[Fe₄L₆]⁸⁺ Cages: Encapsulation and Catalytic Degradation of an Insecticide

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Abstract: Chiral bis(diimine) ligands (derived from chiral enantiopure diamines and 2-formylpyridine) enantioselectively self-assemble with an iron (II) salt to either the tetrahedral cage molecule $\Delta\Delta\Delta\Delta$-[Fe₄L₆]⁸⁺ or its enantiomer, $\Lambda\Lambda\Lambda\Lambda$-[Fe₄L₆]⁸⁺. These versatile water-soluble capsules are capable of binding a wide range of organic guests in their large hydrophobic cavities. Among these guests is the neurotoxic insecticide dichlorvos, for which the $\Delta\Delta\Delta\Delta$-[Fe₄L₆]⁸⁺ coordination capsule serves as a competent supramolecular catalyst for its hydrolysis.

Keywords: Catalytic hydrolysis of insecticides · Host–guest chemistry · Organophosphates · Self-assembly · Supramolecular catalysis

1. Introduction

Originating in biological processes, host–guest chemistry has undergone an enormous development since the discovery of cyclodextrins more than 100 years ago, which has culminated in the preparation of many artificial host molecules capable of mimicking the function of natural proteins.[1] Especially in the last two decades, self-assembled hollow polyhedral coordination cages[2] and organic capsules[3] have been shown not only to encapsulate a variety of guests but also to promote reactions inside their cavities. The behavior of chemical systems can change dramatically when one species is encapsulated by another, prompting effects such as a significant increase in reaction rates,[4] a change in the outcome of a reaction,[5] stabilization of reactive compounds due to shifted equilibria,[6] and activation of inert compounds.[7] Self-assembled coordination cages based on chiral ligands are of particular interest because they provide an asymmetric microenvironment for enantioselective guest recognition and stereoselective reactions.[8]

Recently, the Nitschke group has been developing metal–organic subcomponent self-assembly to allow the construction of supramolecular hosts.[9] While this work incorporates the same principles as those used in the self-assembly of smaller water-soluble cage molecules,[6a,10] the larger ligands used here enable a wider range of guests to be encapsulated. These guests include chiral natural products and insecticides.[11]

## 2. Enantioselective Self-Assembly of Water-soluble [Fe₄L₆]⁸⁺ Cages

Stock solutions of the deep purple tetrahedral cage molecule $\Delta\Delta\Delta\Delta$-**2** were prepared in deuterated water from enantiopure *SS*-**1**, 2-formylpyridine, and FeSO₂ in a 6:12:4 ratio *via* subcomponent self-assembly and used without purification for subsequent experiments (Scheme 1).[11] FTICR mass spectrometry measurements were consistent with an [Fe₄L₆]⁸⁺ formulation, and DOSY (Diffusion Ordered Spectroscopy) NMR measurements gave a

hydrodynamic radius, which was in good agreement with the values derived from molecular modeling.[11]

Despite the distance of the glyceryl substituents of *SS*-**1** from the iron corners, we observed that they dictated the handedness of the iron stereocenters in such a way that the diamine subcomponent *SS*-**1** formed enantioselectively the capsule with all the metal centers having Δ-configuration ($\Delta\Delta\Delta\Delta$-**2**). *RR*-**1** resulted in the enantiomeric cage, $\Lambda\Lambda\Lambda\Lambda$-**2**. The mirror-image CD spectra of these two cage solutions is shown in Fig. 1. As expected, the cage solution prepared with the achiral diamine *RS*-**1** exhibited no optical activity.

