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Fully collapsed “imploded” cryptophanes in solution and the solid state.

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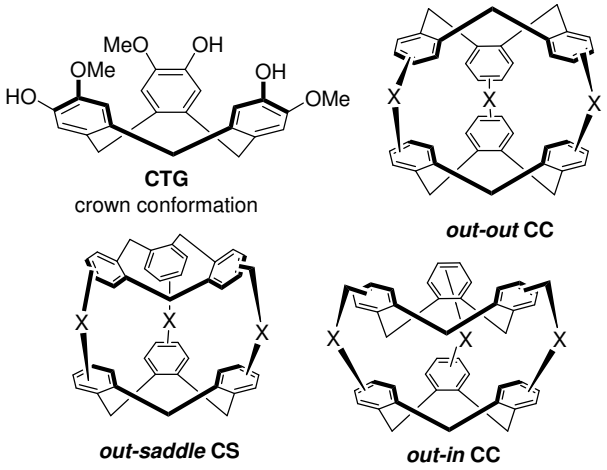
Abstract: Cryptophanes with flexible-linkers derived from (±)-tris-(4-formyl-phenyl)-cyclotriguaiacylene with either bisoxydi(ethylamine) or bis(aminopropyl)ether are isolated as single crystals whose crystal structures show the proposed but previously un-characterised *out-in* conformation where both cyclotriguaiacylene fragments adopt a crown conformation with one crown sitting inside the other. The usual cage-like *out-out* conformation of the cryptophanes is observed on dissolution of the crystals with heating, and these collapse back to the *out-in* isomers over time. In contrast, a cryptophane also derived from (±)-tris-(4-formyl-phenyl)-cyclotriguaiacylene but with rigid dibenzalhydrazine linkers is isolated as the more usual *out-out* isomer.

Cryptophanes are a class of organic cage molecule. They usually feature two cyclotribenzylenes (CTB) moieties joined through three linker groups. [1,2] Most commonly, the CTB moiety is a cyclotriguaiacylene (CTG) derivative. Bowl-shaped *tris*-functionalised CTG units are chiral and cryptophanes can form as the achiral *syn* or chiral *anti* forms. There are various synthetic routes to cryptophanes including template synthesis and capping where preformed CTB units are directly linked together.[1,2] Analogues assembled through coordination bonds [3] or via hydrogen bonding [4] are also known. Cryptophanes are host molecules of diverse guest binding abilities, and may show constrictive guest binding meaning it can be challenging to obtain cryptophanes completely empty of guests.[1] Smaller cryptophanes strongly bind gases such as xenon and hydrocarbons, and the former has led to significant interest in their potential use in biosensors exploiting hyperpolarised ^{129}Xe NMR.[5] Larger cryptophanes and their analogues can complex fullerenes with potential utility in purification of higher fullerenes.[4] CBT cavitands can exist in a bowl-like “crown” or twisted “saddle” conformation. Chiral crown CTBs racemise via the saddle form which is typically 13–16 kJ mol^{-1} higher in energy than the crown conformation.[1] The first kinetically stable saddle structure was reported by Luz who isolated the saddle conformation of cyclotriveratrylene by quenching a high-temperature sample.[6]



Scheme 1. Crown conformation of CTG and different conformations of cryptophanes, *out-in* has never been previously observed.

Conformational exchange can also be observed for cryptophanes, and understanding the conformations adopted and any induced-fit aspects to the molecular recognition behaviour of cryptophanes is important for their continued development as solution and solid state molecular hosts. The typical structure has a crown-crown (CC) *out-out* conformation where the two upper rims the CTBs face one another, Scheme 1. There are a handful of reported examples *out-saddle* conformation that occur where one crown has undergone pseudo-rotation to the twisted saddle form giving a partially “imploded” crown-saddle (CS) structure, Scheme 1.[7-13] The *out-saddle* conformation of imploded cryptophanes was first unequivocally demonstrated by Holman et al with a crystal structure of a *m*-xylyl-linked *anti*-cryptophane,[8] and there has been one further crystal structure of an imploded cryptophane with triallyl-decoration from Dmochowski et al.[10] With the benefit of these well-characterised examples of *out-saddle* cryptophanes, early reports by Collet of *out-out* cryptophanes with highly flexible $O(CH_2)_nO$ (n = 6-10) linkers being in equilibrium with their *out-in* CC conformations (Scheme 1) [7] were subsequently reinterpreted as the *out-saddle* forms, based on signature chemical shifts.[1,8] Furthermore, gas-phase computational studies of the imploded form of cryptophane-E with (OCH_2CH_2O) bridges between CTG units concludes the *saddle-out* conformer is of relatively similar energy to *out-out* forms, and even being slightly lower in energy than guest-free cryptophane.[12] However the *out-in* CC form of cryptophane-E is at least 29 kJ mol^{-1} higher in energy.[12] Formation of imploded cryptophanes is generally attributed to

