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Voltammetric Characterization of Redox-Inactive Guest Binding to Ln^{III}[15-Metallacrown-5] Hosts Based on Competition with a Redox Probe

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Abstract: A novel competitive binding assay was implemented to monitor the binding of a redox inactive substrate to a redox inactive metallacrown host based on its competition with ferrocene carboxylate (FcC^-) using cyclic voltammetry (CV). First, the binding of FcC^- to Ln^{III}[15-$MC_{Cu^{II},N,L\text{-}pheHA}$-5] (LnMC) hosts was characterized by cyclic voltammetry. It was shown that the voltammetric half wave potentials, $E_{1/2}$, shifted to more positive potentials upon the addition of LnMC. The explicit dependence of $E_{1/2}$ with the concentration of LnMC was used to determine the association constants for the complex. The FcC^- binding strength decreased with larger central lanthanide metals in the LnMC hosts, and substantially weaker binding was observed with La^{III}. X-ray crystallography revealed that the hydrophobic host cavity incompletely encapsulated FcC^- when the guest was bound to the nine-coordinate La^{III}, suggesting the LnMC's ligand side chains play a substantial role in guest recognition. With knowledge of the MC-FcC^- solution thermodynamics, the binding affinity of a redox inactive guest was then assessed. Addition of sodium benzoate to a LnMC and FcC^- mixture resulted in $E_{1/2}$ shifting back to the value observed for FcC^- in the absence of LnMC. The association constants between benzoate and LnMC's were calculated via the competitive binding approach. Comparison with literature values suggests this novel assay is a viable method for determining association constants for host–guest systems that exhibit the proper electrochemical behavior. Notably, this CV competitive binding approach does not require the preparation of a modified electrode or a tethered guest, and thus can be generalized to a number of host–guest systems.

Keywords: competitive binding · cyclic voltammetry · host–guest systems · metallacrowns · supramolecular chemistry

Introduction

Electrochemistry has emerged as a viable tool in investigations of molecular recognition phenomenon.[1] Cyclic voltammetry (CV) in particular has been used to probe the binding of redox-active guests to a number of hosts, including cyclodextrins (CD),[2] cucurbiturils,[3] polyammonium macrocycles,[4] calixarenes,[5] cavitands,[6] resorcinarenes,[7] amine-thiophenolate complexes[8] and even DNA.[9] CV is well suited for studying supramolecular host–guest systems, as mechanistic, kinetic, and thermodynamic information can be gathered from the CV curves.[10] For systems, where complex dissociation is fast relative to the scan rate, two significant perturbations to the voltammetric responses are often observed. First, a decrease in the peak currents results because the diffusion coefficient, D, of the encapsulated redox-active probe (i.e., the host–guest complex) is smaller than the uncoordinated redox probe. Second, the apparent half-wave potential, $E_{1/2}$ (i.e., the average of the anodic and cathodic peak potentials) shifts upon complexation, a result of the complex stabilizing the oxidized or reduced forms of the guest. These observable changes in the voltammetric response of the guest can be used to extract thermodynamic information on host–guest binding.[11] Thus CV has the capacity to be especially significant in cases where common techniques for quantifying host–guest interactions are complicated by host properties. Metallacrowns (MCs) are one class of molecular recognition agents[12] where alternative characterization methods can be useful, as their paramagnetism can complicate characterization by highly accessible ^{1}H NMR techniques.

MCs[13] are a class of metallamacrocycle[14] that are structurally analogous to crown ethers.[15] MCs propagate a [M-N-O] ring repeat unit, where M is a metal cation. Numerous

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metallamacrocycles, including certain MCs, have emerged as versatile molecular hosts. Metallamacrocyclic frameworks have been developed with the ability to recognize cations,[16] anions,[17] or neutral molecules.[18] The host–guest chemistry of 15-MC-5 complexes is especially rich, as the host is amenable to variation at the central metal, ring metal, counter anion, and ligand.[19] 15-MC-5 complexes composed of Cu$^{\text{II}}$ ring metals and Ln$^{\text{III}}$ central metals form planar complexes with numerous Lewis acidic sites capable of coordinating anions. Additionally, chiral α-aminohydroxamic acid ligands can be employed to differentiate the faces of the MC and impart chirality in the rotational sense of the ring.[20] MC's synthesized from exclusively L- or D-phenylalanine possess hydrophobic cavities over one face while the other is less sterically encumbered and more hydrophilic (Figure 1 a). When crystallized from methanolic solutions with a nitrate anion, the MC's form resolved helices.[16g,21] Alternatively, crystals grown from water reveal the well-characterized hands-hands structure, with two MC's associating via hydrophobic contacts between ligand phenyl rings to form a molecular compartment. This compartment has been shown to selectively recognize dicarboxylate guests based on size and guest-ligand interactions.[22]

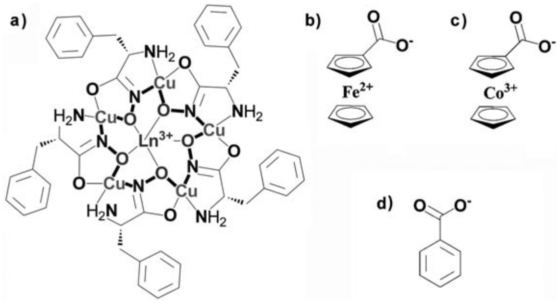


Figure 1. a) LnMC, b) FcC$^-$, c) CocC, d) benzoate.

Recently, information on certain thermodynamic aspects of Ln$^{\text{III}}$[15-MC$_{\text{Cu}^{\text{II}},\text{N},\text{L-pheHA}}$-5] (LnMC) carboxylate binding in solution have been reported. Our investigations with isothermal titration calorimetry (ITC)[23] and results by Tegoni et al. with fluorescence and ^{1}H NMR spectroscopy[24] reveal differential recognition of carboxylate guests based on guest size and hydrophobicity, as well as the central lanthanide in the LnMC host. These studies suggest that both the central metal and hydrophobic cavity play a significant role in guest recognition. However, further studies are needed to understand the solution behavior of these dynamic hosts.

