

Triply interlocked covalent organic cages

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Interlocked molecules comprise two or more separate components that are joined by 'mechanical' rather than covalent bonds. In other words, these molecular assemblies cannot be dissociated without the cleavage of one or more chemical bonds. Although recent progress has enabled the preparation of such topologies through coordination or templating interactions, three-dimensional interlocked covalent architectures remain difficult to prepare. Here, we present a template-free one-pot synthesis of triply interlocked organic cages. These 20-component dimers consist of two tetrahedral monomeric cages each built from four nodes and six linkers. The monomers exhibit axial chirality, which is recognized by their partner cage during the template-free interlocking assembly process. The dimeric cages also include two well-defined cavities per assembly, which for one of the systems studied led to the formation of a supramolecular host-guest chain. These interlocked organic molecules may prove useful as part of a toolkit for the modular construction of complex porous solids and other supramolecular assemblies.

In spite of remarkable progress in recent years, the preparation of complex mechanically interlocked architectures such as catenanes^{1–4}, rotaxanes⁵, Borromean rings^{6–8}, Trefoil knots⁹ and Solomon knots^{6,10,11} remains a formidable synthetic challenge^{12,13}. Most systems are constructed from monocyclic molecules, and interlocked assemblies of bicyclic or tricyclic species are synthetically demanding and comparatively rare.

The first triply interpenetrated molecular topology was realized in 1999 when Fujita and colleagues reported the spontaneous self-assembly of ten components into two interlocked, three-stranded coordination cages¹⁴. This involved a reversible, metal-mediated process with palladium as the cage vertices. Almost a decade later, Hardie and colleagues described cobalt and zinc-based systems with a similar topology¹⁵, and Fukuda and colleagues reported an interlocked arrangement of two four-stranded palladium coordination cages¹⁶. Very recently, Beer and colleagues prepared a multiply interlocked system in which the crossing cycles consisted of covalent entities¹⁷. This assembly was templated by sulfate ions, which remained bound within the dimer after synthesis. Organic cavitands¹⁸ such as cryptophanes¹⁹ and carcerands^{20,21} are cage-like molecules with a permanent internal void space. Such species can in principle interlock in a multiply interpenetrated fashion, but it is challenging to devise molecules with appropriate structures, topologies and symmetries to achieve this in a three-dimensional covalent architecture.

We recently described the synthesis of tetrahedral covalent organic cages formed by a [4 + 6] cycloimination reaction between triformylbenzene and a series of 1,2-vicinal diamines²². These tetrahedral symmetry cages include four windows that are large enough to be penetrated by small molecules such as gases and organic solvents. As a result, the organic crystals can exhibit high levels of permanent microporosity after desolvation, with Brunauer–Emmett–Teller surface areas exceeding 600 m² g^{−1} (ref. 22).

We now show that such cages can be multiply interlocked using dynamic covalent chemistry in the presence of an acid catalyst. These compact, catenated dimers are entirely covalent and assemble without the aid of any additional template (Fig. 1). In general, the synthesis of interlocked molecules and molecular knots relies on multistep synthetic routes, often combined with metal templating^{2,9,12}.

The single-step formation of covalently bonded interlinked organic molecules is challenging, although clearly beneficial^{23–26}. We have combined 20 components to form triply interlocked species in good yield, in one step, and from commercially available precursors. Indeed, a remarkable level of complexity emerges from rather simple starting materials and procedures.

Results

The interlocked dimer **3a** (1,753 g mol^{−1}) was obtained in 60% yield via cycloamination of trialdehyde **1** with 1.5 equiv. of propane-1,2-diamine (**2a**), using acetonitrile as the solvent in the presence of trifluoroacetic acid (TFA). In the absence of TFA, the non-interlocked, monomeric cage (876.5 g mol^{−1}) was formed, as described previously²². The corresponding reaction with (1*R*,2*R*)-1,2-diaminocyclopentane (**2b**) in dichloromethane produced an analogous dimer, **3b** (2,064 g mol^{−1}), in 40% crude yield. Similarly, the reaction of ethane-1,2-diamine (**2c**) in acetonitrile produced dimer **3c** (1,585 g mol^{−1}) in 56% crude yield. Remarkably, the assembly of all three of these complex interlocked dimers is readily accomplished on gram scales in a one-pot reaction that involves 20 precursor molecules. The synthesis requires no additional template other than the solvent and the precursors. It is likely that the water released in the condensation reaction, together with the TFA catalyst, promotes a dynamic equilibrium via reversible imine bond formation^{6,27}.

