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COMMUNICATION

Templated dynamic cryptophane formation in water†‡

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Several dynamic hexaimine cryptophanes, that are built up from two triformylcyclotribenzylene cavitands and three diamino linkers and spontaneously assemble in water in the presence of a suitable templating guest, are reported. X-ray structure, kinetics and thermodynamics of assembly and molecular recognition properties are discussed.

Supramolecular chemistry aims at investigating and understanding molecular assemblies and weak intermolecular interactions, which are ubiquitous in nature and essential for processes that take place in biology.[1] Central to this endeavor has been the design of molecular entities capable of organizing into supramolecular species or supermolecules, which mimic functions of biological systems or display novel properties. In recent years covalent analogues of supermolecules could be realized by using reversible covalent bonds.[2] Like self-assembly processes utilizing hydrogen bonding or other non-covalent interactions, dynamic covalent chemistry is subject to proof reading and error correction but has the advantage of better control over the reversibility of the bond formation.[2a] This not only allows generation of virtual dynamic molecular libraries,[2c] in which components are under constant exchange, but also dynamic covalent syntheses of novel materials, macromolecules, receptors, molecular machines and other molecular devices.[2a,b] Research in our and other laboratories has demonstrated the proficiency of dynamic covalent chemistry for the efficient, multi-component synthesis of molecular container molecules and larger nanocapsules.[3,4] Application of Schiff base chemistry allowed assembly of capsules with varying size and geometry.[3a–d] Nevertheless, the thermodynamic lability of the imine bond in water, which is the desired medium for biomedical applications of such dynamic covalent assemblies, is a disadvantage of this type of chemistry. Our hypothesis has been that template effects, which are essential for the formation of self-assembly capsules using weak non-covalent binding interactions,[4b] may also drive formation of polyimine container molecules in water. To test this hypothesis, we have investigated the possibility to assemble polyimine cryptophanes in aqueous medium. Cryptophanes are an interesting class of spherical container molecules composed of two chiral cyclotriveratrylenes (CTVs) that are three-fold linked.[5] The chiral *anti* form, in which the CTV units have the same handedness, has interesting chiral recognition properties and has helped answer important questions related to the chiroptical properties of perhalogenated alkanes.[6] Due to their exceptional Xe binding properties, cryptophanes show great promise for magnetic resonance imaging involving hyperpolarized Xe, a field, that is continuously evolving.[5c,7] Earlier, our group reported the first quantitative, dynamic cryptophane synthesis that allowed dynamic resolution of cyclotribenzylenes (CTBs) **1** and **2**. If a solution of **1** (or **2**), 1.5 equivalents of (*R*,*R*)-1,2-diaminocyclohexane **3** and catalytic amounts of trifluoroacetic acid was stirred for three weeks at room temperature, cryptophane (*P*,*P*)-**4** formed quantitatively (Chart 1).[3d] Rate limiting in this thermodynamic synthesis of **4** is cup inversion of (*M*)-**1**(**2**) to (*P*)-**1**(**2**). This multi-component assembly, in which the cryptophane is constructed from two CTBs and three linker units, held together by six covalent bonds, represents a conceptionally new way to synthesize cryptophanes, which differs from the traditional *direct assembly method* and the

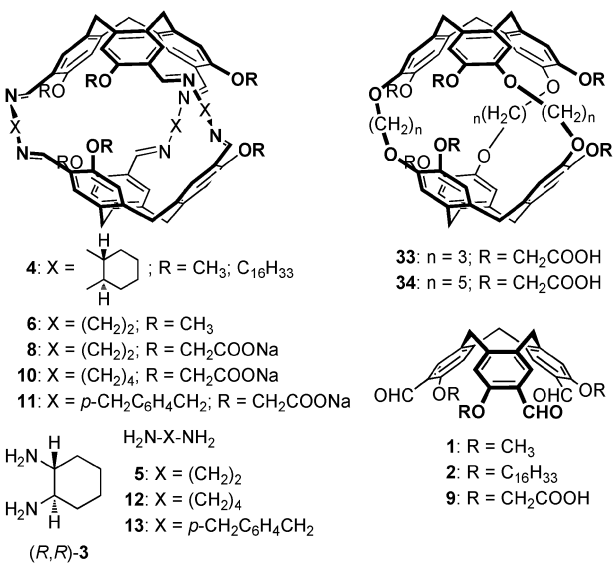

Chart 1 Cryptophanes, triformyltribenzylenes and diamines.

