Host–Guest Systems

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Dangling Arms: A Tetrahedral Supramolecular Host with Partially Encapsulated Guests**

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Supramolecular chemistry takes advantage of self-assembly to prepare large, discrete structures from relatively simple subunits. Using metal–ligand interactions, π stacking, and/or hydrogen bonds to link the various subunits together, many elegant examples of supramolecular assemblies have been synthesized which have been the subject of some excellent review articles.[1–5] Some examples of the utilization of host–guest properties of such clusters to modify guest reactivity include work done by Fujita,[6,7] Reek,[8–10] and Rebek.[11–14] The rational design and properties of self-assembling tetrahedral M_4L_6 supramolecular clusters ($M = Al^{III}$, Fe^{III}, Ga^{III}, Ti^{IV}; H_4L = 1,5-bis(2,3-dihydroxybenzamido)naphthalene) have been described by Raymond and co-workers, with structural features illustrated in Figure 1.[15–19] These chiral assemblies can encapsulate a variety of lipophilic monocationic molecules as guests within the 350–500-Å^3 cavity.[20–22] While encapsulated, guests can undergo reactions—both stoichiometric and catalytic—with significant rate enhancement and improved product selectivity in some cases.[23–25] The catalytic cycle proposed to explain these results requires the substrate to enter the host and react inside the cluster and then the product to exit. For polymer formation, the product must continually exit the host while the cluster remains intact. Can this be achieved using the M_4L_6 assembly?

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

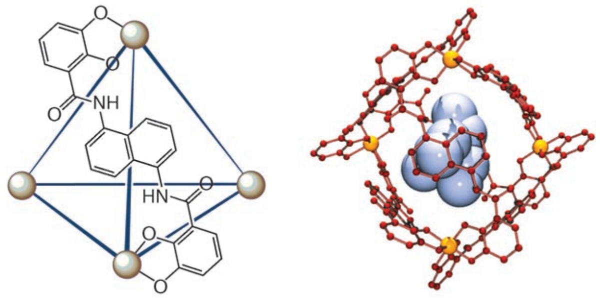
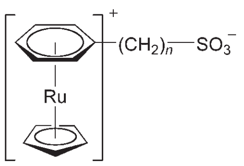


Figure 1. Left: Schematic structure of the M_4L_6 tetrahedral cluster which illustrates the structure of L^{4-} and its coordination to the metal-ion vertices. Right: Illustration of the host–guest complex $[Et_4N\subset Ga_4L_6]^{11-}$ based on the X-ray structure coordinates, with a Et_4N^+ guest shown in blue.

Recently, it was observed that $[Ga_4L_6]^{12-}$ and $[Ti_4L_6]^{8-}$ hosts facilitate guest exchange at essentially the same rate, thus demonstrating that the guest-exchange mechanism does not require a ligand-dissociation step. Small openings exist in the triangular faces of the host, and concerted cluster distortion is proposed as a means to enlarge these gaps for guests to pass through.[26] If a stable host–guest complex was synthesized with part of the guest protruding from the host through this opening, the aperture would have to expand to accommodate the steric bulk introduced by the protrusion. Such a system is analogous to the transition state proposed for nondissociative guest exchange. Rebek and co-workers have reported examples of linear molecules “partially” encapsulated in the hydrophobic pocket of an open-ended cavitand,[27] but no examples have been reported for “closed” self-assembled hosts, such as the M_4L_6 cluster. Herein, the synthesis and characterization of $[RuC_n\subset Ga_4L_6]^{12-}$ ($RuC_n = [CpRu\{\eta_6\text{-}C_6H_5(CH_2)_nSO_3\}]$, $n = 4, 6, 8, 10$; Cp = cyclopentadienyl) is reported in the solution state: a series of host–guest complexes with linear “arms” protruding from the host interior.

With the $[Ga_4L_6]^{12-}$ ion as the host, a suitable guest compound has to be designed with an appendage capable of protruding through the opening of the host into the bulk solvent. Such a guest should have three regions: a lipophilic monocationic head group which exhibits sufficient binding stability for encapsulation, a linear chain of variable length to protrude through the aperture, and a hydrophilic anionic end group to stabilize the arm in aqueous solution. The sandwich complex $[CpRu(\eta_6\text{-}C_6H_6)]^+$ is known to be encapsulated by the $[Ga_4L_6]^{12-}$ ion,[28] and was chosen as the cationic head group for RuC_n (Scheme 1). This series of compounds features linear alkyl chains, with one end bound to the cationic sandwich complex at the phenyl ligand, and the other bound to a sulfonate anion.



