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[17] CCDC-194337 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Structural Memory Reporters

Supramolecular Chirality: A Reporter of Structural Memory**

*Marco Ziegler, Anna V. Davis, Darren W. Johnson, and Kenneth N. Raymond**

Dedicated to Dr. Jide Xu
on the occasion of his 60th birthday

Herein we describe a molecular structure, formed from labile components, that exhibits structural memory. The macroscopic model in Figure 1 demonstrates this principle. The wooden icosohedral puzzle retains its structure (without any glue) despite dissociation of several pieces. These labile pieces can be removed and replaced without disassembly of the original structure. The structure itself is retained, or remembered, throughout the process of component substitution. In short, structural memory describes the substitution process itself and not merely the starting and ending states of the system.

Figure 1. A 3D puzzle made of labile wooden components retains its structure despite dissociation of several pieces.

Like the wooden puzzle, discrete supramolecular assemblies exhibit well-defined topologies, specified by the arrangement and connectivity of the constituent molecular components. If these molecular components can be substituted in a stepwise fashion and the supramolecular structure still persists, then there is structural memory. We describe such structural memory—as reported by retention of chirality—in

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[*] Prof. K. N. Raymond, M. Ziegler, A. V. Davis, D. W. Johnson
Department of Chemistry
University of California
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-486-5283
E-mail: raymond@socrates.berkeley.edu

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a chiral metallo-supramolecular assembly composed exclusively of labile *achiral* components. Although the molecular composition of the assembly is altered, chirality of the original assembly serves as a structural reporter, confirming that the original structure is preserved.

Chiral memory of self-assembled structures has been described previously.[2] In each of those examples, *chiral* molecular components induce supramolecular chirality in the original structure. Replacement of the chiral components by achiral analogues then creates a resolved structure, which is stable from days to years at room temperature. Importantly, without the initial chirally templated structure, the achiral components would assemble racemic, structural analogues. In contrast, we began with a resolved chiral assembly of achiral components in which chirality exists only at the supramolecular level. Stepwise replacement of the achiral components results in preservation of the original supramolecular chirality.

We have described the $[Ga_4L^1_6]^{12-}$ tetrahedron as the product of a rational design strategy; its labile metal and ligand components are programmed to form one predetermined structure.[3,4] The C_3 symmetry of trisbidentate chelation at the four octahedral metal centers and the C_2 symmetry of the six naphthyl-biscatecholamide L^1 ligands drive formation of an $M_4L^1_6$ tetrahedral cluster (Figure 2).[1] An isolated cavity exists within the structure, and it encapsulates guest molecules such as tetraethylammonium. The assembly is truly supramolecular: the lability of the Ga^{III}–catecholate interactions insures that self-assembly of the discrete structure is under thermodynamic control.

The chirality of the $[Ga_4L^1_6]^{12-}$ tetrahedron results from trisbidentate coordination of the metal ion. A simple $[GaL_3]^{3-}$ catecholate complex exists in solution as two rapidly interconverting enantiomers (Λ and Δ).[5] Mechanical coupling of two such metal centers in a $[Ga_2L_3]^{6-}$ helicate complex slows the isomerization rate by a factor of 100 (Figure 3).[6]

Assembly of the $[Ga_4L^1_6]^{12-}$ tetrahedron produces a racemic mixture of homochiral ($\Lambda\Lambda\Lambda\Lambda$ and $\Delta\Delta\Delta\Delta$) structures. We have shown that these assemblies can be resolved by using chiral countercations.[7] Most remarkably, after exchange of the resolving agent for achiral countercations, an aqueous solution of the $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$ cluster retains its enantiopurity for at least eight months, even after extended boiling of the solution. The chirality of this structure, as measured from the circular dichroism spectra, persists even though there is evidence that partial dissociation of the complex occurs on the time scale of seconds.

