Host–Guest Systems

DOI: 10.1002/anie.201000416

Chiral Nanoscale Metal–Organic Tetrahedral Cages: Diastereoselective Self-Assembly and Enantioselective Separation**

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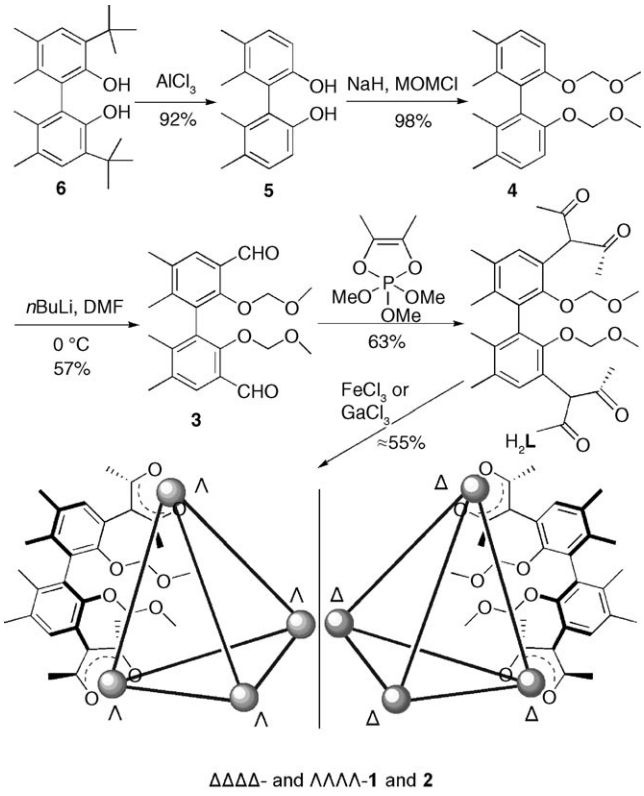
The self-assembly of nanoscale molecular architectures that have inner cavities has received intense attention in the past decade.[1,2] Such hollow polyhedra can be synthesized by recognition-driven self-assembly of complementary subunits. A variety of high-symmetry cages and capsules with distinct geometries have been synthesized with the use of rigid, highly directional multibranched ligands to bind to coordinatively unsaturated metal complexes.[2–4] In particular, starting with the pioneering work of Saalfrank et al.,[3a] a variety of M_xL_y cages have been assembled from octahedral metal centers and C_2- or C_3-symmetric bis- and tris(bidentate) catecholamide or β-diketonate ligands.[3,4] The resolution of racemic anionic M_4L_6 clusters by chiral cations has been described by Raymond and co-workers.[4d] The incorporation of chiral functionalities into such assembled entities can expand their utility in enantioselective processes.[5,6] Nevertheless, asymmetric processes based on chiral cavities still remain relatively unexplored, mainly because of the difficulty in synthesizing large chiral cages in optically pure forms.[6]

1,1′-Biphenyl derivatives with intrinsic C_2 symmetry constitute a class of compounds that are widely employed in chiral recognition processes, in particular as auxiliaries in asymmetric synthesis.[7] We report herein the self-assembly of homochiral tetrahedral cages from the biphenyl bridging ligand 5,5′,6,6′-tetramethyl-3,3′-diketone-2,2′-bis(methoxymethoxy)-biphenyl (H_2L), and potentially C_3-symmetric metal ions. The polyhedra can be used as hosts for crystallization separation of racemic alcohols with an enantioselectivity of up to 99.5%.

The enantiopure atropisomeric H_2L was prepared in four steps in good overall yield (32%) from the readily available chiral 5,5′,6,6′-tetramethyl-3,3′-di-*tert*-butyl-1,1′-biphenyl-2,2′-diol (Scheme 1). Reaction of H_2L with M^{III} chloride (3:2 molar ratio) in DMF followed by layering the solution with methanol afforded the desired complexes M_4L_6 (M = Fe **1**, Ga **2**) in moderate yields. The formation of the tetrameric



Scheme 1. Synthesis of the ligand H_2L and compounds **1** (Fe_4L_6) and **2** (Ga_4L_6). MOM = methoxymethyl.

compounds was supported by ESI-MS, which showed prominent peaks for the desired tetramers $[Fe_4L_6+H]^+$ and $[Ga_4L_6+2H]^{2+}$ at m/z 3370.6 and 1711.8, respectively. The IR spectra of both **1** and **2** showed bands characteristic of chelated acetylacetonate (acac) groups at 1575 cm^{-1}.

