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A new [4]carceplex, and a crystal structure and dynamic combinatorial chemistry of a [5]carceplex

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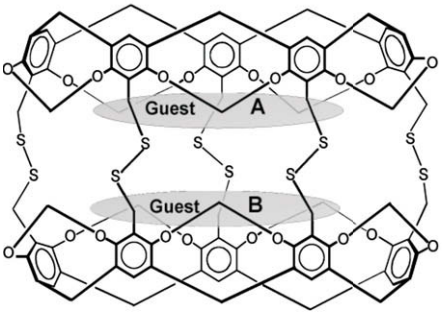
ABSTRACT

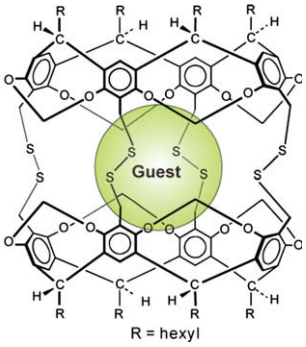
A new [4]carceplex (**2**·guest) is reported. It is composed of two cavitands linked by four disulfide bonds. It forms twistomers, which interconvert on a millisecond timescale. The energy barrier for interconversion of twistomers is guest-dependent. Formation of [4]carceplex **2**·guest is template dependent. The selectivity in templates is flat relative to most previous related template work. Larger kin [5]carceplex **1**·guests were reinvestigated. A crystal structure confirms the twist between the hemispherical cavitands. Use of a redox buffer allowed dynamic combinatorial chemistry to be performed between pairs of templates.

1. Introduction

Disulfide bonds play key roles in biology,[1] materials science,[2] and supramolecular chemistry.[3] For example, disulfides are essential for the tertiary structure of many proteins, and dynamic combinatorial chemistry (DCC) often exploits the reversibility of disulfide bond formation.[3] Caged compounds also continue to captivate supramolecular chemists.[4] Furthermore, in the case of a disulfide-linked cage, a potential release mechanism is incorporated,[5] which may find application in delivery devices. A while back, we reported a penta-disulfide-linked [5]carceplex, **1**·guests.[6] Herein we report further studies on [5]carceplex **1**·guests, including template-driven DCC, and we report the preparation and characterization of its smaller sibling, tetra-disulfide-linked [4]carceplex **2**·guest.



[5]Carceplex **1**•Guests



[4]Carceplex **2**•Guest

2. Results and discussion

2.1. Synthesis

Low yields of [5]carceplex **1**·guests[6] led us to explore the preparation of [4]carceplex **2**·guest (Scheme 1). The study was

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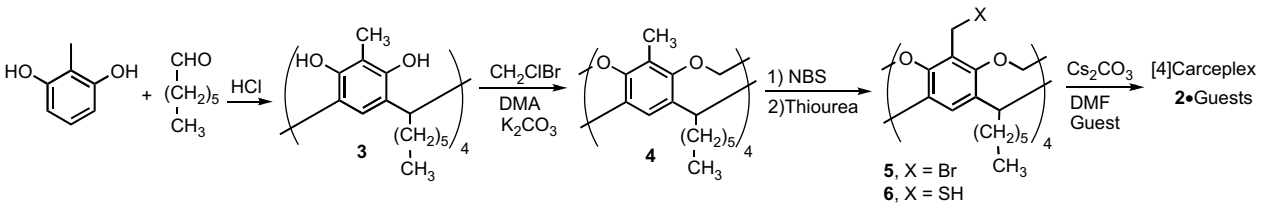


Scheme 1. Synthesis of [4]carceplex **2**·guest.

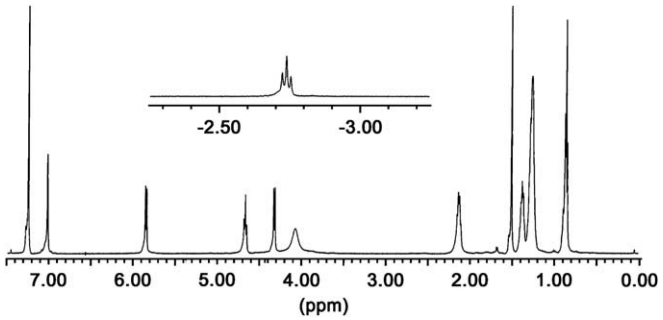


Figure 1. ^{1}H NMR spectrum (500 MHz) of [4]carceplex **2**·diethylsulfide at 300 K in $CDCl_3$. See Experimental for assignments.

driven in part by our curiosity about the potential utility of disulfide-linked carceplexes. But we also wondered if use of template effects and/or DCC could help us overcome the challenge of synthesizing [4]carceplex **2**·guest: we had tried several methods to produce **2**·guest, but none were successful. For example, stirring of tetrabenzylthiol cavitand **6** (prepared via standard procedures shown in Scheme 1) in dimethylformamide (DMF) with Cs_2CO_3 as base for 6 h at room temperature gave no [4]carceplex **2**·guest. Under the same conditions, but in the presence of 2 mol% (% of solvent DMF) of diethylsulfide, we obtained a 15% yield of [4]carceplex **2**·diethylsulfide (Scheme 1) as characterized by ^{1}H NMR (Fig. 1) and MALDI-MS. This demonstrates that DMF is a suitable solvent for this reaction, but not a suitable template. A suitable template is clearly needed, and diethylsulfide is suitable. Thus, judicious choice of template did indeed lead us to a carceplex that had eluded us for some time.