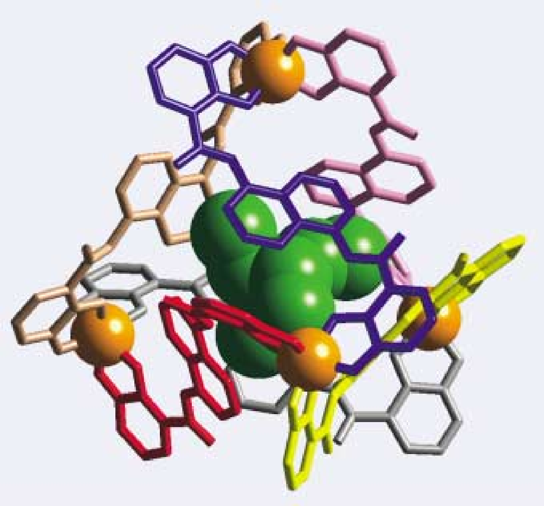

Figure 2. $M_4L^1_6$ tetrahedral assembly composed of biscatecholamide ligands and octahedrally coordinated metal ions.[1] The structure encapsulates guests such as Et_4N^+ ions.

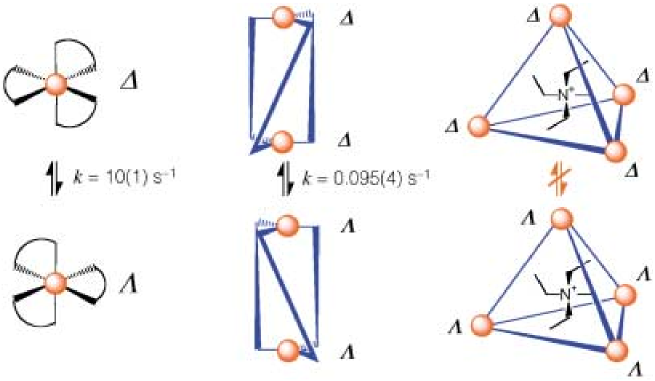

Figure 3. Racemization of a mononuclear $[GaL_3]^{3-}$ catecholate complex occurs 100 times faster than for $[Ga_2L_3]^{6-}$, while mechanical coupling of vertices in $[Ga_4L^1_6]^{12-}$ completely inhibits racemization.

The phenyl biscatecholamide L^2 ligand does not form a tetrahedral structure itself but rather only forms an M_2L_3 helicate when combined with octahedral metal ions (Figure 4).[8] However, ligands L^1 and L^2 share very similar coordination chemistries, as both are biscatecholates. That such supramolecular components are programmed with the information specific to the formation of one self-assembled structure is a central tenet of supramolecular chemistry. In violation of this principle, the robustness of the $[Ga_4L^1_6]^{12-}$ tetrahedral framework is subjected to a radical test. Its ligands are replaced with the nontetrahedral L^2 components in a stepwise fashion. Consequently, the formation of a series of $[Ga_4L^1_nL^2_{6-n}]^{12-}$ mixed-ligand tetrahedra from the homoleptic $[Ga_4L^1_6]^{12-}$ is followed in aqueous solution over time.

The L^1 tetrahedral cluster was prepared and isolated as the $\Delta\Delta\Delta\Delta$-$(Et_4N)_{11}[(Et_4N)\subset Ga_4L^1_6]$ salt, and the ligand L^2 was introduced as the helicate complex $K_6[Ga_2L^2_3]$ (Figure 4).

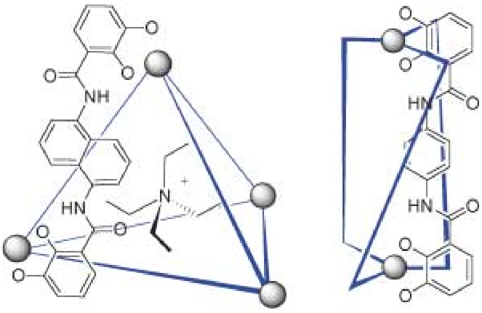

Figure 4. $\Delta\Delta\Delta\Delta$-$[(Et_4N^+)\subset Ga_4L^1_6]^{11-}$ and $[Ga_2L^2_3]^{6-}$ complexes used in the ligand-substitution experiment. Gray spheres represent Ga^{III} ions, while the blue lines represent the ligands of each structure.

