Resolution and Kinetic Stability of a Chiral Supramolecular Assembly Made of Labile Components**

Andreas J. Terpin, Marco Ziegler, Darren W. Johnson, and Kenneth N. Raymond*

The importance of chirality for recognition processes in nature is impressively exemplified by the different tastes of (R)- and (S)-asparagine,[1] and the vastly different pharmacological effects of the two enantiomers of thalidomide.[2] Chirality is not the exclusive domain of organic chemistry, many metals can also serve as centers of chirality.[3] The most frequent case is an octahedral arrangement of three bidentate ligands around a metal center to form D or L absolute configurations. Chirality at metal centers has been found to play an important role in nature, for example, for the siderophore-mediated iron uptake in many organisms.[4]

ΔL/A Isomerization of tris-bidentate complexes of the labile high-spin ferric ion or its closely related gallium(III) analogues is rapid in aqueous solution. Tris(catecholate)gallium(III) complexes, model compounds of iron siderophores, usually racemize fast. Racemization rates of 10(1) s⁻¹ for a mononuclear complex[5] and 0.10(1) s⁻¹ for a dinuclear helix[6] were determined by NMR studies. The isomerization was found to...

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be unimolecular and to proceed through a Bailar twist mechanism. The combination of two chiral metal centers to form a helicate substantially slows the isomerization rate as a result of strong mechanical coupling through the rigid ligands.

Larger supramolecular clusters based on metal–ligand interactions have been designed,[7–10] many of which are intrinsically chiral. In particular, tetrahedral [M₄L₆] assemblies have been prepared from C₂-symmetric bis-catecholate or bis-hydroxamate ligands and octahedral metal ions, which form trigonally symmetric vertices (Figure 1).[11–15] In [Ga₄L₆] the metal vertices are bridged by a ligand that does not discriminate between the A–D or A–A configuration across an edge but does discriminate against the Bailar-twist transition state required for inversion.[11, 12] The result is the formation in solution of all possible isomers (with point group symmetry): ΔΔΔΔ (T), ΔΔΔΔ (C₃), ΔΔΔΔ (S₃), and their mirror images. In contrast, the tetrahedral complex [Ga₂L₆] has strongly coupled metal centers, such that if one metal center initially has an A configuration, the metal center across an edge from it must necessarily also be A. In this case the result is the formation of a racemic mixture of homoconfigurational clusters (ΔΔΔΔ or ΔΔΔΔ).[13] The activation energy for interconversion of a tris(catecholate)gallium(III) center from A to D is 67(1) kJ mol⁻¹.[8] If the tetrahedral structure is truly rigid and the metal centers cannot racemize independently from each other, the activation barrier for isomerizing a [M₄L₆] cluster through a Bailar-twist mechanism would be expected to be much higher. Herein we report the resolution of [Ga₂L₆] and show that the enantiomers are indeed exceedingly stable towards racemization.

Complete resolution of the chiral anionic cluster is accomplished in the presence of the chiral N-methylnicotinium cation (Nic) derived from natural (−)-nicotine and designed to interact stereospecifically with the vertices of the tetrahedron. Interestingly, the cation is encapsulated in the cavity of the cluster [(Nic)⊂Ga₂L₆]⁻, as shown by the large upfield shift of the resonances of the cation in the ¹H spectrum (Figure 2), which is characteristic of encapsulation and has been observed previously for related clusters and guests.[13, 14] The encapsulated chiral cation is an ideal probe to determine the diastereomeric excess (de) of the resolved cluster. The NEt₄⁺ ion readily displaces the chiral guest to form enantiopure ΔΔΔΔ- and ΔΔΔΔ-[Et₄N]⁺[(Et₄N)⊂Ga₂L₆] clusters with complete retention of chirality of the metal centers. Remarkably, an alkaline, aqueous solution of ΔΔΔΔ-[Et₄N]⁺[(Et₄N)⊂Ga₂L₆]⁻ retained its enantiopurity for at least eight months, and even extended boiling of the solution did not lead to racemization.[17]

The absolute configuration and enantiopurity of the clusters was determined from their CD spectra (Figure 3): the π–π* transitions in the catechol moiety at each metal center give rise to a strong exciton coulplet from which the absolute configuration can be determined.[16]

An X-ray crystallographic analysis[19] of ΔΔΔΔ-[Et₄N]⁺[(Et₄N)⊂Ga₂L₆] confirmed the absolute configuration at the metal center (Figure 4). The gallium ions are coordinated in a distorted octahedral fashion (average Ga–O bond length 1.966 Å, with a twist angle at the Ga center of 40.2° and Ga–Ga distances of 12.663 Å). These values are very similar to those found in the crystal structure of the same compound in racemic form.[19]

Chirality at octahedral metal centers can be imposed by chiral ligands,[18] and a tetrahedral bis-catecholate cluster with...
exclusive $A$ configurations at the Ga$^{111}$ metal centers has been reported.[20] To the best of our knowledge, the $\text{AAAA}$- and $\text{AAAAI}$-[Et$_6$N]$_4$-/[Et$_7$N]$_4$-[Ga$_2$]$_2$ clusters are the first examples of enantiopure, nonracemizing clusters formed quantitatively from achiral labile components.[22] Like a wooden house, the rigidity of this molecular tetrahedron results from not the individual components but the way they are assembled. Dissociation of one board followed by reattachment does not change the structure.