2.2. Templation

In all, 42 guests were screened as potential templates, and 6 were found to be suitable. Suitable and unsuitable templates are shown in Charts 1 and 2, respectively. The suitable templates were subjected to competition experiments to determine their relative abilities as templates for formation of [4]carceplex **2**·guest. The results are given in Table 1. The template effect is fairly flat compared to results we have found with other carceplexes.[7,8] Indeed, some of the unsuccessful templates shown in Chart 2 may be only slightly poorer templates than the successful ones in Chart 1. It is likely that the transition state is early (perhaps formation of the second disulfide link) and the lack of inter-cavitand interactions at that stage makes for host–guest complexes of modest stability due to a lack of preorganization. In other systems we have reported, the examples with early transition states were accompanied by charged hydrogen bonds between the cavitands, which provided considerable preorganization.[7] In an example with a late transition

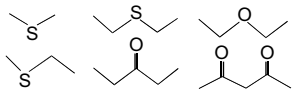


Chart 1. Suitable templates for formation of **2**·guest.

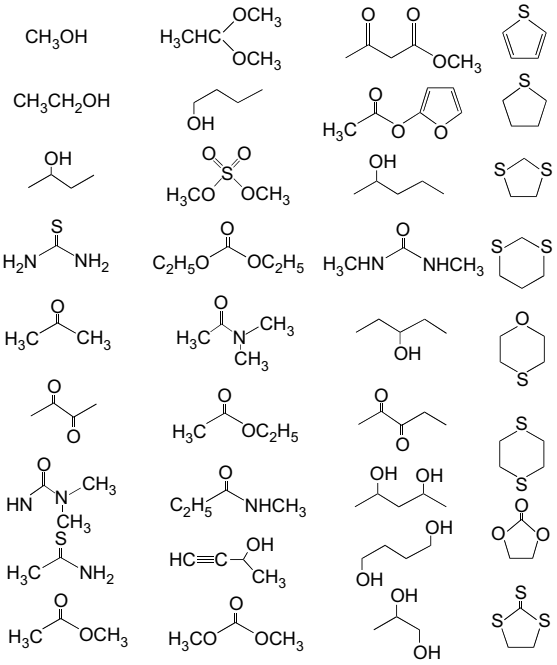


Chart 2. Unsuitable templates for formation of **2**·guest.

state, the multi-bridged intermediate had sufficient inter-cavitand linkages to also create a highly preorganized cavity.[8]

2.3. Twistomers

We reported conformational 'twistomers'[9] for [5]carceplex **1**·guests,[6] and we found similar dynamics for [4]carceplex **2**·guest. Figure 2 shows variable temperature ^{1}H NMR spectra of [4]carceplex **2**·diethylsulfide. The inter-cavitand methylenes appear as a doublet of doublets at lower temperature, but coalesce into a singlet at higher temperatures. These hydrogens are diastereotopic in the twistomer conformation (Fig. 3), but interconvert rapidly on the ^{1}H NMR timescale above room temperature. The $\Delta G^{\ddagger}$ for this process was determined from the ^{1}H NMR coalescence to be 12–15 kcal/mol, depending on the guest (Table 2). Larger guests induce lower activation energies,[9] presumably due to both raising of the ground state partway out of the fully twisted conformation (which has a smaller cavity than the untwisted conformation according to examination of CPK models) and bonding more favorably to the transition state (which appears to have a larger cavity than the ground state).

Table 1
Template ratios in the formation of **2**·guest

Guest	Template ratio
Methylsulfide	50
Ethylmethylsulfide	20
Diethylsulfide	5
Diethylether	5
3-Pentanone	1

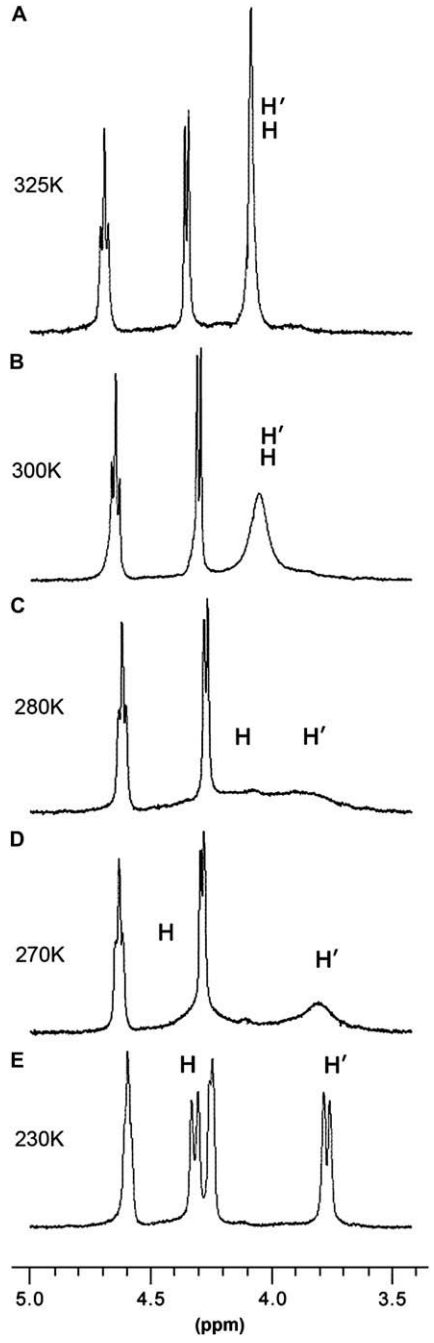


Figure 2. Partial ^{1}H NMR spectra (500 MHz) of [4]carceplex **2**·diethylsulfide in $CDCl_3$ at various temperatures. The diastereotopic benzylic protons are labeled H and H′.