Inspired by the successful utilization of CV in characterizing host–guest interactions with other supramolecular systems, we sought to apply those methods in our investigations of LnMC guest recognition. The LnMCs we are interested in are redox inactive, so the redox active guest ferrocene carboxylate (FcC$^-$) (Figure 1 b) was employed. Herein we report our investigations of the interactions between LnMCs and ferrocene carboxylate (FcC$^-$). A systematic shift in the half-wave potential of the oxidation of FcC$^-$, $E_{1/2}$, was observed upon titration of LnMC. The dependence of $E_{1/2}$ with [LnMC] allows for the determination of complex association constants.[11a]

This electrochemical approach, while effective, is limited in its requirement of a redox active guest. However, we now report a novel method for the determination of a redox inactive guest's binding strength based on its competition with the FcC$^-$ redox probe. Upon the addition of a competitive guest to a mixture of LnMC and FcC$^-$, the FcC$^-$ potential shifts towards the free value. This observation was first reported by Kaifer et al. with a cyclodextrin derivative,[25] although no methods have been reported to determine the association constants between the host and redox inactive guest from such data. The extraction of thermodynamic information on guest complexation via voltammetric competition experiments was first suggested by Lehn et al. in 1981,[4a] and has been successfully utilized with ferricyanide-polyammonium macrocycle complexes;[26] however, this technique required an understanding of the protonation constants associated with guest binding. Competition experiments have also been devised that require either the absorption of a redox active moiety on the electrode surface during the experiment or preparation of a modified electrode.[27] Additionally, competition experiments were performed on systems where the redox probe and molecular host are tethered together.[28] In contrast to these strategies, the CV competitive binding assay described herein is homogeneous, is easily observable with conventional macroelectrodes, and does not require a tethered probe. The only prerequisite information needed is the binding constant of the redox active guest, which can be determined through a straightforward CV titration experiment. Thus, our competitive binding assay can be generalized to a wide variety of systems.

Results

CV experiments were performed in a 1:1 mixture of methanol and water. Methanol was necessary to increase LnMC solubility, while water reduced solution resistance and provided acceptable pH conditions. The KCl electrolyte, chloride LaMC salts, and MOPS buffer were chosen because they are not known to interact with the MCs lanthanide binding site.[23] The pH values reported for these experimental conditions are the $^{s}_{s}$pH meaning the reported pH was measured in the methanol/water mixture using pH electrodes calibrated in aqueous buffers, and corrected using the reported constants.[29] The pH of 7.5 was chosen as the optimal pH to ensure FcC$^-$ deprotonation and LnMC stability. The pK_a values of FcCH and ferrocenium carboxylic acid (FcCH$^+$) in water are reported as 4.20 and 1.3, respectively.[2a] In 50 % methanol, the pK_a of carboxylic acids typically increase 0.75–1 log units.[30] Therefore, the guests should be deprotonated under our conditions. The pK_a of MOPS in a 50 % methanol and 50 % water solution is 6.77.[31] Therefore, the pH 7.5 employed herein is within the buffer range for MOPS.

The cyclic voltammetry of FcC^- behaves reversibly under the utilized conditions. Figure 2a shows the voltammogram for FcC^-. The peak separation, ΔE_p, of 70 mV is consistent with observations from previous reports in aqueous solutions.[2a,c] The formal potential of the FcC^-/FcC couple in the employed electrolytes was estimated from $E_{1/2}$ in the absence of any LaMC and was determined to be 0.337 V vs Ag/AgCl at 25.0 ± 0.1 °C. Upon the addition of LaMC (Figure 1b), the FcC^- wave shifts to more positive potentials with concomitant reduction in peak currents, consistent with complexation of FcC^- by LaMC. The decrease in the peak current results from a the LaMC stabilizing the reduced form of FcC^-, which is reasonable given that the LaMC carries a 3^+ charge, reduced FcC^- has a 1^- charge, and the oxidized complex FcC is neutral. The decreased peak current is indicative of slower diffusion of the LnMC-FcC^- complex to the electrode surface.

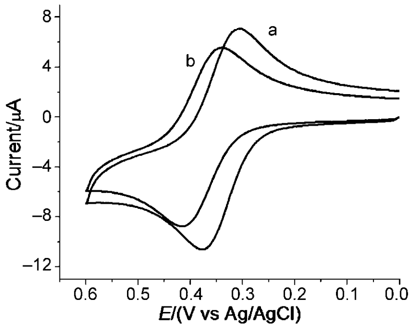


Figure 2. Cyclic voltammograms of FcC^- in the absence (a) and presence (b) of 10.7 equivalents of DyMC. The potential shifts to higher values as a result of DyMC stabilizing the reduced form of FcC^-.

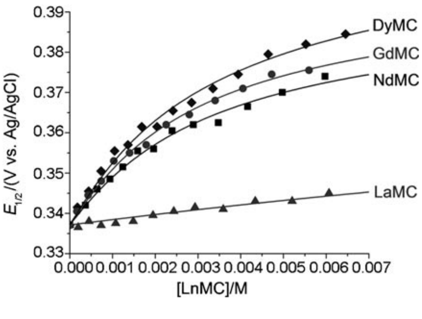
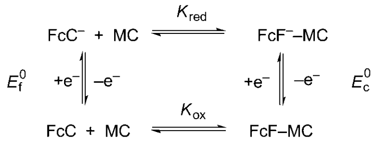


Figure 3. Plots of $E_{1/2}$ versus the concentration of LnMC added to the solution. Data points: ◆: DyMC, ●: GdMC, ■: NdMC, ▲: LaMC. The displayed fits were obtained by simultaneous fitting of K_{red} and K_{ox}. Significantly weaker binding is observed with LaMC due to poor encapsulation of FcC^- when it is bound to the nine-coordinate central metal.

Titrations of LnMCs with various central metals to 0.6 mM solutions of FcC^- were performed. The limited solubility of LnMCs allowed the addition of ~10 equivalents of the host. Plots of $E_{1/2}$ vs LnMC concentration are shown in Figure 3. The largest perturbation in the potential of FcC^- is observed with DyMC, while LaMC causes a very modest shift. The equilibrium between the oxidized and reduced forms of FcC^- and the LnMC is treated with the widely accepted square scheme[11d] (Scheme 1). K_{red} and K_{ox} represent the association constant for FcC^- and FcC, respectively, and $E_f^{0'}$ and $E_c^{0'}$ are the formal potentials of the free and complexed FcC^- determined from the voltammetric responses. The change in $E_{1/2}$ with the change in LnMC concentration can be treated with Equation (1), where $[MC]_f$ is the concentration of free LnMC in solution.



