Host-Guest Chemistry

DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Enantiopure Water-Soluble Fe_4L_6 Cages: Host-Guest Chemistry and Catalytic Activity**

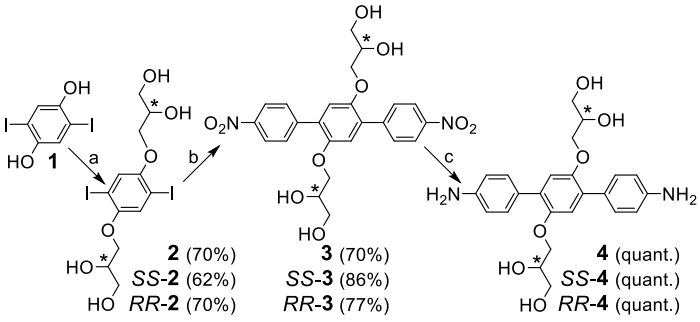
*Jeanne L. Bolliger, Ana M. Belenguer, and Jonathan R. Nitschke**

Host-guest chemistry has its origin in biological processes involving molecular recognition through noncovalent interactions, as for example when substrates bind to enzymes. Over the last decade, organic capsules[1] and self-assembled coordination cages[2] have been prepared that are able to encapsulate a variety of guests, increase the rates of chemical reactions,[1c,3] change the course of reactions involving encapsulated molecules,[2i,4] or shift equilibria to stabilize otherwise unstable species.[5] Self-assembled metal-organic capsules based on chiral ligands are of special interest because they possess a chiral internal void which can not only enable enantioselective guest recognition and separation but can also provide an asymmetric microenvironment for stereoselective reactions.[6]

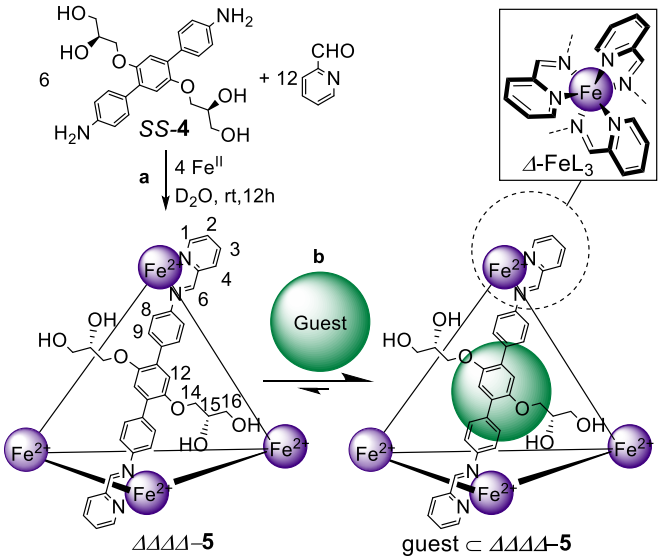
Small guest molecules have been observed[7] to be encapsulated by a water-soluble self-assembled tetrahedral M_4L_6 cage prepared *via* subcomponent self-assembly from amine, aldehyde and Fe^{II} precursors. Here we show how the use of a longer diamino terphenylene subcomponent, bearing chiral glyceryl groups, allows the enantioselective formation of larger water-soluble Fe_4L_6 capsules. This new cage encapsulates a wider range of guests, including larger molecules such as chiral natural products. We also demonstrate our cage's ability to accelerate catalytically the hydrolysis of the acetylcholine esterase inhibitor insecticide dichlorvos, which shares key chemical features with the class of organophosphate chemical warfare agents (CWAs).

Diaminoterphenylenes **4**, *SS*-**4**, and *RR*-**4** were prepared in three steps from diiodohydroquinone **1** as shown in Scheme 1. The studies described below were carried out using aqueous stock solutions of *ΔΔΔΔ*-**5** (or *ΛΛΛΛ*-**5** or **5**) prepared from enantiopure *SS*-**4** (or *RR*-**4** or **4**), 2-formylpyridine, and $Fe^{II}SO_4$ in a 6 : 12 : 4 ratio (Scheme 2). Experimental details and characterization data are provided in the Supporting Information (SI).

A solution of the deep purple capsule *ΔΔΔΔ*-**5** gave FTICR mass spectra consistent with an $[Fe_4L_6]^{8+}$ formulation (SI Fig. SS09). Its hydrodynamic radius, determined from DOSY NMR, was 15.25 (± 0.62) Å, which is consistent with the value of 16.1 Å derived from the model showin in Figure 1. This model was energy-minimized using the universal force field (UFF) of ArgusLabs[9] (SI Fig. S005).