2.4. Crystal structure of 1·(DMA)$_2$

The studies on the twistomers described above for [4]carceplex **2**·guest, and on those reported earlier for [5]carceplex **1**·guests[6] were in solution. We now report a crystal structure of [5]carceplex **1**·(DMA)$_2$, where DMA=dimethylacetamide (Fig. 4). The twist between the two hemispherical cavitands is clear, as are the corresponding inter-cavitand diastereotopic methylenes. The five disulfide linkages are all twisted, but they are not quite equivalent, as the twist varies slightly between the five linkages. The two DMA guests are oriented parallel to one another, and to the equator of the carceplex. This is the orientation predicted earlier based on ^{1}H NMR data in solution.[6] The guests are aligned such that their dipoles oppose each other in an energetically favorable manner.

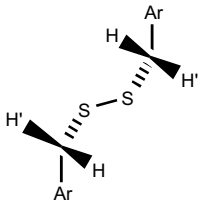


Figure 3. Diastereotopic benzylic protons of [4]carceplex **2**·diethylsulfide (Ar represents a cavitand).

Table 2
$\Delta G^{\ddagger}$ of twistomers of [4]carceplex **2**·guest

Guest (coalescence temperature in K)	$\Delta G^{\ddagger}$ (kcal mol^{-1})
Dimethylsulfide (322)	14.8±0.2
Ethylmethylsulfide (296)	13.6±0.2
Diethylsulfide (283)	12.9±0.2
Diethylether (295)	13.5±0.2
3-Pentanone (268)	12.3±0.2

2.5. Dynamic combinatorial chemistry

We wanted to investigate the potential of a disulfide-linked carceplex in DCC studies. Could we boost our yields by allowing thermodynamics to drive the reaction? What happens if two guests can occupy the cavity? We chose [5]carceplex **1**·guests because the idea of multicomponent templates is intriguing.[10] We sought some improvement in the yield of **1**·guests. For example, the two-step reaction to form the benzylthiols from their methyl precursors (i.e., (1) *N*-bromosuccinimide, (2) thiourea) was achieved in 10% yield in the case of the corresponding [5]cavitand (to yield **9**, Scheme 2),[6] but in 80% yield on the [4]cavitand (to yield **6**). This was attributed to the low solubility of the 'footless' [5]cavitand **7** in CCl_4. Adjustment of temperature and initiator improved our yields from 10% to 40% (See Experimental).

Turning to the carceplex reaction itself, we developed a redox buffer to allow the carceplex to form under reversible conditions: we chose mercaptoethanol (ME_{red}), 2-hydroxyethyldisulfide (ME_{ox}), and triethylamine. When [5]cavitand **9** was subjected to these conditions in DMF, a 50% yield of **1**·(DMF)$_2$ was obtained (Scheme 2). This is a significant improvement over the 25% yield obtained under kinetic conditions.[6] When **1**·(DMF)$_2$ was subjected to ME_{red} and triethylamine in DMF, cavitand **9** was obtained, showing that the reaction can indeed be reversed in the presence of ME_{red} and base in DMF. When **1**·(DMF)$_2$ was subjected to the redox buffer in DMA as solvent, **1**·(DMA)$_2$ was obtained exclusively. In a control experiment where **1**·(DMF)$_2$ was dissolved in DMA in the presence of triethylamine, but neither ME_{red} nor ME_{ox} was present, no guest exchange was observed. Thus, the redox buffer facilitates guest exchange via disulfide bond rupture and reformation.

With the above results in hand, we subjected [5]cavitand **9** to redox buffer in a 1:1 mixture of DMF/DMA solvent. We obtained a mixture of **1**·(DMF)$_2$, **1**·(DMF)(DMA), and **1**·(DMA)$_2$ in a ratio of about 20:5:1. [5]Carceplex **1**·(DMF)(DMA) was characterized by MALDI-MS and by ^{1}H NMR of the mixture of the three carceplexes (Fig. 5). Statistically, one would expect a 1:2:1 ratio of carceplexes, where the mixed carceplex predominates. Clearly DMF is preferred over DMA, presumably due to the smaller size of DMF being more complementary to the size of the [5]cavitands in which they are imbedded.

3. Conclusion

Once elusive [4]carceplex **2**·guest was prepared via exploration and discovery of suitable templates. The relative templating abilities of the suitable templates were found to be flat, likely due to the lack of preorganization at the transition state. The hemispheres of **2** are twisted with respect to one another in solution, similar to larger

