Cage Complexes

International Edition: DOI: 10.1002/anie.201507295
German Edition: DOI: 10.1002/ange.201507295

Spontaneous Resolution of an Electron-Deficient Tetrahedral Fe_4L_4 cage

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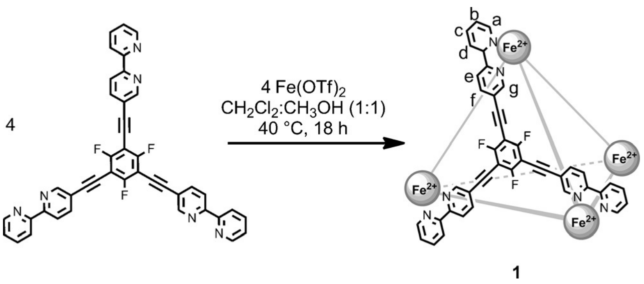
Abstract: *A highly electron-deficient C_3-symmetric tris(bipyridyl) ligand was prepared in four steps and used for the coordination of $Fe(OTf)_2$, thereby resulting in the homochiral assembly of a new family of robust tetrahedral M_4L_4 cages. This homochiral T-symmetric cage containing a relatively large cavity of 330 Å^3 is capable of encapsulating an anionic guest, as was determined by mass spectrometry, ^{19}F NMR spectroscopy, and finally shown from its crystal structure. Moreover, crystallization of the cage from CH_3CN led to crystals containing both ($\Delta\Delta\Delta\Delta$ and $\Lambda\Lambda\Lambda\Lambda$) enantiomers, while crystallization from CH_3OH resulted in crystals containing only the right-handed ($\Delta\Delta\Delta\Delta$) cage. The difference in the crystal packing of the two crystal structures is discussed and a feasible explanation for the unique phenomenon among supramolecular cages—spontaneous resolution—is given.*

Metallosupramolecular cages have attracted a lot of attention in contemporary chemical research, particularly, in terms of the potential applications of their confined cavities.[1] In particular, tetrahedral M_4L_6[1a,2] and M_4L_4[1a,3] coordination cages have been of great interest for the encapsulation of various charged guests,[1a,2b,c,e,f,3b,4] neutral compounds,[2g–k,3e,i,5] and for conducting catalytic reactions.[6] Another interesting aspect of tetrahedral coordination cages is the possibility to prepare chiral supramolecular structures by using chiral or achiral ligands.[7] The introduction of chiral ligands or subcomponents is a common approach to control the stereoconfiguration of the final assembly.[2i,j,3h,8] Interestingly, chiral supramolecular structures can also be prepared using achiral ligands, where the chirality arises from metal centers. Depending on the stability of the metal–ligand bond and the structure of the ligand used, the tetrahedral cages M_4L_6 or M_4L_4 can be obtained as three different diastereomers: homochiral T ($\Delta\Delta\Delta\Delta/\Lambda\Lambda\Lambda\Lambda$), heterochiral C_3 ($\Delta\Delta\Delta\Lambda/\Lambda\Lambda\Lambda\Delta$), or achiral S_4 ($\Delta\Delta\Lambda\Lambda/\Lambda\Lambda\Delta\Delta$), or as mixtures.[7] Racemic tetrahedral cages have been resolved by the addition of chiral counterions.[9] Raymond and co-workers used a resolved enantiopure cage $(NMe_4)_{12}[\Delta\Delta\Delta\Delta\text{-}Ga_4L_6]$ to catalyze an aza-Cope rearrangement.[10] In a very rare case, spontaneous resolution upon crystallization of helicates has been reported.[11]

To attract electron-rich guests inside the cavity, we designed a C_3-symmetric tris(bipyridyl) ligand with a highly electron-deficient[12] fluorine-substituted benzene core with attached 2,2′-bipyridyl binding sites. To the best of our knowledge, this is the first example of a stable C_3-symmetric tris(bipyridyl) ligand to be used for the preparation of M_4L_4 cages.

The ligand (1,3,5-tris[5-ethynyl(2,2′-bipyridyl)]-2,4,6-trifluorobenzene) was synthesized in reasonable yield by Sonogashira coupling of 5-ethynyl-2,2′-bipyridine and 1,3,5-trifluoro-2,4,6-triiodobenzene (see the Supporting Information). Cage **1** was prepared by mixing the ligand with $Fe(OTf)_2$ in a 1:1 ratio in CH_2Cl_2/CH_3OH. As a consequence of the rigidity of the ligand and the octahedral coordination geometry of the Fe^{II} center, only the homochiral T-symmetric Fe_4L_4 cage is formed (Scheme 1), as proven by ^{1}H NMR analysis: only one set of ligand signals is observed (Figure 1, see also Figures S5 and S9). Cage formation was further confirmed by the ESIMS measurement in CH_3CN showing signals for the $[Fe_4L_4]^{8+}$, $[Fe_4L_4OTf]^{7+}$, and $[Fe_4L_4(OTf)_2]^{6+}$ ions (Figure S15). Additionally, a ^{1}H DOSY NMR study



Scheme 1. Synthesis of $[Fe_4L_4(OTf)_8]$ cage **1**; only one ligand structure is shown for clarity.