3. Host–Guest Chemistry

$\Delta\Delta\Delta\Delta$-**2** encapsulates a wide range of organic and organometallic compounds into its large hydrophobic cavity – a selection of these guests are displayed in Scheme 2.[11] Since the corresponding unsubstituted terphenylene cage is neither water-soluble nor binds any guest molecules,[12]
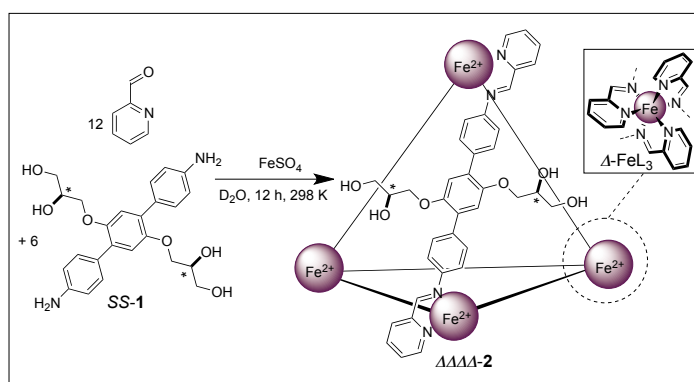
Scheme 1. Enantioselective formation of $\Delta\Delta\Delta\Delta$-**2** in D₂O from *SS*-**1**, 2-formylpyridine, and FeSO₄ by subcomponent self-assembly.

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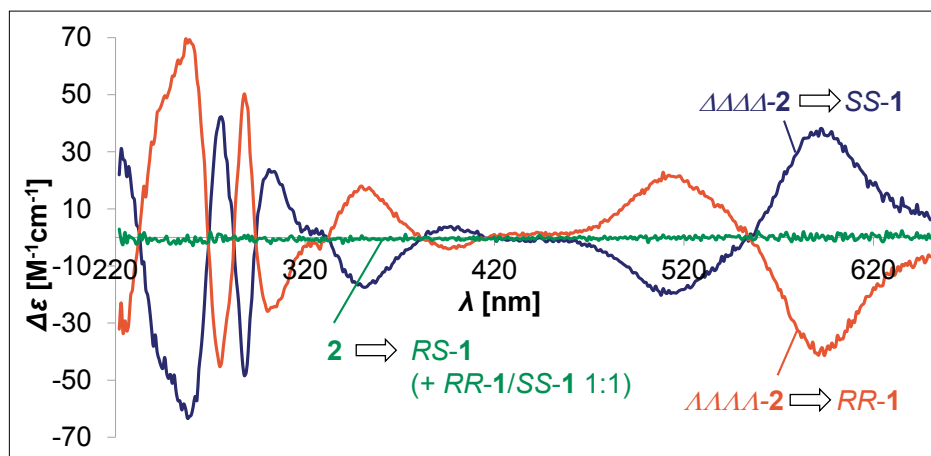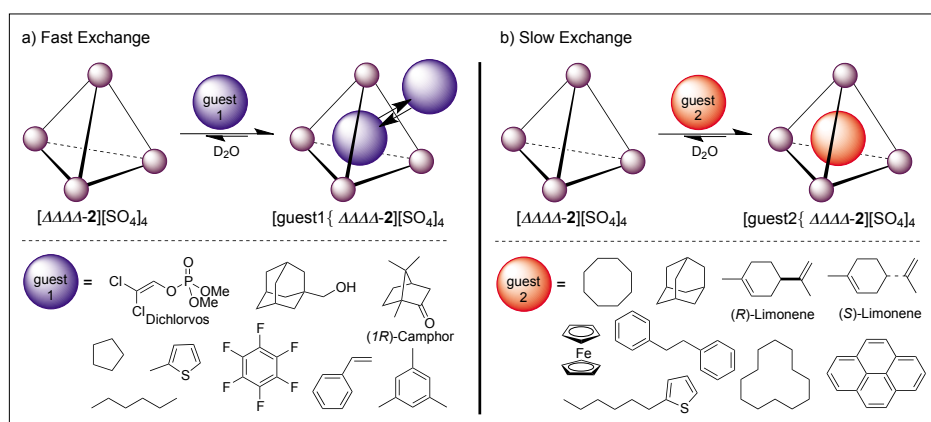E-mail: j.l.bolliger@gmail.com

Fig. 1. CD spectra of $\Delta\Delta\Delta\Delta$-**2** (blue), $\Lambda\Lambda\Lambda\Lambda$-**2** (red), and **2** (green).

Scheme 2. Host-guest chemistry of $\Delta\Delta\Delta\Delta$-**2**. a) Fast exchange on NMR timescale for water-soluble and small guests; b) slow exchange (NMR timescale) for large hydrophobic guests.

we hypothesize that the glyceryl substituents are not only important for the cage's water-solubility but also serve to close the faces of the tetrahedral coordination capsule, with both factors contributing to the encapsulation of neutral guests.