Scheme 1. (a) i. NaOH, EtOH, ii. 3-chloro-1,2-propanediol; (b) 4-nitrophenylboronic acid, K_2CO_3, 0.05 mol% [2,6-bis[(di-1- piperidinyl-phosphino)amino]phenyl] palladium(II) chloride[8]; (c) H_2, 10% Pd / C.



Scheme 2. **a**) Enantioselective formation of *ΔΔΔΔ*-**5** from *SS*-**4**, 2-formylpyridine, and $Fe^{II}SO_4$ by subcomponent self-assembly; **b**) Host guest chemistry of *ΔΔΔΔ*-**5**. Top right: *Δ*–FeL_3 corner.

The shortest $Fe^{II}\cdots Fe^{II}$ distance of *ΔΔΔΔ*-**5** is calculated to be approximately 17.1 Å while the bisbidentate ligand forming the edge of the tetrahedron has a total length of approximately 26.3Å (distance $H^2\cdots H^{2'}$; Scheme 2). We infer that the glyceryl substituents not only render the cage water soluble but also serve to close the faces of the cage, thereby forming a hydrophobic cavity with the glyceryl hydroxy groups directed outward. Based on the molecular model, the volume of the cavity of *ΔΔΔΔ*-**5** was calculated to be 418 $Å^3$. This calculation employed a virtual probe with a radius of 3.0 Å (instead of the usual 1.4 Å), which was the smallest size that remained in the cavity throughout the calculations

[*] Dr. Jeanne L. Bolliger, Dr. Ana M. Belenguer, Dr. Jonathan R. Nitschke, Department of Chemistry, University of Cambridge Lensfield Road, Cambridge, CB2 1EW, UK
E-mail: jrn34@cam.ac.uk
Homepage: http://www-jrn.ch.cam.ac.uk

[**] This work was supported by the Swiss National Science Foundation (SNSF) and the European Research Council. We thank the EPSRC Mass Spectrometry Service at Swansea for conducting FT-ICR MS experiments.

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

(SI Fig. S008). We would therefore expect the void of *ΔΔΔΔ*-**5** to exceed our calculated value.

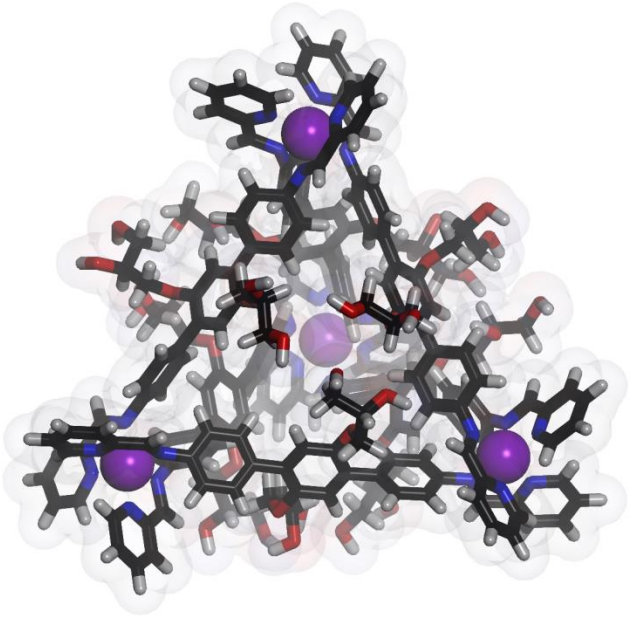


Figure 1. Molecular model of *ΔΔΔΔ*-**5** from molecular mechanics calculations with ArgusLabs through the universal force field (UFF).

We found that the stereochemistry of the glyceryl groups dictated the handedness of the iron(II) stereocenters, despite the distance between these stereochemical elements. The capsules formed from the enantiopure subcomponents *SS*-**4** and *RR*-**4** gave rise to mirror-image CD spectra (SI Fig. S004) indicating enantioselective formation of a $[M_4L_6]^{8+}$ cage with all the metal centers having either Δ or Λ configuration.[2d,6a] By comparing the sign of the Cotton effect at the MLCT transition with observations for similar $Fe^{II}(diimine)_3$ complexes[10] and $[Fe_4L_6]^{8+}$ capsules,[11] we were able to infer that subcomponent *SS*-**4** formed *ΔΔΔΔ*-**5** and its enantiomer *RR*-**4** led to the formation of *ΛΛΛΛ*-**5**. The use of diamine **4**, prepared from racemic starting material, resulted in a mixture of capsules **5**, which exhibited no optical activity (SI Fig. S004).

