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Selective, cofactor-mediated catalytic oxidation of alkanethiols in a self-assembled cage host†

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A spacious Fe(II)-iminopyridine self-assembled cage complex can catalyze the oxidative dimerization of alkanethiols, with air as stoichiometric oxidant. The reaction is aided by selective molecular recognition of the reactants, and the active catalyst is derived from the Fe(II) centers that provide the structural vertices of the host. The host is even capable of size-selective oxidation and can discriminate between alkanethiols of identical reactivity, based solely on size.

Self-assembled metal–ligand cages have been used to promote and catalyze a variety of reactions,[1] from unimolecular rearrangements and cycloadditions,[2] to acid and base-catalyzed additions[3] and organometallic transformations.[4] Encapsulating substrates in host molecules allows a variety of novel reaction behaviors, including rate accelerations,[5] sequestration of reactive intermediates[6] and unusual regioselectivity.[7] Novel outcomes such as size-and-shape or positional selectivity often come from strong binding in an internal cavity. This selectivity comes with a price: often, when exquisite size-selectivity in reactions occurs, then the substrates bind too tightly and turnover can be limited, especially if the hosts are not water-soluble and cannot take advantage of hydrophobic effects.[8]

One other rarity in supramolecular catalysis is the host acting as, or delivering, the active reagent for the reaction. Hosts are mostly used as tiny (''yoctoliter'', in some cases[9]) flasks. Guests are encapsulated and reaction is accelerated due to increased effective concentration. Some cages have internal functional groups,[10] some can be exploited as sensitizers for photochemical reactions[11] and the walls of the vessels can sometimes participate,[12] but mostly, cage hosts just provide separate nanophases for the reaction. Enzymes, on the other hand, actively participate in the reaction, and can exploit metal ion cofactors for the catalyzed processes.[13]

We have recently shown that self-assembled Fe_4L_6 cage complexes can act as hosts for neutral molecules in organic solution, and catalyze polar reactions on the host interior.[14] During our investigations into host-catalyzed thioetherification reactions,[14b] we noticed that oxidative dimerization of alkanethiol nucleophiles was a persistent side reaction that could only be minimized under anaerobic conditions. We then investigated how and why this reaction might occur, and the scope of the process.

The initial test was simple – *n*-octanethiol (**C_8-SH**) was refluxed in CD_3CN in the presence of 5% Fe_4L_6 cage complex **1**[14a,b] for 24 h and monitored by ^1H NMR. After 24 h, all the octanethiol was consumed and only *n*-octyldisulfide could be seen. The cage was mostly intact and the reaction was clean, with no other obvious byproducts. While oxidative disulfide formation is simple and well-known,[15] the rapid reactivity was surprising. As the cage does not decompose, the process must be catalytic, with atmospheric O_2 as stoichiometric oxidant – indeed, if the reaction is repeated under N_2, minimal reaction is seen. The nature of the active catalyst was not obvious, though. While it is obvious that the redox-active Fe(II) ions in the Fe_4L_6 are involved, they are fully saturated in the assembly and have no free coordination sites. No change in oxidation state during the reaction can be seen from the NMR analysis either. The likeliest explanation is that small amounts of Fe(II) ions leach from the assembly, and act as the active catalyst while the bulk of the cage remains intact. We have seen evidence of this phenomenon before when performing post-assembly modifications on Fe-containing cages.[16]

The next step was to see if this was a common phenomenon for Fe-iminopyridine systems, and so we repeated the reaction with **1** and two other differently sized cages: Nitschke's Fe_4L_6 cage **2**,[17] and the Fe_2L_3 helicate **3** (Fig. 1).[18] Again, **C_8-SH** was added to a CD_3CN solution of 5% cage **1** or **2**, or 10% **3** (to ensure the same concentration of Fe) and heated in air. As can be seen in Fig. 2, the reactivity difference is stark – in the presence of **1**, 54% conversion of **C_8-SH** to the corresponding disulfide (**C_8-S)$_2$** is seen after 7.5 h at 80 °C, whereas even at 80 °C for 19 h, minimal (<5%) conversion occurs with either hosts **2** or **3**. In addition, when 25% $Fe(NTf_2)_2$ was added to a solution of **C_8-SH** in CD_3CN and heated for 36 h, no oxidation