The guest molecules in Scheme 2 can be roughly grouped into two classes. The first class of guests (Scheme 2a) consists of small (*e.g.* cyclopentane) and/or water-soluble molecules (*e.g.* dichlorvos) which undergo fast exchange between their free and encapsulated states as observed by ^{1}H NMR and DOSY experiments. The fast exchange leads to only one averaged set of ^{1}H peaks which are found at a higher magnetic field compared to the chemical shift of these molecules in the absence of $\Delta\Delta\Delta\Delta$-**2**. The NOE cross peaks observed between protons of the cage $\Delta\Delta\Delta\Delta$-**2** and the protons of the encapsulated guest also indicate the presence of the expected host–guest complex. The second class of guests (Scheme 2b) consists of larger hydrophobic molecules which appear to be suitably sized for the void of $\Delta\Delta\Delta\Delta$-**2** and form 1:1 host-guest complexes. Only one species (guest$\subset\Delta\Delta\Delta\Delta$-**2**) was observed in solution by ^{1}H NMR. A typical member of this class is adamantane. When excess water-insoluble adamantane was added to an aqueous solution of $\Delta\Delta\Delta\Delta$-**2**, new ^{1}H NMR signals corresponding to adamantane began to appear; comparison of the integrated intensities of these new peaks with those of the host peaks indicated a 1:1 host:adamantane ratio. DOSY NMR measurements indicated that the adamantane shared the host's rate of diffusion, and strong NOE cross peaks were observed between the protons of the guest molecule adamantane and protons of the host $\Delta\Delta\Delta\Delta$-**2**. The hydrophobic guests of this class do not undergo fast exchange on NMR timescale, as shown in racemic mixtures of (*R*)-limonene and (*S*)-limonene – two sets of peaks (assigned to the two diastereomeric host-guest complexes (*R*)-limonene$\subset\Delta\Delta\Delta\Delta$-**2** and (*S*)-limonene$\subset\Delta\Delta\Delta\Delta$-**2**, respectively) are visible in the ^{1}H NMR spectrum.

4. Encapsulation and Catalytic Hydrolysis of the Insecticide Dichlorvos

Organophosphates are widely used as pesticides and chemical warfare agents (CWA), flame retardants and plasticizers. Considering the serious effects of exposure to organophosphate compounds by inhibition of acetylcholinesterase,[13] it is not surprising that many research groups are investigating new pathways to hydrolyze organophosphates to less toxic compounds. Recently, new catalysts have been developed for the hydrolysis of organophosphates,[14] but apart from examples in which CWA are encapsulated and hydrolyzed by cyclodextrins[15] there are no reports for encapsulation leading to increased rates of hydrolysis of CWA or simulants. We have recently demonstrated that the organophosphate insecticide dichlorvos can not only be encapsulated into a self-assembled cage coordination cage but also that hydrolysis of the toxic compound occurs at an increased rate in the presence of $\Delta\Delta\Delta\Delta$-**2**.[11]

The molecular model of dichlorvos$\subset\Delta\Delta\Delta\Delta$-**2** (Fig. 2) was energy-minimized using the universal force field (UFF) of ArgusLabs.[16] According to this model, dichlorvos has a suitable size for the cavity of $\Delta\Delta\Delta\Delta$-**2** and is encapsulated despite its high water-solubility. These results are corroborated by NOE experiments. Belonging to the first class of guests, we observe at pH 7 fast exchange on NMR timescale with the equilibrium far on the side of the host-guest complex.