Both **3a** and **3b** formed crystals that were suitable for X-ray structure analysis. Catenane **3a** crystallized from methanol in space group *R*3̄*c* in the form of the solvate **3a**·7MeOH·3H₂O, whereas crystals of **3b** were obtained as dichloromethane solvates in space group *C*222₁. The crystal structures show that two tetrahedral cages interlock so that three of the four windows in each cage are penetrated by the bisimine linkers of the partner cage (Fig. 2). As a result, each cage accommodates one aryl ring from its partner. The two encaged aryl rings are aligned by π – π stacking. The tetrahedral cages are tricyclic and therefore topologically equivalent to a 3-torus. The dimer can therefore be described as two interlocked 3-tori with six crossing cycles, three from each cage (Fig. 3). Fujita's Pd-complex¹⁴ is interlocked via six crossing cycles, but its monomers are bicyclic and therefore topologically equivalent to a 2-torus. To our knowledge,

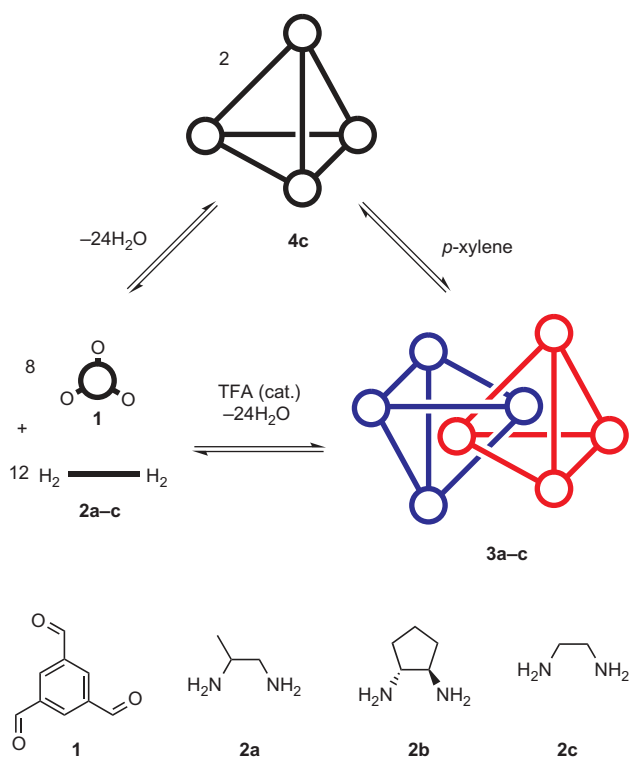


Figure 1 | Synthesis of interlocked cages 3a-c. Reaction of triformylbenzene (1) with propane-1,2-diamine (2a) in the presence of TFA affords the interlocked dimer 3a. The analogous reaction of 1 with (1*R*,2*R*)-1,2-diaminocyclopentane (2b) yields the analogous interlocked dimer 3b. Similarly, the reaction of 1 with ethane-1,2-diamine (2c) yields dimer 3c. In contrast, the monomeric cage 4c is first formed from 2c in the absence of TFA, but subsequently reorganizes in solution into the dimer 3c over longer timescales.

the only other example of an interlocked 3-torus dimer is the metal coordination compound reported by Fukuda and colleagues¹⁶; this, however, has eight crossing cycles (four per monomer). Unlike this structure and that of Fujita¹⁴, in which all cycles are crossing cycles, each cage molecule in dimers 3a and 3b possesses a non-crossing cycle corresponding to its open, non-penetrated window (Fig. 3c). Significantly, the open, non-crossing cycle can be penetrated by other molecules. The open windows of 3a and 3b generate two cavities at opposing ends of the dimer, rather like an ‘egg cup’. These cavities are large enough to accommodate other molecules. For example, the windows of 3a are occupied by methanol when crystallized from this solvent (Fig. 2B). The methyl group in the solvent faces into the hydrophobic interior of the cavity, and the hydroxyl group is hydrogen-bonded to additional interstitial lattice solvent. In contrast to Fujita’s coordination complex, dimers 3a, 3b and 3c are entirely covalent. As a result, the molar mass for 3b is approximately half that of the Fujita assembly, because the structure is composed solely of light elements, even though the dimensions of 3b (22 × 22 × 22 Å; Supplementary Fig. S23) are very similar.

The crystals of 3b are homochiral; the two interlocked cage molecules are crystallographically related via a twofold rotation axis, and the local symmetry of the catenane approximates point group D_3 . In contrast, catenane 3a is arranged around the D_3 symmetry site of space group $R\bar{3}c$ (Wyckoff position a). There are twelve 1,2-propane units in catenated dimer 3a, each of which exhibits positional isomerism. The number of possible positional isomers, z , of a dimer 3 with n types of vertices can be calculated by the expression

$$z = (n^{12} + 3n^6 + 2n^4)/6 \quad (1)$$

There are therefore 720 possible positional isomers for 3a ($n = 2$, owing to the two possible axial orientations per 1,2-propane group). Four of these isomers have point group symmetry D_3 , six are C_3 , 60 are C_2 , and the remaining 650 display C_1 symmetry. Based on their orientation, the six 1,2-propane groups that penetrate the cage windows can exercise different steric effects, depending on whether the methyl groups point towards or away from the window ‘frame’ of the partner cage. As such, the different isomers deviate to varying degrees from the ideal D_3 symmetry and, as a result, the anisotropic displacement parameters are elongated perpendicular to the threefold axis. This disorder explains why the crystals diffracted to only low resolution despite their relatively large size (~1–2 mm).