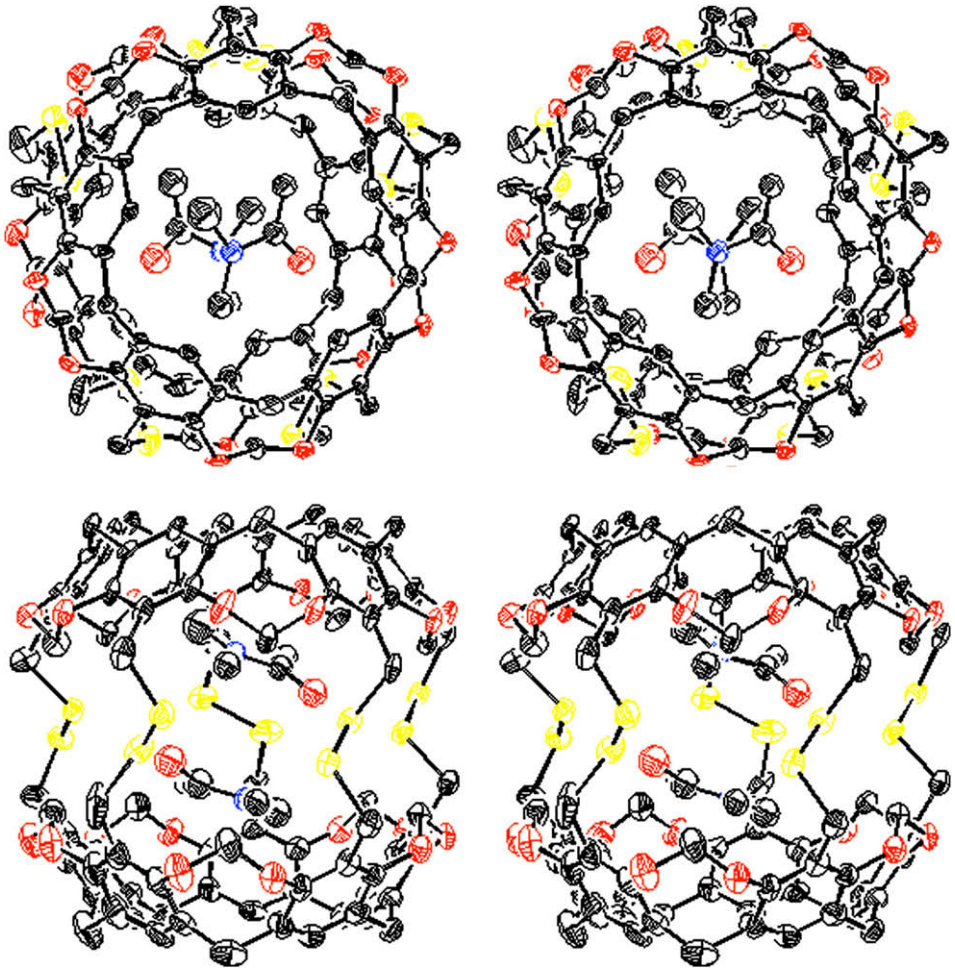
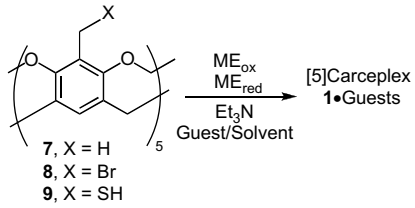


Figure 4. Stereoviews of X-ray crystal structure of [5]carceplex **1**·$(DMA)_2$.



Scheme 2. Synthesis of [5]carceplex **1**·guests from cavitand **9**.

sibling [5]carceplex **1**. In the solid state, the twisting of **1** is clearly evident as is the parallel arrangement of the two entrapped guests. Using a redox buffer, reversible conditions led to a two-fold increase in yield for [5]carceplex **1**·guests. The redox buffer also provided a platform from which combinatorial dynamic chemistry was explored. An added dimension is that the templates used are pairs of molecules. $(DMF)_2$ was found to be a superior template to $(DMA)_2$, and (DMF)(DMA) was found to be intermediate in templating ability. [5]Carceplex **1**·guests and [4]carceplex **2**·guest serve as prototypes for disulfide-linked carceplexes that have potential as DCC systems and as delivery devices.

4. Experimental

4.1. General

All reagents were purchased from Aldrich Chemical Co., Inc. NFP, DMF, DMA were distilled and stored over 4 Å molecular sieves under a N_2 atmosphere. NBS was recrystallized and dried under vacuum over P_2O_5 prior to usage. All other reagents were commercially available at >98% purity and were used without further purification. Silica gel (BDH, 230–430 mesh) was used for column chromatography. Silica gel thin layer chromatography was performed on glass-backed plates (Aldrich, silical gel 60, F_{254},

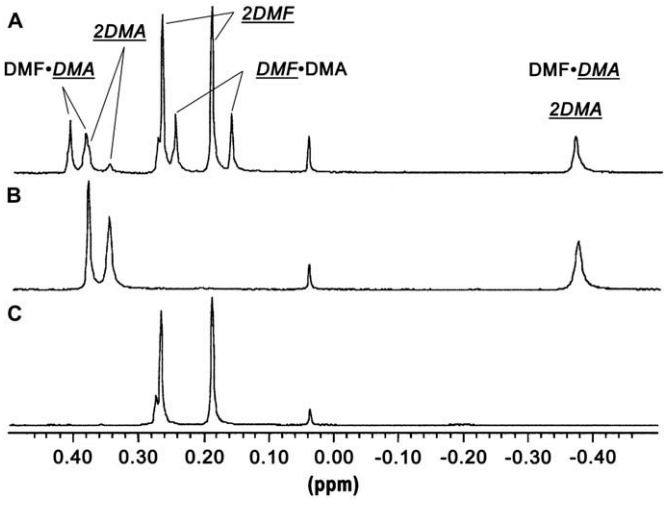
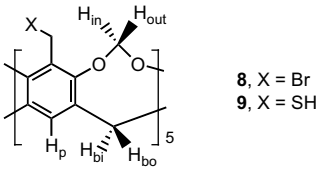


Figure 5. Partial ^{1}H NMR spectra of [5]carceplexes (A) **1**·(DMF)(DMA), (B) **1**$(DMA)_2$, and (C) **1**·$(DMF)_2$. Labeled signals are from italicized guest.