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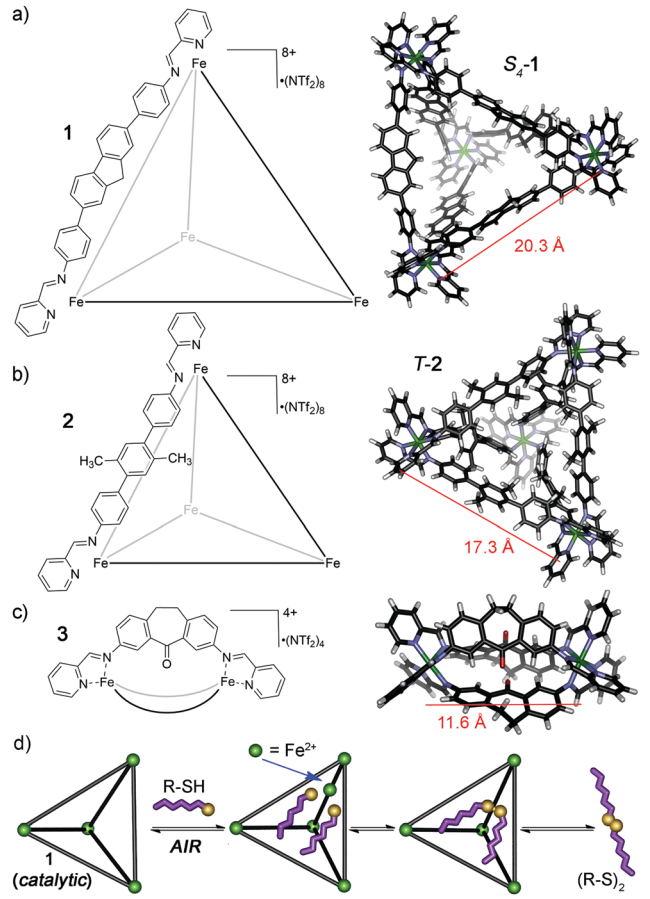


Fig. 1 Self-assembled cage complexes tested. (a) Large Fe_4L_6 host **1**; (b) medium-sized Fe_4L_6 tetrahedron **2**; (c) Fe_4L_6 helicate **3**. (d) Illustration of the oxidation process.

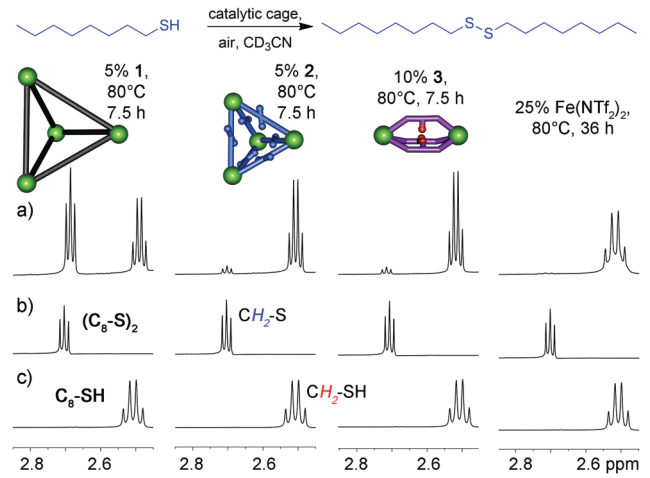


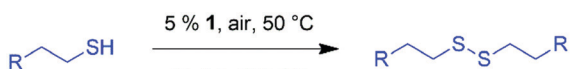
Fig. 2 ^{1}H NMR analysis of the reaction catalyzed by various Fe-containing species. Expansion of the CH_2–S region of the ^{1}H NMR spectra of (a) reaction mixture after reaction for the indicated time; (b) purified disulfide product **(C_8-S)$_2$**; (c) purified thiol starting material **C_8-SH**. CD_3CN, 400 MHz, spectra acquired at 298 K.

product was seen. Oxidation can occur non-catalytically with free Fe^{II} salts under more forcing conditions, but these mild conditions were not sufficient for effective oxidation. Furthermore, adding extra $Fe(NTf_2)_2$ to the cage-catalyzed reaction caused a reduction in conversion (Fig. S7, ESI†). Adding 10, 25 or 50% (with respect to **C_8-SH**) to the **C_8-SH** dimerization reaction with 5% cage **1** gave 35%, 33% and 20% conversion respectively, after 11.5 h at 50 °C.