Scheme 1. Square Scheme depicting the equilibrium between the LnMC, FcC^-, and FcC.

$$E_c^{0'} = E_f^{0'} + \frac{RT}{F}\ln\left(\frac{1+K_{red}[MC]_f}{1+K_{ox}[MC]_f}\right) \tag{1}$$

Examination of this equation reveals that significant changes in the potential result when K_{red} is much larger than K_{ox}. Previous treatments of systems with this behavior operated under the assumption that K_{ox} is negligible, which allows for a straightforward solution for K_{red} based on the observed potential shift upon the addition of host. We felt that this assumption might be an appropriate starting point because intuitively, it seemed likely that the neutral FcC would bind quite weakly to the 3^+ charged host, especially in comparison to FcC^-. Additionally, different studies have revealed association constants of less than $100\,\text{M}^{-1}$ between LnMC's and zwitterionic guests.[32]

Traditional approaches to treating systems with square schemes involve using large excesses of host, and assuming that the concentration of free host in solution is equal to the concentration of host added to solution. However, with only ~10 equivalents of LnMC dissolving in the solution, this assumption is not valid. Therefore, the concentration of free host in solution was solved for explicitly using a previously reported treatment[11a] where $[FcC^-]_0$ and $[MC]_0$ are the concentrations of FcC^- and LnMC added to the solution, respectively, [Eq. (2)].

$$\begin{aligned}
&[MC]_f = \frac{-a+\sqrt{b}}{2K_{red}} \\
&a = 1 + K_{red}[FcC^-]_0 - K_{red}[MC]_0 \\
&b = (1 + K_{red}[FcC^-]_0 - K_{red}[MC]_0)^2 + 4K_{red}[MC]_0
\end{aligned} \tag{2}$$

The change in $E_{1/2}$ with the change in the concentration of LnMC were fit using Equations (1) and (2), yielding the association constants shown in Table 1. Stronger binding is observed with smaller, more Lewis acidic central metals. A similar trend was observed with benzoate.[23] LaMC displays exceptionally weak binding.

Table 1. between LnMC's and FcC$^-$ or FcC and the diffusion coefficient for the LnMC-FcC$^-$ complex.

Host	K_{red}[a] [M^{-1}]	K_{ox}[b] [M^{-1}]	K_{red}[c] [M^{-1}]	K_{ox}[c] [M^{-1}]	D_{com}[d] [$\times 10^{-6}$ cm^2 s^{-1}]
LaMC	55±3	–	60±50	0±40	1.67
NdMC	600±30	–	970±130	130±40	1.94
GdMC	740±40	95±15	1040±100	100±30	1.38
DyMC	940±30	120±20	1120±100	40±30	1.54

[a] Calculated based on the assumption that K_{ox} is zero. [b] calculated by competition equation with CocC. [c] Calculated by simultaneous fitting. [d] Calculated based on the decrease in the anodic peak currents upon titration of LnMC and using K_{red} and K_{ox} values determined by simultaneous fitting.

Armed with information on LnMC-FcC$^-$ complexation, we intended to use FcC$^-$ as a probe for monitoring redox inactive guest binding to LnMC's. This was achieved through a novel competitive binding assay. A typical competition titration involved the addition of the redox inactive benzoate to a ~10:1 mixture of LnMC and FcC$^-$. Addition of the competitive guest displaces FcC$^-$. This increases the concentration of free FcC$^-$ in solution, which shifts the observed potential back towards the free FcC$^-$ value (Figure 4). The peak currents also return to the free FcC$^-$ values. The results of a typical competition titration are shown in Figure 5, where $E_{1/2}$ is plotted against the redox inactive guest concentration. Nearly complete displacement of the FcC$^-$ guest from DyMC was achieved after the addition of 120 equivalents of sodium benzoate under these conditions. Importantly, the addition of benzoate does not alter $E_f^{0\prime}$, indicating that the perturbation in the presence of LnMC is a result of preferential benzoate binding to the host and not merely from changes associated with activity effects/alterations in the electrolyte ionic strength. Additionally, the reversibility of the voltammetric response for FcC$^-$, as gauged by ΔE_p, remains constant throughout the competition titration.

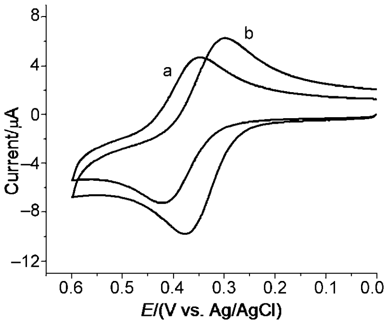


Figure 4. CV responses for FcC$^-$ in the presence of a) 10.8 equivalents of DyMC, b)10.8 equivalents of DyMC and 170 equivalents of sodium benzoate. $E_{1/2}$ shifts towards the free FcC$^-$ value as it is displaced from the DyMC by benzoate.

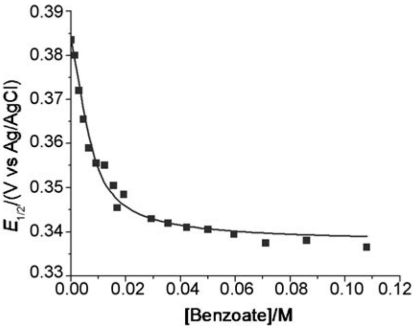
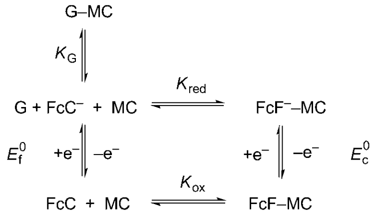


Figure 5. Plot of $E_{1/2}$ vs. the concentration of benzoate obtained during a competition titration. The addition of benzoate to a 10.8:1 mixture of DyMC and FcC$^-$ shifts $E_{1/2}$ to more positive values. $E_{1/2}$ returns to the free value after the addition of 120 equivalents of benzoate. This change can be fit using Equations (1) and (3) to obtain the association constant for the competitive guest. The displayed fit was obtained with simultaneously fit K_{red} and K_{ox} values.

A new method for obtaining binding constants based on this behavior was employed. A modified square scheme describes the equilibrium, where the concentration of free LnMC is affected by the competing equilibrium with the redox inactive guest (Scheme 2). The measured potential can still be accounted for using Equation (1), except now the concentration of free LnMC is solved for using the solution to the cubic equation shown in Equation (3).[33]



Scheme 2. Diagram for the competitive binding equilibrium. The scheme is similar to Scheme 1, except the system is perturbed by the competitive equilibrium between the free LnMC and the competitive guest.

$$[\mathrm{MC}]_f = \frac{-a}{3} + \frac{2}{3}\sqrt{(a^2-3b)}\cos\left(\frac{1}{3}\arccos\left(\frac{-2a^3+9ab-27c}{2\sqrt{(a^2-3b)^3}}\right)\right)$$
$$a = K_{Dred} + K_{DG} + [\mathrm{FcC}^-]_0 + [G]_0 - [\mathrm{MC}]_0$$
$$b = K_{DG}([\mathrm{FcC}^-]_0 - [\mathrm{MC}]_0) + K_{Dred}([G]_0 - [\mathrm{MC}]_0) + K_{Dred}K_{DG}$$
$$c = -K_{Dred}K_{DG}[\mathrm{MC}]_0 \tag{3}$$

K_{Dred} is the dissociation constant between LnMC and FcC$^-$, K_{DG} is the dissociation constant between LnMC and the competitive guest, and $[\mathrm{G}]_0$ is the concentration of the competitive guest added to the solution. An estimate for K_{DG}

can be obtained by fitting the competition titration data using Equations (1) and (3). Binding constants for benzoate to LnMC's were obtained by the CV competition method and are displayed in Table 2.