Scheme 1. Structural formula of RuC_n ($n = 4$, 6, 8, and 10).

Addition of a stoichiometric amount of RuC_n to K_{12}-$[Ga_4L_6]$ in D_2O led to the encapsulation of the ruthenium head group for all chain lengths ($n = 4$–10). The ^1H NMR spectra of the resulting host–guest complexes display signals for the Cp and phenyl rings of the guest shifted to significantly higher fields relative to the values observed in the absence of the host (Figure 2). Such an upfield shift is a diagnostic feature observed for encapsulated guest protons and is caused by the magnetic shielding from the naphthalene groups surrounding the cavity of the $[Ga_4L_6]^{12-}$ ion.[16,18,20] Furthermore, the two sets of mirror-related phenyl protons become diastereotopic upon encapsulation of the sandwich complex by the host because of the chiral environment of the cavity.

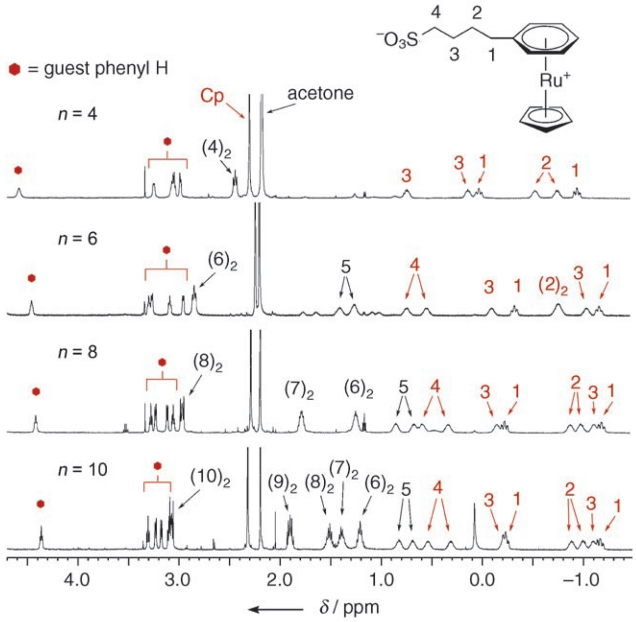


Figure 2. Portions of the ^1H NMR spectra (D_2O, 500 MHz) of the host–guest complexes $[RuC_n\subset Ga_4L_6]^{12-}$. Guest resonance assignments follow the labeling scheme illustrated for RuC_4 (top), with the same numbering pattern used for all chain lengths. Cp denotes the 5H singlet from the Ru-bound cyclopentadiene ring. Interior protons are highlighted with red labels, and signals that integrate to two protons are identified by subscripted labels.

Diastereotopic splitting is also observed for most, but not all, geminal methylene resonances, accompanied by varying upfield shifts. With the aid of 2D COSY and/or TOCSY NMR spectroscopic analysis, all chain protons were fully assigned (Figure 2). Methylene carbon atoms are numbered sequentially along the chain and begin with the carbon atom bound to the sandwich complex. For RuC_4, the geminal methylene protons on C1–C3 become diastereotopic upon encapsulation by the $[Ga_4L_6]^{12-}$ ion, and diastereotopic geminal methylene protons are observed for C1–C5 for encapsulated RuC_6, RuC_8, and RuC_{10}. Upfield shifts tend to increase for protons closer to the head group. In comparison, several methylene protons remain enantiotopic and show little, if any, upfield shift. The signal from the methylene group adjacent to the sulfonate moiety is unsplit and unshifted in all four $[RuC_n{\subset}Ga_4L_6]^{12-}$ host–guest spectra. These ^1H NMR observations indicate that part of the alkyl chain bound to the cationic sandwich complex resides within the chiral host and the rest of that alkyl chain lies outside the cavity with the terminal sulfonate group. At least one methylene group is found outside the host in all four systems. Thus, the $[Ga_4L_6]^{12-}$ cluster encapsulates only part of the RuC_n zwitterion.

The signals for the 72 host protons are typically observed as six sets of 12 protons (Figure 3a), as the catechol and naphthalene ring edges are interrelated in point group *T*, each with three adjacent nonequivalent protons. In the presence of the protruding arm, however, these resonances are split into 24 sets of three protons (Figure 3b). This observation indicates that the overall symmetry is reduced from point group *T* for the host alone to C_3 upon encapsulation of RuC_n. Such a symmetry reduction is expected to occur when the alkyl sulfonate arm of the guest protrudes through the opening in a triangular face of the tetrahedron. This action breaks the ligand twofold symmetry, but retains the C_3 axis running from a Ga^{III} vertex through the aperture of interest. The six ligands that span the edges of the tetrahedron separate into two chemically nonequivalent groups: three "base" ligands that surround the protruding arm and three "side" ligands connected to the Ga^{III} vertex opposite the protrusion, with 12 different protons for each. According to 2D COSY NMR spectroscopy, the 24 host signals originate from four sets of catechol protons and four sets of naphthyl protons (see the Supporting Information).