The large cage **1** evidently displays unusual reactivity, and this is most likely due to its molecular recognition capabilities. The cavity in **1** is much larger than those in **2** or **3** (Fe–Fe distances are shown in Fig. 1), and we have previously shown that it is a strong host for small neutral molecules.[14] Molecular recognition could allow size-selectivity, so we analyzed the relative rate of reaction for differently sized thiols. Six different *n*-alkanethiols were reacted with 5% **1** for 11.5 h at 50 °C in CD_3CN in air, and the observed conversions are shown in Table 1. These conditions were chosen to allow a comparison of the relative rates of reaction. Maximal (>90%) conversion to disulfide product was possible after 22 h reflux in CD_3CN (80 °C), although some decomposition of the cage did occur when heated for extensive periods of time at this temperature. The conversion of the small and medium-sized thiols (**C_5-SH**–**C_{10}-SH**) under the less forcing 50 °C/11.5 h reaction conditions was essentially identical, with 50–60% conversion observed in each case. As the thiol increased in size, however, the efficacy of the process reduced sharply. **C_{11}-SH** was oxidized, albeit slower than C_5–C_{10}, but dodecanethiol was oxidized far more slowly, with only 15% conversion under the conditions.

The binding properties of the different alkanethiols in **1** were analyzed by UV-Vis absorbance spectroscopy. This is the optimal method of determining the association constant and binding stoichiometry for cages such as **1**,[14] which show rapid in/out exchange of neutral small molecule guests on the NMR timescale, making quantitative NMR analysis of the recognition challenging. The alkanethiol guests were no different, and showed rapid in/out exchange by NMR. Each guest was titrated into a 3 μM solution of **1** (or **2**) in CH_3CN, and the changes in absorbance at both 330 and 370 nm (or 275/335 nm for **2**) were recorded and analyzed. In each case, the binding isotherms were fit to both the 1 : 1 and unbiased 1 : 2 binding models and the variances calculated.[19] The significance of the 1 : 2 model was judged based on the inverse ratio of the squared residuals compared to the 1 : 1 model, and quantified *via* *p*-value. The results are summarized in Table 2: for the full fitting details, including fitting curves, variances and error analysis, see ESI.†

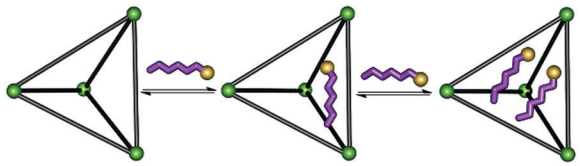
Table 1 Relative reactivity of alkanethiols in cage **1**[a]



Reactant	Conversion, %	Reactant	Conversion, %
C_5-SH	49	**C_{10}-SH**	63
C_6-SH	47	**C_{11}-SH**	43
C_8-SH	54	**C_{12}-SH**	15

[a] Reactions performed at 50 °C, 11.5 h, CD_3CN and analyzed by ^{1}H NMR, concentrations determined using dioxane standard. [**C_x-SH**] = 18.2 mM.

Table 2 Binding affinities of alkanethiols in cage **1**[a]



1 : 2 substrate (**1**)	$K_1 \times 10^3$ M^{-1}	$K_2 \times 10^3$ M^{-1}	α ($4K_2/K_1$)
C_5-SH	2150 ± 650	1.2 ± 3.0	8.7×10^{-4}
C_6-SH	540 ± 130	2.4 ± 1.5	0.018
C_8-SH	174 ± 43	0.78 ± 0.53	0.018

1 : 1 substrate (**1**)	$K_a \times 10^3$ M^{-1}	1 : 1 Substrate (**1**)	$K_a \times 10^3$ M^{-1}
C_{10}-SH	19.7 ± 6.4	**$(C_6\text{-S})_2$**	71.0 ± 14
C_{11}-SH	40.0 ± 19	**$(C_8\text{-S})_2$**	76.1 ± 3.8
C_{12}-SH	2.7 ± 0.6	**$(C_{10}\text{-S})_2$**	27.9 ± 9.4
$(C_3\text{-S})_2$	16.6 ± 2.4	**$(C_{11}\text{-S})_2$**	5.5 ± 0.5
$(C_5\text{-S})_2$	38.8 ± 7.1	**$(C_{12}\text{-S})_2$**	8.4 ± 0.9

1 : 1 substrate (**2**)	$K_a \times 10^3$ M^{-1}
C_6-SH	420 ± 130

[a] In CH_3CN, [**1**], [**2**] = 1.5 μM, absorbance changes measured at 330 nm and 370 nm for **1**, and 278/335 nm for **2**.[19]

The binding affinities of all the alkanethiols for cage **1** were quite high (as we have seen for other guests),[14b] in the range of 2000–40 000 M^{-1}. Most interestingly, the medium-sized (**C_5-SH–C_8-SH**) thiols fit best to a 2 : 1 model, with negative cooperativity. **C_5-SH** had the strongest affinity, but the affinities are broadly similar. As the thiols increase in size (**C_{10}-SH–C_{12}-SH**), error analysis indicates that the 1 : 1 binding motif is more favored, and **C_{12}-SH** has by far the lowest affinity for **1**. As the analysis is based on variance analysis to a fitting model, it is important to state that both modes of binding are possible in each case, just less favored: the cavity of **1** is theoretically big enough to fit two copies of **C_{12}-SH**.