These cage compounds are stable as dry solids for many months, but undergo complex imine interchange reactions in solution under certain conditions. For example, when dissolved in a mixture of dichloromethane and *p*-xylene, the monomeric cage 4c forms a catenane in the absence of added TFA over a period of 50 days to form crystals of 3c:3 *p*-xylene (Fig. 2C). As in the case of 3a and 3b, the interlocked cages in 3c have matched helicity. This spontaneous enantioselective interlocking of cage 4c in the absence of acid suggests that the catenane 3c is a thermodynamically favoured product that in this case is removed from the equilibrium by crystallization. Acid catalysis accelerates the catenation reaction, whereas catenation in the absence of acid requires up to 50 days. In both cases, the catenane is removed from the equilibrium by phase separation. We tentatively suggest that π - π stacking interactions (Fig. 2) may stabilize the formation of the catenated species. This is further supported by control experiments with mesitylene, as described below. Additional studies regarding the effect of solvent and TFA concentration are in progress. Initial findings show that lower TFA concentrations lead to mixtures of catenated and non-catenated species, at least on reaction timescales of a few days (Supplementary Fig. S9).

The crystal structure of 3c:3 *p*-xylene comprises a polymeric host-guest assembly in which *p*-xylene molecules penetrate the open windows of two interlocked dimers (Fig. 2C). Dimer 3c is therefore a linear director, forming infinite one-dimensional chains in the solvated crystal structure, reminiscent of doubly fused calix[4]arenes, which can also form linear inclusion polymers in the presence of suitable connectors^{28,29}. The remaining two *p*-xylene molecules in the crystal are located in channels running between the one-dimensional polymeric host-guest strands (Supplementary Fig. S28).

The very compact nature of these interlocked dimers is apparent in the space filling model given for 3c in Fig. 2E. It is also significant that the interlocked dimers have a helical structure (Fig. 3a). Helicity, or axial chirality, is an intrinsic property of the monomeric cages. All six bisimino vertices must be of the same enantiomer, and the vertex substituents must occupy *exo*-positions to facilitate a tetrahedral molecular structure. It appears that both cages in the dimer must provide ‘threads’ of equivalent helicity to ensure effective interlocking. As a result, the dimer of 3a contains twelve 1,2-propane units of one enantiomer only. This is remarkable, because a racemic diamine, 2a, was used in the synthesis, suggesting a highly selective multicomponent reaction in which each interlocked dimer ‘self-resolves’ its axial chirality in the assembly process. As a result, the dimers are chiral but the crystals are racemic.

Molecular models of the two possible dimers for 3b were generated and optimized using the Materials Studio 5.0 (Accelrys) density functional module *Dmol*³. The dimer consisting of two equivalent cage enantiomers (Fig. 4a) was calculated to be 22.9 kJ mol⁻¹ more stable than the dimer comprising unmatched enantiomers (Fig. 4b). Cages with matched axial chirality interlock more effectively: the closest atom-to-atom contacts are 2.26 Å, compared with 1.99 Å for the dimer comprising mismatched enantiomers. The mismatched dimer model also includes a greater number of close atom-to-atom contacts. These two models are shown in

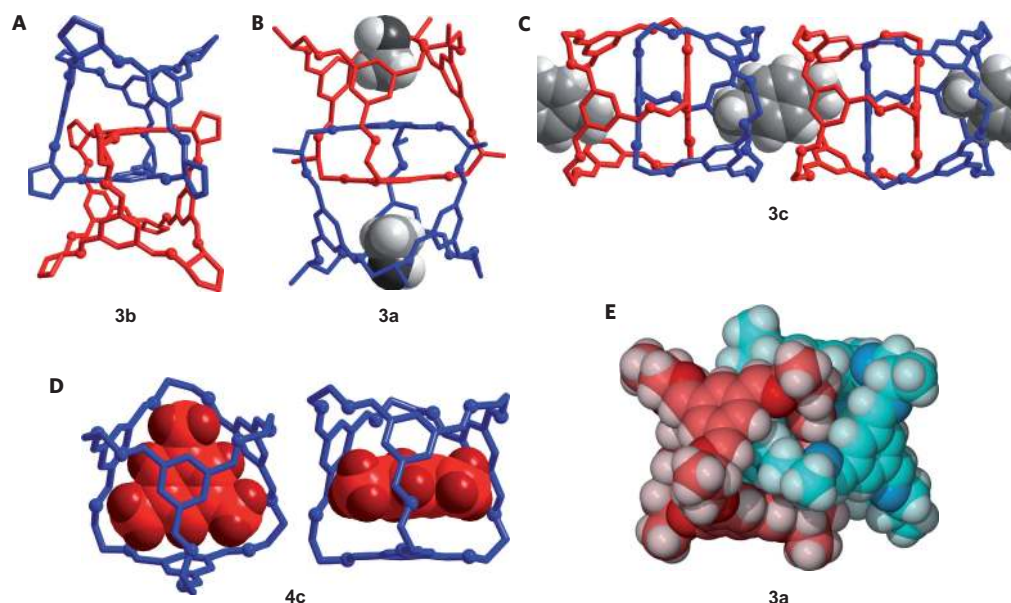


Figure 2 | Structures of triply interlocked cages. **A–D**, Crystal structures of **3b** (**A**); **3a** with methanol guests (**B**); **3c**, which forms a one-dimensional polymeric host-guest assembly with *p*-xylene (**C**); and the host-guest assembly of **4c** C mesitylene (**D**). **E**, Space-filling representation of one of the positional isomers of the triply interlinked dimer **3a**. Light blue and red: C; white: H; dark blue and red: N.

