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Anion Encapsulation Drives the Formation of Dimeric Gd^{III} [15-metallacrown-5] $^{3+}$ Complexes in Aqueous Solution

Carmelo Sgarlata[†], Alessandro Giuffrida[†], Evan R. Trivedi^{‡,§}, Vincent L. Pecoraro^{‡,*}, and Giuseppe Arena^{†,*}

[†]Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Via A. Doria 6, 95125 Catania, Italy

[‡]Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055, United States

Abstract

Metallacrown complexes capable of sequestering dianions, as shown in the solid state, also exist in aqueous solution at neutral pH, as demonstrated by calorimetric and mass spectrometric data. The driving forces for the formation of these dimeric complexes in solution strongly depend on the chain length of the guest rather than its degree of unsaturation.

Molecular capsules have garnered considerable interest over the past several decades as vehicles capable of selective molecular recognition and catalysis.¹ While there are many different categories of such species that include purely covalent organic structures or organic fragments that associate through salt-bridge or hydrogen-bonding interactions,² possibly the most heavily studied are self-assembled architectures that use metal atoms to template the desired molecular environment.³ Paramount among such systems was that reported by Raymond and Bergman, who provided a system with significant catalytic rate acceleration.⁴ In addition, numerous examples with both exchange labile and exchange inert metals have been shown to assemble soluble compartments capable of guest recognition.⁵

One class of metallamacrocycles that has seen applications in guest recognition, molecular magnetism, and luminescent spectroscopy is metallacrowns (MCs).⁶ These molecules are the inorganic analogues of crown ethers, substituting $[\text{M}-\text{N}-\text{O}]_n$ repeat units, formed using hydroxamic acids or other appropriate tetradentate ligands, for the more familiar $[\text{C}-\text{C}-\text{O}]_n$

*Corresponding Authors: vlpec@umich.edu., garena@unict.it.

[§]Present Address: E.R.T.: Department of Chemistry, Oakland University, Rochester, MI 48309-4479.

ORCID

Carmelo Sgarlata: 0000-0002-9284-1303

Evan R. Trivedi: 0000-0002-3651-739X

Giuseppe Arena: 0000-0002-3874-7076

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ASSOCIATED CONTENT

Supporting Information

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ITC and ESI-MS experimental details (PDF)

linkages. Like crown ethers, MCs can be prepared with varying sizes but also can alter the composition of the metal and ligand and total charge. An important subgroup of MCs is that formed as 15-metallacrown-5 (15-MC-5). These can be prepared as three-dimensional structures or planar materials with transition metals such as copper(II) in the MC ring position and lanthanides in the captured central position. Numerous studies have examined the formation, stability, and kinetics of these complexes, and detailed studies describing the structure of M(15-MC-5) with various metals and ligands have appeared.⁷ Most interesting among these complexes are those prepared with chiral ligands, such as phenylalanine hydroxamic acid (pheHA),⁸ which lead to the formation of face-differentiated MC, which places five ligand side chains on the same face (Scheme 1).

These amphipathic molecules associate in the solid state, forming chiral compartments that exhibit nonlinear-optical properties when the proper guest is captured in these cavities.⁹ As a consequence, studies have explored the metrical parameters required to match the host compartment with the desired guest. While crystallographic studies clearly demonstrate that hydrophobic compartments of different volume can be prepared by varying the hydroxamic acid ligand side chain,¹⁰ there is limited information on whether such dimeric structures exist in solution and are competent to sequester guests into the generated molecular capsule.^{8a,f} A continuing issue that has plagued interpretation and implementation of MCs for guest recognition is the understanding of the composition of these molecules in solution. To this end, we have examined the binding features of the well-characterized $\text{Gd}^{\text{III}}[\text{15-MC}_{\text{Cu}}\text{II}_{\text{NpheHA}}\text{-5}]^{3+}$ (**MC**; Scheme 1)^{8e} host with six different dicarboxylate guest molecules (Scheme 1) having variable lengths and different degrees of unsaturation and have explored to what extent MC is still capable of forming effective dimeric complexes in aqueous solution. [Simplified MC nomenclature uses the formula $\text{M}(\text{X})[\# \text{ ring } n^+]$, where M is the captured atoms- $\text{MC}_{\text{M}'(\text{ox})\text{NL}}\text{-\# ring oxygens}$ central ion, X represents ligands that may bridge between the central and ring metals, MC is the abbreviation for a metallacrown, $\text{M}'(\text{ox})$ is the ring ion and oxidation state, N is the oxime nitrogen that forms part of the MC ring, and L is the ligand templating the MC. Thus, $\text{Gd}^{\text{III}}[\text{15-MC}_{\text{Cu}}\text{II}_{\text{NpheHA}}\text{-5}]^{3+}$ is a MC with a 15-membered ring containing five oxygen atoms, five copper(II) ions in the ring, and a gadolinium(III) central ion, which is made from pheHA.]