In summary, we have shown that a racemic mixture of homocentric tetrahedral clusters with labile metal ions can be resolved into its $\text{AAAA}$ and $\text{AAAAI}$ enantiomers, which are stable toward racemization even though related mononuclear or dinuclear metal complexes (helicates) racemize quickly. “Mechanical stiffness” that prevents racemization is provided through the interconnection of all four labile ions, with quantitative yields of both clusters precipitated with various unstoichiometric mixtures of Nic and K ions.

General: All NMR spectra were measured with a Bruker 500 MHz spectrometer. Chemical shifts are reported as $\delta$ downfield from sodium $[D_2]_2$-2,3.3-[3-(trimethylsilyl)]propionate. Absorption spectra were recorded on a Hewlett-Packard 8450A UV/Vis diode array spectrophotometer. Circular dichroism (CD) spectra were measured with a Jasco J-500C spectropolarimeter equipped with an IF-500 II A/D converter. Mass spectral data were acquired using a Bruker Apex II actively shielded FT-ICR mass spectrometer equipped with an Analytica electrospray source (off-axis probe). H$_4$ICR mass spectrometer equipped with an Analytica electrospray source.

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Clusters with the labile AlIII, FeIII, and InIII ions were resolved by the same method and also show exceedingly high stability towards racemization.


Crystal structure of \( \text{AlEt}_4 \cdot \text{Ga}_{2} \cdot \text{X} \cdot (\text{solute}) \): Crystal data were collected using a Siemens SMART diffractometer equipped with a CCD area detector, crystal size 0.30 mm, \( T = -125 \) °C, graphite-monochromated MoK\( \alpha \) radiation (\( \lambda = 0.71073 \) Å), cubic, space group I\( \bar{2} \) (No. 197), \( a = 22.572(1) \) Å, \( V = 11500.5(9) \) Å\(^3\), \( Z = 2 \), \( \mu = 0.528 \) cm\(^{-1}\), \( F(000) = 3706 \), \( \rho_{\text{calc}} = 1.07 \) Mg m\(^{-3}\). 2\( \theta_{\text{max}} \) = 37.64°. Of the 15524 reflections measured, 1510 were unique (\( R_{\text{int}} = 0.087 \)). The structure was solved by direct methods and refined on \( F^2 \) using SHELXTL. Data were corrected for Lorentz and polarization effects. A semi-empirical absorption correction was applied using XPREP (ellipsoidal model, \( R_{\text{int}} = 0.0486, T_{\text{max}} = 0.812, T_{\text{min}} = 0.755 \)).

The carbonyl oxygen atom of the ligand is disordered over two positions with 1/2 occupancy, and the naphthalene backbone of the ligand is disordered across an imaginary line connecting the two carbon atoms affixed to the nitrogen atoms of the amide. This disorder was modeled as a twist of this backbone around its center with both orientations having 1/2 occupancy. A disordered NEt\( \text{t}^+ \) ion is present in the cavity of the cluster. The nitrogen atom is located on the 23 special position, and the methylene groups are disordered over two sites with 1/2 occupancy. The methyl carbon atoms were disordered over the threefold axes and 12 sites with 1/3 occupancy. There was also a high degree of disorder among the other cations and solvent molecules present. As a result, only the encapsulated NEt\( \text{t}^+ \) ion was found and constrained to be rigid in the disorder model described. The other 11 cations and solvent molecules are included as "(solute)" in the chemical formula and accounted for by a SWAT parameter. As a result of the lack of high angle data (1.2 Å resolution) only the gallium atoms, amide nitrogens, and catecholate oxygen atoms were refined anisotropically. All other atoms were refined isotropically. Hydrogen atoms were included on all appropriate atoms of the ligand that were not disordered but were not refined. Weighting scheme: \( 1/[p(F) + (0.1763p)^2 + 2.7183p] \), where \( p = (F^2 + 2F^2)/3 \). Final \( R_{\text{w}} = 0.0837 \) for 1022 reflections with \( F > 4\sigma(F) \) (1162 Friedel unique data, 157 parameters, 6 restraints); for all 1510 data, \( wR_{\text{F}} = 0.269, \text{GOF} = 1.118 \). Flack\(^{27} \) parameter = 0.08(8); max/min residual density +0.28/–0.27 eÅ\(^{-3}\). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145431. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).


Other examples of partially resolved assemblies made from moderately labile octahedral metal ions (Ni\( \text{II} \) and Co\( \text{II} \)) and achiral ligands are dinuclear triple helicates.\(^{12, 23} \)


SMART, Area Detector Software Package, 1995, Siemens Industrial Automation, Inc., Madison, WI, USA.