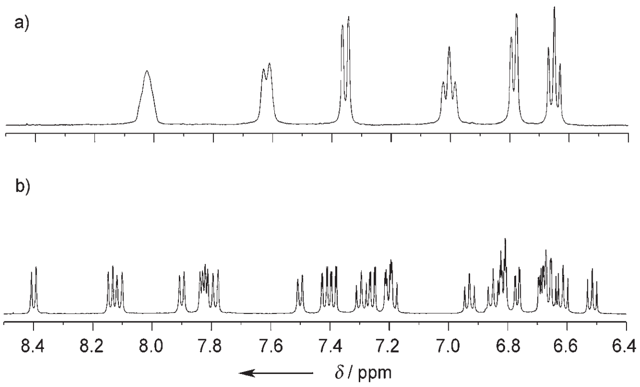


Figure 3. Portions of the ^1H NMR spectra (D_2O) that show the host resonances observed for a) point group *T* typically observed for most host–guest complexes and b) $[RuC_{10}{\subset}Ga_4L_6]^{12-}$ characteristic of C_3 symmetry.

The 2D NOESY NMR spectra of the $[RuC_n{\subset}Ga_4L_6]^{12-}$ system provide additional information about the structures of the host–guest complexes. Figure 4 shows the spectrum of the $[RuC_6{\subset}Ga_4L_6]^{12-}$ system with focus on the cross section between the host and guest resonances. The phenyl and Cp signals of the guest show strong correlations with signals from three out of the four sets of host naphthalene protons. No cross peaks are observed between the phenyl or Cp resonances of the guest and catechol proton signals of the host, thus confirming that the cationic head group is buried deep within the host cavity, near the naphthyl ring walls. Similar 2D NOESY NMR spectroscopic observations have been reported for other guests within the $[Ga_4L_6]^{12-}$ cluster, such as Et_4N^+ and $[CpRu(\eta_6\text{-}C_6H_6)]^+$ ions.[18,28]

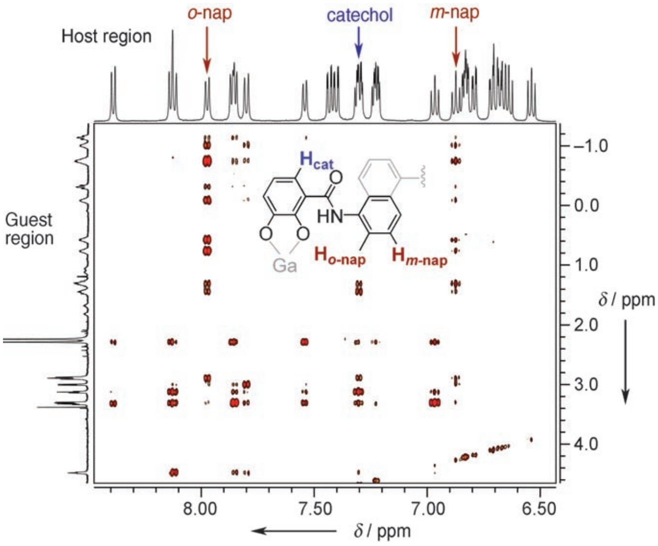


Figure 4. The 2D NOESY NMR spectrum (D_2O, 500 MHz) of the $[RuC_6{\subset}Ga_4L_6]^{12-}$ system shows cross peaks between host resonances (horizontal axis) and guest resonances (vertical axis). Resonances from naphthyl protons that border the aperture, *ortho* and *meta* to the amide nitrogen atom, are highlighted in red. The catechol resonance highlighted in blue shows cross peaks with signals from exterior methylene protons. nap = naphthyl, cat = catechol.

