ln^{3+} complexation capabilities of 15-MC-5 compared to those of 18-C-6.

Conclusions

The $Ca^{2+}-Ln^{3+}$ substitution reaction for $\{Ca^{II}[15\text{-MC}_{Cu^{II}(N)(L)}\text{-5}]\}^{2+}$ complexes is thermodynamically favored for the entire lanthanides(III) series in both methanol/water 9:1 and 99:1 (v/v). The 15-MC-5 scaffold encapsulates the

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Ln^{3+} ions with low selectivity for the La^{3+}-Gd^{3+} series, while a marked selectivity for the Gd^{3+}-Yb^{3+} cations was observed. The latter cations are in fact small enough to fit into the MC cavity, and the selectivity likely has its origins in the size correspondence between the cavity and the core metal. Moreover, the 15-MC-5 scaffold has also been demonstrated to be a better complexing agent toward Ca^{2+} than crown ethers. In particular, Ca^{2+} cannot be removed from the MC cavity even in presence of an excess of 18-crown-6 macrocycle, while the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ formation process thermodynamically drives the Ca^{2+} removal from the 18-C-6 cavity. This marked preference of 15-MC-5 for Ln^{3+} has been attributed to the partial negative charge of the oxygens of the metallacrown ring. The Ca^{2+} and La^{3+} 15-MC-5 complexes are stable in the presence of an excess of Na^{+}, a behavior that is different from that of 15-C-5, which is a better complexation agent for the alkali metals than for Ca^{2+}. These studies for the first time quantitatively compare the metal complexation properties of crowns and metallacrowns. We can conclude that the neutral organic macrocycles are superior chelating agents for alkali metal cations but are less capable of sequestering more highly charged, hard cations than their metallamacrocylic counterparts. Finally, we also demonstrated a high thermodynamic selectivity in lanthanide(III) complexation by 15-MC-5. This suggests that metallacrowns may be useful for Ln^{3+} separation.

Experimental Section

General Information. All chemicals were reagent grade and used as received without further purification. Phenylalanine methyl ester hydrochloride, tryptophan methyl ester hydrochloride, and hydroxylamine hydrochloride were purchased by Fluka. Lanthanide(III) nitrates hydrate (La^{3+}, Nd^{3+}, Gd^{3+}, Dy^{3+}, Er^{3+}, and Yb^{3+}) and 18-crown-6 ether were purchased by Sigma Aldrich. Copper(II) acetate monohydrate and copper(II) chloride dihydrate were purchased by Carlo Erba. Literature procedures were employed for the synthesis of the $\{La^{III}(NO_3)_3[15\text{-}MC_{Cu^{II}(N)(\textit{S})\text{-pheha}}\text{-}5]\}(OH_2)_2$ (**5**)[23] and the Ca^{2+} adduct with 18-crown-6 ether ($[Ca\subset(18\text{-}C\text{-}6)](NO_3)_2$, **6**).[54,55] Deuterated NMR solvents were high purity and purchased by Sigma Aldrich. Buffered methanol/water 9:1 or 99:1 (v/v) were prepared by mixing reagent grade methanol and bidistilled water in proper amounts. MES hydrate (4-morpholineethanesulfonic acid, 4.88 g, 25 mmol) was suspended in 500 mL of the solvent, and saturated NaOH solution in methanol was added dropwise under vigorous stirring up to complete dissolution (pH ca. 6.1−6.2). The pH was then corrected to 6.5 by addition of further NaOH. The buffered stock methanol/water mixture was used within 2 weeks (the pH value was checked 1 week after buffer preparation). Standard KOH solution (ca. 0.1 N) was prepared using Merck Titrisol high purity concentrated solutions. EDTA solution (ca. 0.016 N) was prepared by weight using solid bisodic EDTA dihydrate. All solutions were prepared using freshly boiled, doubly distilled water and standardized with the usual procedure of this laboratory.[56] The purity of the ligands was checked by potentiometric titrations and NMR. ^1H NMR spectra were collected on an Varian Inova 400 MHz and Bruker Avance 300 MHz spectrometers. ESI mass spectra were recorded on a single quadrupole Micromass LCT Mass Spectrometer (Micromass, Manchester, U.K.) fitted with a pneumatically assisted electrospray probe. Data were processed using the spectrometer software (MassLynx NT version 3.4). Visible absorption spectra were collected on a Perkin-Elmer Lambda 25 and a Varian Cary 50 Bio spectrophotometers using matched quartz cells of 1 cm of path length. Elemental analyses were carried out by a Carlo Erba EA1108 microanalyzer. All samples for the spectrophotometric titrations were prepared using a Metrohm Dosimat 665 dispenser provided with 10, 5, and 1 mL burets. All the other samples were prepared using either the Metrohm dispenser or Hamilton Gastight syringes with volumes of 1, 0.5, or 0.25 mL. The pH ($-\log [H^+]$) was measured using a Hamilton microelectrode (P/N 238100) connected to an Orion 720A potentiometer. The reference compartment of the electrode was filled with a 0.1 M (KCl) methanol/water 9:1 solution and left to equilibrate for 24 h. The electrode was calibrated using two methanol/water 9:1 buffer solutions. The buffers were prepared by mixing proper amounts of acetic acid/sodium acetate or conc. ammonium hydroxide/ammonium chloride in methanol/water mixtures to obtain two 0.1 M buffers in methanol/water 9:1 (v/v) at pH 6.84 and 9.21, respectively (corresponding to the pK_a values of CH_3COOH and NH_4^+ in methanol/water 9:1, see Supporting Information).[57]

