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Establishing the Binding Affinity of Organic Carboxylates to 15-Metallacrown-5 Complexes

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The reaction of L-phenylalanine hydroxamic acid (H_2L-pheHA) with copper(II) and lanthanide(III) salts yields 15-Metallacrown-5 structures of the general composition Ln(X)n[Cu(II)(L-pheHA)]$_5^{(3-n)+}$ where X can represent a wide variety of anions. With five copper ions and one central lanthanide ion, the Ln[15-MC-5] complexes have multiple positions where these anionic guests may bind to the metallacrown host. In addition, these metallacrowns are amphiphilic, containing one face that is primarily hydrophobic (due to the five benzyl side chains which are oriented upon the same face of the molecule) and a face that is hydrophilic which has no impediment to solvent access. While it has been known that aromatic carboxylates bind preferentially to the hydrophobic face and short chain aliphatic carboxylates bind preferentially to the hydrophilic face, there have been no quantitative assessments of the stability of these host−guest complexes. Using Isothermal Calorimetry (ITC) we have determined the binding constants for several carboxylate anions to a variety of metallacrown complexes. The affinities of anions that coordinate to the lanthanide ion on the hydrophobic face are related to the hydrophobicities of the guests, with higher binding strength observed for the more hydrophobic carboxylates. Central metal such as La(III) or Nd(III) which are nine coordinate are able to accommodate two guests on the hydrophobic side; however, central metals such as Gd(III) or Dy(III) which are eight coordinate are limited to encapsulating one guest into the hydrophobic pocket. A second guest, bound to the hydrophilic face is often observed with these 8-coordinate lanthanides. The significantly weaker second binding constant between benzoate and Gd(III)[15-MC-5] supports the model that the second benzoate binds to the central metal through the hydrophilic side. Unlike the Gd(III)[15-MC-5], the higher binding constant of the second benzoate with La(III)[15-MC-5] is consistent with the crystallographic model which shows that the second guest binds to the hydrophobic side.

Introduction

Since the first macrocyclic polyether was reported in 1967,[1,2] many scientists have investigated new macrocyclic compounds.[3−8] These investigators have been interested in encapsulating cationic, anionic, or neutral ions in the cavity of the macrocyclic compounds in solution. Today, numerous different molecular structure types have been prepared which not only demonstrate molecular recognition of the desired guest, but also serve numerous practical applications ranging from aides in synthetic chemistry to analytical reagents. More recently, chemical transformations such as 2 + 2 photochemical reactions,[9−11] or 4 + 2 Diels−Alder reactions[12,13] have been reported in solution or in the solid state by the application of an appropriate supramolecular compound for guest alignment.

Metallacrowns, which are analogues of crown ethers, were reported in 1989.[14−16] Despite the intense interest[17−20] in the

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synthesis, structural characterization, and physical properties of metallacrowns, a quantitative description of the host–guest interactions between organic carboxylates and metallacrowns in solution has not appeared. For the most part, these interactions have been described in the solid state,[21−30] and the characterization of solution thermodynamics has been limited to the formation and stability of the metallacrowns themselves, without significant regard to the associated guests.[31−39] Specifically, the site selective binding of guests with hydrophilic or hydrophobic functional groups by metallacrowns with different central metals has not been investigated. Previous work has focused on metallacrowns that bind guests in the solid state.[23,24,29] The unknown binding affinity of the metallacrowns with guests and the binding site selectivity of guests, based on the different coordination number of the central metal, limits the development of metallacrowns for the use as scaffolds for catalytic chemical reactions.

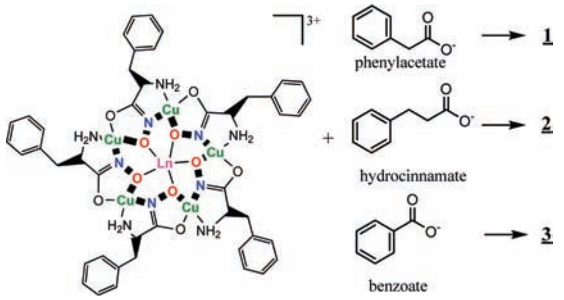

Figure 1. Reaction scheme between Ln(III)[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$-5]$^{3+}$ and organic carboxylates such as benzoate, phenylacetate, and hydrocinnamate in water.

Herein, we probe two new aspects of host guest interactions of amphiphilic metallacrowns in aqueous solution. First, we examine the dependence of the guest affinity for a metallacrown by reacting different benzene carboxylate derivatives (benzoate, phenylacetate, and hydrocinnamate) of varying hydrophobicity in aqueous solution (Figure 1). Second, we explore the difference in guest affinity for the central lanthanide ion, specifically with respect to the coordination number of the central ion. We will show that metallacrowns can encapsulate two guests inside the hydrophobic side of the metallacrown when the central metal has a high coordination number and a large ionic radius such as seen with La(III) while smaller, lower coordination number lanthanides such as Gd(III) can bind only one guest in the hydrophobic pocket. Our studies vary the central metal from La(III) to Dy(III) to observe the change of binding affinity based on the Lewis acidity of the central metal. To understand the possible interactions between metallacrowns and organic carboxylates in solution, we prepared the complexes Gd(III)(phenylacetate)$_2$[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$-5](phenylacetate) (**1**), La(III) (hydrocinnamate)$_2$[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$-5]-(NO$_3$)(**2**), and La(III)(benzoate) [15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$-5]-(benzoate)$_{0.5}(OH)_{1.5}$(**3**). The possible solution binding modes are discussed in relationship to these structures.

Experimental Section

General Information. All chemicals were used as received from Sigma-Aldrich and Fisher Scientific without further purification. Electrospray Ionization Mass Spectra were measured with a Micromass LCT spectrometer and elemental analyses were measured with a Perkin-Elmer 2400 Series II analyzer. Single-crystal X-ray diffraction data were collected at low temperatures using a standard Bruker SMART CCD-based X-ray diffractometer. The collected data were refined with the Bruker SHELXTL (version 2008/3) software package. VP-ITC (Isothermal Titration Calorimetry) from MicroCal, LLC was used to measure binding constants of the guest versus the metallacrown in water.

Preparation of Host Guest Adducts: Gd($C_8H_7O_2$)$_2$[15-MC$_{\mathrm{L\text{-}pheHA}}$-5]($C_8H_7O_2$) (1). Phenylacetic acid (1 g, 7.4 mmol) was added in 10 mL of distilled water. NaOH (0.3 g, 7.4 mmol) was dissolved in 5 mL of water, and then added to a phenylacetic acid solution. After drying the solution, the resultant phenylacetate sodium salt was used to react with the metallacrown. Gd(III)(NO$_3$)$_3$[15-MC$_{\mathrm{L\text{-}pheHA}}$-5] [24] (0.05 mg, 0.032 mmol) was dissolved in 20 mL of water. Phenylacetate sodium salt (0.015 g, 0.095 mmol) was dissolved in 5 mL of water, and then added to the Gd(III)MC solution. Methanol was added until the complex completely dissolved in solution. The solution was slowly evaporated to grow single crystals. Yield 68%. Analysis for ($C_{45}H_{50}N_{10}O_{10}Cu_5Gd$)$_2$ ($C_8H_7O_2$)$_6$ (H_2O)$_{16}$, found (calcd): C = 43.04 (43.30), H = 4.28 (4.58), N = 7.28 (7.32). ESI-MS gave [($C_{45}H_{50}N_{10}O_{10}Cu_5Gd$) ($C_8H_7O_2$)$_2$]$^+$ 1634.8 *m*/*z*.