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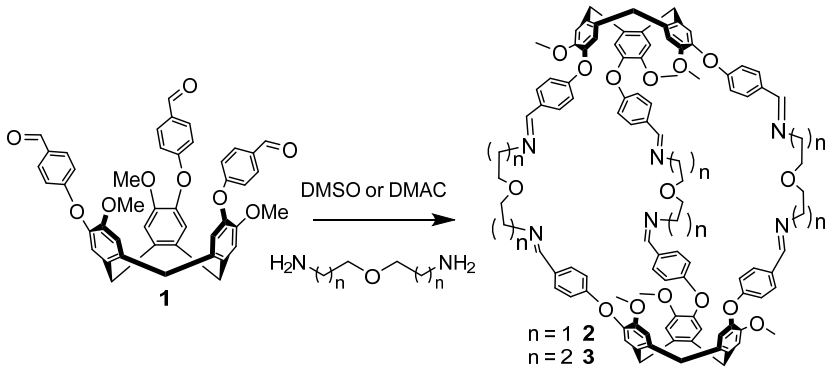
partial collapse of the initially synthesised *out-out* cage structure on removal of included guest molecules, achieved by high temperature evacuation or heating the cage in a solvent that is too large to occupy the cage cavity.[7-12] An exception to this was reported by Berthault and co-workers, who observed spontaneous isomerisation of a water-soluble cryptophane to the *out-saddle* form in de-gassed aqueous solution.[13] The apparent stability of this imploded structure is attributed to the hydrophobicity of the interior of the cryptophane and lack of encapsulation of guest water molecules. The *out-out* form could be reconstituted quantitatively by the introduction of xenon or helium to the aqueous solution to provide a guest molecule.[13] Overall it is likely that if completely evacuated of guests most cryptophanes will implode,[1] unless crown-saddle isomerisation is constricted by very short linkers or in examples where the CTB is a tribenzotriquinacene.[1,14]



Scheme 2. Synthesis of cryptophanes **2** and **3**.

We report herein the first examples of imploded cryptophanes with the fully collapsed *out-in* CC conformation. The *out-in* form has been structurally verified by crystallography, and can be isolated in solution even in the presence of suitable guest molecules. The cryptophanes reported here were synthesised through dynamic covalent chemistry, specifically imine formation. Dynamic covalent chemistry has been a successful approach to the synthesis of various types of organic cage.[14-18] Imine-linked cryptophanes have been previously reported by Warmuth [16,17] and by Kuck,[14] through reaction of aldehyde groups decorating the periphery of CTBs with aliphatic, cyclic or aromatic diamines to give symmetrical capsules, with cage formation sometimes requiring the presence of a guest.[17] This strategy can also be used to generate larger cube-like cages with eight CTB units.[16] We have previously used dynamic di-sulfide bond formation to assemble the world's smallest cryptophane.[18]

(±)-Tris-(4-formyl-phenyl)-cyclotriguaiacylene **1** [19] was reacted with a slight excess of bisoxydi(ethylamine) or bis(aminopropyl)ether in dimethylsulfoxide (DMSO) or dimethylacetamide (DMAC) to afford single crystals of cryptophanes **2** and **3** in low-to-moderate yields, Scheme 2. High dilution conditions were not necessary to be able to isolate clean cryptophanes but monitoring of reaction solutions in d_6-DMSO by NMR indicates other oligomers are being formed in solution. Formation of the cages is supported by mass spectrometry (Figs. S18, S29). The X-ray structure of **2**·4(DMAC)·2(H_2O) was determined in space group *P*-1 from crystals directly synthesised from DMAC solution.[20] The structure of **2** shows that a cryptophane is the outcome of imine bond formation as was expected and with both CTG fragments in the crown conformation. Unexpectedly, the cryptophane is the *out-in* form with the bowl of one CTG unit sitting above the molecular bowl of the other which prevents any guest binding inside the cryptophane, Fig. 1. The two crown CTG units are of opposite enantiomers hence this is a *syn*-cryptophane. The structure has a non-crystallographic C_3 rotation axis. Despite their alignment there are no face-to-face π-π stacking interactions between the two CTG units, and the arene