Synthesis of (*S*)-α-phenylalaninehydroxamic Acid (pheha, 1). The synthesis of this ligand was performed using a procedure reported in the literature,[58] with the following modifications. A volume of 25 mL of a conc. aqueous NH_4OH solution was added to 100 mL of chloroform, and the biphasic mixture was gently stirred for 15 min. The organic layer was separated using a separatory funnel and dried with anhydrous Na_2SO_4. Solid (*S*)-α-phenylalanine methyl ester hydrochloride (8.43 g, 39.1 mmol) was added to the chloroform solution. The obtained suspension was mantained under stirring at room temperature for 1 h, and the precipitate filtered out. The solvent was removed under vacuum, and (*S*)-α-phenylalanine methyl ester was obtained as a pale yellow oil. In a separate flask, a 50 mL solution of KOH (13.1 g, 234 mmol) in methanol was added to a 40 mL solution of hydroxylamine hydrochloride (16.3 mg, 235 mmol) in methanol. The suspension was left to stir for 20 min at 0 °C, and the precipitate filtered out. The methanolic hydroxylamine solution was added to the tryptophan methyl ester oil. The solution was left to stir at room temperature overnight, then kept at 4 °C for 24 h. The product precipitated out as a microcrystalline white powder which was collected by filtration and washed with chloroform (3 × 50 mL). More product precipitated out leaving the solution at 4 °C for additional 48 h. Yield 70%. ^1H NMR [$(CD_3)_2SO$, 400 MHz]: δ 7.23 (m, 5H, Ph), 3.26 (t, $J = 7$ Hz, 1H, $C_\alpha H$), 2.85 (q, $J_1 = 14$ Hz, $J_2 = 7$ Hz, 1H, $C_\beta H$), 2.62 (q, $J_1 = 14$ Hz, $J_2 = 7$ Hz, 1H, $C_\beta H$). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.54. Found: C, 59.7; H, 6.8; N, 15.3.