La($C_9H_9O_2$)$_2$[15-MC$_{\mathrm{L\text{-}pheHA}}$-5](NO$_3$) (2). Hydrocinnamic acid (0.5 g, 3.3 mmol) was dissolved in 10 mL of distilled water. NaOH (0.13 g, 3.3 mmol) was dissolved in 5 mL of water. The sodium hydroxide solution was added to the hydrocinnamic acid solution. After drying the solution, hydrocinnamate sodium salt was used to react with the metallacrown. La(III)-(NO$_3$)$_3$[15-MC$_{\mathrm{L\text{-}pheHA}}$-5][24] (0.05 mg, 0.03 mmol) was dissolved in 20 mL of water. The hydrocinnamate sodium salt (0.011 g, 0.06 mmol) was dissolved in 5 mL of water, and then added to the La(III)MC solution. Methanol was added until the complex completely dissolved in solution. The solution was slowly evaporated to grow single crystals. Yield 57%. Analysis for ($C_{45}H_{50}N_{10}O_{10}Cu_5La$)(NO$_3$)$_2$ ($C_9H_9O_2$) $_4$(H_2O)$_{16}$, found

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(calcd): C = 41.78 (40.90), H = 4.36 (4.58), N = 8.27 (8.33). ESI-MS gave $[(C_{45}H_{50}N_{10}O_{10}Cu_5La)\ (C_9H_9O_2)_2]^+$ 1644.3 *m*/*z*.

La(III)($C_7H_5O_2$)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5]($C_7H_5O_2$)$_{0.5}$-(OH)$_{1.5}$ (3). $La(NO_3)_3$[15-$MC_{L\text{-}pheHA}$-5][24] (0.03 g, 0.019 mmol) was dissolved in 10 mL of water. Sodium benzoate (0.02 g, 0.14 mmol) was added into 2 mL of water and was then added to the metallacrown solution. The solution was slowly evaporated to grow single crystals. Yield 75%. Analysis for $(C_{45}H_{50}N_{10}O_{10}Cu_5La)_2\ (C_7H_5O_2)_3\ (H_2O)_{15}$, found (calcd): C = 41.92 (40.05), H = 4.21 (4.39), N = 7.64 (8.41). ESI-MS gave $[(C_{45}H_{50}N_{10}O_{10}Cu_5La)\ (C_7H_5O_2)]^{2+}$ 733.5 *m*/*z*.

Preparation of solutions for ITC titration experiments. Preparation of La(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$. $CuCl_2 \cdot 2H_2O$ (0.95 g, 5.5 mmol) and L-pheHA (1.0 g, 5.5 mmol) were added to 100 mL of methanol and stirred for 10 min. Sodium hydroxide was added into the solution to adjust pH to around 6.5. $LaCl_3 \cdot 7H_2O$ (0.408 g, 1.1 mmol) was added to the solution and stirred for a day. Additional NaOH was added to adjust the pH to 7. The solution was filtered and slowly evaporated to grow crystals. The collected crystals were vacuum-dried. Yield 55%. Analysis for $(C_{45}H_{50}N_{10}O_{10}Cu_5La)(Cl)_3(H_2O)_{2.5}$, F.W. = 1493.9. found (calcd): C = 36.14 (36.15), H = 3.92 (3.71), N = 9.31 (9.37). La(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.0070 g, 4.69 μmol) was dissolved in 10 mL of 2 mM-MOPS (pH 7.6) solution to prepare 0.469 mM solution. The metallacrown solution was prepared right before each titration experiment and used immediately.

Preparation of Nd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$. $CuCl_2 \cdot 2H_2O$ (0.95 g, 5.5 mmol) and L-pheHA (1.0 g, 5.5 mmol) were added to 100 mL of methanol and stirred for 10 min. Sodium hydroxide was added into the solution to adjust pH to around 6.5. $NdCl_3 \cdot 6H_2O$ (0.39 g, 1.1 mmol) was added to the solution and stirred for a day. Additional NaOH was added to adjust pH to 7. The solution was filtered and slowly evaporated to grow crystals. Yield 69%. Analysis for $(C_{45}H_{50}N_{10}O_{10}Cu_5Nd)(Cl)_3(H_2O)_{15}$, F.W. = 1722, found (calcd): C = 31.32 (31.36), H = 4.73 (4.68), N = 8.04 (8.13). Nd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.0071 g, 4.12 μmol) was dissolved in 10 mL of 2 mM-MOPS (pH 7.6) solution to prepare 0.412 mM solution. The metallacrown solution was prepared right before each titration experiment and used immediately.

Preparation of Gd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$. $CuCl_2 \cdot 2H_2O$ (0.95 g, 5.5 mmol) and L-pheHA (1.0 g, 5.5 mmol) were added to 100 mL of methanol and stirred for 10 min. Sodium hydroxide was added into the solution to adjust pH to around 6.5. $GdCl_3 \cdot 6H_2O$ (0.41 g, 1.1 mmol) was added to the solution and stirred for a day. Additional NaOH was added to adjust pH to 7. The solution was filtered and slowly evaporated to grow crystals. Yield 61%. Analysis for $(C_{45}H_{50}N_{10}O_{10}Cu_5Gd)(Cl)_3(H_2O)_{15}$, F.W. = 1738, found (calcd): C = 30.94 (31.07), H = 4.42 (4.64), N = 8.02 (8.06). Gd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.0079 g, 4.5 μmol) was dissolved in 10 mL of 2 mM-MOPS (pH 7.6) solution to prepare 0.46 mM solution. The metallacrown solution was prepared right before each titration experiment and used immediately.

Preparation of Dy(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$. $CuCl_2 \cdot 2H_2O$ (0.95 g, 5.5 mmol) and L-pheHA (1.0 g, 5.5 mmol) were added to 100 mL of methanol and stirred for 10 min. Sodium hydroxide was added into the solution to adjust pH to around 6.5. $DyCl_3 \cdot 6H_2O$ (0.41 g, 1.1 mmol) was added to the solution and stirred for a day. Additional NaOH was added to adjust pH to 7. The solution was filtered and slowly evaporated to grow crystals. Yield 71%. The collected crystals were vacuum-dried. Analysis for $(C_{45}H_{50}N_{10}O_{10}Cu_5Dy)(Cl)_3(H_2O)_2$, F.W. = 1509.9. Found (calcd): C = 35.91 (35.76), H = 3.80 (3.60), N = 9.29 (9.27). Dy(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.010 g, 6.62 μmol) was dissolved in 10 mL of 2 mM-MOPS (pH 7.6) solution to prepare 0.662 mM solution. The metallacrown solution was prepared right before each titration experiment and used immediately.

Preparation of Sodium Phenylacetate Solution. Phenylacetic acid (0.1410 g, 1.03 mmol) was added to 10 mL of 2 mM-MOPS solution. NaOH (0.0415 g, 1.03 mmol) was added to the solution. A slight amount of NaOH was added to adjust the pH to 7.5.