The large hydrophobic cavities of water-soluble metal-organic capsules *ΔΔΔΔ*-**5**, *ΛΛΛΛ*-**5**, and **5** were expected to bind a variety of hydrophobic guest molecules (Scheme 2b),[1c,4,5a,12] as was observed. The characteristics of the three classes of guests (Figure 2a-c), which are encapsulated in *ΔΔΔΔ*-**5**, are detailed below (more extensive discussion can be found in the SI); divisions between classes are not sharp. We infer that non-encapsulated molecules (Figure 2d) are either too large or too hydrophilic to bind.

The first class of guests (Figure 2a) consists of the largest molecules that can fit within the host cavity. None of these guests were observed to saturate the available host population. The addition of an excess (15-30 equiv) of one of these molecules to an aqueous solution of *ΔΔΔΔ*-**5** resulted in the appearance of a new set of peaks attributed to the guest, although none of these molecules displayed sufficient water solubility to allow their ^{1}H NMR spectra to be recorded in D_2O in the host's absence. Integration of the guest peaks indicated ca. 18% encapsulation of cyclododecane, and 45% of 1,3,5-triisopropylbenzene (Table S1 in the SI provides a complete list). DOSY measurements indicated that the host and guests of this class diffused at rates comparable to that of the free host (Table S2), and nOe cross peaks were observed between host and guest signals.

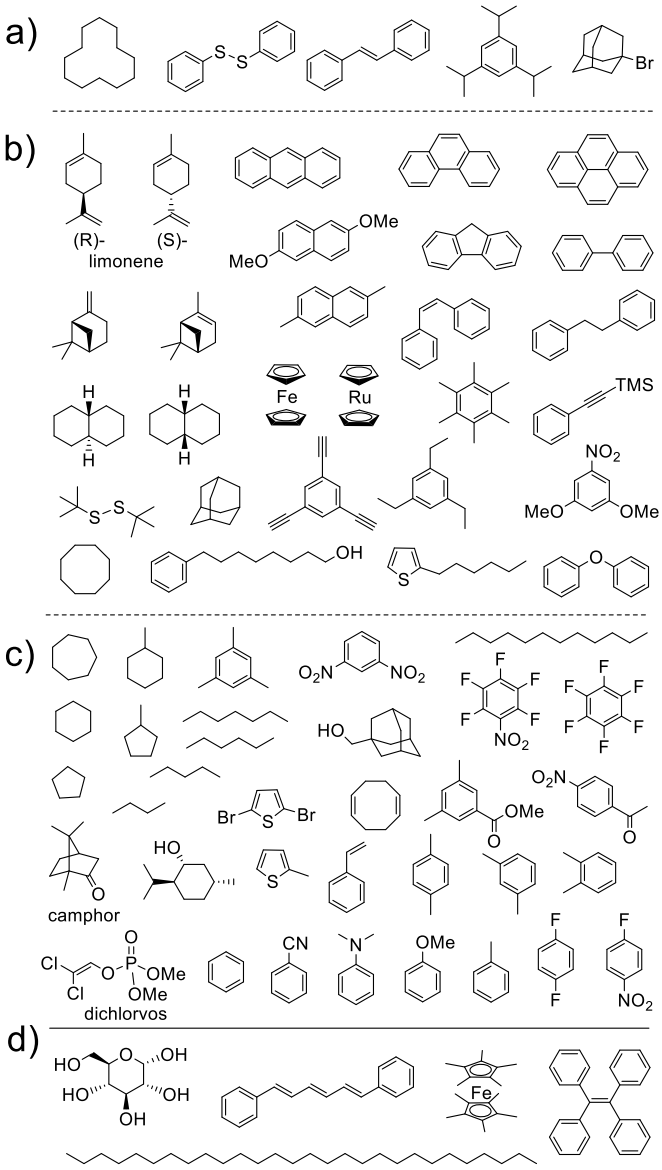


Figure 2. Prospective guest molecules for host *ΔΔΔΔ*-**5**: **a)** larger hydrophobic guests that bound weakly (slow exchange by NMR); **b)** medium-sized hydrophobic guests that bound strongly (slow exchange by NMR); **c)** smaller guests for which fast exchange was observed; **d)** compounds that were not encapsulated.