Synthesis of (*S*)-α-tryptophanhydroxamic Acid (trpha, 2). The synthesis was performed as described for **1**, using 8.23 g (32.3 mmol) of (*S*)-α-tryptophan methyl ester hydrochloride, 13.5 g (194 mmol) of hydroxylamine hydrochloride, and 10.9 g (194 mmol) of KOH. The final solution was left to stir for 24 h. The product precipitated out as a white microcrystalline powder, which was collected by filtration and washed with chloroform (3 × 50 mL). More product precipitated out after 48 h, which was collected by filtration. Yield 55%. ^1H NMR [$(CD_3)_2SO$, 400 MHz]: δ 10.8 (br, 1H, $N_{indole}H$), 7.55 (d, $J = 8$ Hz, 1H, $C_{indole}H$), 7.32 (d, $J = 8$ Hz, 1H, $C_{indole}H$), 7.12 (s, 1H, $C_{indole}H$), 7.06 (t, $J = 8$ Hz, 1H, $C_{indole}H$), 6.96 (t, $J = 8$ Hz, 1H, $C_{indole}H$), 3.34 (t, $J = 7$ Hz, 1H, $C_\alpha H$), 2.99 (q, $J_1 = 14$ Hz, $J_2 = 7$ Hz, 1H, $C_\beta H$), 2.72 (q, $J_1 = 14$ Hz, $J_2 = 7$ Hz, 1H, $C_\beta H$). Anal.

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Calcd for $C_9H_{12}N_2O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.4; H, 5.8, N, 19.3.

Synthesis of $\{Ca^{II}(NO_3)_2[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}(CH_3OH)(OH_2)_{7.5}$ (3). (*S*)-α-tryptophanhydroxamic acid (0.123 g, 0.561 mmol), calcium nitrate tetrahydrate (0.026 g, 0.11 mmol), and copper acetate dihydrate (0.11 g, 0.56 mmol) were added to 30 mL of methanol. The solution was stirred for 24 h. The solution was filtered and slowly evaporated to grow single crystals. Reddish brown crystals were obtained. Yield 28%. ^1H NMR [CD_3OD, 300 MHz]: δ 24.7 (br, 5H, $C_\alpha H$), 12.4 (br, 5H, $C_\beta H$), 7.9 (br, 5H, $C_\beta H$), 7.34 (br s, 15H, Ph), 7.05 (br s, 10H, Ph). ESI-MS: *m*/*z* 1504 ($\{Ca^{II}(NO_3)_2[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}(NO_3)^+$). Anal. Calcd for $C_{46}H_{69}CaCu_5N_{12}O_{24.5}$: C, 35.88; H, 4.52; N, 10.91. Found: C, 35.6; H, 4.3, N, 10.8.

Synthesis of $\{Ca^{II}(NO_3)_2[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}(CH_3OH)_2(OH_2)_4$ (4). (*S*)-α-phenylalaninehydroxamic acid (0.10 g, 0.55 mmol) and copper acetate dihydrate (0.11 g, 0.56 mmol) were dissolved in 50 mL of methanol and stirred for 10 min. Calcium nitrate tetrahydrate (0.026 g, 0.11 mmol) was added to the green solution, and the color changed to brick red. The solution was stirred overnight, and the green insoluble impurities were filtered out. By slow evaporation, brown red crystals were obtained. Yield = 25%. ^1H NMR [CD_3OD, 300 MHz]: δ 29.5 (br, 5H, $C_\alpha H$), 10.2 (br, 5H, $C_\beta H$), 9.5 (br, 5H, $C_\beta H$), 7.39 (br s, 10H, $C_{indole}H$), 7.07 (br, 10H, $C_{indole}H$). ESI-MS: *m*/*z* 1309 ($\{Ca^{II}(NO_3)_2[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}(NO_3)^+$), 624 ($\{Ca^{II}(NO_3)_2[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$). Anal. Calcd for $C_{57}H_{71}CaCu_5N_{17}O_{22}$: C, 40.17; H, 4.20; N, 13.97. Found: C, 40.0; H, 4.1, N, 14.1.

Spectrophotometric Study of 15-MC-5 Equilibria. Standard Ln^{3+} nitrate solutions ($4-5.5 \times 10^{-3}$ M) were prepared by weight in buffered methanol/water 9:1 or 99:1 (v/v, 50 mM MES buffer, pH 6.5). The Ln^{3+} concentrations were determined by titration against standard aqueous EDTA solution (ca. 0.016 N) of about 3 mL of the lanthanide(III) nitrate solution diluted with in 20 mL of aqueous acetate buffer solution (pH 4.5) at 50 °C using Xylenol Orange as indicator. An HCl solution (ca. 0.08 M) in unbuffered methanol/water 9:1 (v/v) was prepared by dilution of conc. HCl (Baker) with proper amounts of reagent grade methanol and bidistilled water. The HCl titer was determined by titration against standard aqueous KOH solution (ca. 0.1 N) using Methyl Orange as indicator.