Preparation of Sodium Hydrocinnamate Solution. Hydrocinnamic acid (1.0 g, 6.6 mmol) was added to 5 mL of water. NaOH (0.27 g, 6.6 mmol) was added into the solution. An excess amount of methanol/ether was added until sodium hydrocinnamate is precipitated. The precipitates were filtered and washed with ether three times and vacuum-dried. Yield 87%. Analysis for $(C_9H_9O_2)(Na)_{1.2}$, F.W. = 176.6. Found (calcd): C = 61.24 (61.14), H = 5.09 (5.13). Sodium hydrocinnamate (0.1413 g, 0.81 mmol) was dissolved in 10 mL of 2 mM-MOPS solution to prepare 81 mM solution. A small amount of NaOH was added to adjust pH to 7.5.

ITC Titrations. Ln(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ Titration with Benzoate. Different central metals of metallacrowns such as La(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.467 mM), Nd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.412 mM), Gd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.811 mM), and Dy(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$ (0.662 mM) were prepared for ITC titration. The metallacrown solution was filled into the sample cell of the ITC, and the syringe was filled with 118 mM-sodium benzoate solution. MOPS (3-(N-morpholino)-propanesulfonic acid) buffer solution (pH 7.6 in water) was used to prepare both the metallacrown and the sodium benzoate solutions to maintain the same pH during the titration. The titration experiments were repeated three times. The sodium benzoate solution was titrated into the MOPS solution to obtain reference data for the heat of dilution, and the MOPS solution was titrated into the metallacrown solution to get the reference data of the heat between the metallacrowns and the MOPS solution. These obtained reference data were subtracted from the reaction heat before the data were fitted. The curve of complex formation heat was fitted with a Sequential Binding (2 site) Model. The thermodynamic parameters were averaged over the results of the three titrations, and the error was calculated as a standard deviation. All titration experiments were done at 298 K (Supporting Information, Figures S1−S4).

Titration of Gd(III)[15-$MC_{Cu(II)N(L\text{-}pheHA)}$-5](Cl)$_3$. The metallacrown (0.409 mM) was titrated with sodium phenylacetate (104 mM) and sodium hydrocinnamate (81.0 mM) at 298 K. MOPS buffer solution (pH 7.6) was used to prepare all solutions used for the ITC titration. The reference data for the heat of dilution for each guest and the reference data of the heat between GdMC and MOPS were collected and subtracted for data fitting. The curve for the heat of complex formation was fitted with a Sequential Binding (2 site) Model. The experiments were repeated three times. The thermodynamic values were averaged over the results, and the error was calculated as a standard deviation (Supporting Information, Figures S5 and S6).

Results

X-ray Crystal Structure Determination. Blue plates of **(1)** and **(2)** from a water/methanol, and blue blocks of **(3)** from a water/methanol were crystallized at 25 °C. A crystal of dimensions 0.48 × 0.36 × 0.18 mm of **(1)**, a crystal of dimensions 0.46 × 0.40 × 0.16 mm of **(2)**, and a crystal of dimensions 0.22 × 0.14 × 0.09 mm of **(3)** were mounted on a standard Bruker SMART 1K CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (λ = 0.71073 Å) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 118(2) K for **(1)** and **(2)**, and 85(1) K for **(3)**; the detector was placed at a distance 4.980 cm from the crystal. A total of 2887 frames

Table 1. Crystallographic Data of Gd(III)(phenylacetate)$_2$[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](phenylacetate) (**1**), La(III)(hydrocinnamate)$_2$[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](NO$_3$)(**2**), and La(III)(benzoate)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](benzoate)$_{0.5}(OH)_{1.5}$(**3**).

	1	**2**	**3**
formula	$C_{69}H_{87}N_{10}O_{24}Cu_5Gd$	$C_{126}H_{164}N_{22}O_{50}Cu_{10}La_2$	$C_{118}H_{153}N_{20}O_{47}Cu_{10}La_2$
space group	*P*2(1)	*P*2(1)	*P*42(1)2
crystal system	monoclinic	monoclinic	tetragonal
M	1915.44	3700.01	3564.82
a/Å	17.748(4)	14.838(5)	32.365(6)
b/Å	16.894(4)	34.563(11)	32.365
c/Å	25.570(6)	15.426(5)	15.134 (3)
α/deg	90.00	90.00	90.00
β/deg	90.886 (3)	108.494 (4)	90.00
γ/deg	90.00	90.00	90.00
V/Å^3	7666(3)	7503(4)	15853 (4)
Z	4	2	4
D_{calcd}	1.660	1.638	1.474
T/K	118(2)	118(2)	85(2)
abs.co./ mm^{-1}	2.297	2.032	1.919
reflections collected/ unique	73614/37567	74561/36527	165121/7379
R_{int}	0.0250	0.0320	0.0569
GOF	1.067	1.065	1.159
wR2[$I > 2\sigma(I)$] [a)]	0.0731	0.1737	0.2039
R1[$I > 2\sigma(I)$] [b]	0.0286	0.0656	0.0835
wR2 (all data)[a)]	0.0751	0.1809	0.2093
R1 (all data)[b]	0.0327	0.0765	0.0923

[a)] $wR2 = |\sum w(|F_o|^2 - |F_c|^2)|/\sum|w(F_o)^2|^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (mP)^2 + nP]$ and $P = [\max(F_o^2,0) + 2F_c^2)]/3$ (*m* and *n* are constants); $\sigma = [\sum[w(F_o^2 - F_c^2)^2]/(n - p)]^{1/2}$. [b] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$.

for **(1)**, 3112 for **(2)**, and 2490 for **(3)** were collected with a scan width of 0.2° in ω for **(1)** and **(2)** and 0.5° for **(3)** and 0.45° in phi for all crystals with an exposure time of 20 s/frame of **(1)**, 45 s/frame of **(2)**, and 60 s/frame of **(3)**. The frames were integrated with the Bruker SAINT software package with a narrow frame algorithm.

The integration of the data of **(1)** yielded a total of 73614 reflections to a maximum 2θ value of 56.64° of which 37567 were independent and 35218 were greater than 2σ(I). The final cell constants (Table 1) were based on the *xyz* centroids of 9508 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group *P*2(1) with $Z = 4$ for the formula $C_{69}H_{87}N_{10}O_{24}Cu_5Gd$. All non-hydrogen atoms were refined anisotropically with the hydrogen placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0286 and wR2 = 0.0731 [based on $I >$ 2sigma(I)], R1 = 0.0327 and wR2 = 0.0751 for all data.

The integration of the data of **(2)** yielded a total of 74561 reflections to a maximum 2θ value of 56.68° of which 36527 were independent and 32098 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the *xyz* centroids of 9032 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group *P*2(1) with $Z = 2$ for the formula $C_{126}H_{164}N_{22}O_{50}Cu_{10}La_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0656 and wR2 = 0.1737 [based on $I >$ 2sigma(I)], R1 = 0.0765, and wR2 = 0.1809 for all data.