Table 2. Binding constants between LnMC's and benzoate determined by the competitive CV assay, ITC, and fluorimetry.

Host	K_g by CV[a] [M^{-1}]	K_g by CV[b] [M^{-1}]	K_g by ITC[c] [M^{-1}]	K_g by fluorimetry[d] [M^{-1}]
LaMC	–	–	370 ± 20	–
NdMC	510 ± 50	680 ± 110	550 ± 10	–
EuMC	–	–	–	389 ± 9
GdMC	560 ± 60	690 ± 120	640 ± 40	–
DyMC	870 ± 80	980 ± 40	760 ± 20	–

[a] Calculated using K_{red} based on K_{ox} is zero. [b] Calculated using simultaneously fit K_{red} and K_{ox} values. CV conditions: methanol and 0.1 M aq MOPS buffer 1:1, pH 7.5, 0.1 M KCl, 25 °C. [c] ITC conditions: pH 7.6 2 mM MOPS in water, 25 °C. The ITC method calculated the binding of a second benzoate, which is not presented here.[23] [d] Fluorimetry conditions: pH 6.0, 0.02 mM hexamethylenetriamine buffer in water at 25 °C.[24]

The binding constants reported heretofore relied on the assumption that K_{ox} is zero. It was necessary to properly assess the veracity of that assumption, as the modest changes in $E_{1/2}$ do not necessarily indicate a minute K_{ox} value. This is most clearly demonstrated with the case of a cucurbit[7]uril host and a ferrocene derivative guest. Though only a 10 mV shift was observed, ^{1}H NMR revealed a K_{red} of 3×10^9 M^{-1} and a similarly large K_{ox}.[3c] To assess whether K_{ox} is truly negligible in our systems, we investigated the interaction between LnMC's and cobaltocenium carboxylic acid hexafluorophosphate (CocC) (Figure 1 c). CocC is thought to be an appropriate mimic of ferrocenium carboxylate due to its similar size and charge.[2d,7b] Additionally, CocC cannot be oxidized at the potentials used in this study.

The CV competitive binding approach was employed with CocCH·PF_6 as the competitive guest. Calculated binding constants of ~100 M^{-1} were obtained for GdMC and DyMC. However, the limited solubility of CocC allowed only a small portion of the displacement curve to be generated (Figure S1), so the accuracy of these values is uncertain. However, examination of the potential shift by the guest provides additional information. CocC shifted the $E_{1/2}$ of LnMC and FcC$^-$ mixtures slightly, revealing that CocC does bind to LnMC. A separate competition titration with tetraethylammonium hexafluorophosphate did not change $E_{1/2}$, indicating the observed potential shift after addition of CocCH·PF_6 was a result of CocC binding. Comparison with benzoate competition titrations reveals a lesser potential shift with CocC. The $E_{1/2}$ of the ~1:10 FcC and DyMC mixture decreased by 5.5 mV upon adding 11 equivalents of CocC per FcC$^-$. A similar 3 mV decrease was observed with LaMC. In contrast, 11 equivalents of benzoate decreased $E_{1/2}$ 24.5 mV with DyMC (Figure 3 b) and 4.5 mV with LaMC. This suggests that the binding strength of CocC to LnMC, and therefore FcC also, is less than benzoate.

Electrospray ionization mass spectrometry (ESI-MS) was utilized to investigate the interaction between LnMC's and CocC further. Spectra of CocC and DyMC or LaMC mixtures revealed low-intensity peaks for the LnMC-CocC complex. Peaks representing the LnMCs with hydroxide or chloride bound had comparable or stronger intensity. No peaks were observed with PF_6^- bound. In contrast, the spectra of LnMC and sodium benzoate mixtures reveal very high intensity peaks for LnMC-benzoate complexes, with minute intensity for chloride or hydroxide complexes.

The influence of K_{ox} can be directly observed in plots of $e^{[F\cdot(E_0-E_{0f})/RT]}$ vs. [LnMC]. If K_{ox} were negligible, a linear relationship would be observed. However, plots for titrations with DyMC possess a slight curvature that reveals a contribution to the electrochemical response by K_{ox} (Figure S2). This observation along with the ESI-MS and electrochemical results with CocC suggests that LnMC's bind FcC weakly. Also, the association constant for FcC should be smaller than benzoate. Based on these observations, it seems that K_2 is small, but likely not negligible. Therefore, we deemed it prudent to account for the contribution of K_{ox} by solving for K_{red} and K_{ox} simultaneously. Simultaneous fitting of K_{red} and K_{ox} introduces the assumption that the complexation of FcC with LnMC does not appreciably affect the concentration of free LnMC in solution. Given the noticeable binding of CocC, we feel this is an appropriate assumption considering the alternative approach relies on the assumption that K_{ox} is zero. K_{red} and K_{ox} values obtained by simultaneous fitting are displayed in Table 1 and the fits are displayed in Figure 3. Binding constants for benzoate obtained by the competitive CV method were recalculated using the K_{red} and K_{ox} values obtained by simultaneous fitting (Table 2).

Further examination of the CV curves reveals a decrease in the peak height upon titration of LnMC. This decrease is a result of the slower diffusion of the FcC$^-$-LnMC complex compared with the free FcC$^-$. A previously reported method[11a] was used to estimate the apparent diffusion constants for the complex based on the change in the anodic peak height and the K_{red} obtained by simultaneous fitting. These values are listed in Table 1. As expected, the values are similar for all lanthanides.

The crystal structure of LaMC with FcC$^-$ is shown in Figure 6. Two FcC$^-$ guests are included in the host's hydrophobic cavity, with one bound bidentate to the central metal in a staggered position, and another bound through a single carboxylate oxygen to a Cu^{II} ring metal with eclipsed cyclopentadienyl rings. The bound guests engage in π–π interactions with the ligand phenyl rings. The La^{III} central metal is nine-coordinate with one water on both the hydrophilic and hydrophobic faces filling the remaining coordination sites. A bound nitrate on the hydrophilic face gives the structure a neutral overall charge.