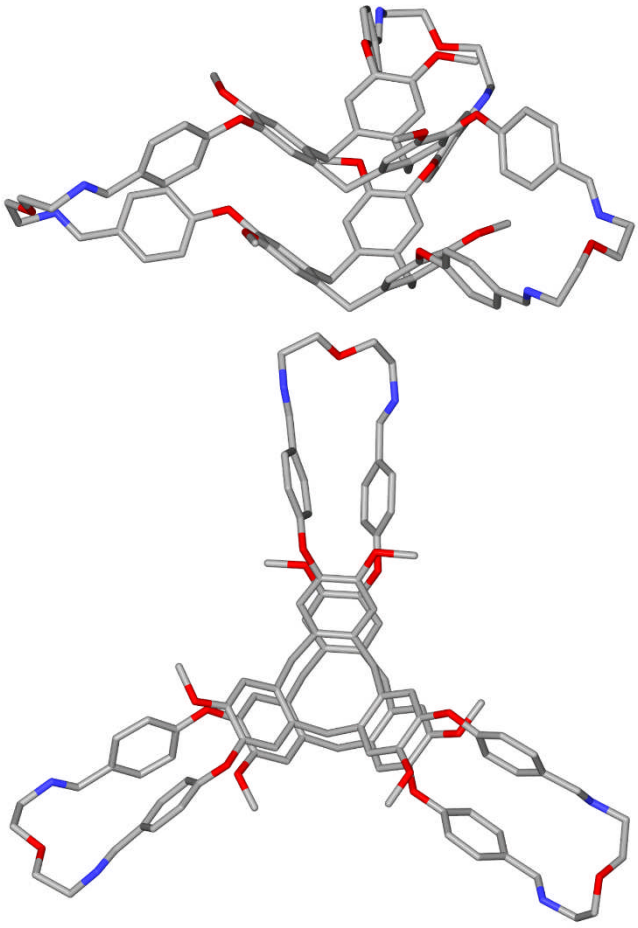


Figure 1. Two views of *out-in* imploded cryptophane from the X-ray structure of **2**·4(DMAC)·2(H_2O).

ring centroid separation is 4.54 Å much longer than the 3.5-3.9 Å that typifies π-stacking. The bowl-in-bowl intramolecular stacking motif extends to the crystal lattice with stacks of cryptophanes forming along the *b* crystallographic axis. The intermolecular distance between CTG units is slightly shorter than the intramolecular distance, at the arene ring centroid separation of 4.51 Å. All imine groups adopt the expected *E*-configuration. The material is a clathrate with solvent molecules of DMAC and water

occupying channels created by the packing of the cryptophanes, Fig. S36.

Single crystals of **3** were obtained from DMSO but were too small and poorly diffracting to give a refineable X-ray structure. A partial solution obtained in space group *R*3 is consistent with the structure of **2**, and clearly shows the *out-in* CC conformation, and columnar packing of cryptophanes, Figs. S37-38. The shortest unit cell length is also indicative of columnar stacking, and is nearly the same for both **2** (9.0936(3) Å) and for **3** (9.0223(14) Å, see SI). Columnar stacking motifs in crown-CTB clathrates results in a shortest unit cell length of 9.61 and 9.78 Å for the achiral cyclotriveratrylene,[21] and ca. 9.1-9.3 Å for enantiomeric CTG-type derivatives.[22]

Crystalline **2** or **3** can be re-dissolved in d_6-DMSO by briefly heating to reflux temperatures. The ^{1}H NMR of **2** shows an initial major and minor species, and a third product that grows in with time to become the dominant product over 2 weeks, Fig. 2 and S5. The solution behaviour of **3** (see SI Figs S20-7 for details) is similar to that of **2** however spectral changes occur at a significantly slower rate, and had not equilibrated after 36 days. In both cases the initial major product is identified as the *out-out* CC isomer, with a highly symmetric ^{1}H NMR spectrum and axial and equatorial methylenic bridging protons appearing as a set of doublets (at 4.90 and 3.70 ppm for **2**) which is characteristic of the CTG crown conformation. The appearance of the central bridging propyl protons in the ^{1}H NMR of **3** is indicative of the *anti*-isomer,[23] which is consistent with inversion of one crown unit from the *syn*-arrangement seen in crystal structures of the *out-in* cryptophanes. The final dominant product is identified as the *out-in* CC cryptophane with the minor species likely to be the intermediate *out-saddle* CS conformation. The conversion to *out-in* does not quite proceed to 100 % completion.