0.25 mm). ^{1}H NMR spectra were acquired using Bruker AV-300, AV-400, AMX-500 spectrometers at ambient temperature (300 K) using the residual $CHCl_3$ as a reference (δ=7.24 ppm) unless noted otherwise. Liquid secondary ion mass spectra (LSIMS) were recorded on a Kratos Concept IIHQ. Matrix assisted laser desorption ionization (MALDI) mass spectra were recorded on a Bruker Biflex IV in reflectron mode. MALDI samples were prepared using 4-nitroaniline as the matrix, and in most cases, silver acetate was added to simplify the spectra by reducing the signals from $M\cdot H^+$, $M\cdot Na^+$, and $M\cdot K^+$. Microanalyses were performed on a Carlo-Erba elemental analyzer, model 1106 or model 1108. X-ray crystallography measurements were made on a Rigaku/ADSC CCD area detector with graphite monochromated Mo Kα radiation machine and the data analysis was performed using teXsan crystallographic software package. Melting points were recorded on a Thomas Hoover capillary melting point apparatus, and are uncorrected.

4.2. Modified synthesis of [5]carceplex 1·guests[6]



8, X = Br
9, X = SH

4.2.1. [5]Cavitand benzylbromide *8*

[5]Cavitand **7** (148.0 mg, 0.2 mmol)[11] was dissolved in CCl_4 (100 mL), and this solution was bubbled with N_2 for 2 h. NBS (185.1 mg, 1.04 mmol, 5.2 equiv) and benzoyl peroxide (50 mg) were added. The reaction mixture was stirred at 50 °C under a 100 W tungsten filament lamp for 12 h under the protection of N_2. Then the solvent was removed in vacuo. Ethanol (20 mL) was added, and the resulting suspension was sonicated for 5 min. Filtration of the suspension afforded a white solid, which was dried at 100 °C under vacuum for 24 h. This crude product was used directly for the next reaction without purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.31 (s, 5H, H_p), 6.09 (d, 5H, J=7.5 Hz, H_{out}), 4.66 (d, 5H, J=7.5 Hz, H_{in}), 4.58 (s, 10H, CH_2–Br), 4.37 (d, 5H, J=13.1 Hz, H_{bo}), 3.39 (d, 5H, J=13.1 Hz, H_{bi}).

4.2.2. [5]Cavitand benzylthiol *9*

A solution of crude **8** (obtained from 103.6 mg [5]cavitand **7**, 0.14 mmol) and thiourea (110.0 mg, 6.58 mmol) in DMF (20 mL) was bubbled by N_2 for 2 h, then stirred at room temperature for 18 h under the protection of N_2. The reaction mixture was then transferred into a 2 M aqueous solution of degassed NaOH (30 mL) through a cannula, and stirred for an additional 1 h. The reaction mixture was then poured into a 2 M aqueous solution of HCl (100 mL). The resultant gelatinous suspension was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with water (30 mL). After removing the solvent in vacuo, a pale yellow residue was obtained. The latter material was passed through a short silica gel column ($CHCl_3$ eluent) to yield a white solid, which upon recrystallization from $CHCl_3$/ethanol afforded **9** as a white crystal (54.2 mg, 43% yield for the two-step reaction from cavitand[5] **7**). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.25 (s, 5H, H_p), 6.03 (d, 5H, J=7.3 Hz, H_{out}), 4.56 (d, 5H, J=7.3 Hz, H_{in}), 4.37 (d, 5H, J=13.0 Hz, H_{bo}), 3.75 (d, 10H, J=7.1 Hz, CH_2–S), 3.39 (d, 5H, J=13.0 Hz, H_{bi}), 1.55 (t, 5H, J=7.1 Hz, SH). MALDI-MS (positive mode): 901 ($M+H^+$); calcd ($M+H^+$) 901.

Compounds **1**·$(DMF)_2$ and **1**·$(DMA)_2$ were prepared as described previously.[6]

4.3. Redox reactions of 1·guests

4.3.1. Reduction of *1·(DMF)$_2$*

Compound **1**·$(DMF)_2$ (2 mg), DMF (1 mL), and triethylamine (50 μL) were mixed and degassed completely by bubbling through argon for 2 h. Degassed ME_{red} (0.1 mL, excess) was added. The mixture was stirred at room temperature for 20 h under the protection of argon, then 2 M HCl (10 ml) was added to quench the reaction. The suspension was then extracted with $CHCl_3$ (3×5 mL). The combined organic extracts were washed with water and condensed in vacuo. The obtained crude product was dissolved in $CDCl_3$ and performed on the ^{1}H NMR directly to monitor the result of the reaction.

