Host–Guest Chemistry

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Synthesis and Methane-Binding Properties of Disulfide-Linked Cryptophane-0.0.0**

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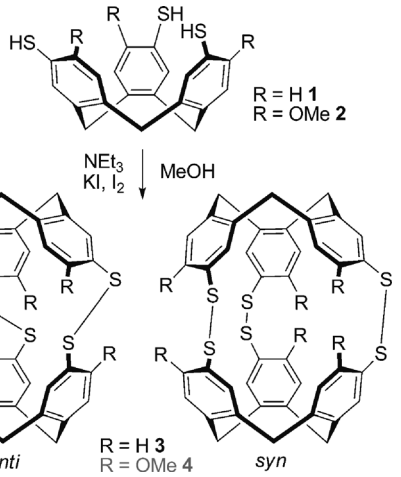
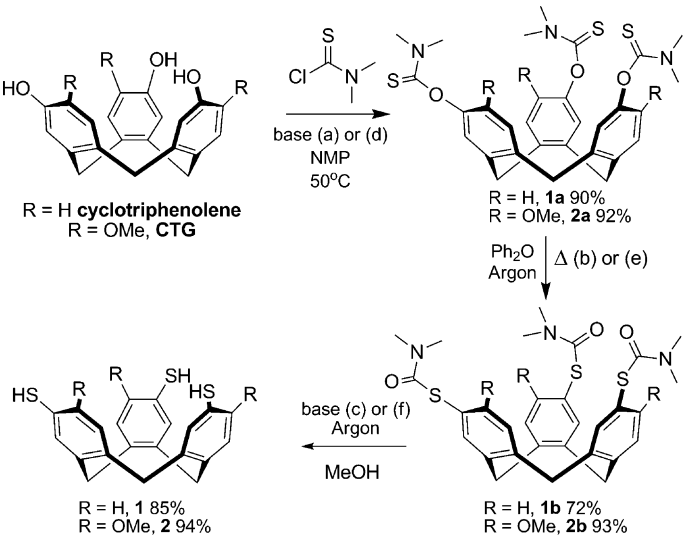
Cryptophanes are cage-like host molecules constructed from two bowl-shaped cyclotriveratrylene (CTV) fragments covalently linked in a head-to-head fashion by three O-$(CH_2)_n$-O bridges.[1] There are two possible geometric isomers, the D_3-symmetric *anti*-isomer which is chiral and the C_{3h}-symmetric *syn*-isomer. Cryptophanes have a well-structured internal molecular cavity, and a rich host–guest chemistry has been established for them.[1] Cryptophanes are often designated by the number of -CH_2- groups in the linking alkyl chains. The smallest reported cryptophane is cryptophane-1.1.1 with O-CH_2-O linkages between the aryl groups of the two host fragments.[2–4] Cryptophane-1.1.1 has good binding properties for small guest molecules including small hydrocarbons[3] and shows remarkably strong binding of xenon.[4] Xenon binding by cryptophanes has garnered much recent interest owing to the potential application of hyperpolarized ^{129}Xe NMR for medical imaging and sensing.[5] The hydrocarbon-binding properties of cryptophanes-2.2.2[6] and −3.3.3 have seen them incorporated into methane-sensing devices.[7] To generate even smaller cryptophanes for potentially improved small-guest binding a direct linkage between heteroatoms at the upper (that is, wider) rims of the CTV-type fragments to give cryptophane-0.0.0 is required. An attractive approach to generating such cryptophanes is to link cyclotriveratrylene analogues with thiol groups at their upper rims through disulfide bond formation, as shown in Scheme 1. Thiolated cryptophanes are known,[8] however all reported examples have traditional O-$(CH_2)_n$-O linkages forming the cryptophane, with the methylthiol or other RS groups in an *ortho* position on the aryl rings. Other types of cage-like species incorporating molecular hosts joined by disulfide links are known.[9]

The novel cavitand cyclotrithiophenolene **1** was synthesized from cyclotriphenolene in three steps (Scheme 2). Cyclotriphenolene was synthesized by a variation on the two-step literature procedure,[2a,4] which involves cyclization of 3-methoxybenzyl alcohol in the presence of P_2O_5, then demethylation with BBr_3. We have significantly improved the yield on this cyclization step from the reported 6% to 14% through use of high dilution and a very slow addition of the 3-methoxybenzyl alcohol. Cyclotriphenolene **1** is deprotonated with Cs_2CO_3 in *N*-methylpyrrolidone, addition of a large excess of *N*,*N*-dimethylthiocarbamoyl chloride then gives the



Scheme 1. Proposed S-cryptophane-0.0.0 synthesis through disulfide bond formation.



Scheme 2. The synthesis of cyclotrithiophenolene **1** and cyclotrithioguaiacylene **2**. Additional details of conditions for **1**: a) Cs_2CO_3; b) 305 °C; c) 4 M KOH. Additional details of conditions for **2**: d) DABCO; e) 255 °C; f) 4 M NaOH. DABCO = 1,4-diazabicyclo-[2.2.2]octane.