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‡ Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for **6**, **8**–**11** and cryptophane complexes. Yield of **8**·CH_2Cl_2 as a function of pD. CCDC 809740 (**6**·CH_2Cl_2). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10510h

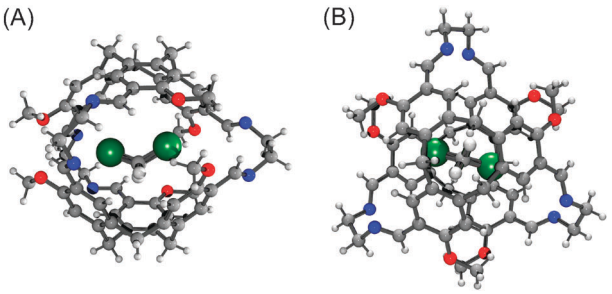


Fig. 1 Ball and stick models of an X-ray structure of **6**·CH_2Cl_2. Side view (A) and top view (B).

templated approach, both pioneered by Collet,[5a] or the *CTV-coupling route* introduced by Cram and coworkers.[8] Closest, perhaps, is the recent metal-coordination approach developed by Zhong *et al.*, in which both CTVs are assembled through six dative Pd–ligand (CTV) bonds.[9] As we will show below, our multi-component approach is versatile and highly efficient, if dynamic covalent bonds are utilized.

Substitution of **3** for **5** gave quantitatively cryptophane **6** under the same conditions as described for the synthesis of **4**. MALDI-TOF and ^{1}H-NMR spectra of the reaction mixture were consistent with formation of either achiral (*P*,*M*)-**7** or racemic (*M*,*M*)-**6**/(*P*,*P*)-**6**. X-Ray crystallography confirmed a self-sorting process leading exclusively to **6**. Cryptophane **6** crystallized from CH_2Cl_2/CH_3OH with one encapsulated CH_2Cl_2 guest (Fig. 1) and has C_{3v} symmetry. Both cavitands are rotated against each other by 60° around the polar C_3 axis, which reduces the cavity volume to 110 Å^3. As a result, space occupancy inside the cavity is close to optimal. The CH_2Cl_2 guest is six-fold disordered and oriented such that one H forms a perfect CH–π interaction with one of the host's arenes. Both Cl atoms are located in the equatorial plane of **6** and form multiple contacts with arenes of the upper and lower CTBs. We wondered, if an array of stabilizing host–guest interactions could drive formation of an equivalent cryptophane complex **8**·Guest in water. Indeed, addition of small amounts of $N(CH_3)_4OH$ or CH_2Cl_2 to water-soluble CTB **9** and two equivalents of **5** in D_2O at pD > 11 leads to spontaneous formation of cryptophane complexes **8**·Guest in close to quantitative yield (Fig. 2C and D and Scheme 1). Yields maximized after approximately two hours. Furthermore, lowering or raising the pD of the medium allowed controlling the apparent stability of **8**·Guest, since its formation requires free **5**. Hence, essentially no complex is observed below pD 9, but maximizes above pD 12.5 (Fig. S11). The following observations further support reversibility of the system and the requirement for a suitable templating guest: when a solution of **8**·CH_2Cl_2 was left standing at rt for several days, whereby excess and complexed CH_2Cl_2 evaporated, **8** rearranged into oligomeric aggregates. The same aggregates form, if **9** and two equivalents of **5** are mixed at pD > 11 in D_2O in the absence of a template (Fig. 2A and B), or in the presence of a potential template that is too big for the inner cavity of **8**, such as acetophenone. The latter experiments also demonstrate that **5** is not a suitable template, which is surprising at first, since the van der Waals volume of **5** (V_{vdW} = 65 Å^3) is about the same as that of CH_2Cl_2 (V_{vdW} = 57 Å^3).§ We speculate that