A D_2O solution of an equimolar ratio of the two complex (5.5 mM each) was prepared and buffered at pD 7.8. (The $K_6[Ga_2L^2_3]$ helicate provides a soluble source of L^2.)[9] This solution was heated to 75 °C, and the ligand-exchange reaction was monitored over 24 h by ^1H NMR and CD spectroscopies (Figure 5 and Figure 6, respectively).

The encapsulated Et_4N^+ ion acts as a structural probe in these experiments—it is only encapsulated in the M_4L_6 tetrahedra, as demonstrated by a large, characteristic upfield shift of its ^1H NMR resonance signals. The initial ^1H NMR spectrum of this reaction solution shows only one type of encapsulated Et_4N^+ ion, corresponding to the $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$ starting material. The ^1H NMR data reveal formation of $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_nL^2_{6-n}]^{11-}$ species over time, as new resonance signals for the encapsulated Et_4N^+ ion grow into the ^1H NMR spectra. (Identification of these species is corroborated by MS data.[10]) These mixed-ligand structures are the result of stepwise ligand replacement of L^1 by L^2 in the initial $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$ tetrahedron. The CD spectra recorded at each time point show that the L^2-substituted $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_nL^2_{6-n}]^{11-}$ tetrahedra maintain their full chirality throughout the substitution reaction. Stepwise ligand replacements do not compromise the structural or chiral memory of the initial tetrahedron! In fact at 24 h, little of the initial $[(Et_4N)\subset Ga_4L^1_6]^{11-}$ remains, while the initial tetrahedral structure and $\Delta\Delta\Delta\Delta$ configuration are fully preserved in the L^2-substituted products.[11]

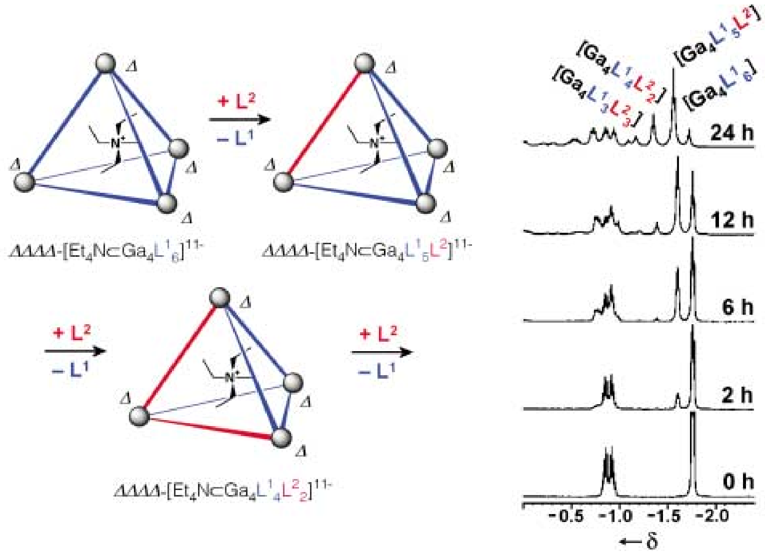

Figure 5. Left: schematic representation of L^2 ligand substitution into $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$. Right: ^1H NMR spectral region showing signals of the Et_4N^+ guest. New guest signals appear as tetrahedra with different ligand combinations are formed. The methyl resonance signals of these guest species are labeled with the composition of the host tetrahedron.