The integration of the data **(3)** yielded a total of 165121 reflections to a maximum 2θ value of 40.06° of which 7379 were independent and 6650 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the *xyz* centroids of 6650 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection. The crystal was determined to be a non-merohedral twin based on indexing by CELL_NOW. The two domains are related by a 178.6 degree rotation about the reciprocal and direct (−1 1 0) axis. The data were processed with TWINABS and corrected for absorption. For this refinement, single and composite reflections belonging to the major component were used in preparing a HKLF 4 reflection file. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group *P*42(1)2 with $Z = 4$ for the formula $C_{118}H_{153}N_{20}O_{47}Cu_{10}La_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen placed in idealized positions. Because of the limited resolution of the data, restraints were applied as needed (SIMU/DELU/SAME) to maintain chemical sensibility channels along 4-fold axes of the crystal lattice. Although different electron density maps of these regions were essentially featureless, these channels quite likely contain disordered water molecules. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0835 and wR2 = 0.2039 [based on $I >$ 2sigma(I)], R1 = 0.0923, and wR2 = 0.2093 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file for **(1)**, **(2)**, and **(3)**.

Description of Host Guest Complexes in the Solid State. Representations of each structure are given in Figures 2−5. Table 2 and Figure 5 illustrate the encapsulation of the guest(s) within the metallacrown compartment and the relative orientation of the two metallacrowns across the hydrophobic cavities. All three metallacrowns adopt the previously described 15-MC-5 structure with five Cu(II) ring metals and a captured lanthanide(III) ion in

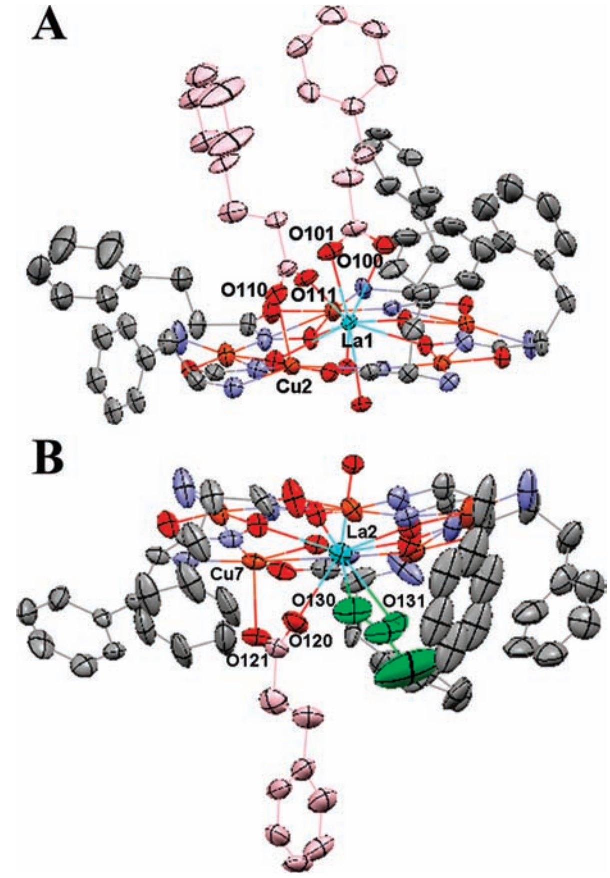


Figure 2. Anisotropic ORTEP Diagrams of La(III)(hydrocinnamate)$_2$[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](NO$_3$) (**2**). (A) Two hydrocinnamates are bound to La(III) on the hydrophobic face of this metallacrown. (B) Hydrocinnamate and nitrate (green) anions are occupying the hydrophobic face of the top metallacrown. Hydrocinnamates have interactions with phenyl side chains of the metallacrown (3.79−3.94 Å). Phenyl side chains of each metallacrown also have interactions with phenyl side chains of the counterpart of the metallacrown at 3.71−4.11 Å. Color scheme: red, oxygens; dark blue, nitrogens; brown, ring Cu(II) ions; black, carbon atoms; cyan spheres, La(III); pink, hydrocinnamates; Green, nitrate. Bound waters and anions on the hydrophilic face were removed for clarity. Important atoms are labeled.

the cavity. As is often the case, La(III) metallacrowns have a nine coordinate central lanthanide, whereas the smaller Gd(III) is eight coordinate within the metallacrown cavity.

Complex **2** shows that three hydrocinnamates (pink spheres) bind within a hydrophobic compartment (Figure 2). One oxygen atom of a hydrocinnamate and two oxygen atoms of a nitrate (green spheres) are bound to a nine coordinate La(III) on the top metallacrown. The second carboxylate oxygen of the hydrocinnamate bridges to one of the ring Cu(II) ions. Two hydrocinnamate guests are attached to the bottom metallacrown with one guest bound in a bidentate fashion to the nine coordinate La(III) as was found for the nitrate of the top metallacrown and the second hydrocinnamate bridging between the La(III) and ring Cu(II) as was also described for the top metallacrown. Solvent molecules fill the ninth coordination site of the La(III) ions on the hydrophilic side of the molecule in both cases. In addition to the direct coordination bonds of the oxygen atoms of the nitrate and hydrocinnamate guests, the guest's phenyl group interacts with phenyl side chains of the metallacrown at a ~4.1 Å distance.

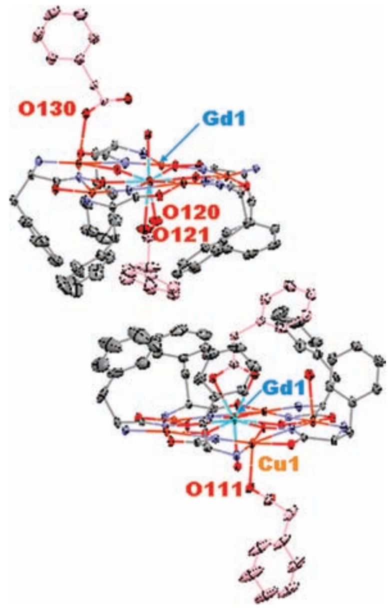


Figure 3. Crystal structure of Gd(III)(phenylacetate)$_2$[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](phenylacetate) (**1**). Each GdMC has a phenylacetate in both hydrophobic and hydrophilic sides. Color scheme: red, oxygens; dark blue, nitrogens; brown, ring Cu(II) ions; black, carbon atoms; cyan spheres, Gd(III); pink, phenylacetate; green, nitrate. Bound waters and anions on the hydrophilic face were removed for clarity. Important atoms are labeled.

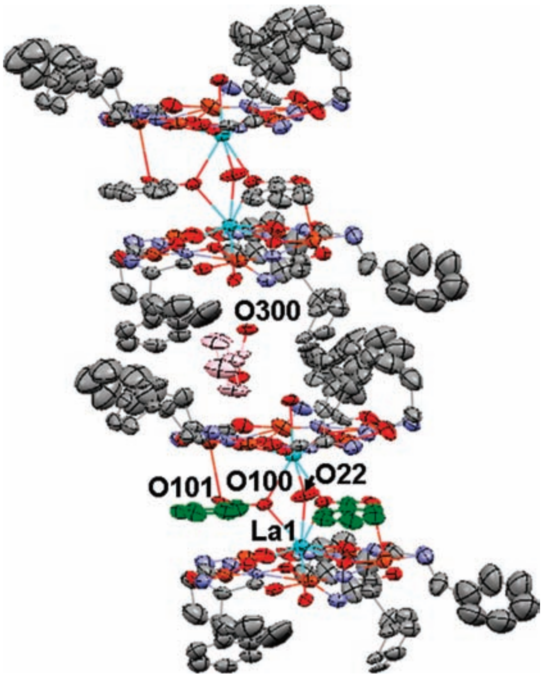


Figure 4. Diagram of La(III)(benzoate)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$-5](benzoate)$_{0.5}(OH)_{1.5}$ (**3**). A benzoate (pink) is encapsulated between adjacent metallacrowns in the hydrophobic pocket surrounded by 10 phenyl side chains of the metallacrowns. Both carboxylate oxygens of this benzoate are interacting with ring coppers of both metallacrowns (3.155 Å distance). Two benzoates (green) are bridging two metallacrowns across the hydrophilic face. These benzoates bridge the central La(III) ions and also form a bond with ring coppers of opposite metallacrowns. Color scheme: red, oxygens; dark blue, nitrogens; brown, ring Cu(II) ions; black, carbon atoms; cyan spheres, La(III); lavender, benzoate guest bridging hydrophobic face; green, carbon atoms of benzoate bridging hydrophilic face. Important atoms are labeled.