The $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ solutions (ca. 1×10^{-3} M, H_2L = pheha or trpha) in buffered methanol/water 9:1 (v/v) were prepared by weight dissolving the solid compounds **3** and **4** in 180 mL of solvent (0.18 mmol, 277 mg and 306 mg of **3** and **4**, respectively). The $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$ solution (ca. 1×10^{-3} M) in buffered methanol/water 99:1 (v/v) was prepared by weight dissolving the solid compound **4** (309 mg, 0.181 mmol) in 180 mL of solvent.

The $Ca^{2+}-Ln^{3+}$ substitution equilibria for $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ complexes were studied by means of batch (out of cell) spectrophotometric titrations of the buffered 15-MC-5 solutions (50 mM MES buffer, pH 6.5) in methanol/water 9:1 (H_2L = pheha or trpha) or 99:1 (H_2L = trpha) with Ln^{3+} nitrate solutions. The solutions of **3** or **4** were divided into 19 samples (1.5 mL each), and each vial was added with increasing aliquots of buffered Ln^{3+} nitrate solutions. The Ln^{3+}/**3** or **4** ranged from 0 to 1.4−2.0 (methanol/water 9:1) or 1.7−2.0 (methanol/water 99:1). The vials were left to equilibrate for 72 h at room temperature, and the absorption spectra were collected in the visible range (400−800 nm). After the equilibration time, the color of the solutions resulted brick-red to violet for increasing Ln^{3+} concentrations.

The self-assembly equilibria of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ species (H_2L = pheha and trpha) were studied by batch (out of cell) pH-metric titrations of compounds **3** or **4** in unbuffered methanol/water 9:1 (v/v) solutions with standard HCl. Solutions of **3** or **4** (ca. 7.5×10^{-4} M) were prepared by weight, dissolving the solids (ca. 26.3×10^{-3} mmol, 40 mg or 44 mg for **3** and **4**, respectively) in 35 mL of methanol/water 9:1 (v/v). These solutions were divided into 16 samples (2.0 mL each), and each vial was added with standard HCl in methanol/water 9:1 up to a total HCl concentration 3.9×10^{-3} M. The vials were left to equilibrate for 72 h at room temperature. The pH of the solutions and the visible absorption spectra (400−800 nm) were then registered. The color of the solution changed from brick red to deep green, then to pale green for increasing HCl concentration. The pH ranged from 3.6 to 7.4 for **3**, and 3.3 to 6.8 for **4**, respectively.

Crown Ether/Metallacrown Competition Studies. The titration of a $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$ solution with the 18-crown-6 were performed in an unbuffered methanol/water 9:1 (v/v) solution. A solution of **4** (4.23×10^{-4} M) was prepared by weight dissolving the solid (1.44 mg, 8.45×10^{-4} mmol) in 2 mL of methanol/water 9:1. A solution of 18-C-6 (5.47×10^{-3} M) was prepared by weight dissolving the solid ligand (4.34 mg, 0.0164 mmol) in 3 mL of a methanol/water 9:1 solution. The solution of $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}trpha}\text{-}5]\}^{2+}$ was titrated with increasing aliquots of 18-C-6 (0.25 mL each, corresponding to 1.6 equiv of crown ether) up to 1.25 mL (8.0 equiv). The spectra were collected 5 min after the crown ether addition. The last spectra (corresponding to 8.0 equiv of 18-C-6) was also recorded 24 h after the sample preparation.

The study of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ self-assembly in presence and in absence of 18-C-6 was studied by dissolving copper(II) acetate monohydrate (15.5 mg, 0.0776 mmol) and pheha (17.3 mg, 0.0960 mmol) in 10 mL of methanol/water 9:1, obtaining a green solution which has been microfiltered (Cu/pheha = 1:1.24). The solution was divided into two samples of 5 mL each, and solid calcium nitrate tetrahydrate (4.7 mg, 0.0199 mmol) or **6** (8.5 mg, 0.0198 mmol) were added to each sample (Ca/Cu = 1.28/5). The solutions turned into brick red in few hours. The samples were left to equilibrate at room temperature for 2 weeks, and the visible absorption spectra collected.