Fig. 4 with all close contacts shorter than 2.5 Å highlighted in red. The closest contacts occur between the N=C(H) hydrogen of one cage and the β-position hydrogen on the cyclopentane vertex of the partner cage. This structural feature is also found in **3a**, in that case involving the methyl-group hydrogen atoms.

Evidence for positional isomerism in **3a** was also found using high-pressure liquid chromatography–mass spectrometry (HPLC-MS), with seven separate peaks being observed in the chromatogram, each corresponding to the molecular mass of **3a** (1,755 *m/z*) (Supplementary Fig. S7). Gel permeation chromatography (GPC)

showed a shorter retention time for dimer **3a** compared with that of the corresponding monomeric cage²², consistent with its larger size (Supplementary Fig. S9). The Fourier transform infrared (FTIR) spectrum for **3a** was essentially identical to that of the non-interlocked cage (Supplementary Fig. S10). In contrast, peaks in the ¹H nuclear magnetic resonance (NMR) spectrum for **3a** showed pronounced shifts and peak broadening with respect to the monomeric cage, in keeping with the increased number of non-equivalent environments in the catenated dimer (Fig. 5a). The ¹H–¹³C heteronuclear single quantum coherence (HSQC) NMR for **3a** (Fig. 5b) suggests at least three different environments for imino-H-nuclei, together with two distinct aryl-H sites.

Crystal structures reveal that π–π stacking is a dominant intermolecular interaction for these catenated dimers, quite in contrast to the packing mode observed for the monomeric cage formed from **2a**, for which no π–π stacking interactions are apparent²². We therefore believe that π–π stacking plays a key role in the assembly process. To explore this, we carried out a control reaction involving ethane-1,2-diamine and **1** in the presence of excess mesitylene, which mimics the shape and symmetry of the 1,3,5-connected

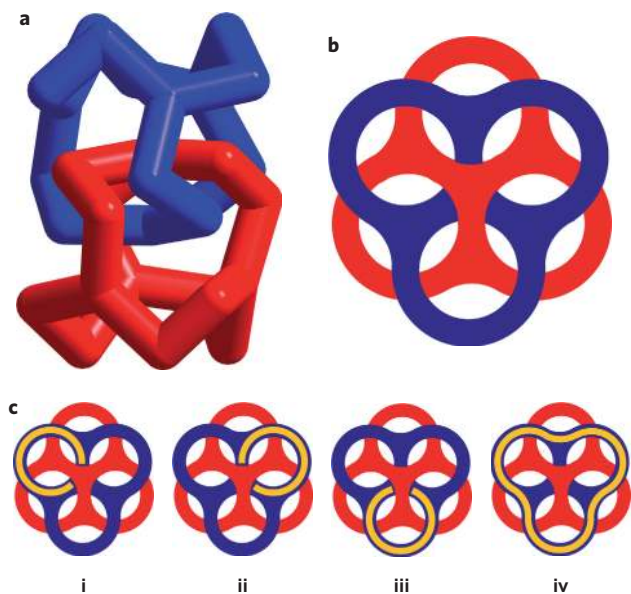


Figure 3 | Topology of triply interlocked cages. **a**, Schematic representation emphasizing the helical structure of interlocked dimers. **b**, Topology of the triply interlocked 3-torus dimer. **c**, Illustration of the three crossing cycles (i–iii) and the non-crossing cycle (iv) of a cage molecule in the interlocked dimer, as highlighted in yellow. The non-crossing cycle (iv) corresponds to the open, non-penetrated window of the cage molecule.

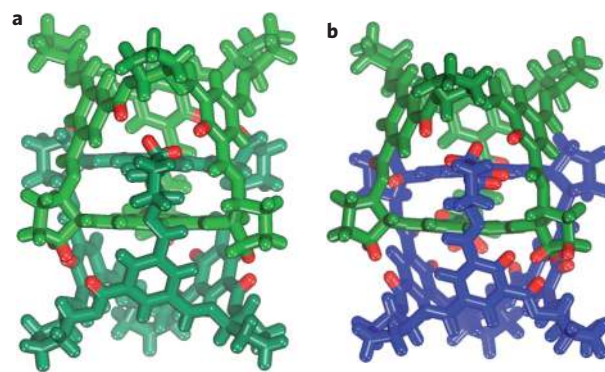


Figure 4 | Matched cage enantiomers interlock more effectively.

a, b, Geometry optimized models for two dimers of **3b** consisting of matched cage enantiomers (**a**) and mismatched cage enantiomers (**b**). Close contacts (less than 2.5 Å) are highlighted in red.