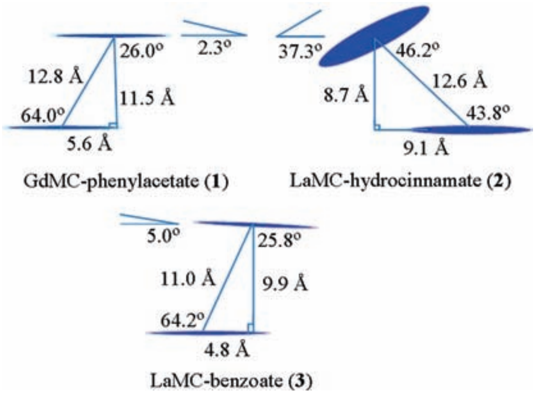
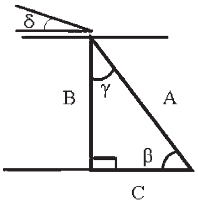


Figure 5. Diagram which shows bond distances and angles between metallacrowns and each guest compound in the crystal structure. Thin ovals mean the plane of the metallacrowns.

Table 2. Distances and Angles of Various Guests to Ln(III)[15-$MC_{L\text{-pheHA}}$-5][a]



	(1)	(2)	(3)
A	12.8 Å	12.6 Å	11.0 Å
B	11.5 Å	8.7 Å	9.9 Å
C	5.6 Å	9.1 Å	4.8 Å
β	64.0 Å	43.8 Å	64.2 Å
γ	26.0 Å	46.2 Å	25.8 Å
δ	2.3 Å	37.3 Å	5.0 Å

[a] A: distance between two centers of the planes. B: the closest distance between a center of one plane to the other plane. C: shifted distance of a metallacrown to the other one. δ: angle between two planes.

The Gd(III) containing complex **1** is shown in Figure 3. The metallacrown ring oxygen to Gd(III) distances are ~0.1 Å shorter than any of the La(III) complexes reflecting the generally smaller size of Gd(III) and the lower coordination number of this ion. For this reason, the Gd (III) is displaced less from the metallacrown ring than is La(III) in any of the complexes. There is one phenylacetate (pink) bound to the Gd(III) in the hydrophobic compartment and a second guest weakly coordinated on the hydrophilic face to a ring copper atom. The eighth coordination site of the Gd(III) is occupied by water.

The host guest complex with La(III) and benzoate is shown in Figure 4. Once again, the La(III) is nine coordinate and displaced significantly from the 5 oxygen atoms of the metallacrown ring. However, this structure differs significantly from the hydrocinnamate complex **2**. First, the La(III) sits on the hydrophilic face rather than within the cavity formed on the hydrophobic side of the metallacrown. Second, benzoate guests bind in two completely different modes than seen in **2**. There are two benzoates (shown in green) that are found on the hydrophilic face serving to bridge two La(III) ions of adjacent metallacrowns. A hydroxide ion, derived from solvent also forms a bridge between the La(III) ions. Thus, this structure is best described as an $\{[La(III)(15\text{-}MC\text{-}5)]_2(\mu_2\text{-benzoate})_2(\mu_2\text{-}OH)]^{3+}$ complex. The two hydrophilic face benzoates are further stabilized by an interaction with ring Cu(II) ions of alternate metallacrowns. There is a third benzoate (pink) which bridges across the hydrophobic faces of two adjacent metallacrowns. The benzoate is held weakly by ring coppers of each metallacrown (Cu−O distances 3.17 and 3.19 Å). The resultant structure associates metallacrowns across both the hydrophilic and hydrophobic faces. The hydrophilic side interaction is very strong, with a short La−La distance (4.19 Å) and close ring plane distances with nearest interactions less than 6 Å. A nicely formed compartment is observed across the hydrophobic faces. The Ln(III)−Ln(III) distance of 11.05 Å is slightly shorter than often seen across the hydrophobic compartments formed by phenylalanine hydroxamate metallacrowns; however, this separation is usually associated with lanthanide ions displaced toward the hydrophobic cavity, not toward the hydrophilic side as observed here. One might have expected a longer La−La separation in this structure. In fact, the metallacrown rings themselves are much closer than usually seen for phenylalanine hydroxamate metallacrowns with a Cu(II)−Cu(II) distance (across the benzoate bridge) of 8.5 Å. This separation is exactly what was observed when nitrate bridged two ring copper atoms in tyrosine hydroxamate metallacrowns; however, unlike the phenylalanine side chain, tyrosine has a hydroxylated phenyl group that was capable of binding to the Cu(II) of an adjacent metallacrown, pulling it closer than might otherwise be expected.[23] Hence, this structure is the first example of such a short metallacrown separation across an unsupported hydrophobic face.

Discussion

Solid State. We have previously demonstrated that the 15-metallacrown-5 structure type composed with phenylalanine hydroxamic acid or related ligands is capable of forming compartments in the solid state which will encapsulate carboxylate anions.[24] The earliest studies demonstrated that aromatic carboxylates such as benzoate and terephthalate could be captured within the hydrophobic cavity generated by the five pheHA phenyl groups, while aliphatic carboxylates such as succinate or glutarate were bound solely to the hydrophilic face of the metallacrown.[24] Aromatic dicarboxylate structures exhibited a compartment in the solid state which fully encapsulated the guest. Subsequent studies demonstrated that one could vary the cylindrical length of the compartment and the shape of the compartment by choice of guest and the propensity of the guest to bind to the central lanthanide and/or the ring copper atoms.[29] Similar cavities are observed for the present complexes as is shown in Figure 5.