The second class of guests consists of slightly smaller, hydrophobic molecules (Figure 2b). These molecules appear to be suitably-sized for the void of *ΔΔΔΔ*-**5**, forming 1:1 host-guest complexes. Only one species was observed in solution, assigned to guest ⊂ *ΔΔΔΔ*-**5**. In DOSY spectra guests of this class were observed to diffuse at the same rate as the host (Table S2); the observation of host-guest nOe cross peaks lends further support for the inference of encapsulation. The proton signals of these hydrophobic guests experienced an upfield shift compared to the guests' chemical shifts in the absence of host; this observation is consistent with what has been observed in other cases of hydrophobic guest binding in water.[2i,5c,6b,7]

The third class of guests (Figure 2c) are either small (cyclopentane), water-soluble (dichlorvos), or both (benzene), and

exhibited fast exchange between their free and encapsulated states as observed by ^{1}H NMR and DOSY experiments. NOe cross peaks indicated encapsulation of these guest molecules. Further discussion of the cycloalkanes, a representative set of guests in this class, is presented in the SI (Fig. S011).

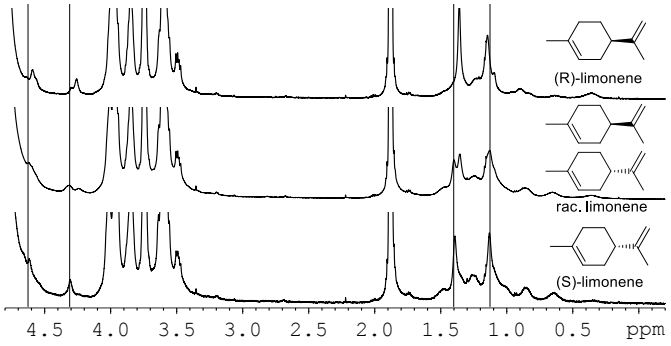


Figure 3. ^{1}H NMR spectra (500 MHz, D_2O) of diastereomeric host-guest complexes upon encapsulation of chiral guests in *ΔΔΔΔ*–**5**. Top: (R)-limonene ⊂ *ΔΔΔΔ*–**5**; middle: diastereomeric mixture (R)-limonene ⊂ *ΔΔΔΔ*–**5** and (S)-limonene ⊂ *ΔΔΔΔ*–**5**; bottom: (S)-limonene ⊂ *ΔΔΔΔ*–**5.**

Host *ΔΔΔΔ*-**5** was observed to interact differentially with the two enantiomers of limonene, as shown by the ^{1}H NMR spectra of Figure 3. The diastereomeric host-guest complexes (*R*)-limonene ⊂ *ΔΔΔΔ*–**5** and (*S*)-limonene ⊂ *ΔΔΔΔ*–**5** enable distinction of both enantiomeric guests, thereby allowing the host to be used as an encapsulative chiral shift reagent. When racemic limonene was used, both diastereomeric host-guest complexes were observed by ^{1}H NMR, but preferential encapsulation of one enantiomer over the other was not observed at 298 K or 278K.

Since *ΔΔΔΔ*-**5** possesses a large cavity in combination with flexible glyceryl groups that surround the pores on the faces of the tetrahedral M_4L_6 capsule, we were not surprised to observe fast exchange with small organic guests for which a smaller rigid M_4L_6 capsule would appear to be more suitable.[7] Even large, slowly-exchanging guests were observed to be fully encapsulated after less than one hour, however. We infer the flexible glyceryl substituents to allow *ΔΔΔΔ*-**5** both to dynamically open its pores and to adapt the volume of its void to the size of the encapsulated guest, thus enabling the binding of guests too large for optimal encapsulation in accordance with the 55% rule.[13]

Organophosphates are widely used as pesticides and CWAs and much effort has been devoted to the investigation of new methods of hydrolysis of organophosphates to less toxic compounds.[14] As shown in Figure 4, we observed *ΔΔΔΔ*-**5** to act as a catalyst in the hydrolysis of the pesticide and CWA simulant dichlorvos, generating the products dimethyl phosphoric acid (DMP, major) and dichlorovinylmethyl phosphoric acid (DVMP, minor). In the presence of 1 mol% of *ΔΔΔΔ*-**5**, an increased rate of hydrolysis of dichlorvos at pH 7 was observed.