In this report, we demonstrate that chiral, amphipathic MCs indeed form dimeric complexes when sequestering dicarboxylic acids and that the chain length of the guest is a more important criterion for recognition than is the degree of molecular unsaturation. Previous attempts to examine guest binding to MC quantitatively in solution using NMR failed because of the severe line broadening due to the presence of copper(II) in the MC backbone; likewise, the use of UV-vis was precluded by the essentially nonexistent change in the extinction coefficient upon going from host to host-guest complexes. Because the calorimetric technique has been proven to be a straightforward, convenient, and accurate method for assessing the stoichiometries and binding affinities of different guests with several hosts^{8d,11,12} the interaction of **MC** with guests **1–6** in water was probed using isothermal titration calorimetry (ITC).^{13,14} An example of typical experimental results is shown in Figure 1.

The experiments shown in the inset expand the region before the first injection of full scan titrations, shifting the equilibrium between the 1:1 (MC–guest) and 2:1 (MC–guest–MC) species toward the formation of MC–guest–MC species due to the MC excess; this allows one to observe the formation of species that would not be otherwise detectable. Guests **2–4** give power curves similar to the one depicted in Figure 1 (Figures S1–S3), while maleate and oxalate deserve their own chapter. Full-scan and expanded titrations were analyzed together (see the Supporting Information, SI)¹⁵ to yield the species and associated thermodynamic parameters illustrated in Figure 2 (and Table S1). It is worth noting that different species and combinations thereof were examined and invariably converged to the species and values reported in Table S1 and Figure 2.

Guests **1–4**, for which we obtain both the 1:1 MC–guest and the MC₂–guest complex, all show ΔG°_2 values greater than ΔG°_1 values, indicating that there is a cooperative effect that somehow favors formation of the MC₂–guest complex over the simple MC–guest species in solution. The first binding step (Figure 2A) is entropy-driven for all dicarboxylates, and this is attributed to a solvophobic effect,¹⁶ which means the entropy resulting from desolvation of the interacting particles compensates for the loss of enthalpy upon complex formation.^{17,18} For the 1:1 MC–guest complexes formed with the longer dicarboxylates, we cannot address whether the guest binds to the hydrophilic face, the hydrophobic face, or either face. For the very short oxalate guest, we believe that this ligand forms a bidentate chelate to the gadolinium(III) ion, with one oxygen atom from each carboxylate moiety bound to the metal. This is supported by the observation of a larger ΔG°_1 of formation for this complex compared to the other dicarboxylates.

In all remaining guests, it is believed that the carboxylate binds using both oxygen atoms as a bidentate ligand to the gadolinium(III) ion.

The binding of the second MC leads to MC₂–guest species for the longer dicarboxylates. While still being entropically driven for terephthalate, it is almost equally favored by the entropic and enthalpic changes for adipate and is enthalpically driven for muconate and fumarate.^{19,20} If we assume that the species detected in solution maintain the structure obtained in the solid state, this difference may be ascribed to the π – π interaction between the phenyl groups from the two MCs contacting one another; in other words, the ring interactions are optimized when the guest is located between the two closer pheHA pendants of the MC. Examination of ring contacts in the solid state confirms this conclusion for the adipate and fumarate systems. The situation is a bit more complex for terephthalate and muconate. In the case of terephthalate, the guest is too long and straight for the phenyl rings from the second MC to favorably interact with the side chains from the first. Therefore, we observe only a large entropic component stabilizing the MC₂–guest complex. Muconate, as long as terephthalate, slides the two MCs slightly to the side with respect to the Gd^{III}–guest–Gd^{III} axis, stabilizing the phenyl ring contacts between the side chains of the compartment (Figure S11).