Cross peaks are also observed between several host resonances and most, if not all, methylene groups on the alkyl chain. The first six to eight methylene groups all show cross peaks with the same two host resonances—one doublet and one triplet, which are highlighted in Figure 4. According to molecular-modeling studies (Figure 5) and 2D COSY NMR spectra, these signals originate from two adjacent naphtha-

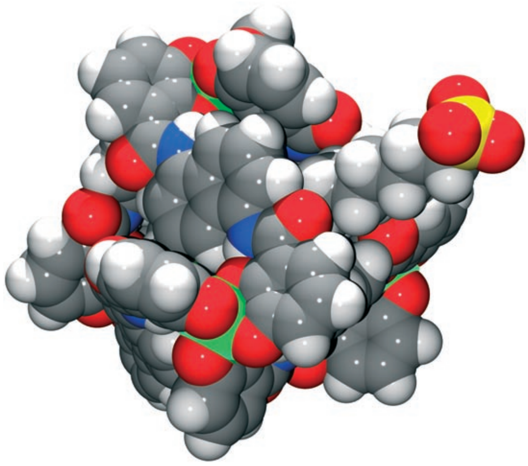


Figure 5. MM3 minimized structural model of the $[RuC_{10}{\subset}Ga_4L_6]^{12-}$ system

lene protons, located *ortho* and *meta* to the amide nitrogen atom. Because of the orientation of the naphthyl ring, the *para* proton is directed away from the alkyl chain and strong cross peaks are not observed with the guest. Relative distances between the host and guest protons in the $[\mathrm{RuC_6{\subset}Ga_4L_6}]^{12-}$ system were determined from NOE interaction growth rates and show these two protons are the closest to the protruding alkyl chain on the C_3-related edges of the three naphthalene rings that surround the aperture. These hydrogen atoms are directed away from the cluster center and can be used as boundary markers to distinguish the host interior from the exterior. Methylene groups 4 and 5 are closest to the boundary, whereas methylene group 1 is the farthest. This difference suggests that the two naphthyl protons are situated between the C4 and C5 of the alkyl chain, with C4 on the interior side and C5 on the exterior side of the cavity boundary. C1, immediately adjacent to the encapsulated cationic head group, lies deep within the cluster. Future NOE interaction growth studies will address the specific conformations of the alkyl chain for guests with different chain lengths.

High-resolution negative ion electrospray mass spectrometry (ESI MS) confirmed the formation of host–guest complexes (Figure 6). Spectra were obtained for solutions of the $[\mathrm{RuC_4{\subset}Ga_4L_6}]^{12-}$, $[\mathrm{RuC_6{\subset}Ga_4L_6}]^{12-}$, $[\mathrm{RuC_8{\subset}Ga_4L_6}]^{12-}$, and $[\mathrm{RuC_{10}{\subset}Ga_4L_6}]^{12-}$ systems, and the resulting spectra showed peaks for the $z=-3$ and -4 charge states of the host–guest complexes with K^+, Na^+, and/or H^+ counterions. The mass spectra of the $[\mathrm{RuC_4{\subset}Ga_4L_6}]^{12-}$ and $[\mathrm{RuC_{10}{\subset}Ga_4L_6}]^{12-}$ systems show additional peaks that correspond to the $z=-5$ charge state of the host–guest complex.

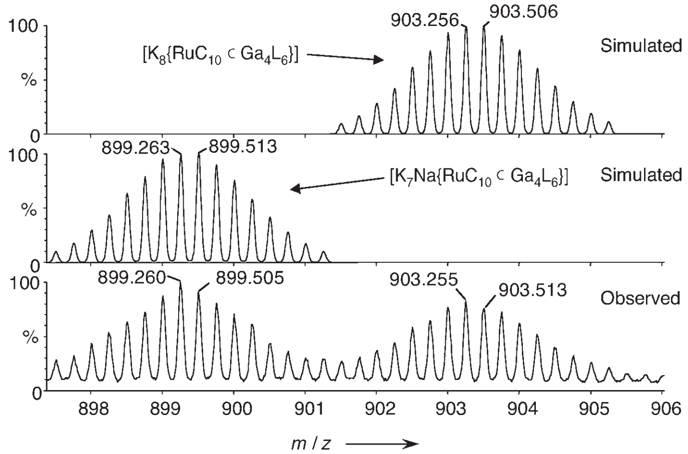


Figure 6. Portion of the electrospray mass spectrum of the $[\mathrm{RuC_{10}{\subset}Ga_4L_6}]^{12-}$ system that shows two adjacent peaks for the $z=-4$ charge state, with predicted isotopic distribution patterns for two particular fragment ion formulae.

This study shows that the $[\mathrm{Ga_4L_6}]^{12-}$ tetrahedron remains intact upon incorporation of the cationic head of a zwitterion, while the link to the anionic tail passes through one of the small openings at the centers of the triangular faces. This process is fully consistent with the nondissociative guest-exchange mechanism recently described.[26] If a guest can extend out of the cavity, new reactions may be envisioned, such as linear polymerizations, with the product extending out of the host cavity as it forms.

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