In the presence of 1 mol% of $\Delta\Delta\Delta\Delta$-**2** we measure an increased rate of hydrolysis at pH 7 at room temperature compared to a reference sample containing only buffer solution. We believe that $\Delta\Delta\Delta\Delta$-**2** is acting as a supramolecular catalyst in the hydrolysis of dichlorvos to dimethyl phosphate (DMP) and dichloroacetaldehyde (hydrate) or, alternatively, to dichlorovinylmethyl phosphate (DVMP) and methanol (Scheme 3). A possible mechanistic explanation for this catalytic acceleration is
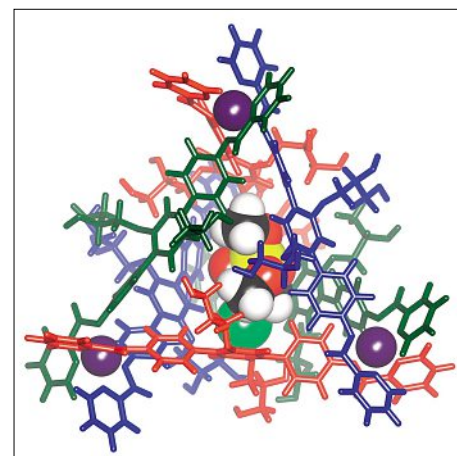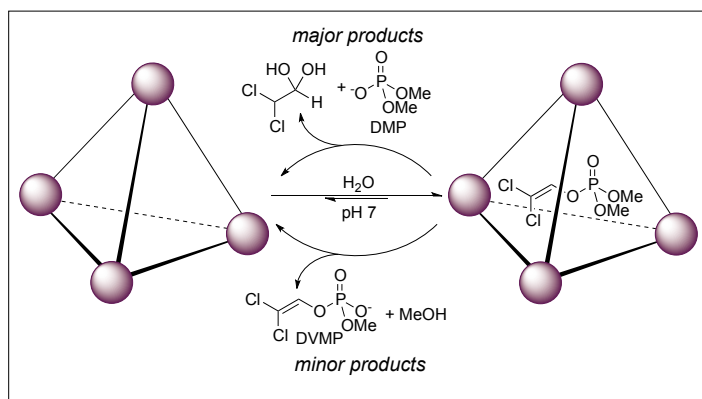

Fig. 2. Molecular model of dichlorvos$\subset\Delta\Delta\Delta\Delta$-**2** from molecular mechanics calculations with ArgusLabs through the universal force field (UFF). Space-filled atoms represent the iron corners (purple) or the encapsulated dichlorvos. Two of the six ligands are colored blue, green, or red, respectively.

Scheme 3. Reversible encapsulation of dichlorvos into $\Delta\Delta\Delta\Delta$-**2** and catalytic hydrolysis at pH 7 to dimethyl phosphate (DMP) and dichloroacetaldehyde (hydrate) as major products and dichlorovinylmethyl phosphate (DVMP) and methanol as minor products.
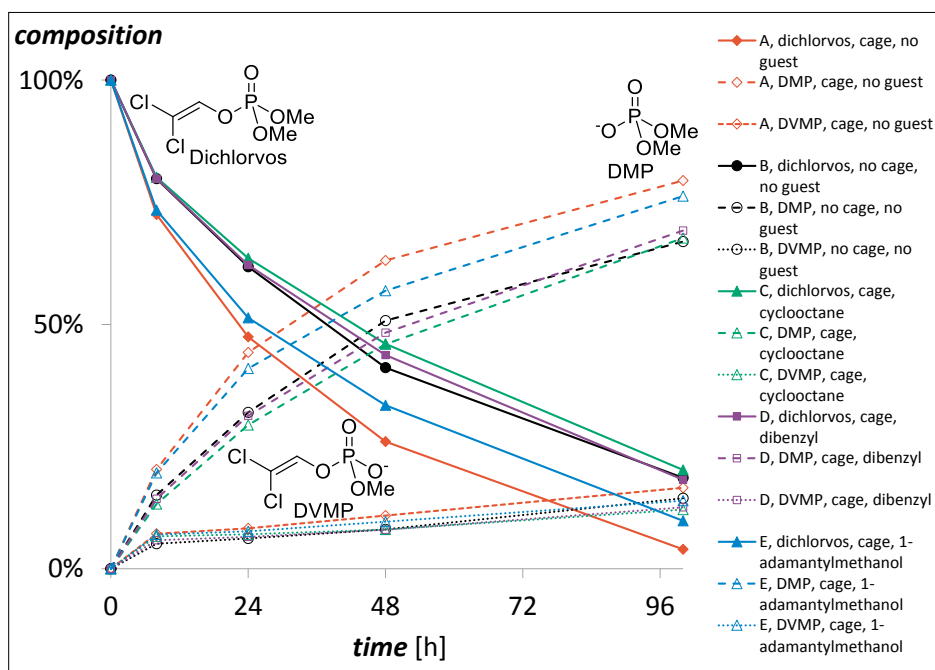

