VIP Host–Guest Chemistry

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Enantiopure Water-Soluble $[Fe_4L_6]$ Cages: Host–Guest Chemistry and Catalytic Activity**

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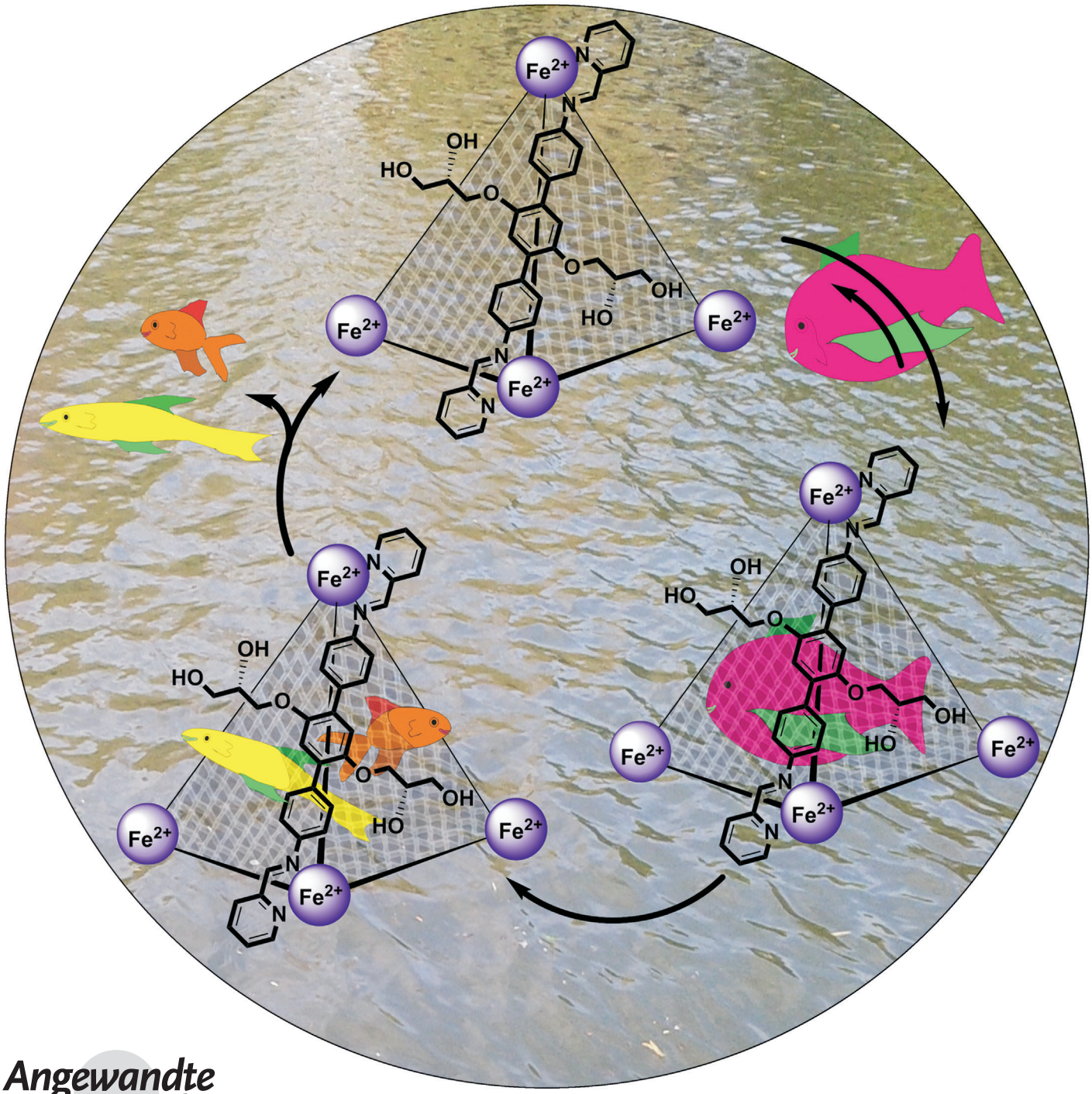