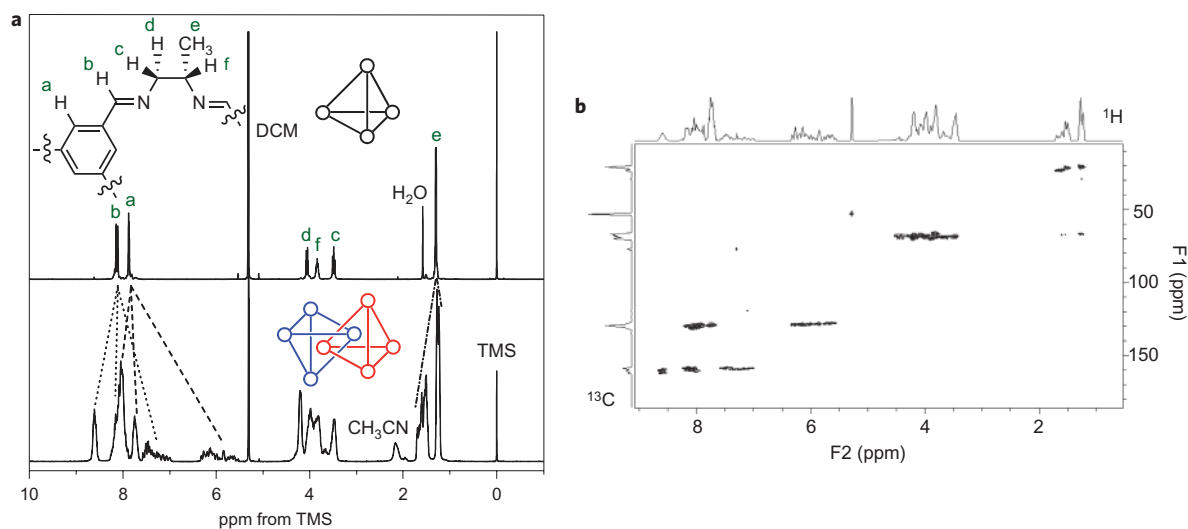


Figure 5 | Characterization of the monomeric cage, 4a, and catenated cage dimer, 3a. **a**, One-dimensional proton NMR for the monomeric cage **4a** (top) and the catenated dimer **3a** (bottom). Dashed lines show the large shifts of the imine, aromatic and methyl protons as the cage symmetry is lost through the formation of the dimer. Part of the structure is shown in the inset that identifies the protons a-f. TMS: tetramethylsilane. **b**, ^1H - ^{13}C HSQC NMR spectrum for catenane **3a**.

benzene rings in these cages. The resulting crystals, **4c** C mesitylene-3 mesitylene (space group $P-1$), contain four molecules of mesitylene per cage. One of these mesitylene molecules is trapped in the centre of the cage (Fig. 2D), forming a π - π stacking interaction with the cage that is analogous to that observed in catenanes **3a-c**. The methyl groups of the mesitylene guest point through the cage windows. Catenanes **3a-c** also show significant intermolecular interactions in addition to π - π stacking. There are six short aryl-H \cdots C=N contacts between the two engaged arene rings and the six penetrating bis(imino) strands in dimers **3a** and **3b**. These range from 2.68 to 2.82 Å in **3b**, which is well below the sum of the van der Waals radii and illustrates the compact structure of the interlocked dimer. This suggests that aryl-H \cdots imino interactions may assist the assembly process by promoting the three bis(imino) strands to curl around the central arene ring of the partner cage.

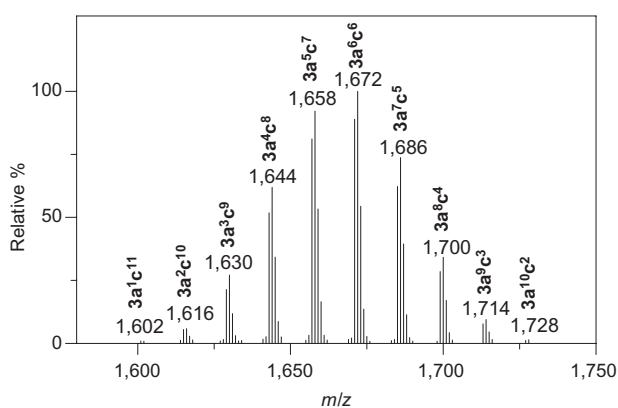


Figure 6 | Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrum for a mixed cage dimer. The number of vertex types, n , is equal to 3 for the interlinked species **5**, which follows a binomial distribution. The superscripts refer to the number of propane- and ethane-functionalized vertices, respectively. The dominant peak for **3-a**^{6c} therefore represents 1:1 incorporation of the diamines. The multiple mass signals for each species arise from the natural abundance of ^{13}C that is incorporated in these assemblies, which comprise between 96 and 108 carbon atoms per dimer. There are 88,965 possible positional isomers for this catenated molecule.

The 'host' cavity in these cages can be considered to be prescribed by the plane formed between the three aryl hydrogens at each cage window. Similarly, the encapsulated arene ring from the partner cage in **3a-c** (or the mesitylene in **4c**) can be considered as the guest. Using these definitions, the van der Waals packing coefficients for **3a** and **4c** C mesitylene were calculated to be 77.7% and 79.5%, respectively; that is, the guest fills more than 75% of the free volume in the cages, as calculated from the atomic van der Waals radii. This significantly exceeds the '55% solution', in which it was hypothesized by Rebek³⁰ that 55% filling represents the best compromise between entropic freedom for the encapsulated guest and the enthalpic gain achieved by close host-guest contacts.