The crystal structure of ferrocene dicarboxylate (FcDC^{2-}) bound to LaMC is displayed in Figure 7. Crystals containing FcDC^{2-} bound to GdMC were isostructural with the displayed structure. FcDC^{2-} bridges the hydrophilic faces

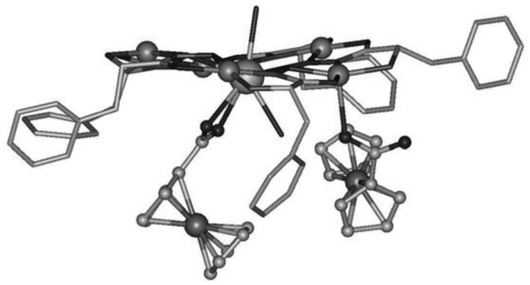


Figure 6. Weblabviewer Pro image of $La^{III}(FcC^{-})_2[15\text{-}MC_{Cu^{II},N,L\text{-}pheHA}\text{-}5](NO_3)$. Two FcC^{-} (ball and stick representation) are encapsulated in the hydrophobic cavity. One is bound monodentate to a copper ring metal with eclipsed cp rings. The other is bound bidentate to La^{III} with staggered cp rings. The carboxylate of FcC^{-} is diagonal to the MC plane when bound to the nine-coordinate La^{III}, which extends much of the ferrocene group outside of the hydrophobic cavity. Unbound or Cu-coordinated solvent, nitrate, and hydrogens were removed for clarity.

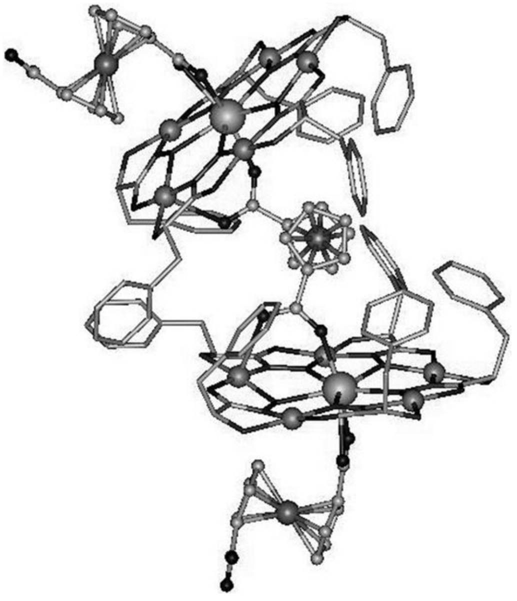


Figure 7. Weblabviewer Pro image of $La^{III}(FcDC^{-})[15\text{-}MC_{Cu^{II},N,L\text{-}pheHA}\text{-}5](NO_3)_{0.5}(OH)_{0.5}$. $FcDC^{2-}$ (ball and stick representation) is bound bidentate to La^{III} and a Cu^{II} ring metal in the hydrophobic compartment. An 11.14 Å distance separates the La^{III} central metals across the hydrophobic faces. The hydrophilic faces are also bridged by $FcDC^{2-}$, which is bound bidentate to the central La^{III}. Hydrogen atoms, solvent, and unbound anions were removed for clarity.

through bidentate coordination to the central metal. $FcDC^{2-}$ is in an anticlinal conformation with a twist angle of 131.3°. $FcDC^{2-}$ also bridges the hydrophobic faces, being bound to both the central metal and a Cu^{II} ring metal. Thus infinite chains of $FcDC^{2-}$ bridged LnMC compartments are formed (Figure S3). The La–La distance is 11.14 Å, a distance consistent with the compartment size typically observed with LnMCs.[22b] The encapsulated $FcDC^{2-}$ has a twist angle of 131.7°. This rotation is likely enforced by the LnMC compartment in order to maintain a La–La distance where π–π interactions between the ligands of opposite LnMCs can be maintained. π–π interactions between the encapsulated $FcDC^{2-}$ and the ligand side chains are observed which likely drive the encapsulation of the guest in the compartment.

The crystal structure of benzoate bound to DyMC is shown in Figure 8. Benzoate is bound bidentate to an eight coordinate Dy^{III} on the hydrophobic face, Guest–ligand π–π interactions are again observed in the hydrophobic pocket. On the hydrophilic face, benzoate is bound monodentate to the central metal, and is engaged in a hydrogen bond through the unbound carboxylate to a water bound to a copper ring metal. In contrast, the structure reported with an eight-coordinate Eu^{III} central metal had benzoate-bound monodentate to a copper ring metal,[24] with the unbound carboxylate hydrogen bonded with a water on the central metal.

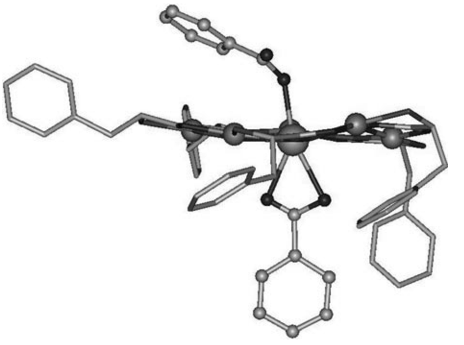


Figure 8. Weblabviewer Pro image of $Dy^{III}(benzoate)_2[15\text{-}MC_{Cu^{II},N,L\text{-}pheHA}\text{-}5](benzoate)$. Benzoate (ball and stick representation) is bound bidentate to the 8-coordinate Dy^{III} on the hydrophobic face and monodentate on the hydrophilic face. Benzoate is perpendicular to the metallacrown plane when coordinated to the eight coordinate metal. Hydrogens, unbound benzoate, and unbound and Cu-coordinated solvent were removed for clarity.

Discussion

Voltammetric methods have been integral in the study of molecular inclusion phenomena. With the pioneering reports by Peter et al.[4a] and Matsue et al.[2a] and work by numerous research groups, of which the Kaifer group is particularly noteworthy, the study of redox active guest binding has grown significantly. Quantitative studies of guest binding are particularly helpful in developing our understanding of host–guest chemistry, and CV has been effective in this pursuit when redox active guests are employed. However, the quantitative study of redox inactive guest binding to redox inactive hosts using electrochemical methods is less well developed. This could be due in part to the viability and accessibility of ^1H NMR techniques. Unfortunately, not all hosts are amenable to ^1H NMR characterization, which creates a need for alternative methods. Many alternative techniques, such as ITC, require expensive equipment which might not be available to non-specialists. Additionally, it is always advantageous to have a large analytical repertoire so that a measurement's accuracy can be confirmed. Thus, it is worthwhile to explore alternative approaches to guest binding that utilize highly accessible instrumentation, and can be generalized to a variety of host–guest systems.