Control experiments involving the addition of 12 mol% of 2-formylpyridine, 6 mol% of *SS*-**4**, 4 mol% of $FeSO_4$, or 4 mol% of a mononuclear iron complex formed from 2-formylpyridine and aniline to the buffered solution at pH 7 showed no acceleration of the rate of hydrolysis of dichlorvos (SI Figs. S013 through S019). Similarly, acceleration of dichlorvos hydrolysis was not observed in the presence of the tightly bound hydrophobic guests cyclooctane or bibenzyl, which we infer to have blocked the cavity of *ΔΔΔΔ*-**5**. The addition of the slightly-water-soluble guest 1-adamantylmethanol reduced the rate of *ΔΔΔΔ*-**5**-catalyzed dichlorvos hydrolysis only to a small degree (Figs. S014 and S015 in the SI). Although dichlorvos is water-soluble and observed to undergo rapid exchange between bound and unbound states on the NMR timescale, nOe cross-peaks indicated the formation of a host-guest complex (SI Fig. S149). We infer that the hydrolysis products DMP and DVMP most likely are not encapsulated because their observed chemical shifts do not change in the presence of *ΔΔΔΔ*-**5** (SI Figs. S017b and S017c).

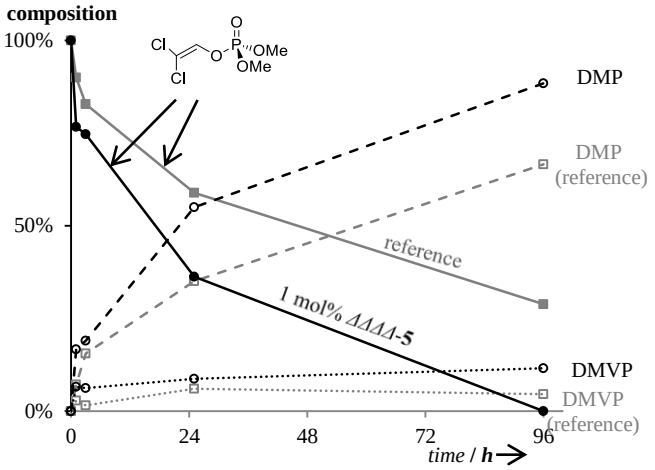


Figure 4. Hydrolysis of dichlorvos in 0.1M phosphate buffer at pH 7 and 298 K. Gray squares: reference; black circles: in presence of 1 mol% of *ΔΔΔΔ*-**5**. —— dichlorvos — — dimethyl phosphoric acid (DMP) ▪▪▪▪ dichlorovinylmethyl phosphoric acid (DVMP).

Possible mechanistic explanations for this catalytic acceleration include the involvement of the hydroxyl groups in a manner similar to those involved in CWA hydrolysis by cylodextrins[14e] or to the recognition of the CWA Soman recently demonstrated by Sambrook, Gale *et. al*.[15] Polarization of the encapsulated dichlorvos by the positively charged cage molecule would also facilitate nucleophilic attack at the phosphorus center. To our knowledge, this is the first example of use of a metal-organic capsule to increase the rate of hydrolysis of an organophosphate.

In conclusion, we have prepared the new enantiopure cage molecules *ΔΔΔΔ*-**5** and *ΛΛΛΛ*-**5** by subcomponent self-assembly. Considering that the chiral centers are remote from the metal corners, the formation of a single cage diastereomer is remarkable. Cage *ΔΔΔΔ*-**5** was observed to bind a wide range of organic guests, enabling distinction between the enantiomers of a chiral organic guest. Host *ΔΔΔΔ*-**5** also served as a catalyst for the hydrolysis of the neurotoxic organophosphate dichlorvos.