Initial experiments indicate that triply interpenetrated catenated cages can also be formed with mixed functionalities. For example, when an equimolar mixture of diamines **2a** and **2c** was used, a statistical distribution of catenated products was obtained corresponding to the general formula **3-a** ^{x} **c** ^{y} ($x+y=12$) where x and y represent the number of propane- and ethane-functionalized vertices in the dimers, respectively. The intensity ratio in the mass spectrum for this material (Fig. 6) exhibits a binomial distribution. The dimer has 12 vertices, which can be occupied by either propane or ethane groups. Hence, the number of combinations for any composition **3-a** ^{x} **c** ^{y} is given by

$$\binom{12}{x} = \frac{12!}{x!(12-x)!} \quad (2)$$

The mass spectrum for this material shows somewhat lower intensities for isomers rich in propane groups compared to their ethane rich counterparts. Although this mass spectrometry technique is not quantitative in nature, this suggests enhanced incorporation of **2c** in the mixed interlocked dimers over **2a**. Because **2a** was applied as a racemic mixture, the take-up of **2a** must be preceded by the discrimination of its enantiomers, which reduces the hit-rate of **2a** compared to that of **2c**. In addition, the greater steric demand might also disfavour the take-up of **2a**. Given that each vertex consists of either an ethane group or a propane group with one of two possible orientations, then n is equal to 3. Hence, there are 88,965 possible positional isomers for this mixed interlocked dimer.

Conclusions

We have demonstrated for the first time that multiply interlocked catenanes can be formed from purely covalent organic entities without reversible metal coordination bonds^{14–16} or templating ions¹⁷, reinforcing Fujita's statement that interlocked species can be thermodynamically more stable than the corresponding monomeric structures¹⁴. This synthetic route tolerates variation in the precursor molecules; three distinct vicinal diamines were shown to produce analogous structures, and a mixture of diamines was shown to lead to a statistical distribution of triply interlocked products. The interlocked dimers also have two non-crossing cycles, which allows them to function as di-receptors in the formation of one-dimensional supramolecular chains.

Although these materials do not themselves display permanent microporosity, the open, non-crossing cycle in the assembly leads to two well-defined cavities per catenated dimer. We believe that such mechanically interlocked species could prove useful for the modular construction of complex porous materials from preformed 'porous' building blocks²², or as hydrophobic di-receptors for the self-assembly of supramolecular polymers^{31,32}.

Methods

A representative synthesis is given for interlinked product **3a**. Further details of synthesis, including products **3b**, **3c**, **4c** and **5**, as well as full characterization and chemical details, are given in the Supplementary Information.

Materials. 1,3,5-triformylbenzene was purchased from Manchester Organics and used as received. All other chemicals were purchased from Sigma-Aldrich and used as received.

Synthesis. Acetonitrile (300 ml) was added slowly to 1,3,5-triformylbenzene (1 g, 6.17 mmol) in a 500-ml round-bottomed flask at room temperature. After 5 min, trifluoroacetic acid (200 μ l, 2.7 mmol) was added, followed by a solution of 1,2-diaminopropane (685 mg, 9.26 mmol) in CH₃CN (100 ml). The resulting mixture was left covered for 7 days without stirring. After 5 days, a clear pale yellow solution containing large crystals with cubic-like morphology was observed, together with a thin layer of amorphous precipitate at the bottom of the reaction flask. The solids were removed by filtration, re-dissolved in dichloromethane (DCM), and filtered to remove the insoluble precipitate (yield, ~60%). Single crystal data were obtained from a crystal grown by evaporation of DCM with a layer of methanol added to the surface.

IR (KBr pellet, ν) 2,967 (m), 2,931 (w), 2,862 (s), 1,649 (s), 1,599 (w), 1,446 (m), 1,368 (m), 1,323 (m), 1,281 (w), 1,236 (w), 1,160 (m), 1,136 (m), 1,082 (w), 1,041 (m), 971 (m), 924 (w), 886 (m) cm⁻¹. ESI-MS (CH₃OH) m/z : 1,754.93 for C₁₀₈H₁₂₀N₂₄ [M + H]⁺, 1,776.96 for C₁₀₈H₁₂₀N₂₄ [M + Na]⁺. NMR data are shown in Fig. 5 and in more detail in the Supplementary Information.