For **2** some material precipitates after two weeks standing and the remaining cryptophane in solution is largely the *out-in* CC conformer. This ^{1}H spectrum is of lower symmetry with the two CTG bowls in different chemical environments, and the spectrum can be assigned, Fig. 2 and S6. Overlap of the imine proton resonances (Hg/g') with two of the benzamine proton resonances (Hc/c'/d/d') was confirmed by HSQC and HMBC (Figs. S8-9). The four benzamine proton resonances are inequivalent, presumably due to hindered rotation, which was confirmed by TOCSY which showed all four are on the same spin system, Fig. S11. The benzamine proton resonances of the *in* (Hc'-f') and *out* (Hc-f) bowls happen to be coincident. There are two sets of axial and equatorial methylenic bridging protons that can be clearly

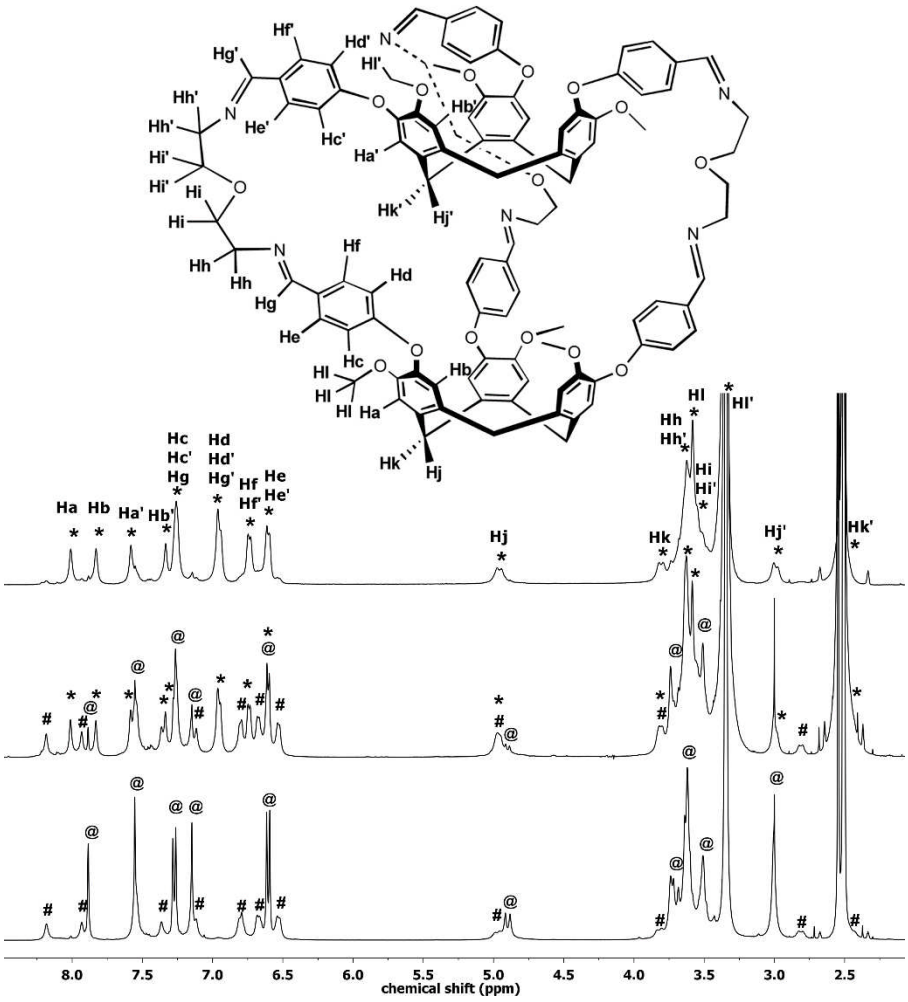


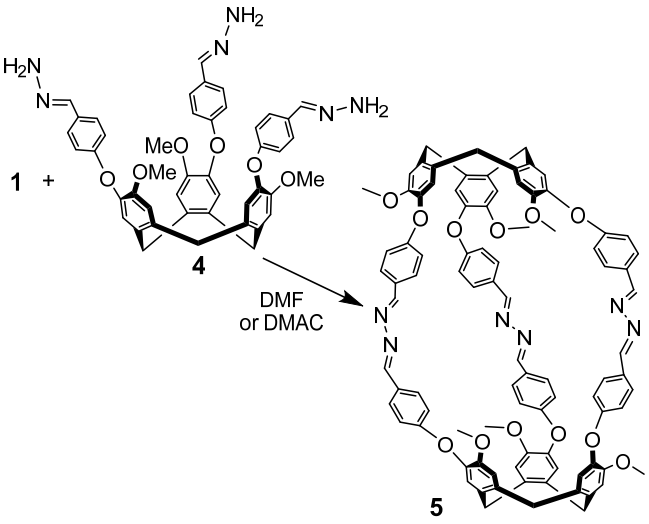
Figure 2. Timecourse ^{1}H NMR (500 MHz) of **2** in d_6-DMSO showing (a) initial spectrum; (b) after 45 hours standing; (c) filtered solution of after 2 weeks. @ designates resonances from *out-out* form; # intermediate kinetic form; * *out-in* form.

identified using COSY (Fig. S12) and HSQC, resonating at 4.91 and 3.76 ppm ($\Delta\delta$= 1.15 ppm) for the *out* bowl and at 2.94 and 2.43 ppm ($\Delta\delta$= 0.51 ppm) for the *in* bowl. Although the *out* bowl shift differences are similar to those observed for many out crown species ($\Delta\delta$= ~1.2 ppm), a separation of only 0.14 ppm was observed for Holman's purified *out-saddle* cryptophane [8] which is significantly different to the observed 0.51 ppm difference observed in this example. The methoxy groups of the two CTG bowls of *out-in* **2** are in different environments resonating at 3.53 and 3.29 ppm. Again, the chemical shifts