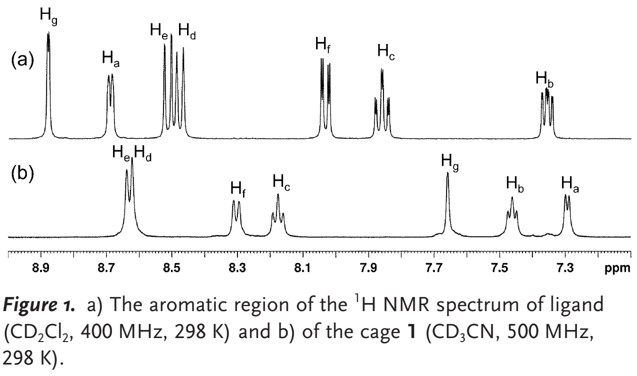


Figure 1. a) The aromatic region of the ^{1}H NMR spectrum of ligand (CD_2Cl_2, 400 MHz, 298 K) and b) of the cage **1** (CD_3CN, 500 MHz, 298 K).

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507295.

unambiguously shows a single band for a single species with a hydrodynamic radius of 1.3 nm (Figures S7d and S11d).

Slow diffusion of Et_2O into a solution of **1** in CH_3CN results in the cage crystallizing in the centrosymmetric monoclinic space group $P2_1/c$ as a pair of ΔΔΔΔ/ΛΛΛΛ cages in the asymmetric unit. The single-crystal X-ray analysis confirms the expected T-symmetric configuration of the cage, with all the metal centers having the same Δ or Λ stereochemistry (Figure 2a). The X-ray structure deviates slightly from the perfect T symmetry, with the Fe⋯Fe distances varying between 14.75 and 15.49 Å (average: 15 Å). The very electron-deficient cavity has a volume of 330 $Å^3$ (calculated by PLATON).[13]

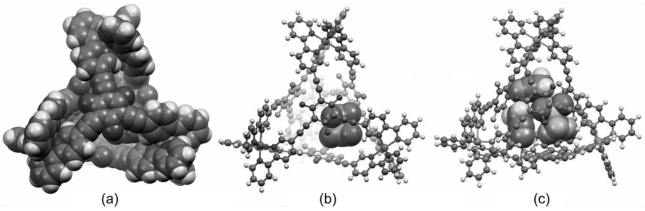

Figure 2. The crystal structure of **1**-ACN [only one cage, ΛΛΛΛ-**1**, is shown in (a) and (b)] and the molecular model of $[(OTf^- + 2\,ACN)\subset\mathbf{1}]$ (c, SPARTAN,[14] MM level).

Despite the poor diffraction quality of the crystals, the X-ray structure unambiguously reveals one OTf^- ion (Figure 2a,b) entrapped inside each cage. The overall shape and size of the cage determined from the X-ray structure and from molecular modeling studies (Figures S16 and S17) are very similar. As only one triflate anion is found to reside inside the cage, molecular modeling studies of the cage with guest molecules were performed. In the X-ray structure, the triflate anion resides in the cavity close to the corner of the cage, with some unresolvable electron density elsewhere in the cavity, while the molecular modeling study suggests that a triflate anion alone would occupy the center of the cavity (Figure S17). The packing coefficient P_c for only one triflate anion ($V_{OTf} = 86$ $Å^3$) is 0.26, which is much lower than the optimal P_c value of 0.55.[15] The inclusion of two triflate ions would result in a much more reasonable P_c value (0.52), but the charge repulsion would prevent the simultaneous encapsulation of two triflate anions in the cavity. The corner location and the impossibility of encapsulating two anions suggest the inclusion of an auxiliary guest(s). This proposal is supported by the DOSY NMR spectrum, where a signal, possibly originating from entrapped solvent molecules, has the same diffusion coefficient as the cage (Figures S7d and S11d). Molecular modeling studies of a triflate anion and two acetonitrile molecules inside the cavity results in a very similar location of the triflate anion: close to the corner of the cage (Figure 2c).

Encapsulation of one triflate anion inside the cage is supported by the ESIMS spectrum of **1** (Figure S15), in which the ion containing a single triflate anion, $[Fe_4L_4OTf]^{7+}$, is observed as the most abundant signal. The gas-phase collision-induced dissociation (CID) experiment on the $[Fe_4L_4OTf]^{7+}$ ion also clearly shows that the cage breaks before the triflate ion is released, thus unambiguously confirming the endo nature of the triflate anion (Figure 3). Variable-temperature ^{19}F NMR measurements suggest that the OTf^- ion is in fast exchange at room temperature, as indicated by a single signal for the anion. At 253 K, the OTf^- signal splits into two, thus indicating encapsulated and free OTf^- ions (Figure S13).