Crystal data. Crystal data were collected on a Bruker APEX diffractometer with MoK α radiation ($\lambda = 0.71073$ Å) at $T = 100(2)$ K. Crystal structures were refined with full-matrix least-squares against F^2 using all data (SHELXL)³³. Absorption corrections were carried out based on symmetrically equivalent reflections obtained by multiscans. Analyses of entanglements of this kind can be performed using the program TOPOS (ref. 34). **3a**: (C₅₉H₆₆N₁₂)₂(CH₃OH)₂(H₂O)₃, $M = 2,032.62$, colourless prism, $0.6 \times 0.3 \times 0.5$ mm³, trigonal, space group $R\bar{3}c$ (no. 167), $a = b = 20.043(3)$, $c = 55.912(11)$ Å, $V = 19,452(5)$ Å³, $Z = 6$, $D_c = 1.041$ g cm⁻³, $\mu = 0.068$ mm⁻¹, $2\theta_{\max} = 40.8^\circ$, 19,959 reflections collected, 2,150 unique ($R_{\text{int}} = 0.0332$), $R1$ ($I > 2(I)$) = 0.1286, $wR2 = 0.3111$ (all data), 234 parameters, 216 restraints, $\mu = 0.068$ mm⁻¹. Crystals of **3a** diffracted to only low resolution, thus the data were truncated at $2\theta = 40.8^\circ$. **3b**: (C₆₆H₇₂N₁₂)₂(CH₂Cl₂)₁₅, $M = 3,340.60$, colourless prism, $0.5 \times 0.2 \times 0.1$ mm³, orthorhombic, space group $C22_1$ (no. 20), $a = 16.861(3)$, $b = 32.059(6)$, $c = 29.480(6)$ Å, $V = 15,935(5)$ Å³, $Z = 4$, $D_c = 1.392$ g cm⁻³, $\mu = 0.568$ mm⁻¹, $2\theta_{\max} = 46.8^\circ$, 31,493 reflections collected, 11,417 unique ($R_{\text{int}} = 0.0982$), $R1$ ($I > 2(I)$) = 0.1006, $wR2 = 0.2551$ (all data), 778 parameters, absolute structure parameter = 0.2(1). The SQUEEZE routine in PLATON³⁵ was used for removing the contributions of diffuse solvent from diffraction intensities. **3c**: (C₄₈H₄₈N₁₂)₂(C₈H₁₀)₂, $M = 1,902.43$, colourless prism, $0.50 \times 0.40 \times 0.30$ mm³, monoclinic, space group $C2/c$ (no. 15), $a = 25.511(9)$, $b = 16.802(6)$, $c = 24.782(8)$ Å, $\beta = 101.733(5)^\circ$, $V = 10,401(6)$ Å³, $Z = 4$, $D_c = 1.215$ g cm⁻³, $\mu = 0.074$ mm⁻¹, $2\theta_{\max} = 48.2^\circ$, 22,439 reflections collected, 8,247 unique ($R_{\text{int}} = 0.0556$), $R1$ ($I > 2\sigma(I)$) = 0.0591, $wR2 = 0.1395$ (all data), 652 parameters, 0 restraints. **4c** C mesitylene: (C₄₈H₄₈N₁₂)₂(C₉H₁₂)₃ C (C₉H₁₂), $M = 1,273.73$, colourless prism, $0.5 \times 0.2 \times 0.2$ mm³, triclinic, space group $P-1$ (no. 2), $a = 10.8757(17)$, $b = 14.151(2)$, $c = 26.065(4)$ Å, $\alpha = 92.550(3)^\circ$, $\beta = 99.061(3)^\circ$, $\gamma = 104.570(3)^\circ$, $V = 3,819.1(10)$ Å³, $Z = 2$, $D_c = 1.108$ g cm⁻³, $\mu = 0.066$ mm⁻¹, $2\theta_{\max} = 46.5^\circ$, 16,014 reflections collected, 10,774 unique ($R_{\text{int}} = 0.0692$), $R1$ ($I > 2(I)$) = 0.1063, $wR2$ (all data) = 0.1750, 877 parameters. These data can be obtained free of charge from The Cambridge

Crystallographic Data centre at www.ccdc.cam.ac.uk/data_request/cif. Deposition numbers: **3a** (765991); **3b** (765992); **3c** (765993); **4c** C mesitylene (768582).