CV is highly accessible, and we felt that a competitive binding approach that utilized a redox probe could be effective for characterizing the thermodynamics of redox-inactive guest binding in solution. Electrochemical competitive binding methods are known to be suitable for electrochemically silent guests, however, they are not especially accessible. One approach coupled potentiometry and CV to study pH-dependent binding equilibria. However, the requirement of the presence and understanding of a protonation step associated with guest binding limited this technique's applicability to only select hosts, such as polyammonium macrocycles.[26] Additionally, methods are known that require the preparation of modified electrodes or substrate absorption, which limits the accessibility of the techniques.[27] A strategy where the host is tethered to the redox active unit has also been employed.[28] The binding assay we have developed uses standard electrodes, is entirely homogeneous, and does not require a chemically modified host. It can be applied to any host with a redox active guest that exhibits one-way shift behavior. In developing our assay, we have applied Wang's mathematical expression[33] to relate the binding constant of the redox-inactive guest to the potential shift of the redox probe. Notably, the only previous knowledge this method requires is the binding constant of the redox active guest, which can be determined electrochemically. Thus, our assay allows for the quantitative study of host–guest complexation using CV exclusively, which makes it highly accessible.

We wished to assess the viability of this novel assay using a well characterized system. Additionally, we wanted to apply the method to LnMC hosts. Their paramagnetism has prevented extensive solution studies with ^{1}H NMR, which makes them well suited for this alternative technique. LnMC guest recognition has been extensively studied in the solid state using X-ray crystallography.[17a,20b,22] However, the potential application of LnMC hosts as mediators of organic reactions has led to increased interest in LnMC–guest solution dynamics. To probe the effectiveness of the CV competitive binding assay using LnMC hosts, we selected benzoate as the redox-inactive guest, as its binding strength has been reported by two groups.[23,24] It was our hope that this study would demonstrate the value of this new approach, as well as lay the foundation for continued voltammetric investigations of the poorly understood aspects of LnMC guest binding in solution.

Before performing the competition experiments, we needed to determine the binding constant of the FcC$^-$ redox probe. We utilized an established method which relied on the assumption that the binding of the oxidized moiety, FcC, was zero. We assessed the veracity of that assumption by using CocC as a mimic of FcC, and examining its binding. CV competition titrations and ESI-MS revealed the CocC does bind, though more weakly than benzoate. Therefore, we felt that the assumption that K_{ox} was zero may not be appropriate for our system and elected to fit K_{red} and K_{ox} simultaneously.

In our fitting, we decided to neglect the binding of a second guest. Crystallographic analysis of LnMC systems often reveals the binding of multiple guests. However, the second binding constants determined for benzoate by ITC were small (50 M^{-1} or less),[23] and sequential binding could not be detected by fluorescence.[24] Based on these results, we felt that treating only the first binding would adequately describe the system.

Based on X-ray crystallography, we ascribe the binding constants for FcC$^-$ (Table 1) and benzoate (Table 2) as primarily representing complexation in the hydrophobic cavity to the central lanthanide. Typically, carboxylate guests are observed binding bidentate to the central metal, such as in the LaMC-FcC$^-$ and DyMC-benzoate structures reported herein (Figures 6 and 8). Certainly, other coordination modes have been observed in the solid state, such as with the LaMC-FcDC^{2-} structure (Figure 7), however, these can often be attributed to packing effects and are less common. Additionally, the binding constants for FcC$^-$ to the LnMC hosts mimic the trends in the Lewis acidity of the central metal, further supporting the central metal as the preferred binding site. A similar trend was observed with benzoate.

Having determined the binding constants for FcC$^-$, we utilized the CV competitive binding assay to quantify the binding of benzoate. This approach allowed for the determination of association constants that closely match the reported values. The differences in the conditions between the various techniques should be noted, especially given the high electrolyte concentration employed in the electrochemical measurements. Nevertheless, the similar values support the viability of the competition technique. Considering the variety of functional groups that can be appended to redox active moieties such as ferrocene, the CV competition approach could be readily generalized to many host systems provided certain conditions are met. First, a detectable dependence of $E_{1/2}$ with concentration of the host is required for this method. This condition is satisfied if either the affinity constant for the redox probe-host is large and/or the concentration of the host is large. Similarly, competitive binding of the redox-inactive host must be sufficiently strong to compete with the binding of the redox active host. This condition is met if the concentration of the redox-inactive competing guest is high and/or its affinity constant with the host is comparable to the affinity constant for the redox probe-host. We estimate that guests with binding strengths within two orders of magnitude of the probe can be measured with this technique, though greater precision could likely be achieved through judicious selection of the conditions and redox probe, and by using a more accurate method for measuring $E_{1/2}$. If these conditions are achievable, the quantitative accuracy of the method is acceptable. When these conditions are not met, the quantitative accuracy suffers, as evidenced by the data for LaMC.

It is worth assessing the FcC$^-$-LnMC binding constants, because though they clearly follow the trend in the Lewis acidity of the central metal, the value for LaMC seems exceptionally low. This value is even more surprising when compared to the binding constant trends seen by ITC for benzoate. Benzoate binds twice as strongly to DyMC compared with LaMC. We detected over 20 times stronger FcC^- binding to DyMC than to LaMC. The primary differences between La^{III} and Dy^{III} are the increased Lewis-acidity and smaller size of Dy^{III}. While one would expect stronger binding to the more acidic metal, the Lewis acidity alone cannot account for the disparity between benzoate and FcC^-. The most significant factor, therefore, is the size of the metal. The larger La^{III} is typically nine-coordinate as is seen for the LaMC-FcC^- complex (Figure 6), while Dy^{III} is typically eight-coordinate, as observed with the DyMC-benzoate structure (Figure 8). Such weak FcC^- binding by LaMC indicates poor guest recognition when bound to the nine-coordinate metal. Crystal structures of LnMC's with ferrocene carboxylate guests are especially helpful in revealing the effects of the central metal coordination number.

With FcC^- bound to the nine-coordinate metal (Figure 6), the guest is positioned such that the hydrophobic ferrocene group extends away from the MC face and outside of the cavity. This orientation results in minimal hydrophobic contacts with the ligand side chains and poor encapsulation inside of the cavity. Such poor guest recognition by the MC with a nine-coordinate metal is reflected in the small binding constant.

Unfortunately, X-ray quality crystals of FcC^- bound to an eight-coordinate LnMC could not be obtained. However, a structure of LnMC's with a ferrocene dicarboxylate ($FcDC^{2-}$) guest is illustrative of FcC^- recognition by an eight-coordinate central metal. Figure 9 shows part of the crystal structure of the LaMC-$FcDC^{2-}$. The LnMC hydrophobic face and encapsulated $FcDC^{2-}$ guest is displayed in order to demonstrate how FcC^- would be positioned in the cavity when coordinated to an eight-coordinate central metal. The $FcDC^{2-}$ on the hydrophilic face, the second LaMC in the compartment, and the carboxylate group at the 1′ position are removed for clarity. In Figure 9, the carboxylate group on $FcDC^{2-}$ is positioned perpendicular to the MC plane on the hydrophobic face. The perpendicular arrangement of the carboxylate orients the ferrocene group roughly parallel to the MC plane. With this coordination mode, the hydrophobic ferrocene group is held within the hydrophobic cavity, where π–π interactions and the hydrophobic effect would significantly contribute to the binding strength. This perpendicular arrangement of the carboxylate relative to the LnMC plane leads to enhanced FcC^- recognition by the cavity. With a bidentate coordinated carboxylate, the perpendicular binding can only occur with an eight-coordinate metal. With the nine-coordinate metal, the ferrocene group extends out of the cavity, so binding is weaker.