The ^1H and ^{13}C NMR spectra of **2** show well-resolved signals for a single ligand environment; most of these signals have a slight upfield shift with respect to the free ligand (Figure 1). The C_2 symmetry of the biphenyl ligand is preserved in the complex, as could be deduced from the number of signals in the NMR spectra. The absence of the proton signal of Hacac at $\delta = 16.71$ ppm in the spectrum of H_2L supports the complete metal–ligand complexation. The resonances of methyl protons of each acac group are equivalent on the NMR time scale, with a signal at $\delta =$ 1.96 ppm in H_2L, but the resonances become obviously nonequivalent with separate signals at $\delta = 1.75$ and 1.99 ppm in **2**. All the proton signals are very sharp, which is indicative of the formation of discrete metal complexes rather than higher oligomeric species. Therefore, the forma-

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[**] This work was supported by NSFC-20971085, "973" Programs (2007CB209701 and 2009CB930403) and the Major Fundamental Research of Shanghai Science and Technology Committee and the key project of the State Education Ministry.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000416.

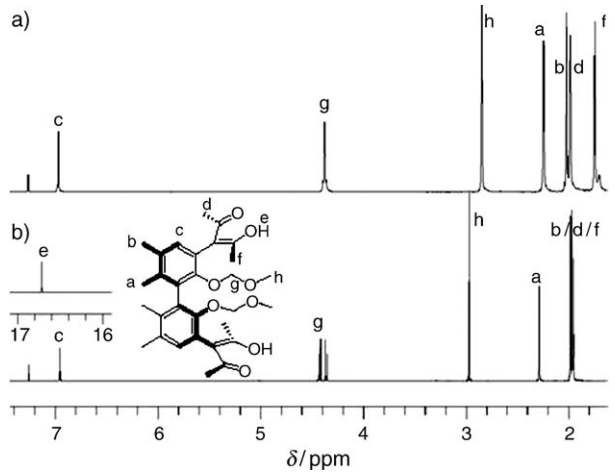


Figure 1. ^{1}H NMR spectra of a) **2** and b) H_2L in $CDCl_3$. The proton signal of Hacac of H_2L is shown as inset. The singlet signal at 7.26 ppm corresponds to $CDCl_3$.

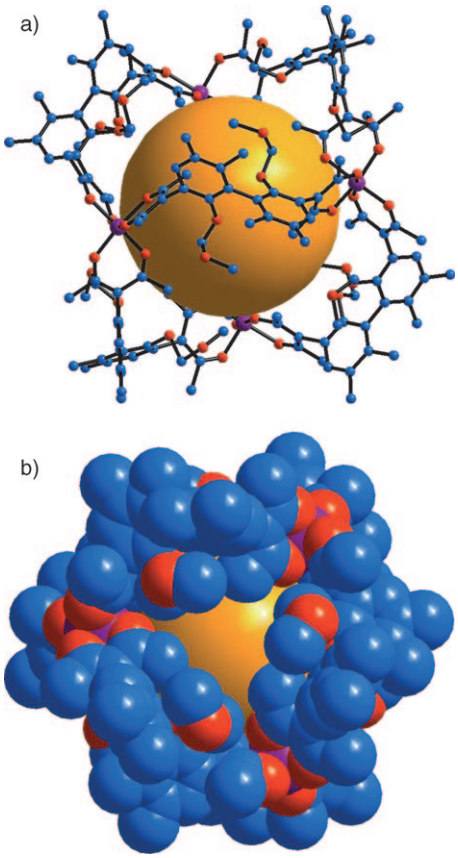


Figure 2. a) View of the molecular structure of **1** and b) its space filling model. (purple Fe, blue C, red O; the cavity is highlighted by a yellow sphere).

tion of tetrameric species with differently configured metal centers can be excluded because the spectra would be more complicated as the ligand would lose its symmetry in this case. We thus believe that the self-assembly of chiral clusters based on H_2L proceeded with high diastereoselectivity and only one single diastereomer was formed. The clusters possess an ideal tetrahedral symmetry, and contain metal centers with either ΔΔΔΔ or ΛΛΛΛ symmetry.