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O-aryl *N,N*-dimethylthiocarbamate derivative **1a** in high yields. **1a** undergoes a Newman–Kwart rearrangement to the *S*-aryl *N,N*-dimethylthiocarbamate **1b** through heating at 305 °C in diphenyl ether for 6.5 h under argon, and purified by column chromatography. Finally, cleavage of the thiocarbamate groups from **1b** by KOH in methanol gives **1** in good yields.

The synthesis of cyclotrithioguaiacylene **2** was recently reported by Chambron and co-workers.[10] They investigated two strategies, with the most successful involving Pummerer methodology to give **2** in two steps from cyclotrimethylthioguaiacylene. The other route was based on a Newman–Kwart rearrangement. This gave **2** in an overall yield of approximately 20% in three steps from cyclotriguaiacylene (CTG), although both the rearranged precursor and hence **2** were not considered to be sufficiently pure. We were simultaneously developing a Newman–Kwart route to **2** also outlined in Scheme 2, and can report a significantly better overall yield of approximately 80% for this approach, with excellent product purity.

The synthesis is similar to that for **1** as well as to Chambron's synthesis, but utilizes different reagents and reaction conditions. As before, the first step was treatment of CTG with base (DABCO) and then a large excess of *N,N*-dimethylthiocarbamoyl chloride to give the *O*-aryl *N,N*-dimethylthiocarbamate derivative **2a** in near quantitative yield (Scheme 2). This compares favorably with the 30% reported by Chambron for this step.[10] Compound **2a** undergoes a Newman–Kwart rearrangement to the *S*-aryl *N,N*-dimethylthiocarbamate **2b** through heating at 255 °C in diphenyl ether for 3 h under argon. This rearrangement is particularly sensitive to conditions: heating at lower temperatures or for shorter times leads to incomplete rearrangement, while longer heating times or higher temperatures leads to decomposition. Finally, cleavage of the thiocarbamate groups from **2b** by NaOH in methanol gives **2** in high yields.

X-Ray quality crystals of **2** and its precursor host molecules **2a** and **2b** were grown, and the molecular structures are shown in Figure 1.[11] None of these structures are clathrate, nor inclusion, complexes and there are no additional guest molecules (Supporting Information).

The coupling dimerization of cyclotrithiophenolene **1** to S-cryptophane-0.0.0 **3** proceeds at room temperature in methanol with initial addition of NEt_3 base and KI, then iodine, Scheme 1. A small amount of insoluble polymeric product was separated by filtration, solvent removed, and the residue purified by column chromatography to give **3** in 21% yield. S-cryptophane-0.0.0 **3** was identified by ^{1}H NMR spectroscopy, mass spectrometry, IR spectroscopy, and X-ray crystallography. The room-temperature ^{1}H NMR spectrum is symmetric, does not show the signal at $\delta = 3.34$ ppm attributed to the SH proton of the precursor **1**, and exhibits the pair of doublets for the endo and exo protons of the -CH_2- groups which are characteristic of the bowl conformation of cryptophanes and CTVs. ES-MS gave a *m*/*z* signal at 765.0318 corresponding to {**3**} K^+, and the IR spectrum did not show the peak for ν_{SH} at 2553 cm^{-1}. Attempts to directly couple **2** in the presence of a base and oxidant to give the desired S-cryptophane-0.0.0 **4** were not successful, and only oligomeric and polymeric disulfide products were obtained. This is probably due to steric effects of the methoxy groups.

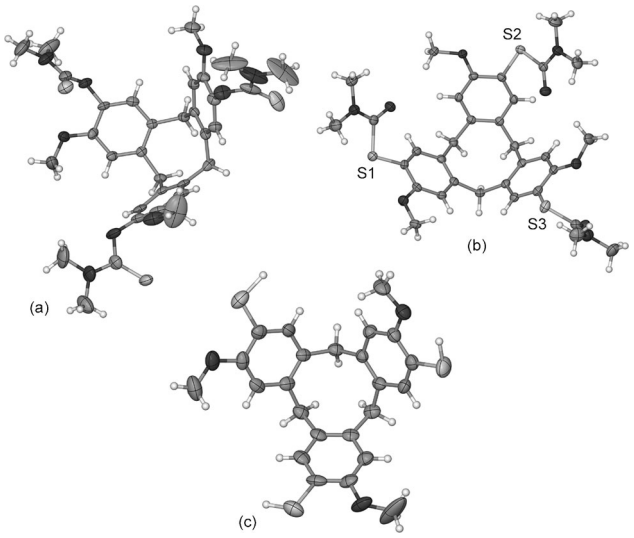

Figure 1. X-Ray crystal structures showing a) **2a**; b) **2b**; c) one molecule from the asymmetric unit of **2**. Thermal ellipsoids set at 50% probability.