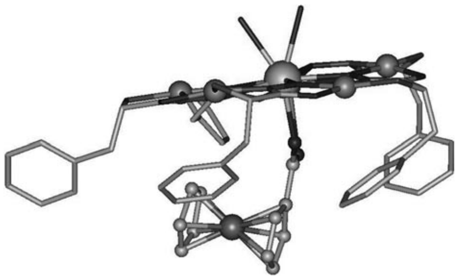


Figure 9. Weblabviewer Pro image of $La^{III}(FcDC^-)[15\text{-}MC_{Cu^{II},N,L\text{-}pheHA}\text{-}5](NO_3)_{0.5}(OH)_{0.5}$ that highlights the orientation of the ferrocene group in the hydrophobic cavity. $FcDC^-$ (ball and stick representation) is bound bidentate to La^{III} and a Cu^{II} ring metal. The carboxylate is perpendicular to the MC-plane, which orients the ferrocene group parallel to the plane and within the cavity. The additional carboxylate on $FcDC^{2-}$, hydrogens, solvent, and other anions were removed for clarity.

Such a large difference between the association constants with La^{III} and Dy^{III} was not observed with benzoate because of its smaller hydrophobic group. Benzoate's phenyl ring is reasonably well encapsulated by the hydrophobic cavity when bound perpendicular to the MC plane with an eight-coordinate metal (Figure 8). Presumably, the phenyl ring would also be sufficiently included in the cavity when bound at a more acute angle with a nine-coordinate metal. Due to the protruding cyclopentadienyl ring on FcC^-, the degree of the encapsulation of the ferrocene group within the hydrophobic cavity is highly dependent on how the carboxylate is oriented relative to the MC plane. Therefore, a more significant difference in binding strength is observed between eight- and nine-coordinate metals with FcC^-. Notably, this demonstrates that significant selectivity can be realized through considerations of the central metal.

Conclusion

A novel, highly accessible CV competitive binding assay was introduced which allows for the straightforward determination the association constants between a redox-inactive guest and host based on the competition with a redox probe. The technique can be readily generalized to a variety of host–guest systems through considerations of the conditions and redox-active component. The method reproduced known association constants between LnMCs and benzoate, confirming the viability of the technique and establishing a method for further investigation of LnMC guest complexation dynamics in solution. In addition, drastically different binding strengths were observed based on the central metal and how effectively the LnMC host's hydrophobic cavity encapsulated the guest, which suggests that significant selectivity could be realized through thoughtful implementation of metals and ligand side-chains in the host's design. We intend to use the CV competitive binding assay to probe differences in binding strength with different ligands and guests. Furthermore, much weaker binding was observed for FcC compared to FcC^-, suggesting that LnMC–guest complexation could be controlled electrochemically. Numerous applications for supramolecular systems under redox control have been realized, such as molecular machines, sensing, and molecular transport, and we are investigating the possibility of utilizing LnMC's in these applications.

Experimental Section

Materials and methods: Distilled, deionized water was used in all experiments. All other solvents were HPLC grade. All chemicals were of reagent grade or better and used as received. Ln^{III}[15-MC$_{L\text{-pheHA}}$-5]Cl$_3$ complexes[23] and cobaltocenium carboxylic acid hexafluorophosphate[34] were prepared as previously reported.

FcC$^-$ sodium salt: Ferrocene carboxylic acid (0.2 g) dissolved in methanol (5 mL) was added to a solution of NaOH (0.05 g) in water (10 mL). The solvent was removed under vacuum, and the solid dissolved in a minimum amount of methanol (~5 mL). FcC sodium salt was precipitated with Et$_2$O (75 mL), filtered, washed with an additional Et$_2$O (25 mL), and air dried to yield an orange powder (0.1445 g, 66 %). Elemental analysis calcd (%) for C$_{11}$H$_9$FeNaO$_2$: C 52.42, H 3.60; found: C 52.46, H 3.57.

La^{III}(FcC$^-$)$_2$[15-MC$_{L\text{-pheHA}}$-5](NO$_3$): La^{III}[15-MC$_{L\text{-pheHA}}$-5](NO$_3$)$_3$ (30 mg, 0.018 mmol) and FcC sodium salt (10 mg) were dissolved in ethanol and acetonitrile 1:1 (8 mL). Slow evaporation of the solution while protected from light yielded crystals within one month (16.5 mg, 43 %). Elemental analysis calcd (%) for LaCu$_5$C$_{71}$H$_{98}$N$_{11}$O$_{28}$Fe$_2$: C 40.19, H 4.66, N 7.26; found C 39.94, H 4.11, N 7.22.

La^{III}(FcDC$^-$)[15-MC$_{L\text{-pheHA}}$-5](NO$_3$): Sodium hydroxide (0.130 g) was dissolved in methanol (15 mL). 1,1′-Ferrocene dicarboxylic acid (0.100 g) was added and quickly changed from a red color to orange. Et$_2$O (100 mL) was added to the solution. The solution was cooled on ice, and filtered to obtain an orange powder of the ferrocene dicarboxylate disodium salt. The powder was washed with Et$_2$O and air dried. La^{III}[15-MC$_{L\text{-pheHA}}$-5](NO$_3$)$_3$ (30 mg, 0.018 mmol) was added to this powder (6 mg) and dissolved in ethanol and water 1:1 (5 mL). Slow evaporation of the solution while protected from light yielded crystals within one month (20.6 mg, 60 %). ESI-MS: *m*/*z*: found: 809 [LaCu$_5$C$_{45}$H$_{50}$N$_{10}$O$_{10}$(FeC$_{12}$H$_8$O$_4$)]$^{2+}$, 1620 [LaCu$_5$C$_{45}$H$_{50}$N$_{10}$O$_{10}$(FeC$_{12}$H$_9$O$_4$)]$^+$; elemental analysis calcd (%) for LaCu$_5$FeC$_{57.5}$H$_{83}$N$_{11}$O$_{29}$: C 36.26, H 4.39, 8.09; found C 37.08, H 4.08, N 8.32.