In future work we will explore enantioselective encapsulation of chiral guests and investigate the binding and hydrolysis of other organophosphates with *ΔΔΔΔ*-**5** and its analogs.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: supramolecular chemistry · chirality · organophosphates · self-assembly · host-guest systems

[1] a) M. W. Schneider, I. M. Oppel, A. Griffin, M. Mastalerz, *Angew. Chem.* **2013**, DOI 10.1002/ange.201208156; *Angew. Chem.Int. Ed.*

2013, DOI 10.1002/anie.201208156; b) K. Kondo, A. Suzuki, M. Akita, M. Yoshizawa, *Angew. Chem.* 2013, *125*, 2364-2368; *Angew. Chem. Int. Ed*. **2013**, *52*, 2308–2312; c) T. Taira, D. Ajami, J. Rebek, *Chem. Commun.* **2012**, *48*, 8508–8510; d) Y. Hua, R. O. Ramabhadran, J. A. Karty, K. Raghavachari, A. H. Flood, *Chem. Commun.* **2011**, *47*, 5979–5981; e) M.-K. Chung, K. Severin, S. J. Lee, M. L. Waters, M. R. Gagné, *Chem. Sci.* **2011**, *2*, 744–747; f) J. A. Riddle, X. Jiang, D. Lee, *Analyst* **2008**, *133*, 417–422; g) T. Mitra, K. E. Jelfs, M. Schmidtmann, A. Ahmed, S. Y. Chong, D. J. Adams, A. I. Cooper, *Nat Chem* **2013**, DOI 10.1038/nchem.1550.

[2] a) M. Han, R. Michel, B. He, Y.-S. Chen, D. Stalke, M. John, G. H. Clever, *Angew. Chem.* **2013**, *125*, 1358-1362; *Angew. Chem. Int. Ed*. **2013**, *52*, 1319–1323; b) N. J. Young, B. P. Hay, *Chem. Commun*. **2013**, *49*, 1354–1379; c) R. W. Troff, R. Hovorka, T. Weilandt, A. Lützen, M. Cetina, M. Nieger, D. Lentz, K. Rissanen, C. A. Schalley, *Dalton Trans*. **2012**, *41*, 8410–8420; d) O. Chepelin, J. Ujma, X. Wu, A. M. Z. Slawin, M. B. Pitak, S. J. Coles, J. Michel, A. C. Jones, P. E. Barran, P. J. Lusby, *J. Am. Chem. Soc.* **2012**, *134*, 19334–19337; e) X.-P. Zhou, J. Liu, S.-Z. Zhan, J.-R. Yang, D. Li, K.-M. Ng, R. W.-Y. Sun, C.-M. Che, *J. Am. Chem. Soc*. **2012**, *134*, 8042–8045; f) S. Turega, M. Whitehead, B. R. Hall, M. F. Haddow, C. A. Hunter, M. D. Ward, *Chem. Commun.* **2012**, *48*, 2752; g) H. Takezawa, T. Murase, M. Fujita, *J. Am. Chem. Soc*. **2012**, *134*, 17420–17423; h) G. H. Clever, W. Kawamura, M. Shionoya, *Inorg. Chem.* **2011**, *50*, 4689–4691; i) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88.

[3] a) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100–103; b) D. Samanta, S. Mukherjee, Y. P. Patil, P. S. Mukherjee, *Chem. Eur. J*. **2012**, *18*, 12322–12329.

[4] M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251–254.

[5] a) W. M. Hart-Cooper, K. N. Clary, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2012**, *134*, 17873–17876; b) P. Mal, B. Breiner, K. Rissanen, J. R. Nitschke, *Science* **2009**, *324*, 1697–1699; c) L. Trembleau, J. Rebek, *Science* **2003**, *301*, 1219–1220.

[6] a) T. Liu, Y. Liu, W. Xuan, Y. Cui, *Angew. Chem.* **2010**, *122*, 4215-4218; *Angew. Chem. Int. Ed*. **2010**, *49*, 4121–4124; b) J. M. Rivera, T. Martín, J. Rebek, *Science* **1998**, *279*, 1021–1023; c) M. Albrecht, E. Isaak, M. Baumert, V. Gossen, G. Raabe, R. Froehlich, *Angew. Chem.* **2011**, *123*, 2903-2906; *Angew. Chem. Int. Ed.* **2011**, *50*, 2850–2853; d) C. J. Brown, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2009**, *131*, 17530–17531; e) T. D. Hamilton, L. R. MacGillivray, *Cryst. Growth Des.* **2004**, *4*, 419–430.

[7] P. Mal, D. Schultz, K. Beyeh, K. Rissanen, J. R. Nitschke, *Angew. Chem.* **2008**, *120*, 8421-8425; *Angew. Chem. Int. Ed.* **2008**, *47*, 8297–8301.