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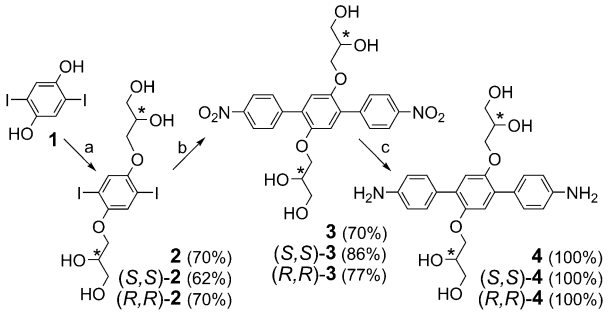
Host–guest chemistry has its origin in biological processes involving molecular recognition through noncovalent interactions, as for example when substrates bind to enzymes. Over the last decade, organic capsules[1] and self-assembled coordination cages[2] have been prepared that are able to encapsulate a variety of guests, increase the rates of chemical reactions,[1c,3] change the course of reactions involving encapsulated molecules,[2i,4] or to stabilize otherwise unstable species.[5] Self-assembled metal–organic capsules based on chiral ligands are of special interest because they have a chirotopic 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 by subcomponent self-assembly from amine, aldehyde and Fe^{II} precursors. Herein 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).

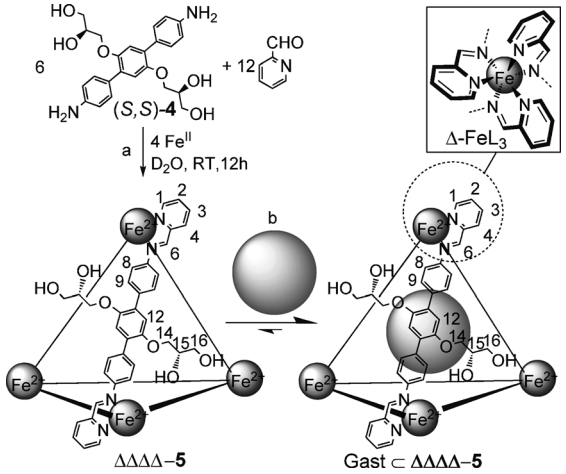
Diaminoterphenylenes **4**, (*S*,*S*)-**4**, and (*R*,*R*)-**4** were prepared in three steps from diiodohydroquinone (**1**) as shown in Scheme 1. The studies described below were carried out using aqueous stock solutions of ΔΔΔΔ-**5** (or ΛΛΛΛ-**5** or **5**) prepared from enantiopure (*S*,*S*)-**4** (or (*R*,*R*)-**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.

A solution of the deep-purple capsule ΔΔΔΔ-**5** gave FTICR mass spectra consistent with an $[Fe_4L_6]^{8+}$ formulation (Figure S009 in the Supporting Information). Its hydrodynamic radius, determined from DOSY NMR spectroscopy, was (15.25 ± 0.62) Å, which is consistent with the value of 16.1 Å derived from the model shown in in Figure 1. This model was energy-minimized using the universal force field (UFF) of ArgusLabs[9] (Figure S005).

The shortest $Fe^{II}\cdots Fe^{II}$ distance of ΔΔΔΔ-**5** is calculated to be approximately 17.1 Å while the bis-bidentate ligand forming the edge of the tetrahedron has a total length of approximately 26.3 Å (distance $H^2\cdots H^2$; Scheme 2). We infer



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



Scheme 2. a) Enantioselective formation of ΔΔΔΔ-**5** from (*S*,*S*)-**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.