4.3.2. Compound *1·(DMF)$_2$* from redox buffer

[5]Cavitand benzylthiol **9** (10 mg, 0.011 mmol), ME_{red} (25.7 mg, 0.22 mmol, 20 equiv), and DMF (7.5 mL) were mixed and degassed completely by bubbling argon for 2 h. This formed solution (**A**). ME_{ox} (17.0 mg, 0.11 mmol, 10 equiv), triethylamine (700 μL, excess), and DMF (7.5 mL) were mixed and degassed completely by bubbling argon for 2 h. This formed solution (**B**). Solution (**A**) and solution (**B**) were combined and mixed through a cannula. The final buffer system was composed of **9** (0.73 mM), ME_{red} (14.7 mM, 20 equiv), ME_{ox} (7.3 mM, 10 equiv), triethylamine (excess), and DMF (15 mL). The mixture was stirred at room temperature for 24 h under the protection of argon, then 2 M HCl (50 mL) was added to quench the reaction. The suspension was then extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were washed with water and condensed in vacuo. The obtained crude product was dissolved in $CDCl_3$ for analysis by ^{1}H NMR. The yield was calculated from the integration of the host and guest peaks (estimated yield 50%).

4.3.3. Compound *1·(DMA)$_2$* from redox buffer

Similar to the procedure above, except that DMA was used as solvent and guest instead of DMF (yield calculated from ^{1}H NMR spectrum, 42%).

4.3.4. Guest exchange reaction

ME_{red} (15.4 mg, 0.2 mmol, 40 equiv) and DMA (7.5 mL) were mixed and degassed completely by bubbling argon for 2 h. This formed solution (**A**). Compound **1**·$(DMF)_2$ (10 mg, 0.005 mmol), ME_{ox} (15.4 mg, 0.1 mmol, 20 equiv), triethylamine (700 μL, excess), and DMA (7.5 mL) were mixed and degassed completely by bubbling argon for 2 h. This formed solution (**B**). Solution (**A**) and solution (**B**) were combined and mixed through a cannula. The final buffer system was composed of **1**·$(DMF)_2$ (0.33 mM), ME_{red} (13.3 mM, 40 equiv), ME_{ox} (6.7 mM, 20 equiv.), triethylamine (excess), and DMA (15 mL). The mixture was stirred at room temperature for 24 h under the protection of argon, then 2 M HCl (50 mL) was added to quench the reaction. The suspension was then extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were washed with water and condensed in vacuo. The obtained crude product was dissolved in $CDCl_3$ and performed on ^{1}H NMR directly to monitor the result of the reaction.

4.3.5. Competition experiment in redox buffer

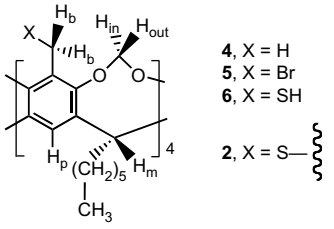
Similar to the procedure above, except that a mixed solvent of DMA/DMF=1:1 was used as solvent and guest instead of only DMF. The obtained crude product was dissolved in $CDCl_3$ for analysis by ^{1}H NMR.

4.4. Synthesis of [4]carceplex 2·guest

4.4.1. Octol *3*

Heptanal (180 mL, 1.29 mol) was added (dropwise) to a solution of 2-methylresorcinol (160.2 g, 1.29 mol) and concd HCl (160 mL) in

ethanol (600 mL) at 0 °C. The mixture was gradually heated (precipitation was observed within an hour of heating) to reflux and maintained at this temperature for 36 h. The resultant precipitate was filtered off and washed with water until the filtrate tested neutral pH. Recrystallization from acetone/hexanes furnished the octol as a white solid (138 g, 48%). Mp>300 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.91 (s, 8H, O*H*), 7.41 (s, 4H, H_p), 4.38 (t, J=7.9 Hz, 4H, H_m), 2.23–231 (m, 8H, $CH_2(CH_2)_4$), 2.04 (s, 12H, ArCH_3), 1.29–1.41 (m, 32H, $(CH_2)_4CH_3$), 0.89 (t, J=7.1 Hz, 12H, $(CH_2)_4CH_3$). MS LSIMS (negative mode): 879 ($M-H^+$); calcd 879 ($M-H^+$). Anal. Calcd for $C_{56}H_{80}O_8$: C, 76.31; H, 9.16; O, 14.53. Found: C, 76.46; H, 9.06; O, 14.48.



*4.4.2. 2-Methyl [4]cavitand **4***

To a slurry of K_2CO_3 (60.2 g, 436 mmol) in CH_2BrCl (25 mL, 385 mmol) and DMA (600 mL) at room temperature was added (via syringe pump) a solution of octol **3** (31.4 g, 36 mmol) in DMA (100 mL) over 48 h. The mixture was subsequently heated to 75 °C and stirred at this temperature for 48 h, with daily addition of 10 equiv of CH_2BrCl. The reaction mixture was cooled, filtered through a Celite® pad, and the excess solvent removed in vacuo. The residue was dissolved in $CHCl_3$ (600 mL), and the organic solution successively washed with 2 M HCl, water (2×300 mL of each), and brine (200 mL), and finally dried with $MgSO_4$. Purification by column chromatography (7:3 $CHCl_3$/hexanes eluent) and subsequent recrystallization ($CHCl_3$/hexanes) of the isolated foam gave 2-methyl [4]cavitand **4** (20 g, 62%) as a white solid. Mp: 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 4H, H_p), 5.86 (d, J=7.1 Hz, 4H, H_{out}), 4.75 (t, J=7.9 Hz, 4H, H_m), 4.24 (d, J=7.1 Hz, 4H, H_{in}), 2.13–2.23 (m, 8H, $CH_2(CH_2)_4$), 1.96 (s, 12H, ArCH_3), 1.28–1.42 (m, 32H, $(CH_2)_4CH_3$), 0.88 (t, J=7.1 Hz, 12H, $(CH_2)_4CH_3$). MS LSIMS (positive mode): 929 ($M+H^+$); calcd 929 ($M+H^+$). Anal. Calcd for $C_{60}H_{80}O_8$: C, 77.54; H, 8.68; O, 13.78. Found: C, 77.53; H, 8.59; O, 13.88.