[8] a) J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem.* **2007**, *119*, 6634-6637; *Angew. Chem. Int. Ed.* **2007**, *46*, 6514–6517; b) J. L. Bolliger, C. M. Frech, *Adv. Synth. Catal.* **2010**, *352*, 1075–1080.

[9] M. Thompson, *ArgusLab*, Planaria Software LLC, Seattle,WA, **1996**.

[10] S. E. Howson, L. E. N. Allan, N. P. Chmel, G. J. Clarkson, R. van Gorkum, P. Scott, *Chem. Commun.* **2009**, 1727–1729.

[11] N. Ousaka, J. K. Clegg, J. R. Nitschke, *Angew. Chem.* **2012**, *124*, 1493-1497; *Angew. Chem. Int. Ed.* **2012**, *51*, 1464–1468.

[12] a) H. Gan, B. C. Gibb, *Chem. Commun.* **2012**, *48*, 1656–1658; b) A. Ustinov, H. Weissman, E. Shirman, I. Pinkas, X. Zuo, B. Rybtchinski, *J. Am. Chem. Soc.* **2011**, *133*, 16201–16211.

[13] S. Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016–1022.

[14] a) Z. Radić, T. Dale, Z. Kovarik, S. Berend, E. Garcia, L. Zhang, G. Amitai, C. Green, B. Radić, B. M. Duggan, D. Ajami, J. Rebek, P, Taylor, *Biochem. J.* **2013**, *450*, 231–242; b) P.-C. Tsai, N. Fox, A. N. Bigley, S. P. Harvey, D. P. Barondeau, F. M. Raushel, *Biochemistry* **2012**, *51*, 6463–6475; c) M. M. Ibrahim, G. A. M. Mersal, *J. Inorg. Biochem.* **2010**, *104*, 1195–1204; d) M. Erdem, R. Say, A. Ersöz, A. Denizli, H. Türk, *React. Funct. Polym.* **2010**, *70*, 238–243; e) S. Müller, M. Koller, R. Le Provost, O. Lafont, F. Estour, T. Wille, H. Thiermann, F. Worek, G. Reiter, *Toxicol. Lett.* **2011**, *200*, 53–58.

[15] M. R. Sambrook, J. R. Hiscock, A. Cook, A. C. Green, I. Holden, J. C. Vincent, P. A. Gale, *Chem. Commun.* **2012**, *48*, 5605–5607.

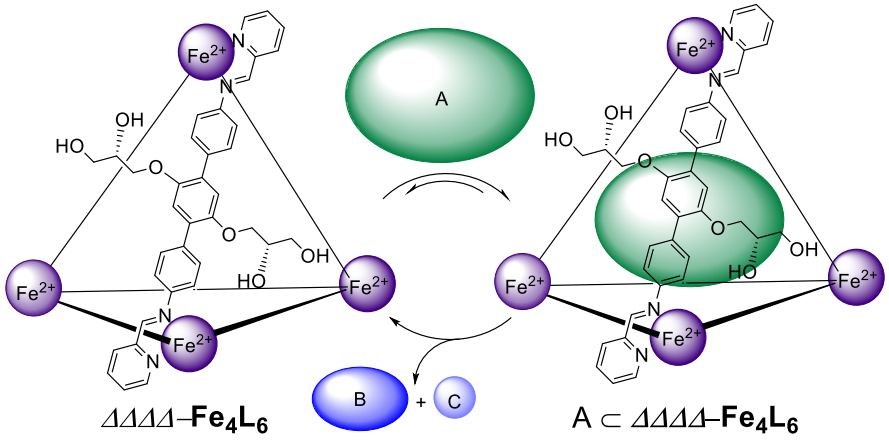
Entry for the Table of Contents

Host-Guest Chemistry

Jeanne L. Bolliger, Ana M. Belenguer, and Jonathan R. Nitschke*

Page – Page

Enantiopure Water-Soluble Fe_4L_6 Cages: Host-Guest Chemistry and Catalytic Activity



Remote control over enantioselective self-assembly: The new enantiopure cage molecule $\Delta\Delta\Delta\Delta$-5 (and its enantiomer, $\Lambda\Lambda\Lambda\Lambda$-5) was prepared by subcomponent self-assembly. It is capable of binding a wide range of organic guests in its cavity and distinguishing between the enantiomers of a chiral organic guest. Host $\Delta\Delta\Delta\Delta$-5 also serves as a catalyst for the hydrolysis of the neurotoxic organophosphate dichlorvos.