The integrity of the $\{La^{III}[15\text{-}MC_{Cu^{II}(N)(S)\text{-}pheha}\text{-}5]\}^{3+}$ (compound **5**) in presence of 18-C-6 was tested by adding 1.25 mL of a 5.5×10^{-3} M solution of 18-crown-6 ether (14 mg, 0.053 mmol in 9.6 mL methanol/water 9:1) to 2 mL of a 4.3×10^{-3} M solution of **5** (3.4 mg, 0.022 mmol in 5 mL metahnol/water 9:1). The visible spectra were registered 48 h after sample preparation.

Na^+/Ca^{2+} Competition Studies. A solution of **3** (ca. 2.02×10^{-4} M) was prepared by dissolving the solid (7.20 mg, 5.06 mmol) in 25 mL of methanol/water 9:1. The solution was divided in 2 samples (3 mL each). To one of the samples, solid NaCl (8.9 mg, 0.15 mmol) was added to obtain a 50 mM Na^+ concentration. Two similar samples were prepared using compound **5** (3.13 mg, 1.99 mmol in 10 mL of methanol/water 9:1). The samples in presence and absence of NaCl were left to equilibrate for 72 h, and the visible absorption spectra were registered.

Calculations. Thermodynamic constants (log *K*) for the $Ca^{2+}-Ln^{3+}$ substitution equilibria for $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ were calculated from visible spectrophotometric data using the Hyperquad 2006 program.[59] Formation constants (log *K*) for the equilibria of self-assembly of the $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$ complexes (corresponding to the $Ca^{2+} + 5Cu^{2+} + 5HL^- = \{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+} + 5H^+$ equilibrium) were calculated from visible spectrophotometric data at different pH using the Specfit32 program.[9,60] Least-square treatment was performed by minimization of the sample standard deviation $\sigma = [\sum_i (A_i^o - A_i^c)^2/(n-m)]^{1/2}$, where A_i^o, A_i^c are the experimental and calculated absorbance values, *n* is the number

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(59) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739–1753.

(60) *SPECFIT/32*, version 3.0.35; Spectrum Software Associates: Oshkosh, WI, 2004.

of observations, and *m* is the number of parameters refined. Estimated errors of the titrant volume (0.008 mL) was considered in the weighting of the spectrophotometric data. Calculated absorbances and equilibrium constants were determined taking into account the reactant concentrations and, for the self-assembly equilibria, of the experimental pH values. For the determination of the equilibrium constants of the $Ca^{2+}-Ln^{3+}$ substitution reactions, the molar absorbances of Nd^{3+} and Er^{3+} nitrates were introduced as fixed parameters. For the determination of the formation constants of $\{Ca^{II}[15\text{-}MC_{Cu^{II}(N)(L)}\text{-}5]\}^{2+}$, the formation constants and calculated spectra of the species of the binary system Cu^{2+}/L (H_2L = pheha or trpha) were those previously published and treated as fixed parameters.[9,10] The speciation diagrams were plotted with the Hyss 2006 program.[61]

List of Abbreviations

Glossary

pheha	(*S*)-α-phenylalaninehydroxamic acid
trpha	(*S*)-α-tryptophanhydroxamic acid
SB15-C-5	3′-sulfobenzo-15-crown-5
15-C-5	15-crown-5
B15−C-5	benzo-15-crown-5
S15−C-5	stilbene-15-crown-5
4tBuB15-C-5	4-*tert*-butylbenzo-15-crown-5

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Supporting Information Available: Additional representative spectral data, distribution diagrams, calculated spectra for the $Ca^{2+}/Cu^{2+}/$**1** or **2** binary and ternary species, representative results of spectral data fit, and experimental procedures and data treatment for the preparation of buffer solutions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(61) Alderighi, L.; Gans, P.; Ienco, A.; Peters, D.; Sabatini, A.; Vacca, A. *Coord. Chem. Rev.* **1999**, *184*, 311–318.