One potentially useful variation of these metallacrowns is the centrally bound cation. We and others have shown that a wide variety of cations may be sequestered within the roughly planar 15-MC-5 cavity.[24,29,33,40] Depending on the choice of cation, the number of ligand binding sites

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(40) Seda, S. H.; Janczak, J.; Lisowski *Eur. J. Inorg. Chem.* **2007**, 3015–3022.

and their affinities for guests may be modified. A clear illustration of this point is a comparison of the chemistry of La(III) and Gd(III) 15-MC-5 complexes. In general, La(III) is nine-coordinate with slightly longer bonds than that of the corresponding 8-coordinate Gd(III). Because La(III) is too large to fit within the metallacrown ring plane, it is displaced toward either the hydrophilic or hydrophobic sides. When solely water or hydroxide are bound to La(III), the La(III) is located on the hydrophilic face with three ligands oriented toward the solvent and one ligand in the hydrophobic cavity. In contrast, when anionic ligands such as aromatic carboxylates are bound to the La(III), the ligands appear within the hydrophobic compartment. The compartment is sufficiently large to allow two guests, (e.g., two hydrocinnamates on the bottom metallacrown in Figure 2) or a hydrocinnamate and a nitrate (top metallacrown in Figure 2). One should note that in all cases the hydrocinnamates are bound as bidentate chelates. In the first case, both carboxylate oxygens are bound to the La(III) ion. The remaining two carboxylates form a bridge between the La(III) and an adjacent ring Cu(II) ion. It is interesting to note that in one case, the hydrocinnamate could have been bound bidentate to the La(III) and the nitrate could have bound as the bridging ligand; however, the opposite is true. This preference may be indicating that nitrate has a higher affinity for the La(III) than does the carboxylate ligand. Alternatively, it may be that binding the hydrocinnamate as a bidentate ligand to the La(III) of the top metallacrown may cause steric clashes with the other hydrocinnamates bound to the bottom metallacrown of the compartment. This may also explain why a nitrate, rather than a fourth hydrocinnamate, is found in the cavity.

The host guest complexes isolated with Gd(III) are quite different because of the smaller size and the lower coordination number of the ion. Complex **2** has guests bound on both the hydrophilic and the hydrophobic sides. The stronger interaction is within the hydrophobic cavity where both carboxylates are coordinated to the Gd(III). The hydrophilic side guest is monodentate and bound to copper, not gadolinium, making the association far weaker than the guest in the hydrophobic core. Because Gd(III) is eight coordinate, the orientation of the guests is different than observed with the nine coordinate La(III). The carbon alpha to the bidentate carboxylate is essential orthogonal to the metallacrown ring plane in the Gd(III) structure whereas it is at a considerable angle in the hydrocinnamate complex. This changes in geometry has direct impact on the relative extension of ligands within the cavity and is reminiscent of the structural differences observed for terephthalate bridged Gd(III) and La(III) metallacrowns.

Our general observation of numerous studies is that aliphatic mono and dicarboxylate ligands with 6 carbons or less are excluded from the hydrophobic (phenyl ring) side of the metallacrown; however, carboxylates containing aromatic groups or double bonds can be found on either side of the metallacrown.[24] An example of this is illustrated with the benzoate structure **3** of Figure 4. Unlike **1** or **2**, the metallacrowns are much more closely associated across the hydrophilic face in this structure. There is a benzoate that binds within the cavity; however, the interaction is weak and to Cu(II) not La(III). This is because the La(III) ion has been pulled to the hydrophilic side of the metallacrown to form the very strong La(III)$_2$(μ_2-benzoate)$_2$(μ_2-OH) core. The result is the rare case where an aromatic carboxylate appears to have higher affinity for the hydrophilic face relative to the hydrophobic compartment.

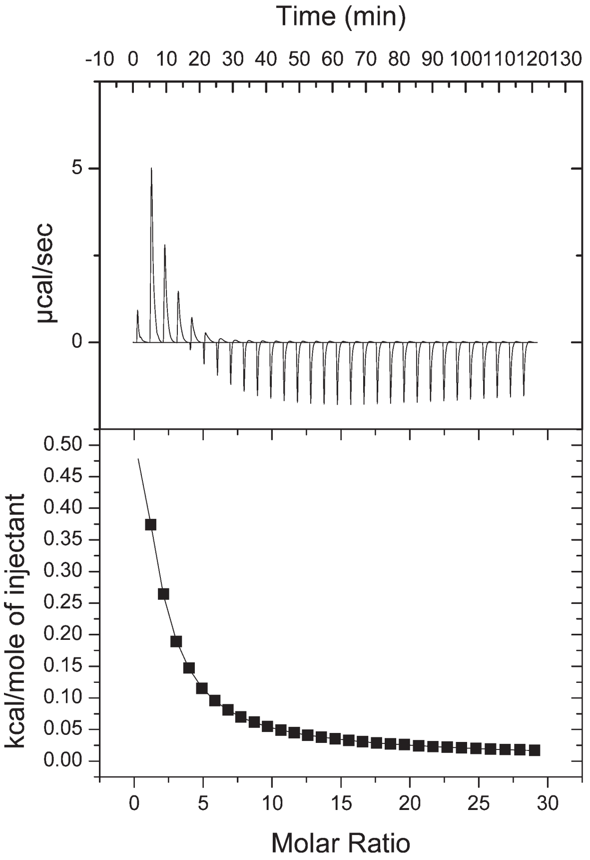

Figure 6. Isothermal titration calorimetry graph showing the titration of Gd(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$ (0.811 mM) with sodium benzoate (117.8 mM) at 298 K in water. Both solutions were prepared with 2 mM-MOPS solution. The molar ratio is the ratio of guest/metallacrown. The methodology for fitting the data is provided in the text.

Host Guest Complexation in Solution. The interaction of metallacrown hosts with monocarboxylate guests in water was probed using Isothermal Titration Calorimetry (ITC).[41,42] Previously we had qualitatively examined guest binding using UV−vis and NMR spectroscopies; however, neither of these techniques were useful for obtaining quantitative determinations of host−guest affinities. Since Cu(II) ion is a paramagnetic metal, severe line broadening was observed (even using La metallacrowns) which prohibited accurate determinations of host, guest, or host−guest complexes. Furthermore, the essentially non-existent change in extinction coefficient upon going from host to host−guest complexes precluded the use of UV−vis spectroscopy. Nevertheless, ITC proved to be a straightforward, convenient, and accurate method for assessing the binding affinities of different guests with several hosts. An example of typical experimental results is shown in Figure 6.

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(41) Benniston, A. C.; Gunning, P.; Peacock, R. D. *J. Org. Chem.* **2005**, *70*, 115–123.

(42) Jadhav, V. D.; Schmidtchen, F. P. *Org. Lett.* **2006**, *8*, 2329–2332.

Table 3. Thermal Parameters Obtained by Titrating Sodium Benzoate Solutions into Ln(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$ at 298 K in Aqueous Solution

	LaMC(Cl)$_3$[a]	NdMC(Cl)$_3$[a]	GdMC(Cl)$_3$[a]	DyMC(Cl)$_3$[a]
Ka_1 (L/mol)	3.7 (2) × 10^2	5.5 (1) × 10^2	6.4 (4) × 10^2	7.6 (2) × 10^2
$\Delta G°_1$ (kcal/mol)	−3.50 (3)	−3.74 (1)	−3.82 (4)	−3.93(2)
ΔH_1 (kcal/mol)	0.61 (3)	0.83 (5)	1.46 (6)	1.52 (4)
ΔS_1 (cal/mol·K)	13.8 (0)	15.3 (1)	17.7 (1)	18.3 (1)
Ka_2 (L/mol)	55 (2)	50 (1)	29 (7)	28 (2)
$\Delta G°_2$ (kcal/mol)	−2.37 (2)	−2.31 (1)	−2.0 (13)	−1.96 (5)
ΔH_2 (kcal/mol)	0.90 (3)	1.67 (8)	1.9 (3)	2.9 (2)
ΔS_2 (cal/mol·K)	11.0 (1)	13.4 (3)	13.1 (4)	16.5 (4)

[a] All solutions were prepared with pH 7.6, 2 mM-MOPS aqueous solution. The binding constants increase as the atomic number in lanthanide metals increases. All titration experiments were repeated three times with reported error values as standard deviations. Ka_1, $\Delta G°_1$, ΔH_1, and ΔS_1 are values for the hydrophobic site. Ka_2, ΔS_2, ΔH_2, and $\Delta G°_2$ are obtained from the hydrophilic site. See Supporting Information, Tables S1−S4 for thermal parameters of each titration experiment.