Cryptophane **3** was identified as the *anti* isomer by analytical chiral HPLC, as the two enantiomers were observed to separate on the column. This was confirmed by the crystal structure of the clathrate complex **3**·$(NMP)_2$ where NMP = *N*-methylpyrrolidone (Figure 2).[11] The three S–S linkages are the same within errors, with S–S bond lengths 2.0457(15), 2.0453(16), and 2.0462(15) Å and C-S-S-C torsion angles of −67.81(17), −66.24(18), and −66.55(16)°. There are no guest molecules inside the cryptophane as NMP is too large to fit inside the cavity, which its estimated volume is around 40 $Å^3$.

If the sulfide dimerization is performed on a larger scale then small amounts (< 5%) of the *syn* isomer are obtained, however this cannot be separated from the *anti* isomer. *Syn*-S-cryptophane-0.0.0 has an identical mass spectrum to the *anti* isomer, but a distinct ^{1}H NMR spectrum (see Supporting Information).

S-Cryptophane-0.0.0 **3** has the smallest cavity yet known for a cryptophane. According to Rebek's ideal guest–host

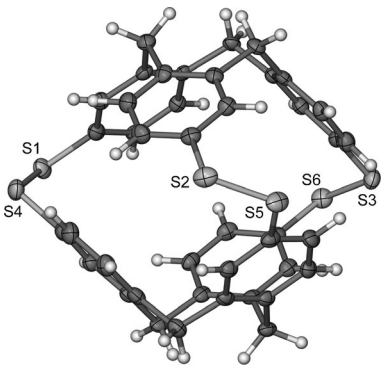

Figure 2. S-cryptophane-0.0.0 **3** from the crystal structure of **3**·$(NMP)_2$. Thermal ellipsoids set at 50% probability.

volume ratio of 0.55,[12] this is a good cavity-size match for a single molecule of methane which has an estimated molecular volume of approximately 28 Å^3. Indeed, ^{1}H NMR studies show that *anti*-S-cryptophane-0.0.0 reversibly binds methane in either CD_2Cl_2 or $CDCl_3$ solution with a K_a(220 K) of 91 and 103 M^{-1} respectively. Association is enthalpy driven with enthalpies of association −19.08 and −37.08 kJ mol^{-1} in CD_2Cl_2 or $CDCl_3$, respectively, and entropies of association −52.5 and −129.8 J mol^{-1} K^{-1}, as determined from the van't Hoff plot (see Supporting Information). Similarly to previous studies of CH_4 binding by cryptophanes,[3] free methane is observed in $CDCl_3$ solution with a chemical shift of $\delta =$ 0.19 ppm at room temperature. On cooling the solution, a second sharp NMR signal appears to high field ($\delta =$ −5.99 ppm at 220 K) attributed to the encapsulated methane (Figure 3). The transition from fast to slow exchange of methane binding to the cryptophane is also apparent through the occurrence of a second set of signals for the cryptophane protons, showing both guest encapsulating cryptophane and free cryptophane in solution. At room temperature an ABX type pattern is observed for the H_A, H_C, and H_B protons. At low temperatures the spin system is AMX-like, the near degeneracy of the H_A and H_C protons being lost as the chemical environment of these protons becomes more dissimilar in the presence of the captured methane (see Supporting Information). Similarly, a second set of doublets is also seen for the exo methylene group. The *syn*-S-cryptophane-0.0.0 shows similar binding properties (see Supporting Information). Interestingly the same NMR spectral trends were observed when the cryptophane was exposed to a nitrogen atmosphere, indicating binding of nitrogen (see Supporting Information). However when H_2 was introduced the ^{1}H NMR spectrum was invariant to temperature hence any H_2 binding is fast on the NMR timescale. Likewise there were no spectral changes on introduction of CO_2, though this is because CO_2 is too large to bind rather than being in fast exchange. The temperature dependence of the spectrum of **3** in the absence of gaseous molecules (i.e. in vacuo) was monitored, and a single set of signals was observed (see Supporting Information).

In summary, we have synthesized the smallest known cryptophane: S-cryptophane-0.0.0 **3**. Preliminary binding studies show that the cryptophane binds dissolved gases in solution including methane and nitrogen.

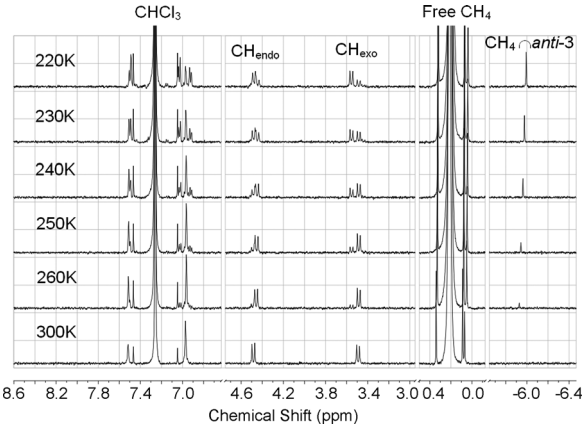

Figure 3. Portion of the variable-temperature ^{1}H NMR spectra of $(CH_4)\cap$*anti*-**3** in $CDCl_3$.

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[11] See Supporting Information for details on the X-Ray structure analyses. CCDC 842783 (**2a**), 842784 (**2b**), 842782 (**2**) and 842785 (**3**·$(NMP)_2$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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