A single-crystal X-ray diffraction study on **1** and **2** unambiguously revealed the formation of nanosized chiral, porous clusters.[8] Both **1** and **2** crystallize in chiral trigonal P_3 space group, and the asymmetric unit is formed from one-third of each of three cages. Each tetrameric cluster has noncrystallographic tetrahedral symmetry constructed from four C_3-symmetric metal centers and six C_2-symmetric (*S*)-L ligands (Figure 2). Within each polyhedron, the metal centers adopt a nearly idealized octahedral geometry by coordinating three chelated acac anions from three different ligands with reasonable metal–oxygen distances. Although the tris(bidentate) coordination at each metal center can form either a Δ or Λ configuration, the overall structure of the cluster when composed of chiral (*S*)-L may be homochiral ΛΛΛΛ-*fac*. Each of the six ligands possesses the same handedness of chirality and coordinates to two metal centers through its two chelating acac groups with an average metal–metal separation of approximately 12.0 Å for both **1** and **2**. This arrangement of metal ions and coordination ligands thus leads to a molecular tetrahedron with the vertices occupied by the metal ions and the edges of the L ligands. The two phenyl rings of the L ligands are twisted along the pivotal C–C bond at the 1,1′-positions with dihedral angles of 74.1–81.5° for **1** and 76.8–79.1° for **2**; the bulk of the biphenyl moieties point away from the cavity of the molecular tetrahedron to give rise to a porous cluster.

A space-filling representation of **1** and **2** clearly shows the formation of a porous, nanosized cage with wide apertures (Figure 2b). The overall sizes of the clusters are approximately 24.1 Å, while the aperture on each face has approximate diagonal distances of 7.0 × 7.0 Å. Each cage of both **1** and **2** has an open cavity that has an approximate volume of 1800 Å^3 and is accessible to guest molecules. The packing of tetrahedral clusters in **1** and **2** leads to an occupation of around 33% of the total volume by guest molecules.[9] Clusters **1** and **2** are rare examples of homochiral molecular polyhedra that bear additional inwardly directed functional groups that have been crystallographically characterized.[10]

The electronic spectrum of H_2L is characterized by two π–π* transitions of diketone and biphenyl groups at 283 and 238 nm, respectively. These π–π* transitions occur at 276 and 241 nm for **1** and 303 and 239 nm for **2** (Figure 3). In addition, there are two new bands around 461 and 369 nm for **1**, which probably arise from ligand-to-metal charge transfer (LMCT) and metal-to-ligand charge transfer (MLCT) processes, respectively.

The CD spectra of **1** and **2**, which are formed from *S*- and *R*-enantiomers of H_2L, are mirror images of each other, thus demonstrating their absolute configuration and enantiopurity. The CD spectra of (*S*)- and (*R*)-**1** each exhibit an acac π–π* band at 302 nm and an MLCT band at 374 nm, as well as a bisignate LMCT band at 493 and 428 nm. The exciton coupling of two identical phenyl chromophores[11] results in the corresponding positive and negative exciton splitting patterns centered at 250 nm for (*S*)- and (*R*)-**1**.

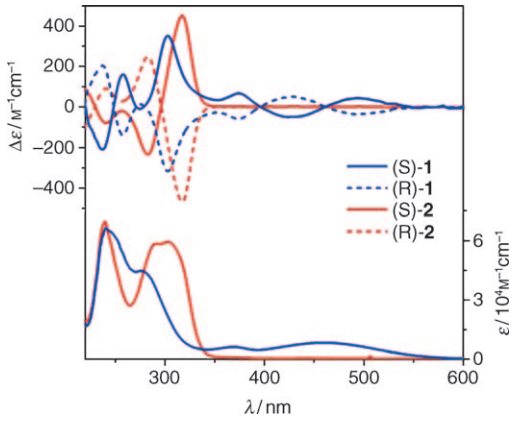
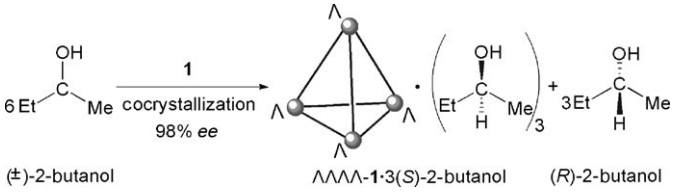


Figure 3. CD (top) and UV/Vis (bottom) spectra of **1** and **2** in THF.