To test this view, we investigated the cis isomer of **4** [maleate (**5**)], which for geometric reasons is shorter than its trans isomer, and oxalate (**6**), which is much shorter and does not possess unsaturated centers. Figure 2A shows that maleate interacts with the MC to yield the

1:1 (MC–guest) complex; however, the 2:1 MC species is not formed (Figure 2B). The spatial disposition of the two carboxylate groups, resulting from the *cis* configuration of this butenedioic acid, does not permit formation of the MC₂–guest complex. Reiterating, for all other dicarboxylates, the guest–MC interaction that leads to the 1:1 species is driven entropically. The set of full-scan titrations with oxalate (Figure 3) follows the same trend. However, expanding the initial part of the titrations provides an unexpected result: unlike for all of the other guests, for the shortest dicarboxylate, the portion of the power curve focusing on large MC–guest ratios is exothermic (Figure 3, inset).

Attempts to obtain a 2:1 species by varying the concentrations as well as the guest–MC ratio were unsuccessful. Oxalate has a geometrical arrangement that is likely different from that found for the interaction of longer guests with MC. The different behavior (i.e., arrangement) is corroborated by its larger ΔG° of formation compared to the other dicarboxylates. In other words, the short aliphatic oxalate anion cannot trigger the formation of MC₂–guest species because of its dimensions.

In order to further assess the above view, all systems were investigated by high-resolution electrospray ionization mass spectrometry (ESI-MS) under the same conditions as those used for the ITC experiments. The data obtained from mass spectrometry nicely support the speciation derived via ITC (Figure 4 and Table S2).

The signals associated with the MC₂–guest complex are detected at m/z 977.96 and are ascribed to [(MC₂–muconate)-NO₃]³⁺; along with the MC₂–guest species, the 1:1 complex is also detected at m/z 1567.95, which corresponds to [(MC–muconate)NO₃]⁺. The typical isotopic distribution of the MC₂–guest complex is clearly visible in the spectrum and represents its unequivocal “fingerprint”. The calculated spectrum (Figure S12) nicely reproduces the experimental spectrum. The uncomplexed MC signal was detected at m/z 1488.92, while the signals relating to either dimeric or trimeric MC species were not detected in the absence of the guest. This last observation is consistent with the guest triggering formation of the MC₂–guest complex. A similar behavior is observed for the spectra of all systems (Table S1).

In summary, we have demonstrated that MC forms supra-molecular species with both aromatic and aliphatic dicarboxylates in aqueous solution at neutral pH. The formation of MC–guest species is always entropically driven. The driving forces for formation of the MC₂–guest complex depend on the guest. For example, terephthalate exhibits a strong entropic component for MC₂–guest formation, which is not observed for fumarate. The size and shape, rather than unsaturation, are the key factors for guest encapsulation within the MC–guest–MC species in solution. Oxalate is too short to trigger the formation of a 2:1 species. These data resolve the long-standing question as to whether these MC–guest–MC complexes exist in solution and show for the first time that their formation is a consequence of the host–guest interaction. Future work will focus on the development of intermolecular contacts, such as hydrogen bonding, that will stabilize (MC)₂ structures prior to guest encapsulation as well as on the effect of the C shape and size on the formation of effective guest-induced MC–guest–MC species in solution.

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Figure 1.

ITC titration of terephthalate into **MC** at 25 °C in buffered aqueous solution [pH 7.2, 50 mM 3-morpholinopropane-1-sulfonic acid (MOPS)]. Full scan: $C_{MC} = 0.3$ mM; the final guest–MC ratio was 8.5. Inset: expanded titration; $C_{MC} = 0.9$ mM; the final guest–MC was 0.4.

Figure 2.

Thermodynamic parameters for the species obtained by titrating the appropriate dicarboxylate solution into MC at 25 °C in a buffered aqueous solution (pH 7.2, 50 mM MOPS). *: detected in neither ITC nor ESI-MS experiments. Concentrations, guest–MC ratios, and methodology for fitting the data are provided in the SI.

Figure 3. ITC titration of oxalate into MC at 25 °C in a buffered aqueous solution (pH 7.2, 50 mM MOPS). Full scan: $C_{MC} = 0.4$ mM; the final guest–MC ratio was 6. Inset: expanded titration; $C_{MC} = 1.1$ mM; the final guest–MC ratio was 0.3.

Figure 4.
ESI-MS spectrum for the MC_2 -muconate complex in positive mode from a solution at pH 7.2.

Scheme 1.

Schematic Illustrations of the MC Ligand and Carboxylate Guests (1, Terephthalate; 2, *trans,trans*-Muconate; 3, Adipate; 4, Fumarate; 5, Maleate; 6, Oxalate)