Fig. 3. Hydrolysis of dichlorvos in the presence of competing guests in 0.1 M phosphate buffer at pH 7 and 295 K. A) 0.8 mol% $\Delta\Delta\Delta\Delta$-**2**, B) reference, C) 0.8% cyclooctane⊂$\Delta\Delta\Delta\Delta$-**2**, D) 0.8% dibenzyl⊂$\Delta\Delta\Delta\Delta$-**2**, E) 0.8% $\Delta\Delta\Delta\Delta$-**2** + 1-adamantylmethanol.

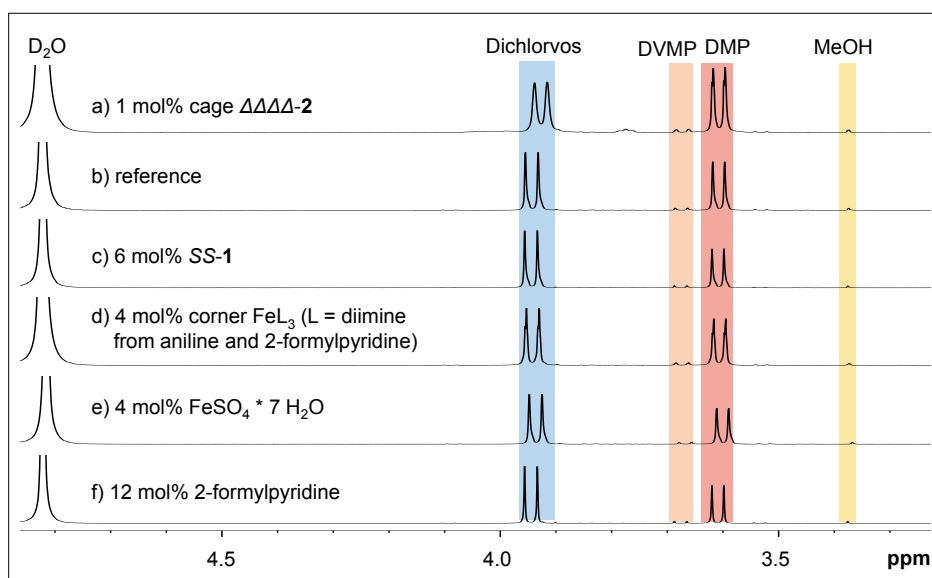

Fig. 4. ^{1}H NMR after 24 h of the hydrolysis of dichlorvos in the presence of 1 mol% of $\Delta\Delta\Delta\Delta$-**2** (a), with no additive (b), or in the presence of an equimolar amount of the corresponding subcomponent of $\Delta\Delta\Delta\Delta$-**2** (c-f), respectively.

thus: the (reversible) encapsulation of the insecticide by the highly positively charged cage molecule leads to the polarization of the phosphorus–oxygen bonds, facilitating a nucleophilic attack at the phosphorus atom and leading to the observed higher rate of hydrolysis in the presence of the cage molecule.

Reference reactions carried out in the presence of competing guests from the first class (1-adamantylmethanol, Scheme 2a) and inhibiting guests belonging to the second class (cyclooctane and dibenzyl, Scheme 2b) support our hypothesis that the encapsulation of dichlorvos into $\Delta\Delta\Delta\Delta$-**2** leads to faster hydrolysis (Fig. 3). The hydrophobic guests cyclooctane (Fig. 3, sample C) and dibenzyl (Fig. 3, sample D) from the second class inhibit the catalytic acceleration by forming a strong host-guest complex with $\Delta\Delta\Delta\Delta$-**2**, thereby preventing dichlorvos from binding and resulting in the same rate of reaction as the reference sample (Fig. 3, sample B). On the other hand, the competing guest 1-adamantylmethanol (1st class, Fig. 3, sample E) was seen to slow the hydrolysis reaction to a rate somewhere between the reference sample (Fig. 3, sample B) and the sample in the presence of pure $\Delta\Delta\Delta\Delta$-**2** (Fig. 3, sample A).