*4.4.3. 2-Bromomethyl [4]Cavitand **5***

NBS (4.05 g, 22.8 mmol) was added to a solution of 2-methyl [4]cavitand **4** (5.04 g, 4.42 mmol) in CCl_4 (500 mL), and the resulting suspension was briefly sonicated (till the vast majority of NBS had dissolved). AIBN (~25 mg) was added, and the reaction mixture stirred at room temperature under a 100 W tungsten filament lamp until all the starting material was consumed. Filtration, followed by removal of the excess solvent afforded a golden foam which, upon filtration through a short silica gel pad (CH_2Cl_2 eluent) gave a white foam. Subsequent recrystallization from CH_2Cl_2/ethanol yielded **5** as white needles (4.87 g, 88%). Mp: 178 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 4H, H_p), 6.01 (d, J=6.6 Hz, 4H, H_{out}), 4.76 (t, J=8.0 Hz, 4H, H_m), 4.55 (d, J=6.6 Hz, 4H, H_{in}), 4.40 (s, 8H, H_b), 2.13–2.24 (m, 8H, $CH_2(CH_2)_4$), 1.22–1.42 (m, 32H, $(CH_2)_4CH_3$), 0.88 (t, J=6.9 Hz, 12H, $(CH_2)_4CH_3$). MS LSIMS (positive mode): 1244 ($M+H^+$); calcd 1244 ($M+H^+$).

*4.4.4. Tetrathiol **6***

A solution of 2-bromomethyl [4]cavitand **5** (2.27 g, 1.78 mmol) and thiourea (829 mg, 10.9 mmol) in DMF (50 mL) was stirred at room temperature for 18 h. The reaction mixture was then poured into a degassed solution of 1 M NaOH (50 mL), stirred for an additional 45 min, and finally acidified to ~pH 4 by careful addition of concd HCl. The resultant gelatinous suspension was extracted with $CHCl_3$ (3×30 mL), and the combined organic extracts washed with water and brine (30 mL of each), dried with $MgSO_4$, and concentrated in vacuo to a colorless syrup. The latter material was passed through a short silica gel pad (CH_2Cl_2 eluent) to yield an opaque foam, which upon crystallization from CH_2Cl_2/ethanol afforded tetrathiol **6** as a white solid (1.55 g, 82%). Mp: 135 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 4H, H_p), 5.94 (d, J=7.0 Hz, 4H, H_{out}), 4.74 (t, J=8.0 Hz, 4H, H_m), 4.45 (d, J=7.0 Hz, 4H, H_{in}), 3.56 (d, J=7.2 Hz, 8H, H_b), 2.13–2.23 (m, 8H, $CH_2(CH_2)_4$), 1.87 (t, J=7.2 Hz, 4H, *SH*), 1.24–1.49 (m, 32H, $(CH_2)_4CH_3$), 0.88 (t, J=6.9 Hz, 12H, $(CH_2)_4CH_3$). ESI-MS (negative mode): 1055 ($M-H^+$); calcd 1055 ($M-H^+$). Anal. Calcd for $C_{60}H_{80}O_8S_4$: C, 68.15; H, 7.63; O, 12.11; S, 12.11. Found: C, 68.17; H, 7.50; S, 12.30.

*4.4.5. Compound **2**·diethylsulfide*

Cs_2CO_3 (91.0 mg, 0.28 mmol, 10 equiv per benzylthiol) was added to DMF (30 mL) and stirred for 2 min. Diethylsulfide (0.90 mL, 2 mol % of DMF) and **6** (30.0 mg, 0.028 mmol) were added to the mixture. The system was closed and stirred at room temperature for 48 h, then poured into a 2 M aqueous solution of HCl (50 mL). The resultant suspension was extracted with $CHCl_3$ (3×10 mL). The $CHCl_3$ extracts were combined and the solvent was removed in vacuo. The resulting white residue was dried under vacuum overnight, then purified through silica gel column, eluting with $CHCl_3$/hexanes (1:4). Precipitation of the product from $CHCl_3$/hexanes gave a white solid. (4.8 mg, 15%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.01 (s, 8H, H_p), 5.84 (d, 8H, J=7.6 Hz, H_{out}), 4.67 (t, 8H, J=8.0 Hz, H_m), 4.32 (d, 8H, J=7.6 Hz, H_{in}), 4.07 (br, 16H, CH_2–SS), 2.13 (m, 16H, CH–CH_2), 1.24–1.49 (m, 64H, feet $(CH_2)_4$), 0.86 (t, 24H, J=6.6 Hz, feet CH_3), 0.87 (overcovered, 4H, guest SCH_2CH_3) −2.74 (t, 6H, J=7.5 Hz, SCH_2CH_3). MALDI-MS (positive mode): 2302 ($M+Ag^+$); calcd ($M+Ag^+$) 2302.