Dy^{III}(benzoate)$_2$[15-MC$_{L\text{-pheHA}}$-5](benzoate)$_{0.75}$Cl$_{0.25}$: A solution of Dy^{III}[15-MC$_{L\text{-pheHA}}$-5]Cl$_3$ (99.28 mg, 0.063 mmol), sodium benzoate (86.6 mg, 0.601 mmol), and sodium ferrocene carboxylate (1.5 mg, 0.006 mmol) in methanol and pH 7.5 0.1 M aq MOPS 1:1 (10 mL) was slowly evaporated to yield block-shaped crystals (0.0981 g, 81 %). ESI-MS: *m*/*z*: found: 746 [DyCu$_5$C$_{45}$H$_{50}$N$_{10}$O$_{10}$(C$_7$H$_5$O$_2$)]$^{2+}$, 1613 [DyCu$_5$C$_{45}$H$_{50}$N$_{10}$O$_{10}$(C$_7$H$_5$O$_2$)$_2$]$^+$; elemental analysis calcd (%) for Dy$_2$Cu$_{10}$C$_{132.25}$H$_{174.25}$N$_{20}$O$_{52.5}$Cl$_{0.25}$: C 41.22, H 4.57, N 7.27; found C 42.02, H 4.22, N 7.22.

Cyclic Voltammetry: CV measurements were performed with a BAS Epsilon potentiostat and a C3 cell stand. The working electrode was a 0.0707 cm^2 glassy carbon disk that was polished with 0.05 μm polishing alumina on velvet, rinsed, and sonicated in distilled deionized water before each scan. A Pt wire counter electrode and aqueous Ag/AgCl reference electrode (BASi) were used. The electrochemical cell was water jacketed and held at a constant temperature (±0.1 °C) with a VWR 1145 refrigerated constant temperature controller. It should be noted that strict temperature control was required for the competition titration experiments. The cell's exposure to light was limited to prevent FcC$^-$ decomposition.[35] No evidence for decomposition was observed through the course of the experiments. The solution was purged with argon and kept under an argon atmosphere during the experiments. Electrochemical measurements with LnMCs were performed in 10 mL of a 0.1 M KCl solution containing 50 % methanol, 50 % 0.1 M aq MOPS buffer solution that had a ${}^{s}_{s}$pH of 7.5. The solution resistance was compensated electronically. A scan rate of 200 mV s^{-1} was used. The concentration of host was adjusted from 0–12 mM by adding solid host weighed on a Mettler AT201 balance. No significant changes in the pH were observed through the course of the experiments.

X-ray Crystallography: Crystals were mounted on a standard Bruker SMART-APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube ($\lambda = 0.71073$ A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(2) K; the detector was placed at a distance 5.055 cm from the crystal. Frames were integrated with the Bruker SAINT software package[36] with a narrow frame algorithm. Analysis of the data showed negligible decay during data collection; the data were processed with SADABS[37] and corrected for absorption. The structures were solved by direct methods and refined with the Bruker SHELXTL (version 2008/4) software package[38] by the full-matrix least-squares method on F^2. Hydrogen atoms were placed on idealized positions using a riding model.

Crystal data for La^{III}(FcC$^-$)$_2$(NO$_3$)[15-MC$_{L\text{-pheHA}}$-5]: For a crystal of dimensions 0.45 × 0.30 × 0.22 mm, a total of 4825 frames were collected with a scan width of 0.5° in ω and 0.45° in ϕ with an exposure time of 20 s per frame. The structure was solved with formula LaCu$_5$C$_{71}$H$_{98}$N$_{11}$O$_{28}$Fe$_2$, $M = 2121.92$ g mol^{-1}, orthorhombic space group $P2_12_12_1$, $a = 16.3243(11)$, $b = 17.5101(11)$, $c = 30.507(2)$ Å, $V = 8720.1(10)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.616$ mg cm^{-3}, $\mu = 2.077$ mm^{-1}, max. and min. transmission 0.6579 and 0.4550, respectively, 830 restraints, 1239 parameters, 405 792 reflections (R(int) = 0.0421), 24 529 independent reflections, for observed data $R_1 = 0.0496$, $wR^2 = 0.1364$, for all data $R_1 = 0.0549$, $wR^2 = 0.1431$, largest diff. peak and hole 3.199 and −1.145 e Å cm^{-3}.

Crystal data for La^{III}(FcDC$^-$)[15-MC$_{L\text{-pheHA}}$-5](NO$_3$): For a crystal of dimensions 0.26 × 0.16 × 0.10 mm, A total of 4460 frames were collected with a scan width of 0.5° in ω and 0.45° in ϕ with an exposure time of 25 s per frame. The structure was solved with formula LaCu$_5$FeC$_{57.5}$H$_{83}$N$_{11}$O$_{29}$, $M = 1874.83$ g mol^{-1}, orthorhombic space group $I2_12_12_1$, $a = 13.8915(9)$, $b = 30.956(2)$, $c = 35.708(2)$ Å, $V = 15\,355.6(17)$ Å^3, $Z = 8$, $\rho_{\text{calcd}} = 1.648$ mg cm^{-3}, $\mu = 2.170$ mm^{-1}, max. and min. transmission 0.8122 and 0.6022, respectively, 322 restraints, 1094 parameters, 302 773 reflections (R(int) = 0.0495), 21 700 independent reflections, for observed data $R_1 = 0.0337$, $wR^2 = 0.0948$, for all data $R_1 = 0.0374$, $wR^2 = 0.0982$, largest diff. peak and hole 1.515 and −0.862 e Å cm^{-3}.

Dy^{III}(benzoate)$_2$[15-MC$_{L\text{-pheHA}}$-5](benzoate)$_{0.75}$Cl$_{0.25}$: For a crystal of dimensions 0.44 × 0.34 × 0.12 mm, a total of 5190 frames were collected with a scan width of 0.5° in ω and 0.45° in ϕ with an exposure time of 10 s per frame. The structure was solved with formula Dy$_2$Cu$_{10}$C$_{132.25}$H$_{174.25}$N$_{20}$O$_{52.5}$Cl$_{0.25}$, $M = 3853.74$ g mol^{-1}, monoclinic space group $P2_1$, $a = 15.5327(7)$, $b = 25.4741(12)$, $c = 19.7410(9)$ Å, $\beta = 98.379(1)°$, $V = 7727.8(6)$ Å^3, $Z = 2$, $\rho_{\text{calcd}} = 1.656$ mg cm^{-3}, $\mu = 2.394$ mm^{-1}, max. and min. transmission 0.6299 and 0.5109, respectively, 555 restraints, 2171 parameters, 299 821 reflections (R(int) = 0.0309), 43 365 independent reflections, for observed data $R_1 = 0.0353$, $wR^2 = 0.0909$, for all data $R_1 = 0.0384$, $wR^2 = 0.0931$, largest diff. peak and hole 1.287 and −0.872 e Å cm^{-3}.

CCDC-752675, -752676, -752847 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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