The CD spectra of (*S*)- and (*R*)-**2** show a phenyl π–π* band at 240 nm and do not show exciton coupling of the phenyl groups, whereas intense positive and negative exciton splitting patterns of acac groups centered at 296 nm were observed for (*S*)- and (*R*)-**2**, respectively. Based on the exciton chirality method for the absolute configuration assignment of tris(acac) metal complexes,[12] the positive exciton pattern indicates that each Ga center in (*S*)-**2** is in the Λ form, which is consistent with the crystal structure; the negative pattern indicates each Ga center in (*R*)-**2** is in the Δ form. The configuration of the newly formed stereogenic metal centers is thus controlled by the configuration of the biphenyl platform. Exciton coupling of acac chromophores can be clearly observed for **2**, as they may be free from overlapping transitions,[11c] as evidenced by the significant red shift of their π–π* transition in the absorption spectra.

Upon addition of 2-butanol to apohost **2** in $CHCl_3$, the expected formation of the kinetically stable host–guest complex could not observed by ^{1}H NMR spectroscopy. However, the inclusion of 2-butanol could be readily achieved through cocrystallization of the evacuated host and racemic alcohols in $CHCl_3$ at room temperature (Scheme 2). The desorbed 2-butanol from (*S*)-**1** was analyzed by using GC on a chiral support, which showed that the enantiomeric excess (*ee*) value was 98.8 %, and the absolute configuration of (*S*)-2-butanol was confirmed by comparison of the retention time with that of a reported sample.[13e] Similar enantioselective inclusion behavior was observed for racemic 3-methyl-2-butanol, whereby (*R*)-**1** exhibited remarkable selective inclusion of the *R* enantiomer over the *S* enantiomer. The *ee* value of the desorbed guests was 99.5 %. On the basis of microanalysis and thermogravimetric analysis (TGA), the inclusion



Scheme 2. Selective inclusion of (*S*)-2-butanol by ΛΛΛΛ-**1**.

complexes, which were not particularly soluble in common organic solvents, can be formulated as **1**·(2-butanol)$_3$ and **1**·(3-methyl-2-butanol)$_3$. The chiral nature of the included molecule is determined by the handedness of host, as further evidenced by the remarkable inclusion preference of (*R*)-**1** for the *R* enantiomer of 2-butanol over the *S* enantiomer (99.2 % *ee*). Control experiments indicated that the ligand H_2L itself can not resolve the enantiomers of 2-butanol under otherwise identical conditions.

Although many artificial hosts have been developed for chiral recognition of alcohols in the solid state, there are few examples of the highly enantioselective inclusion of small alcohols.[13] In particular, in the case of secondary alcohols, it is difficult to recognize chirality because the subtle structural difference between the enantiomers as methyl groups and hydrogen atoms attached to the chiral carbon atom have to be discriminated. In this case, success may result from the combination of the chiral cage with the amphiphilic cavity interior that is lined with flexible methoxymethyl ethers; this combination leads to bioanalogous interaction of the host with guest species during the crystallization process.[13g] Attempts to obtain single crystals of the inclusion adducts have been unsuccessful. Further investigations on the resolution behavior and resolution of other racemic organic species are in progress.

In conclusion, we have presented the diastereoselective self-assembly of chiral neutral metal–organic cages and demonstrated their highly enantioselective abilities to resolve small racemic alcohols by crystallization inclusion. Further work is aimed at enlarging the open channels and further functionalization of the interiors of the cages through modifications of organic linkers for enantioselective processes.

Experimental Section

Synthesis of **1** and **2**: A solution of $FeCl_3$ (10.8 mg, 0.067 mmol) in DMF (1 mL) was added dropwise to a solution of (*S*)- or (*R*)-H_2L (52.6 mg, 0.1 mmol) in DMF (4 mL) at room temperature. The resulting solution turned dark purple and was stirred for 10 minutes, after which time the solution was layered with methanol. After two weeks, dark-red crystals of **1** suitable for X-ray crystallography were collected by filtration, washed with ethanol and ether, and dried in air. Yield: 57 %. IR (KBr): $\tilde{\nu}$ = 2918 (b), 1575 (vs), 1443 (s), 1357 (s), 1271 (w), 1155 (m), 1081 (w), 1030 (m), 970 (w), 935 (w), 817 (w), 699 (w), 682 (w), 602 (w), 449 cm^{-1} (w); elemental analysis calcd (%) for $C_{192}H_{292}Fe_4N_4O_{76}$ ([Fe_4**L**$_6$]·4DMF·24H_2O): C 56.30, H 7.19; found: C 56.01, H 7.14. The guest molecules could be removed by heating in vacuum to further confirm the composition of the apohost [Fe_4**L**$_6$]: calcd (%) for $C_{180}H_{216}Fe_4O_{48}$: C 64.13, H 6.46; found: C 63.98, H 6.40.