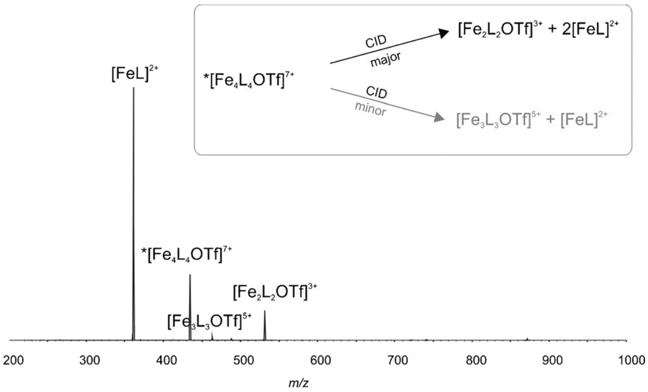

Figure 3. The ESI-QTOF CID spectrum for the isolated $[Fe_4L_4(OTf)]^{7+}$ ion (marked with a star) and its fragmentation pathway.

Interestingly, when changing the crystallization conditions to a slow diffusion of $i$$Pr_2O$ into a CH_3OH solution, unexpected spontaneous resolution of the homochiral cages occurs. Under these conditions, the cage crystallizes in the cubic chiral space group $I23$ and $Z = 2$ (1/12 part of the cage in the asymmetric unit). The cage has perfect T symmetry, with Fe⋯Fe distances of 15.09 Å. Despite the poor crystal quality (the two triflate anions and possible solvent molecules could not be located, see the Supporting Information), the cage is unambiguously the ΔΔΔΔ enantiomer of **1** (Figure S18).[16]

The monoclinic crystal lattice holds a pair of ΔΔΔΔ and ΛΛΛΛ enantiomers (Figure S16), which interact through nesting of the $[Fe(bipy)_3]^{2+}$ moieties of the ΔΔΔΔ cage in the open side of the ΛΛΛΛ cage. These ΔΔΔΔ/ΛΛΛΛ nesting pairs are then connected to the adjacent row of enantiomeric pairs through packing of the $[Fe(bipy)_3]^{2+}$ moieties of the ΛΛΛΛ cages (Figure S19a,b). The third dimension is completed through a weak sideways oriented interaction of the $[Fe(bipy)_3]^{2+}$ moiety with the F_3Ph moiety of the adjacent cage (Figure S19c).

The packing in the chiral cubic $I23$ crystal lattice is completely different, as the lattice contains only ΔΔΔΔ cages, with no nesting between the cages. The four $[Fe(bipy)_3]^{2+}$ moieties of the cage cap the F_3Ph moieties of the four adjacent cages perpendicularly (Figure S20a). Correspondingly, the four F_3Ph moieties of the cage are capped by the $[Fe(bipy)_3]^{2+}$ moieties of four adjacent cages (Figure S20b). These eight tetrahedrally oriented (for one cage) "head-to-wall" interactions result in a chiral MOF-like structure.

Our study introduces a new family of stable electron-deficient tris(bipyridyl) ligands which can form robust M_4L_4 cages with highly electron-deficient cavities. Cage **1** crystallizes as a racemic ΛΛΛΛ/ΔΔΔΔ pair from acetonitrile and entraps one triflate anion inside the cage. In contrast, concentration (crystallization) from methanol results in intermolecular interactions that lead to tetrahedral "head-to-wall" packing of the cages. These interactions do not occur in acetonitrile and result from the solvation of the cages by the solvent methanol molecules. This subsequently leads to spontaneous resolution, with the chiral cubic crystal lattice containing only the ΔΔΔΔ enantiomer.

Acknowledgements

The Academy of Finland (grant nos. 265328 and 263256 to K.R., nos. 284562 and 278743 to E.K.) and the University of Jyväskylä are kindly acknowledged for financial support. Johanna Lind and M. Sc. Esa Haapaniemi are gratefully acknowledged for their help with the MS and NMR experiments. Prof. Janne Ihalainen and Dr. Heli Lehtivuori are acknowledged for their help with CD measurements.

Keywords: cage complexes · chirality · metallosupramolecular chemistry · spontaneous resolution · X-ray crystallography

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14890–14893
Angew. Chem. **2015**, *127*, 15103–15106

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[16] We have not yet succeeded in finding a single crystal of the ΛΛΛΛ enantiomer for X-ray crystal structure determination. All the larger crystals studied turned out to be of the ΔΔΔΔ enantiomer, while the smaller ones did not diffract sufficiently well. These two types of crystals were morphologically different and to investigate the chirality of **1** more thoroughly, we isolated a large number of single crystals (from methanol) and their circular dichroism (CD) was measured. To our disappointment,

the number of isolated single crystals was not sufficient to have sufficient concentration to obtain CD spectra of high enough quality. We also measured the CD spectrum of the whole crystallization batch and no CD signal was obtained, thus indicating that the bulk of crystallization product is indeed a racemic mixture (Figure S21).

Received: August 5, 2015