and shift separations are notably different to those observed in Holman's *out-saddle* cryptophane where methoxy groups were at 3.87 (out) and 2.82 (saddle) ppm, with the large time-average upfield shift of the *saddle* methoxy attributed to it residing as the guest inside the bowl of the *out* crown.[8] This type of internal guest arrangement is not consistent with the *out-in* cryptophane structure and we do not observe such a large upfield shift of the methoxy, supporting that the dominant species on equilibration of **2** has a different conformation.

NOESY and ROESY spectra of **2** recorded after 2 weeks in solution (Fig. S13-15) corroborates that the two CTG bowls are distinguishable and show the through space couplings that are expected within each CTG bowl between the two aryl proton environments at 8.01, 7.82 *ppm* (Ha, Hb) for the *out* bowl and 7.58, 7.31 ppm (Ha', Hb') for the *in* bowl. There are also couplings between protons on the benzamine units that shows the two bowls are in close proximity (between He/e' and Hf/f' and Hc/c' and Hd/d'), and between the methoxys of the *out* and *in* bowls with benzamine Hc/c' and Hd/d' respectively (Fig. S14). This is consistent with the crystal structure of **2** where H···H separations between methoxy protons of one bowl and those benzamine protons of the other are at separations 2.51 - 2.82 Å. 2D DOSY NMR of the same solution (Fig. S16) shows the presence of two large species with diffusion coefficients of D = 1.083 x10^{-10} m^2 for the small amount of the larger *out-out* cryptophane that remains in solution, and D = 1.377 x10^{-10} m^2 for the smaller *out-in* species. DOSY NMR of **3** (Fig. S26) taken after 27 days equilibration shows three large species, commensurate with the slower rate of conformational exchange.