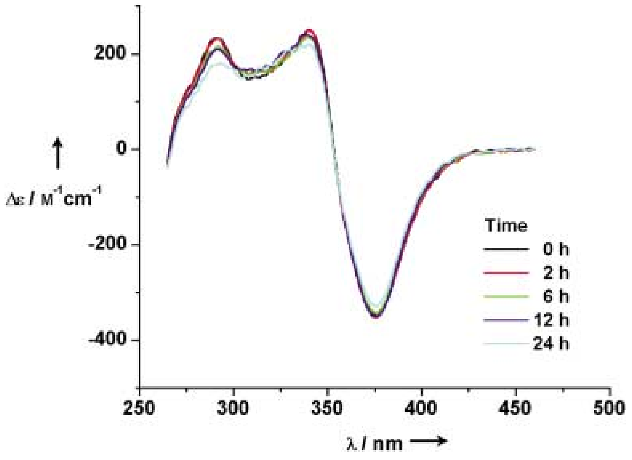

Figure 6. The chirality of the $[(Et_4N)\subset Ga_4L^1_nL^2_{6-n}]^{11-}$ tetrahedra is monitored by CD over time. Some change in the CD spectra is seen in the ligand-based absorptions due to the difference in chromophoric groups of the L^1 and L^2 ligands. However, these spectra show very little change in CD activity, demonstrating retention of chirality and thus structural memory of the tetrahedral system.

We have previously described the formation of libraries of mixed-ligand M_4L_6 tetrahedra, created from combinations of ligands, some of which form homoleptic tetrahedra and some of which do not; the formation of mixed-ligand supramolecular assemblies is not itself unprecedented.[10] However, we present here a different phenomenon: a tetrahedral assembly undergoes ligand substitution to generate a mixture of hybrid assemblies that retain the originally imprinted *chiral* tetrahedral structure. The chirality of the original structure—a property of the structure itself and not of its constituent components—acts as a structural reporter; retention of chirality throughout the substitution reaction distinguishes substitution into the original structure from disassembly of the original structure and *de novo* assembly of the new mixed species. This result is a consequence of the inertness of the resolved homochiral structure to racemization. Just as resolved $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$ is not the thermodynamic product of the self-assembly of L^1 and Ga^{III}, resolved $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_nL^2_{6-n}]^{11-}$ cannot be simply the thermodynamic product of the current substitution reaction. Therefore, we assert that the $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_nL^2_{6-n}]^{11-}$ tetrahedra retain the structure, and consequently the chirality, of their $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4L^1_6]^{11-}$ progenitors. This is a remarkable demonstration of structural and chiral memory in a single molecular species.

Experimental Section

General: ^1H NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer. Circular dichroism spectra were measured with a Jasco J-500C spectropolarimeter, equipped with an IF-500 II A/D converter, and a Varian Cary 300 spectrophotometer was used to collect UV/Vis spectra. $\Delta\Delta\Delta\Delta$-$(Et_4N)_{11}[(Et_4N)\subset Ga_4L^1_6]$ and $K_6[Ga_2L^2_3]$ were synthesized as previously reported.[1,7,8]

Ligand substitution: A solution of $K_6[Ga_2L^2_3]$ (5.5 mM) and $\Delta\Delta\Delta\Delta$-$(Et_4N)_{11}[(Et_4N)\subset Ga_4L^1_6]$ (5.5 mM) was prepared in a KD_2PO_4/D_2O buffer adjusted to pD 7.8 with NaOD. The solution was heated in an NMR tube at 75 °C. At each time point the tube was cooled to room temperature, and an NMR spectrum was recorded.

For CD spectral measurements, aliquots of the reaction solution were removed at each time point and diluted to 0.52 mM with 2 mM KOH(aq). CD samples were measured in a 0.1 mm quartz cell. The absorption spectrum of each diluted aliquot was measured to verify aliquot concentration. Some material precipitated from the D_2O solution over the course of the reaction. This material was redissolved and was found to contain the same mixture of species as the reaction solution (as evidenced by ^{1}H NMR spectroscopy) and the same CD spectrum.

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