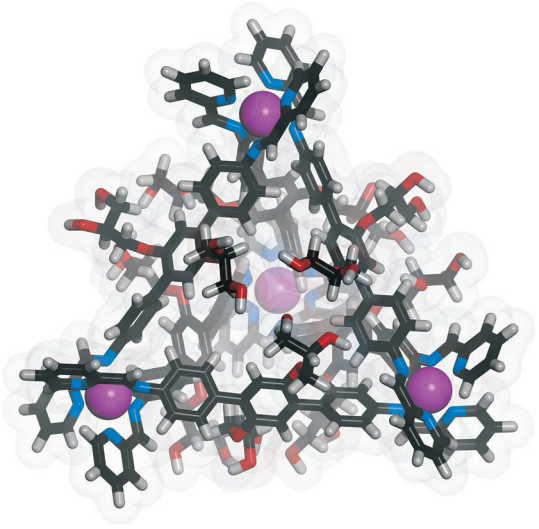


Figure 1. Molecular model of ΔΔΔΔ-**5** from molecular mechanics calculations with ArgusLabs through the universal force field (UFF). Black C, gray H, violet Fe, blue N, red O.

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that the glyceryl substituents not only make 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 (Figure S008). We would therefore expect the void of ΔΔΔΔ-**5** to exceed our calculated value.

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 (*S*,*S*)-**4** and (*R*,*R*)-**4** gave rise to mirror-image circular dichroism (CD) spectra (Figure 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 metal-to-ligand charge-transfer (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 (*S*,*S*)-**4** formed ΔΔΔΔ-**5** and its enantiomer (*R*,*R*)-**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 (Figure 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 is in the Supporting Information); 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 was observed to saturate the available host population. The addition of an excess (15–30 equivalents) of one of these molecules to an aqueous solution of ΔΔΔΔ-**5** resulted in the appearance of a new set of ^{1}H NMR resonances attributed to the guest, although none of these molecules was sufficiently water soluble to allow their ^{1}H NMR spectra to be recorded in D_2O in the host's absence. Integration of the guest peaks indicated approximately 18% encapsulation of cyclododecane, and 45% of 1,3,5-triisopropylbenzene (Table S1 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 nuclear Overhauser effect (nOe) cross peaks were observed between host and guest signals.

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

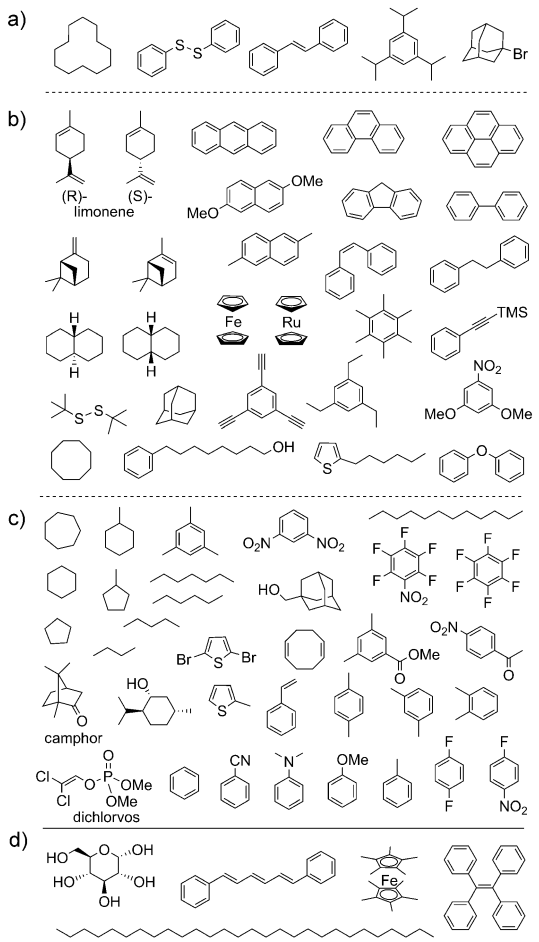

Figure 2. Prospective guest molecules for host ΔΔΔΔ-**5**: a) larger hydrophobic guests that bound weakly (slow exchange as determined by NMR spectroscopy); b) medium-sized hydrophobic guests that bound strongly (slow exchange as determined by NMR spectroscopy); c) smaller guests for which fast exchange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

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 detected 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 in the Supporting Information (Figure S011).