Other control experiments (Fig. 4c–f) were conducted in solutions (buffered to pH 7) of single subcomponents in the same concentration as in the cage solution (Fig. 4a). These experiments showed no effect on the rate of hydrolysis relative to the buffered reference solution (Fig. 4b). Attention is drawn to the upfield shift of the dichlorvos signal in Fig. 4a, indicating encapsulation of the insecticide into $\Delta\Delta\Delta\Delta$-**2**. The signals of hydrolysis products DVMP, DMP, and methanol appear at the same chemical shift as in the reference samples and are believed to be not encapsulated due to their smaller size and also their significantly higher water-solubility. This indicates that our system does not suffer from product inhibition – a common occurrence in supramolecular catalysis.

5. Conclusions

In conclusion, we have prepared the enantiopure cage molecules $\Delta\Delta\Delta\Delta$-**2** and $\Lambda\Lambda\Lambda\Lambda$-**2** by subcomponent self-assembly and studied the host-guest chemistry of $\Delta\Delta\Delta\Delta$-**2** in water. Due to the hydrophobic effect, $\Delta\Delta\Delta\Delta$-**2** binds a wide range of organic guests in its cavity and enables the distinction of chiral organic molecules from their enantiomers by formation of diastereomeric host-guest complexes. The presence of 0.8–1 mol% of $\Delta\Delta\Delta\Delta$-**2** resulted in an increased rate of hydrolysis of dichlorvos, which is to our knowledge

the first example of self-assembled metal-organic cage used for catalytic hydrolysis of a CWA simulant.

[1] a) E. A. Kataev, C. Müller, *Tetrahedron* **2014**, *70*, 137; b) L. A. Joyce, S. H. Shabbir, E. V. Anslyn, *Chem. Soc. Rev.* **2010**, *39*, 3621.

[2] a) N. J. Young, B. P. Hay, *Chem. Commun.* **2013**, *49*, 1354; b) I. S. Tidmarsh, B. F. Taylor, M. J. Hardie, L. Russo, W. Clegg, M. D. Ward, *New J. Chem.* **2009**, *33*, 366; c) T. Sawada, M. Yoshizawa, S. Sato, M. Fujita, *Nat. Chem.* **2009**, *1*, 53; d) S. Turega, M. Whitehead, B. R. Hall, A. J. H. M. Meijer, C. A. Hunter, M. D. Ward, *Inorg. Chem.* **2013**, *52*, 1122; e) R. A. Bilbeisi, J. K. Clegg, N. Elgrishi, X. de Hatten, M. Devillard, B. Breiner, P. Mal, J. R. Nitschke, *J. Am. Chem. Soc.* **2012**, *134*, 5110.

[3] a) T. Taira, D. Ajami, J. Rebek, *Chem. Commun.* **2012**, *48*, 8508; b) T. Mitra, K. E. Jelfs, M. Schmidtmann, A. Ahmed, S. Y. Chong, D. J. Adams, A. I. Cooper, *Nat. Chem.* **2013**, *5*, 276; c) M. W. Schneider, I. M. Oppel, A. Griffin, M. Mastalerz, *Angew. Chem. Int. Ed.* **2013**, *52*, 3611; d) Y. Hua, R. O. Ramabhadran, J. A. Karty, K. Raghavachari, A. H. Flood, *Chem. Commun.* **2011**, *47*, 5979; e) J. Mosquera, S. Zarra, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2014**, *53*, 1556.

[4] a) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100; b) C. J. Hastings, M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2010**, *132*, 6938; c) T. Murase, Y. Nishijima, M. Fujita, *J. Am. Chem. Soc.* **2012**, *134*, 162; d) D. Samanta, S. Mukherjee, Y. P. Patil, P. S. Mukherjee, *Chem. Eur. J.* **2012**, *18*, 12322.