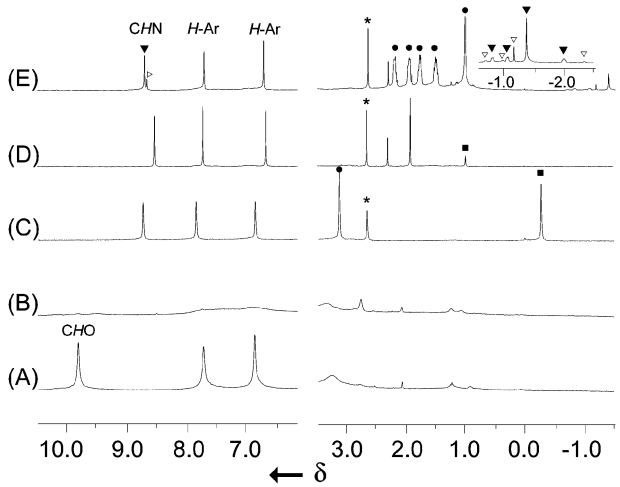
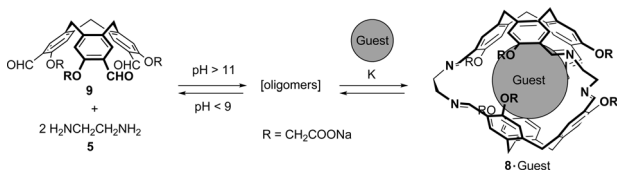


Fig. 2 ^{1}H NMR spectra showing the templated formation dynamic cryptophane complexes in D_2O at pD >11. (A) **9** alone (300 MHz; 25 °C; D_2O; NaOD). (B) **9** and two equiv. **5** (300 MHz; 25 °C; D_2O; NaOD). (C) **9**, two equiv. **5** and 1.1 equiv. of $N(CH_3)_4OH$ (300 MHz; 25 °C; D_2O; NaOD). (D) **9**, two equiv. **5** and excess CH_2Cl_2 (400 MHz; 25 °C; D_2O; NaOD). (E) **9**, two equiv. **5** and excess **24** (500 MHz; 25 °C; D_2O; NaOD; after H/D exchange). Signals are marked as follows: excess **5** (*), free guest (●); complexed CH_2Cl_2 and $N(CH_3)_4^+$ (■); minor (▽) and major (▼) diastereomers of **8**·**24**.



Scheme 1 Templated, reversible complex **8**·Guest formation in D_2O.

the reactivity of encapsulated **5** towards the imine bonds prevents formation/observation of hypothetical **8**·**5**. If the latter complex would form, the high inner phase molarity of **5** ([**5**] = 15 mol L^{-1}) likely results in an instantaneous trans-imination reaction, breaking **8** open. Thus, **8**·**5** should be thermodynamically strongly destabilized and may exist only in trace amounts, if at all.

Not knowing the concentration of hypothetical free **8**, we defined the stability constant of **8**·Guest as K = [**8**·Guest]/[oligomers][Guest]$_{free}$ = 1600 M^{-1} for CH_2Cl_2 (ΔG_{298K} = −4.4 kcal mol^{-1}; Scheme 1). Cryptophane binds a large spectrum of different guests, whose van der Waals volume ranges from 57 Å^3 (CH_2Cl_2) to 118 Å^3 (choline **27**) (Chart 2). Maximum binding strength is observed for $CHCl_3$. Guests that are too large in one or multiple dimensions, such as acetophenone, toluene or $[N(n\text{-}Bu)_4]^+$, or too reactive (*e.g.* 2,3-cyclohexenone) did not template formation of **8**. We attribute the high binding versatility of **8** to its ability to adapt to the size of the guest by a wrapping/unwrapping motion around the polar C_3 axis.[7c] Competition experiments for guests **14**, **15**, **17**, **19**, **21**, **24** and **27**, did not give a smooth bell-shaped selectivity plot, which is typically observed for cryptophanes in organic solvents.[5a] This must be attributed to the different hydrophobicity of the guests, which will lead to substantially different dehydration energies.¶ However, size complementarity between