*4.4.6. Compound **2**·diethylether*

Similar to the above procedure. Compound **6** (30 mg, 0.028 mmol), Cs_2CO_3 (91 mg, 0.28 mmol), DMF (30 mL), diethylether (0.87 mL, 2 mol % of DMF). Compound **2**·diethylether was obtained as a white solid (2.0 mg, 6%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.04 (s, 8H, H_p), 5.84 (d, 8H, J=7.6 Hz, H_{out}), 4.66 (t, 8H, J=8.0 Hz, H_m), 4.32 (d, 8H, J=7.6 Hz, H_{in}), 3.75–4.60 (br, 16H, CH_2–SS), 2.14 (m, 16H, CH–CH_2), 1.78 (q, 4H, J=7.1 Hz, OCH_2CH_3), 1.24–1.49 (m, 64H, feet $(CH_2)_4$), 0.86 (t, 24H, J=6.6 Hz, feet CH_3), −2.33 (t, 6H, J=7.1 Hz, OCH_2CH_3). MALDI-MS (positive mode): 2286 ($M+Ag^+$); calcd ($M+Ag^+$) 2286.

*4.4.7. Compound **2**·**3**-pentanone*

Similar to the above procedure. Compound **6** (30 mg, 0.028 mmol), Cs_2CO_3 (91 mg, 0.28 mmol), DMF (30 mL), 3-pentanone (0.87 mL, 2 mol % of DMF). Compound **2**·3-pentanone was obtained as a white solid (1.0 mg, 3%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.03 (s, 8H, H_p), 5.84 (d, 8H, J=7.6 Hz, H_{out}), 4.66 (t, 8H, J=8.0 Hz, H_m), 4.32 (d, 8H, J=7.6 Hz, H_{in}), 3.75–4.33 (br, 16H, CH_2–SS), 2.12 (m, 16H, CH–CH_2), 1.24–1.49 (m, 64H, feet $(CH_2)_4$), 0.86 (t, 24H, J=6.6 Hz, feet CH_3), 0.84 (overcovered, 4H, guest $COCH_2CH_3$), −2.33 (t, 6H, J=7.1 Hz, guest $COCH_2CH_3$). MALDI-MS (positive mode): 2298 ($M+Ag^+$); calcd ($M+Ag^+$) 2298.

*4.4.8. Compound **2**·ethylmethylsulfide*

Similar to the above procedure. Compound **6** (30 mg, 0.028 mmol), Cs_2CO_3 (91 mg, 0.28 mmol), DMF (30 mL), ethylmethylsulfide (0.75 mL, 2 mol % of DMF). Compound **2**·ethylmethylsulfide was obtained as a white solid (4.9 mg, 16%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.04 (s, 4H, H_p), 7.01 (s, 4H, H_p'), 5.87 (d, 4H, J=7.5 Hz, H_{out}), 5.82 (d, 4H, J=7.6 Hz, H_{out}'), 4.66 (m, 8H, H_m), 4.61 (d, 4H, J=7.6 Hz, H_{in}), 4.19 (d, 4H, J=7.5 Hz, H_{in}'), 3.55–4.50 (br, 16H, CH_2–SS), 2.13 (m, 16H, CH–CH_2), 1.24–1.49 (m, 64H, feet $(CH_2)_4$), 1.28 (overcovered, 4H, guest SCH_2CH_3), 0.86 (t, 24H,

J=6.6 Hz, feet CH_3), 0.87 (overcovered, 2H, guest S$CH_2$$CH_3$), −1.37 (t, 3H, J=7.4 Hz, S$CH_2$$CH_3$), −1.90 (s, 3H, CH_3S). MALDI-MS (positive mode): 2288 ($M+Ag^+$); calcd ($M+Ag^+$) 2288.

*4.4.9. Compound **2**·methylsulfide*

Similar to the above procedure. Compound **6** (30 mg, 0.028 mmol), Cs_2CO_3 (91 mg, 0.28 mmol), DMF (30 mL), methylsulfide (0.75 mL, 2 mol% of DMF). Compound **2**·methylsulfide was obtained as a white solid (4.4 mg, 14%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.03 (s, 8H, H_p), 5.84 (d, 8H, J=7.5 Hz, H_{out}), 4.68 (t, 8H, J=7.8 Hz, H_m), 4.45 (d, 8H, J=7.5 Hz, H_{in}), 4.34 (br, 8H, CH_2–SS), 3.82 (br, 8H, CH_2–SS), 2.16 (m, 16H, CH–CH_2), 1.24–1.49 (m, 64H, feet $(CH_2)_4$), 0.86 (t, 24H, J=6.6 Hz, feet CH_3), −0.65 (s, 6H, guest SCH_3). MALDI-MS (positive mode): 2274 ($M+Ag^+$); calcd ($M+Ag^+$) 2274.

4.5. Competition experiments

Cs_2CO_3 (45.0 mg, 0.14 mmol, 10 equiv per benzylthiol) was added to DMF (15 mL) and stirred for 2 min. Guest **1**, guest **2** (both are 2 mol% of DMF), and tetrathiol **6** (15.0 mg, 0.014 mmol) were added to the mixture. The system was closed and stirred at room temperature for 48 h, then poured into a 2 M aqueous solution of HCl (25 mL). The resultant suspension was extracted with $CHCl_3$ (3×10 mL). The $CHCl_3$ extracts were combined and the solvent was removed in vacuo. The product mixture was then passed through a short silica gel column, eluting with $CHCl_3$/hexanes (1:2), to get rid of polymer byproducts. Product ratios were calculated from the ^{1}H NMR spectra by integration of each set of guest signals. The error in the integration is estimated to be ±10%.

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Supplementary data

Crystallographic data are available. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 696212. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.110.

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