The larger products only fit to a 1 : 1 model, as might be expected. The binding affinities of the products correlate nicely with the observation that "mid-sized" thiols react fastest in **1**: the strongest affinities are for **$(C6\text{-S})_2$** and **$(C_8\text{-S})_2$**, whereas smaller (C_3, C_5) and larger (C_{10}–C_{12}) products are less favored. Importantly, when thiols, even small ones such as **C_6-SH**, were titrated into xylene cage **2**, the binding only fit to a 1 : 1 model, and 2 : 1 binding was highly unlikely. Minimized structures (SPARTAN, AM 1 forcefield) are shown in Fig. 3, and support this observed selectivity: cage **1** has a large cavity and can encapsulate two molecules of **C_8-SH** (Fig. 3d), whereas cage **2** is much smaller and only one guest can fit (Fig. 3e). Larger guests (**C_{10}-SH–C_{12}-SH**) would fill the cavity of **1**, disfavoring 2 : 1 binding. The models show that the large panel gaps do not prevent ingress/egress of the reactants and allow protrusion of the alkyl arms of the guest(s), if needs be, and that the exact orientation of the guest(s) in cavity will be quite variable. Notably, all of the products have some affinity for the cage, even **$(C_{12}\text{-S})_2$**, which shows that while large reactants favor 1 : 1 binding, 2 : 1 binding is possible and reaction can still occur. As the binding affinities of reactant and product are generally of the same order, there is minimal product inhibition seen, as one species does not dominate the binding.

The strong binding of the targets in host **1**, and the opportunity for encapsulation, provides an explanation for the unusual reactivity of **1** when compared to other Fe-based assemblies. We have no evidence that the intact cage itself acts as the catalyst, so the theory that a small amount of Fe^{II} released from cage **1** in solution is the active catalyst in the reaction is the most plausible, with atmospheric oxygen as stoichiometric oxidant. This process could obviously occur in free solution, but coencapsulation of the guests increases their effective concentration, smoothing the reaction process. Cages with small (or no) cavities such as **2** or **3** are not capable of this reactivity. Interestingly, even though cage **2** can bind thiols in a 1 : 1 manner, no reactivity is seen, indicating that coencapsulation is needed. Addition of superstoichiometric (with respect to cage) amounts of $Fe(NTf_2)_2$ slowed the reaction down, which suggests that in this case the additional ions are competitive guests for the cage, displacing the thiol guests and slowing reaction. There appears to be a "sweet spot" in [Fe] that allows both the guests and the active Fe(II) ion catalyst to bind in host **1**. The small amounts of Fe(II) active catalyst act as "cofactors" for this biomimetic reaction in the host. Cofactor-mediated catalysis, namely the use of an additional reactant bound inside the parent "apoenzyme" host to effect reactivity, is usually only seen with large superstructures.[20]

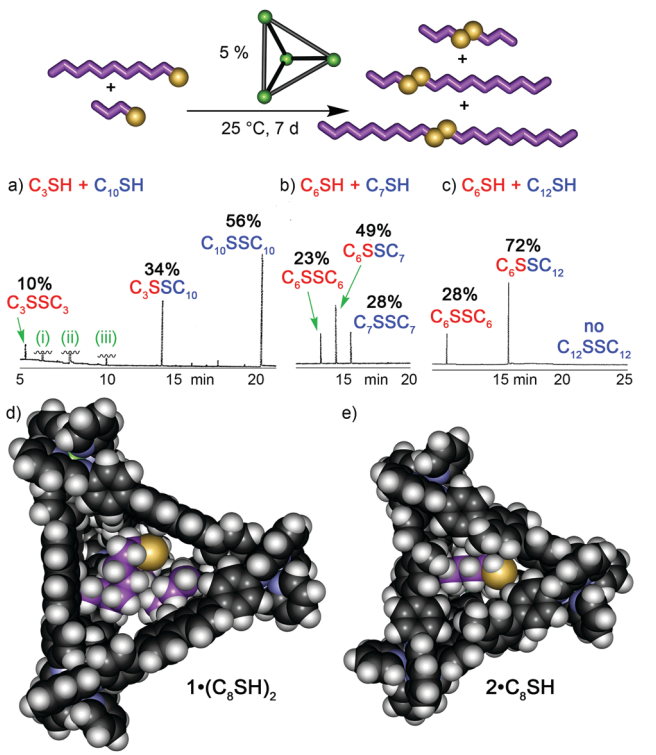
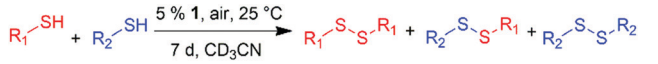