(*S*)- and (*R*)-**2** were synthesized by following a similar method. Yield: 51 %. IR (KBr): $\tilde{\nu}$ = 2918 (b), 1575 (vs), 1443 (s), 1357 (s), 1271 (w), 1155 (m), 1081 (w), 1030 (m), 970 (w), 935 (w), 817 (w), 699 (w), 682 (w), 602 (w), 449 cm^{-1} (w); elemental analysis calcd (%) for $C_{192}H_{284}Ga_4N_4O_{72}$ ([Ga_4L_6]·4DMF·20H_2O): C 56.53, H 7.02; found: C 56.60, H 7.00. The guest molecules were also removed by heating, and the resulting apohost characterized: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (s, 6H), 1.99 (s, 6H), 2.03 (s, 6H), 2.25 (s, 6H), 2.85 (s, 6H), 4.36–4.40 (t, 4H), 6.97 ppm (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 17.1, 20.2, 27.6, 27.8, 56.4, 98.1, 111.1, 130.6, 132.3, 132.8, 133.7, 135.9, 152.4, 190.5, 194.2 ppm. Elemental analysis calcd (%) for $C_{180}H_{216}Ga_4O_{48}$: C 63.09, H 6.35; found: C 62.92, H 6.33.

Crystallization separation experiment: Racemic 2-butanol (4 mL) or 3-methyl-2-butanol (4 mL) was added dropwise to a solution of the apohost **1** (40 mg) in dry $CHCl_3$ at room temperature. The resulting solutions were allowed to evaporate slowly; the inclusion solids formed after two days. The solid were filtered and washed with diethyl ether to remove surface solvent molecules. The guest alcohols were removed from the inclusion solids of **1**·(guest)$_3$ by washing with MeOH. Elemental analysis calcd (%) for the adduct $C_{192}H_{246}Fe_4O_{51}$ (**1**·(2-butanol)$_3$): C 64.18, H 6.90; found: C 64.28, H 6.87. Calcd (%) for the adduct $C_{195}H_{252}Fe_4O_{51}$ ([Fe_4**L**$_6$]·(3-methyl-2-butanol)$_3$): C 64.42, H 6.99; found: C 64.32, H 6.90. Optical purity of the guests was determined by GC using a Chiral-G-TA capillary column (ASTEC Company; 30 m × 0.25 mm internal diameter). Other experimental details are given in the Supporting Information.

Received: January 23, 2010
Revised: April 7, 2010
Published online: May 10, 2010

Keywords: chiral resolution · chirality · host–guest systems · inclusion compounds · self-assembly

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[8] Crystal data for **1**: trigonal, *P*3, $a = 34.020(2)$, $c = 17.221(2)$ Å, $V = 17261(3)$ Å^3, $Z = 3$, $T = 123$ K, $F(000) = 5532$, $\rho_{calcd} = 0.972$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.308$ mm^{-1} ($\lambda = 0.71073$ Å), $R1 = 0.1043$ [$I > 2.0\sigma(I)$], $wR2 = 0.2430$, Flack parameter = 0.11(3) and GOF = 0.910. **2**: trigonal, *P*3, $a = 33.8989(3)$, $c = 16.9424(3)$ Å, $V = 16860.7(4)$ Å^3, $Z = 3$, $T = 123$ K, $F(000) = 5406$, $\rho_{calcd} = 1.012$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 1.062$ mm^{-1} ($\lambda = 1.54178$ Å), $R1 = 0.1206$ ($I > 2.0\sigma(I)$), $wR2 = 0.3087$, Flack parameter = 0.10(3) and GOF = 0.878. Contributions to scattering arising from the highly disordered solvent molecules were removed using the SQUEEZE routine of PLATON;[9] structures were then refined again using the data generated. CCDC 721358 and 721359 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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