There are two types of equilibria that will be examined. The first is the measurement of the binding constants between benzoate and different central metal types of the metallacrown [La(III), Nd(III), Gd(III), and Dy(III)]. These studies provide information on the relative binding affinity of metallacrowns to guests by the change of the central metals, which have different metal ion size. The second set of equilibria being considered is between a Gd(III) metallacrown and different guests such as benzoate, phenylacetate, and hydrocinnamate. These guests successively increase the number of methylene groups situated between the carboxylate and phenyl group of the guests. Therefore, each guest from benzoate to hydrocinnamate has an additional carbon−carbon bond difference in length, which allows for the comparison of binding affinity associated with slight changes of the size and hydrophobicity of the guests.

For the first set of equilibria, four different metallacrowns were prepared including La(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$, Nd(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$, Gd(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$, and Dy(III)[15-MC$_{\text{L-pheHA}}$-5](Cl)$_3$. Chloride was chosen as the counteranion for these metallacrowns since it is known that chloride does not directly bind to the central lanthanide ions in the metallacrown while nitrate competes with the guest for the central metal.[23] Twenty-nine to 58 equiv of sodium benzoate solution was individually titrated into four different metallacrown solutions until there is no heat change during the titration, and binding constants were measured. It is expected based on previous observations that the guest bound within the hydrophobic interior would have the highest affinity for the metallacrown with subsequent binding of the second guest occurring on the hydrophilic face.[24] A guest on the hydrophobic side has electrostatic interactions with the central metal, and $\pi-\pi$ interactions with side phenyl groups of the metallacrown while a guest bound on the hydrophilic side only has electrostatic interactions with the central (or ring) metal and competes with solvent water to bind the metal.[24] Therefore, we assigned Ka_1 to the binding affinity at the hydrophobic side and Ka_2 to the binding affinity at the hydrophilic side of the metallacrown.

Table 3 shows that Ka_1, the binding constant assigned to be between benzoate and metallacrowns on the hydrophobic side, increases monotonically across the series. The binding affinity for the guest on the hydrophobic face increased by a factor of 2 on proceeding from La^{3+} (370 M^{-1}) to Dy^{3+} (760 M^{-1}). While this is a subtle change, it is clearly outside the experimental error of the experiment and demonstrates for the first time differential guest recognition in 15-MC-5 based on the central cation. It is probable that the primary factor influencing the trend in binding constants from La(III)MC to Dy(III)MC is the increasing Lewis acidity as one traverses the lanthanide series.[43,44]

As shown in Table 3, Ka_1 is much greater than Ka_2. This observation is consistent with Ka_2 being assigned as the binding constant for the guest to the hydrophilic face; however, the situation is complicated by the coordination number preference of the central lanthanide. The binding affinity (~30 M^{-1}) for the second benzoate for the eight coordinate Gd(III)MC and Dy(III)MC clearly represents binding of the guest to the hydrophilic face. This complexation may occur as a monodentate coordination via a single carboxylate oxygen to the central lanthanide or to the ring copper, or it may represent a bridging bidentate binding mode between the central lanthanide and a ring copper. The localization of the guest becomes more complex when considering the larger La(III) and Nd(III) ions (which can be nine coordinate) in metallacrowns. X-ray analysis of such complexes suggests that these central ions would bind two guests on the hydrophobic face. The second binding constant ~50 M^{-1} for La(III)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$−5]$^{3+}$ or Nd(III)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$−5]$^{3+}$ is twice that of the second binding affinity of Gd(III)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$−5] or Dy(III)[15-MC$_{\text{Cu(II)N(L-pheHA)}}$−5]. More important, the ratio Ka_1/Ka_2 for La(III), which is almost certainly 9-coordinate, and Dy(III), which is almost certainly 8-coordinate, is less than 7 whereas the smaller lanthanide has a ratio of nearly 30 (27.2). Thus, not only the specificity but also the selectivity of guest binding is enhanced with Dy(III). We believe that the relatively higher Ka_2 for La(III) versus Dy(III) is due to the enhanced affinity of the second guest for the hydrophobic pocket available to guests binding to La(III)MC and Nd(III)MC but not to Gd(III)MC and Dy(III)MC. It is notable that Nd(III), which can possibly have a coordination number of 8 or 9 in solution, shows a 50 M^{-1} binding constant. The high second binding constant indicates that Nd(III) is likely nine coordinate in water. Thermodynamic parameters of Table 3 suggest

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(43) Panyushkin, V. T.; Afanasev, Y. A.; Garnovskii, A. D.; Osipov, O. A. *Russ. Chem. Rev.* **1977**, *46*, 2105–2138.

(44) *Chemistry of the f-block Elements*; Aspinall, H. C., Ed.; Gordon and Breach Science Publishers: Langhorne, PA, 2001; Advanced Chemistry Texts, Volume 5.

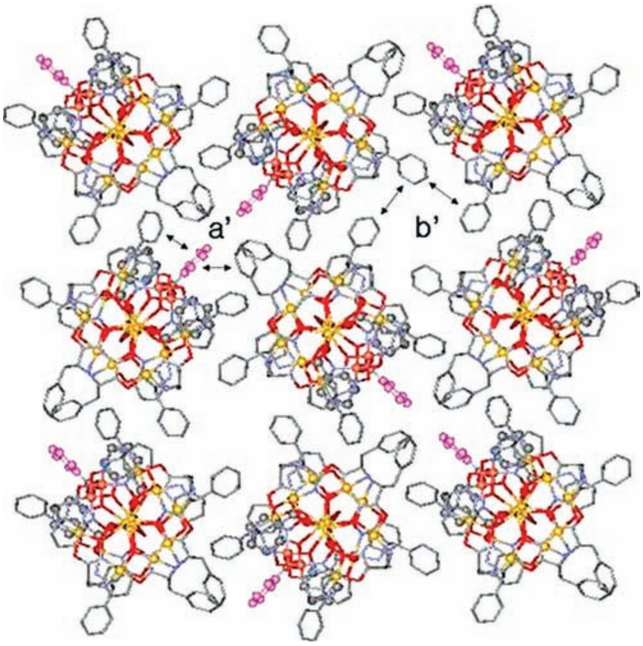

Figure 7. Packing Diagram of La(III)(benzoate)[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$-5](benzoate)$_{0.5}(OH)_{1.5}$ (**3**). The benzoate in the hydrophobic side forms phenyl interactions with neighboring phenyl side chains of metallacrowns within 3.8 Å−4.1 Å in the a′ region, and phenyl side arms of metallacrowns also have interactions each other in ~4.3 Å distance in the b′ region on the x,y plane. Color scheme: red sphere, carboxylic oxygens on La(III); gray tube, carbon; gray sphere, bound benzoate on the hydrophilic side; blue tube, nitrogens; cyan sphere, La(III) ion; violet sphere, benzoate on the hydrophobic side; gold sphere, ring Cu(II) ions. Bound waters and anions on hydrophilic side were removed for clarity.