[5] a) Y. Kohyama, T. Murase, M. Fujita, *Chem. Commun.* **2012**, *48*, 7811; b) C. J. Hastings, M. P. Backlund, R. G. Bergman, K. N. Raymond, *Angew. Chem. Int. Ed.* **2011**, *50*, 10570; c) A. G. Salles, S. Zarra, R. M. Turner, J. R. Nitschke, *J. Am. Chem. Soc.* **2013**, *135*, 19143; d) Y. Yamauchi, M. Fujita, *Chem. Commun.* **2010**, *46*, 5897; e) H. Takezawa, T. Murase, M. Fujita, *J. Am. Chem. Soc.* **2012**, *134*, 17420.

[6] a) P. Mal, B. Breiner, K. Rissanen, J. R. Nitschke, *Science* **2009**, *324*, 1697; b) W. M. Hart-Cooper, K. N. Clary, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2012**, *134*, 17873.

[7] Y. Nishioka, T. Yamaguchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2007**, *129*, 7000.

[8] a) C. Zhao, Q.-F. Sun, W. M. Hart-Cooper, A. G. DiPasquale, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2013**, *135*, 18802; b) T. Liu, Y. Liu, W. Xuan, Y. Cui, *Angew. Chem. Int. Ed.* **2010**, *49*, 4121; c) J. M. Rivera, T. Martín, J. Rebek, *Science* **1998**, *279*, 1021; d) C. J. Brown, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2009**, *131*, 17530.

[9] T. K. Ronson, S. Zarra, S. P. Black, J. R. Nitschke, *Chem. Commun.* **2013**, *49*, 2476.

[10] a) P. Mal, D. Schultz, K. Beyeh, K. Rissanen, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2008**, *47*, 8297; b) T. K. Ronson, C. Giri, N. Kodiah Beyeh, A. Minkkinen, F. Topic, J. J. Holstein, K. Rissanen, J. R. Nitschke, *Chem. Eur. J.* **2013**, *19*, 3374; c) M. M. J. Smulders, S. Zarra, J. R. Nitschke, *J. Am. Chem. Soc.* **2013**, *135*, 7039; d) M. M. J. Smulders, J. R. Nitschke, *Chem. Sci.* **2012**, *3*, 785; e) S. Zarra, M. M. J. Smulders, Q. Lefebvre, J. K. Clegg, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2012**, *51*, 6882.

[11] J. L. Bolliger, A. M. Belenguer, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2013**, *52*, 7958.

[12] W. Meng, J. K. Clegg, J. D. Thoburn, J. R. Nitschke, *J. Am. Chem. Soc.* **2011**, *133*, 13652.

[13] S. Karami-Mohajeri, M. Abdollahi, *Hum. Exp. Toxicol.* **2011**, *30*, 1119.

[14] a) P.-C. Tsai, N. Fox, A. N. Bigley, S. P. Harvey, D. P. Barondeau, F. M. Raushel, *Biochemistry (Mosc.)* **2012**, *51*, 6463; b) M. M. Ibrahim, G. A. M. Mersal, *J. Inorg. Biochem.* **2010**, *104*, 1195; c) M. Erdem, R. Say, A. Ersöz, A. Denizli, H. Türk, *React. Funct. Polym.* **2010**, *70*, 238; d) B. Desire, S. Saint-Andre, *Fundam. Appl. Toxicol.* **1986**, *7*, 646.

[15] a) T. Wille, O. Tenberken, G. Reiter, S. Müller, R. Le Provost, O. Lafont, F. Estour, H. Thiermann, F. Worek, *Toxicology* **2009**, *265*, 96; b) F. Estour, S. Letort, S. Müller, R. K. Kalakuntla, R. Le Provost, T. Wille, G. Reiter, F. Worek, O. Lafont, G. Gouhier, *Chem. Biol. Interact.* **2013**, *203*, 202; c) S. Müller, M. Koller, R. Le Provost, O. Lafont, F. Estour, T. Wille, H. Thiermann, F. Worek, G. Reiter, *Toxicol. Lett.* **2011**, *200*, 53.

[16] M. Thomson, ArgusLab, Planaria Software LLC, Seattle WA, **1996**.