The intermediate kinetic species that is present at low concentrations could not be isolated and is tentatively assigned as the *out-saddle* intermediate that would occur if conversion of *out-out* **2** to *out-in* **2** occurs via racemisation of one crown. Another possibility is that cryptophane rearrangement occurs through partial hydrolysis then reformation of the imine bonds, however this can be discounted by the lack of an aldehyde resonance for the observed intermediate. Addition of the potential guest molecules ferrocene [17] or *o*-carborane [24] to DMSO solutions of *out-in* **2** does not result in substantial changes to the NMR spectrum. Likewise *o*-carborane addition to *out-out* cryptophane **2** does not prevent the conformational transformation, Fig S17. DMSO is itself a known guest for CTG-type cavitands.[24] Hence, the fully imploded structure occurs even in the presence of viable guests and, in contrast to most reported examples of the partially-imploded *out-saddle* cryptophanes, the introduction of new potential guest molecules does not drive the cryptophane back to the *out-out* form which only occurs on heating to DMSO boiling point.[26]

We investigated a cryptophane that was also derived from **1** by dynamic covalent bond formation but with shorter and more rigid linkers. Reaction of **1** with (±)-tris-(4-benzaldehydehydrazone)-cyclotriguaiacylene **4** in DMAC or DMF under conditions of high dilution and heat affords the hydrazine-linked cryptophane **5**, Scheme 3. Cryptophane **5** is extremely insoluble and single crystals of **5**·n(DMAC) were obtained directly from the reaction mixture after several weeks of standing. The crystal structure of **5**·n(DMAC) [20] has three different cryptophanes in the asymmetric unit each with differences in rotations of their dibenzalhydrazine linkers and/or CTG methoxy groups, Fig. S39. All imine groups are in the *E*-configuration. Each cryptophane is in the expected *out-out* CC conformation with *anti* stereoisomerism and with two molecules of DMAC acting as guest molecules within the cavities, shown for one cryptophane in Fig. 3. All guest DMAC are oriented such that the methyl attached to the carbonyl is directed into the cavitand bowl. This is a pertinent illustration that CTG-derivatives and cryptophanes bind solvents of this ilk as guests. Formation of the cage in d_7-DMF can be monitored by ^{1}H NMR (Fig. S32) and is also consistent with the *out-out* CC species, and the cage is observed by mass spectrometry (Fig. S33). Once the material has precipitated it could not be re-dissolved.



Scheme 3. Synthesis of hydrazine-linked cryptophane **5**.

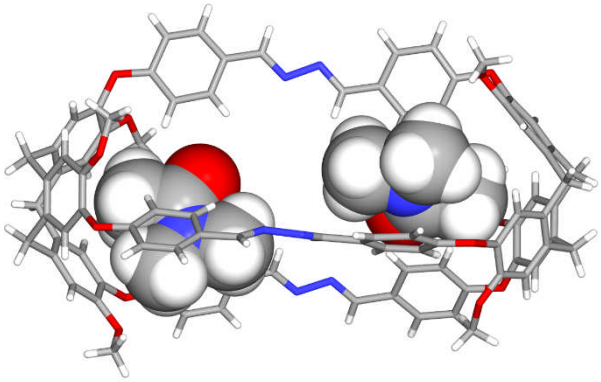


Figure 3. From the crystal structure of **5**·n(DMAC) with guest DMAC shown in space-filling mode.

In summary, we have demonstrated that dynamic imine formation is a successful strategy for development of cryptophanes with extended linkers, noting there are relatively few examples of larger cryptophanes.[7,27] Two of the new cryptophanes show new behaviour for a cryptophane, forming the completely imploded *out-in* cryptophane in both the solid state and in solution, and for these examples, are the equilibrated conformer. The cryptophane with shorter and more inflexible linkers gives the more anticipated *out-out* form. Most remarkably, the collapsed structures occur in the presence of potential guest molecules. This is unexpected as previous examples have only unequivocally shown that implosion leads to the *out-saddle* form, and that such implosion usually occurs on active guest exclusion. While cryptophanes with short linkers are not expected to fully collapse as this would cause high

strain, such collapse might be more expected for those with long and flexible linkers, however this was not the case for previous examples with C_6-C_{10} alkyl-chain linkers,[1] which are more flexible than the imine moieties here. Furthermore, of **2** and **3** reported here, the cryptophane with the longest and most flexible linkers actually showed the slowest rearrangement.

Acknowledgements

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Data accessibility: data supporting this study are available at https://doi.org/10.5518/543.

Keywords: cryptophane • dynamic covalent chemistry • cage conformations • host-guest • supramolecular

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