that the driving force for the first and second guest binding to the metallacrown is entropy driven and attributed to a solvophobic effect, which means the entropy compensates for the loss of enthalpy upon complex formation.[45,46]

Even though the solution data suggest that two benzoates are bound to the hydrophobic side of La(III)MC, the X-ray diffraction model represented in Figure 4 shows that benzoates bind to the La(III) on the hydrophilic face. This behavior is in contrast to the La(III)MC-hydrocinnamate structure (Figure 2). It is likely that the discrepancy between solution and solid phase data is a result of the dimerization of the La(III)MCs across the hydrophilic face. In this orientation, with such a tightly packed structure in the solid state, the primary ring interactions for the benzoates are optimized when the guest is located between the two closer metallacrown rings. Notice that benzoate binds to both the La(III) and the Cu(II) of a metallacrown. The copper interaction, in particular, is expected to be very weak in solution as the high concentration of solvent should displace this benzoate bond. These interactions are illustrated in Figure 7. It should be noted, however, that even the benzoate guest bound in the hydrophobic cavity is weakly complexed by the Cu(II) ring ions, not the La(III). We suspect that the solid state structure is partially a consequence of the length of benzoate and the more efficient packing of metallacrowns in the present structure. This guest is not long enough to form strong $\pi-\pi$ interactions with the phenyl side chains of the metallacrown when it is bound as a bidentate ligand to the metallacrown. In dilute solution, the phenyl side chains of the host are the best hydrophobic contact that can be made for the benzoate rings. However, in the crystal, where the concentration of metallacrowns is high, the benzoate can optimize phenyl−phenyl interactions with the phenyl side chains of neighboring metallacrowns (Figure 7) rather than being restricted to its host's phenyl groups. Probably most important, the two metallacrowns could not approach the very close distance (~8.6 Å) observed in this structure if two benzoates were bound to the La(III) ions of adjacent metallacrowns that form the hydrophobic cavity. The benzoate on the hydrophilic side is also bridging two metallacrowns across the hydrophilic face (Figure 2) and has similar contacts in the solid. Thus, the solid state structure in this case probably is an artifact of the dimerization and close packing of the solid. Structures such as those described previously and in Figure 2 are more representative in solution.

Table 4. Thermal Parameters Obtained by the Titration of Gd(III)[15-MC$_{\mathrm{L\text{-}pheHA}}$-5](Cl)$_3$ with Benzoate, Phenylacetate, and Hydrocinnamate

	benzoate[a]	phenylacetate[a]	hydro-cinnamate[a]
Ka_1 (L/mol)	6.4 (4) × 10^2	3.06 (8) × 10^2	3.7 (2) × 10^2
$\Delta G°_1$ (kcal/mol)	−3.82 (4)	−3.39 (1)	−3.51 (3)
ΔH_1 (kcal/mol)	1.46 (6)	1.8 (2)	1.9 (3)
ΔS_1 (cal/mol·K)	17.7 (1)	17.5 (6)	18 (1)
Ka_2 (L/mol)	29 (7)	11 (3)	25 (3)
$\Delta G°_2$ (kcal/mol)	−2.0 (1)	−1.4 (2)	−1.90 (7)
ΔH_2 (kcal/mol)	1.9 (3)	5 (2)	4 (2)
ΔS_2 (cal/mol·K)	13.1 (4)	23 (5)	19 (5)

[a] Benzoate, phenylacetate, and hydrocinnamate were titrated at 298 K. All titration experiments were repeated three times. Binding constants and thermodynamic values were averaged over the three titrations, and error was calculated as standard deviation. See Supporting Information, Tables S5 and S6 for detailed parameters.

The second set of solution equilibria that we investigated focused on differentiating the affinities of different guests for a representative metallacrown. The metallacrown chosen was Gd(III)[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$−5](Cl)$_3$ as numerous structures with this host are known, making it the quintessential representative of metallacrowns containing 8-coordinate central lanthanide ions. The Gd(III)-MC was titrated with 51 equiv of phenylacetate and 40 equiv of hydrocinnamate to understand how these guests differentially bind to the metallacrown. The binding constant, Ka_1, of benzoate (determined above) with Gd(III)[15-MC$_{\mathrm{Cu(II)N(L\text{-}pheHA)}}$−5]$^{3+}$ shows the highest binding affinity (640 M^{-1}) among three guests in Table 4. It is possible that the relatively higher binding constant is caused by forming a stronger coordination bond with the central metal which is implied by Hammett ρ value (1.0). Unlike binding to the 9-coordinate La(III), the benzoate ligand will bind orthogonally to the metallacrown ring in the 8-coordinate Gd(III) host. Thus, the benzoate fits perfectly within the preformed hydrophobic cavity even though it has less inherent hydrophobic stabilization than the other two guests.[47] This is not the

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case for the slightly longer phenylacetate; however, this poor fit is not a consequence of the length but rather of the orientation of the phenyl group after complexation. Because phenylacetate contains a methylene group between the phenyl and the carboxylate functionalities, the phenyl group is oriented at an approximately 109° angle to the bidentate chelate formed by the carboxylate moiety to the Gd(III). This change causes the phenyl group to be projected through the protection of the host phenyl groups and into aqueous solution. The guest could rearrange to orient the phenyl group within the cavity more effectively; however, this would require shifting from a bidentate to a monodentate carboxylate coordinate mode which is enthalpically less favored. Although hydrocinnamate is longer still, it has a slightly higher binding constant (370 M^{-1}) than phenylacetate (306 M^{-1}). This observation is despite the fact that its Hammett ρ value (0.212) is lower than that (0.489) of phenylacetate. It appears that an "even-odd" effect, as often seen in polymer chemistry, is operative in this case. The addition of a second methylene allows the phenyl group to reorient (or recover) so that the phenyl group may again be symmetrically placed within the hydrophobic cavity. On the basis of this viewpoint, the phenylacetate guest is discriminated against by a combination of the host phenyl ring fence that defines the cavity and the 8-coordinate central ion's propensity to bind carboxylates in a bidentate manner forcing the ligand to extend initially perpendicular to the metallacrown ring plane. This observation may be useful for defining future design parameters to enhance host guest recognition within this molecular class.

Conclusion

The present study provides the only quantitative assessment of host−guest binding affinities for the 15-MC-5 structure type. As such, it provides definitive proof that guests will bind to metallacrowns in aqueous solution. The results demonstrate that host−guest recognition can be fine-tuned through expeditious choice of the central cation, with large ions showing lower affinity than that of their smaller counterparts that are likely to flip onto the hydrophobic face from the hydrophilic face by the access of the aromatic guest to the hydrophobic side. Furthermore, we have demonstrated for the first time that the combination of the central metal and side chain conformation of the metallacrown host provides a construct upon which one may differentiate different guests that have identical binding functionalities. While initially modest, these developments suggest that host−guest systems using metallacrowns may afford a large range of affinities for different guests by varying the central cation (e.g., with Ca(II) or Pb(II)) and the side chain architecture. Future work will assess to what extent this molecular recognition can be realized.

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Supporting Information Available: Complete X-ray crystallographic data for **1**, **2**, and **3** (CIF). Tables S1−S6, thermodynamic parameters of ITC. Figures S1−S6, isothermal graphs of ITC. Figure S7 provides an ORTEP of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.