Host ΔΔΔΔ-**5** interacted 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

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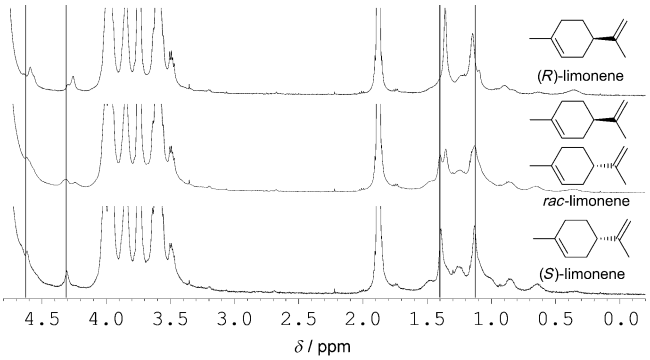

Figure 3. ^{1}H NMR spectra (500 MHz, D_2O) of diastereomeric host–guest complexes upon encapsulation of chiral guests in ΔΔΔΔ-**5**. Top: (*R*)-limonene⊂ΔΔΔΔ-**5**; middle: diastereomeric mixture (*R*)-limonene⊂ΔΔΔΔ-**5** and (*S*)-limonene⊂ΔΔΔΔ-**5**; bottom: (*S*)-limonene⊂ΔΔΔΔ-**5**.

complexes were detected by ^{1}H NMR spectroscopy, but preferential encapsulation of one enantiomer over the other was not observed at 298 K or 278 K.

Since ΔΔΔΔ-**5** has 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. 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, ΔΔΔΔ-**5** acts 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**, the rate of hydrolysis of dichlorvos at pH 7 increased.

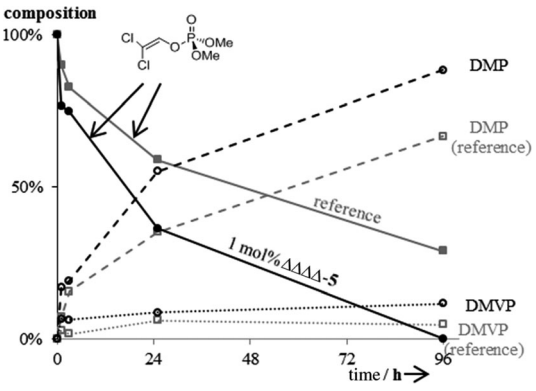

Figure 4. Hydrolysis of dichlorvos in 0.1 M phosphate buffer at pH 7 and 298 K. Gray squares: reference; black circles: in presence of 1 mol % of ΔΔΔΔ-**5**. (—) dichlorvos, (– – –) dimethyl phosphoric acid (DMP), (•••••) dichlorovinylmethyl phosphoric acid (DVMP).

Control experiments involving the addition of 12 mol % of 2-formylpyridine, 6 mol % of (*S*,*S*)-**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 (Figures S013–S019). Similarly, acceleration of dichlorvos hydrolysis was not observed in the presence of the tightly binding 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 only decreased the rate of ΔΔΔΔ-**5**-catalyzed dichlorvos hydrolysis by a small degree (Figures S014 and S015). 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 (Figure S149). We infer that the hydrolysis products DMP and DVMP most likely are not encapsulated because in the NMR spectra their chemical shifts do not change in the presence of ΔΔΔΔ-**5** (Figures S017b and S017c).

Possible mechanistic explanations for this catalytic acceleration include the involvement of the hydroxy 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 the 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 the enantioselective encapsulation of chiral guests and investigate the binding and hydrolysis of other organophosphates with ΔΔΔΔ-**5** and its analogues.

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[1] a) M. W. Schneider, I. M. Oppel, A. Griffin, M. Mastalerz, *Angew. Chem.* **2013**, *125*, 3699 – 3703; *Angew. Chem. Int. Ed.* **2013**, *52*, 3611 – 3615; 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.

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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**, *5*, 276 – 281.

[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 – 2754; 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.

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