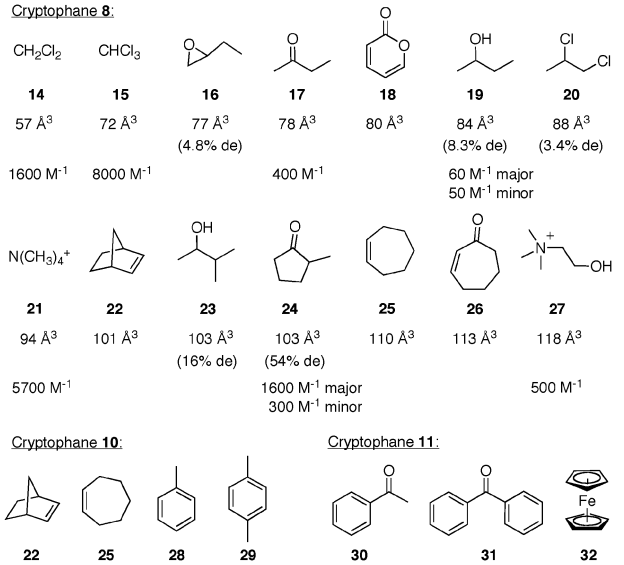


Chart 2 Templates for cryptophanes **8**, **10** and **11**, van der Waals volume,§ de (in parenthesis) and complex stability constant *K*. The error of *K* is 10%.

guest and cavity is observed in a comparison between **8** and water-soluble cryptophanes E3 (**33**) and O (**34**), which have five and seven atom O–$(CH_2)_n$–O linkers, respectively. For these hosts, binding affinity for $N(CH_3)_4^+$ increases in the order **33** (K = 320 M^{-1}) < **34** (K = 2700 M^{-1}), < **8** (K = 5700 M^{-1}) and for the larger choline in the order **33** (K = 350 M^{-1}) < **8** (K = 500 M^{-1}) ≪ **34** (K = 7300 M^{-1}).[10] Thus, optimal match between guest and cavity is observed with a six-atom linker for $N(CH_3)_4^+$ and shifts towards longer linkers for choline. Unfortunately, the instability of acetylcholine at pD > 11 prevented us to measure the choline/acetylcholine selectivity.

The chiral recognition properties revealed additional interesting features of **8**. Diastereomeric excess (de) of chiral guests **16**, **19**, **20**, **23** and **24** range from de = 3.4% to 54% for 2-methylcyclopentanone (Fig. 2E), and roughly scales with guest size (Chart 2). In order to get insight into the kinetic selectivity of **8**, we performed EXSY NMR experiments on diastereomeric **8**·**24**. Interestingly, the chiral selectivity of **8** is reversed in the transition state (TS) for guest exchange. Formation of the minor diastereomer was two-fold faster than that of the major (k^+_{minor}/k^+_{major} = 2; $\Delta\Delta G^{\ddagger}$ = 0.4 kcal mol^{-1}) and dissociation of the minor seven times faster than that of the major (k^-_{minor}/k^-_{major} = 7; $\Delta\Delta G^{\ddagger}$ = 1.15 kcal mol^{-1}). Constrictive binding energy (=$\Delta G^{\ddagger}$ for complexation) for both diastereomeric complexes are 3 and 3.4 kcal mol^{-1} higher than observed for **8**·CH_2Cl_2 ($\Delta G^{\ddagger}$ = 13.1 kcal mol^{-1}), which is consistent with guest size and steric interactions in the TS. Kinetic chiral selectivity is an important property of **8**, since the two diastereomeric TSs for guest exchange may represent good models for stereoselectivity in through-shell reactions between a bulk phase reactant that interacts in a portal with an encapsulated catalyst or reactant.[11] Work is currently in progress to increase selectivity by increasing bulk and rigidity of the linkers of **8**.

We were also able to prepare larger hexaimine cryptophanes **10** and **11** by reacting **8** with 1,4-diaminobutane **12** or *p*-xylylenediamine **13**, respectively, in the presence of suitable guests (Chart 2). Signals for encapsulated guests could only be observed in the NMR spectra of **10**·**22** and **10**·**25**. In all other cases, only signals of **10** and **11** were present. However, differences in chemical shifts of host protons suggest that guests are encapsulated, but exchange rapidly on the NMR scale with free guest and that cryptophane formation is templated by the guest additive in all cases.

In summary, we have developed water-soluble, dynamic hexaimine cryptophanes, that spontaneously assemble in aqueous medium from two triformylcyclotribenzylenes and three diamino linkers in the presence of a suitable template. Guest templation is essential for the formation of these container molecules. The dynamic cryptophanes display great diversity and interesting chiral selectivity in their molecular recognition properties that makes them promising prototypes for the development of responsive molecular materials, sensors and nanoreactors.

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Notes and references

§ Volumes were calculated from energy minimized structures (MM3) using the program Swiss-PdbViewer; http://www.expasy.org/spdbv/.
¶ The octanol–water partition coefficient log *P* increase in the order **17** < **19** < **24** < **14** < **15**.

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