Fig. 3 Size-selective reactivity. Expansions of the GC traces obtained after reaction between different thiols (25 °C, 7 days, CD_3CN, 5% **1**). (a) **C_3-SH** and **C_{10}-SH**; (b) **C_6-SH** and **C_7-SH**; (c) **C_6-SH** and **C_{12}-SH**. Minimized structures of (d) **1·$(C_8$-SH)2** (e) and **2·C_8-SH** (SPARTAN). (i) dodecane; (ii) unreacted **C_{10}-SH**; (iii) impurity in the GC column.

Table 3 Heterodimerization selectivity of alkanethiols in cage **1**[a]



R_1	R_2	Conversion, %	R_1R_1	R_1R_2	R_2R_2
C_3	C_8	19	7	35	58
C_3	C_{10}	20	10	34	56
C_6	C_7	20	23	49	28
C_6	C_{10}	18	19	42	39
C_6	C_{12}	12	28	72	0

[a] Reactions performed at 25 °C, 7 d, CD_3CN and analyzed by GC, concentrations determined using dodecane as internal standard. Equimolar amounts of each thiol used, overall [C_x-SH] = 18.2 mM.

While the size-selectivity of the reaction in **1** is modest when comparing homodimerization of *n*-alkanethiols, we were interested in determining whether any selectivity could be seen when reacting two different thiols. The heterodimerization products of reaction between *n*-alkanethiols of different length cannot be distinguished by NMR, as might be expected, so a GC method is required. Initial tests run at 80 °C for 24 h were not encouraging, as statistical mixtures were seen. However, mixtures of RSH + RSSR are well-known to equilibrate over time, especially at high temperature.[21] To remove this equilibration, we analyzed the reactions between sets of equimolar amounts of two different alkanethiols in the presence of 5% **1** at 25 °C for 7 days. The observed conversions were <20% in each case, and allow a view of the initial selectivity. The combinations tested were C_3/C_8, C_3/C_{10}, C_6/C_7, C_6/C_{10} and C_6/C_{12} – Fig. 3a–c shows GC data for three of these reactions (see ESI† for full, uncropped GC traces), and Table 3 shows the product distributions.

In these non-equilibrated kinetic experiments, the selectivity for differently sized alkanethiols is obvious, and quite impressive. While minimal selectivity is seen when C_6-SH and C_7-SH are combined, as might be expected, other combinations showed significant excesses of one product. For example, when C_3-SH and C_8-SH were reacted, $(C_8\text{-S})_2$ was favored in an 8.6 : 5.5 : 1 ratio over C_8-S-S-C_3 and $(C_3\text{-S})_2$, respectively. Similar product ratios were observed for the C_3/C_{10} combination, but the selectivity towards $(C_{10}\text{-S})_2$ was slightly lower. Consistent with the observation that larger alkanethiols ($\geq C_{10}$) were not favorably coencapsulated, the combination of C_6-SH and C_{12}-SH gave only two products, with the C_6-S-S-C_{12} heterodimer being formed in a 3.6 : 1 excess over $(C_6\text{-S})_2$, and no $(C_{12}\text{-S})_2$ was observed at all. The most favored combinations are those with approximately 13–18 carbon atoms, *i.e.* C_3-S-S-C_{10}, C_6-S-S-C_{10} or C_6-S-S-C_{12}, which corresponds with the observation that medium-sized thiols such as C_8-SH are favorably coencapsulated and the reaction rate drops off as the guests increase in size.

In conclusion, we have shown that small amounts of a self-assembled host are capable of the catalytic oxidation of alkanethiols to their corresponding disulfides. The reaction requires coencapsulation to proceed effectively, and the host is capable of distinguishing between alkanethiols of differing size, but identical reactivity, all while showing good turnover. This selectivity is unusual, and we are currently investigating its applications in dynamic combinatorial libraries.

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Conflicts of interest

There are no conflicts to declare.

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