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References

- Claessens, C. G. & Stoddart, J. F. Pi–pi interactions in self-assembly. *J. Phys. Org. Chem.* **10**, 254–272 (1997).
- Hubin, T. J. & Busch D. H. Template routes to interlocked molecular structures and orderly molecular entanglements. *Coord. Chem. Rev.* **200**, 5–52 (2000).
- Leigh, D. A., Wong, J. K. Y., Dehez, F. & Zerbetto, F. Unidirectional rotation in a mechanically interlocked molecular rotor. *Nature* **424**, 174–179 (2003).
- Fujita, M. Self-assembly of [2]catenanes containing metals in their backbones. *Acc. Chem. Res.* **32**, 53–61 (1999).
- Jager, R. & Vogtle, F. A new synthetic strategy towards molecules with mechanical bonds: nonionic template synthesis of amide-linked catenanes and rotaxanes. *Angew. Chem. Int. Ed.* **36**, 930–944 (1997).
- Meyer, C. D., Joiner, C. S. & Stoddart, J. F. Template-directed synthesis employing reversible imine bond formation. *Chem. Soc. Rev.* **36**, 1705–1723 (2007).
- Chichak, K. S. *et al.* Molecular Borromean rings. *Science* **304**, 1308–1312 (2004).
- Peters, A. J., Chichak, K. S., Cantrill, S. J. & Stoddart, J. F. Nanoscale Borromean links for real. *Chem. Commun.* **27**, 3394–3396 (2005).
- Guo, J., Mayers, P. C., Breault, G. A. & Hunter, C. A. Synthesis of a molecular trefoil knot by folding and closing on an octahedral coordination template. *Nature Chem.* **2**, 218–222 (2010).
- Siegel, J. S. Chemical topology and interlocking molecules. *Science* **304**, 1256–1258 (2004).
- Pentecost, C. D. *et al.* A molecular Solomon link. *Angew. Chem. Int. Ed.* **46**, 218–222 (2007).
- Breault, G. A., Hunter, C. A. & Mayers, P. C. Supramolecular topology. *Tetrahedron* **55**, 5265–5293 (1999).
- Safarowsky, O., Windisch, B., Mohry, A. & Vogtle, F. Nomenclature for catenanes, rotaxanes, molecular knots and assemblies derived from these structural elements. *J. Prakt. Chem.* **342**, 437–444 (2000).
- Fujita, M., Fujita, N., Ogura, K. & Yamaguchi, K. Spontaneous assembly of ten components into two interlocked, identical coordination cages. *Nature* **400**, 52–55 (1999).
- Westcott, A., Fisher, J., Harding, L. P., Rizkallah, P. & Hardie, M. J. Self-assembly of a 3-D triply interlocked chiral [2]catenane. *J. Am. Chem. Soc.* **130**, 2950–2951 (2008).
- Fukuda, M., Sekiya, R. & Kuroda, R. A quadruply stranded metallohelicite and its spontaneous dimerization into an interlocked metallohelicite. *Angew. Chem. Int. Ed.* **47**, 706–710 (2008).
- Li, Y., Mullen, K. M., Claridge, T. D. W., Costa, P. J., Felix, V. & Beer, P. D. Sulfate anion templated synthesis of a triply interlocked capsule. *Chem. Commun.* **46**, 7134–7136 (2009).
- Cram, D. J. Cavitands—organic hosts with enforced cavities. *Science* **219**, 1177–1183 (1983).
- Collet, A. Cyclotrivertatrylenes and cryptophanes. *Tetrahedron* **43**, 5725–5759 (1987).
- Leontiev, A. V. & Rudkevich, D. M. Encapsulation of gases in the solid state. *Chem. Commun.* 1468–1469 (2004).
- Liu, X. J., Liu, Y., Li, G. & Warmuth, R. One-pot, 18-component synthesis of an octahedral nanocontainer molecule. *Angew. Chem. Int. Ed.* **45**, 901–904 (2006).
- Tozawa, T. *et al.* Porous organic cages. *Nature Mater.* **8**, 973–978 (2009).
- Johnson, A. G., Leigh, D. A., Nezhad, L., Smart, J. P. & Deegan, M. D. Structurally diverse and dynamically versatile benzylic amide [2]catenanes assembled directly from commercially available precursors. *Angew. Chem. Int. Ed.* **34**, 1212–1216 (1995).
- Hamilton, D. G., Feeder, N., Teat, S. J. & Sanders, J. K. M. Reversible synthesis of pi-associated [2]catenanes by ring-closing metathesis: towards dynamic combinatorial libraries of catenanes. *New J. Chem.* **22**, 1019–1021 (1998).
- Hausmann, P. C. & Stoddart, J. F. Synthesizing interlocked molecules dynamically. *Chem. Rec.* **9**, 136–154 (2009).
- Au-Yeung, H. Y., Pantos, G. D. & Sanders, K. M. Amplifying different [2]catenanes in an aqueous donor–acceptor dynamic combinatorial library. *J. Am. Chem. Soc.* **131**, 16030–16032 (2009).
- Rowan, S. J., Cantrill, S. J., Cousins, G. R. L., Sanders, J. K. M. & Stoddart, J. F. Dynamic covalent chemistry. *Angew. Chem. Int. Ed.* **41**, 898–952 (2002).
- Hosseini, M. W. & De Cian, A. Crystal engineering: molecular networks based on inclusion phenomena. *Chem. Commun.* **7**, 727–733 (1998).
- Hosseini, M. W. Molecular tectonics: from simple tectons to complex molecular networks. *Acc. Chem. Res.* **38**, 313–323 (2005).
- Mecozzi, S. & Rebek, J. The 55% solution: a formula for molecular recognition in the liquid state. *Chem. Eur. J.* **4**, 1016–1022 (1998).

31. Roosma, J., Mes, T., Leclere, P., Palmans, A. R. A. & Meijer, E. W. Supramolecular materials from benzene-1,3,5-tricarboxamide-based nanorods. *J. Am. Chem. Soc.* **130**, 1120–1121 (2008).
32. Brunsveld, L., Folmer, B. J. B., Meijer, E. W. & Sijbesma, R. P. Supramolecular polymers. *Chem. Rev.* **101**, 4071–4097 (2001).
33. Sheldrick, G. M. A short history of SHELX. *Acta Crystallogr.* **64**, 112–122 (2008).
34. Blatov, V. A. Multipurpose crystallochemical analysis with the program package TOPOS. *IUCr CompComm. Newsletter* **8**, 4–38 (2006).
35. Spek, A. L. Single-crystal structure validation with the program PLATON. *J. Appl. Cryst.* **36**, 7–13 (2003).

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Author contributions

A.C., T.H. and D.A. conceived and designed the experiments. The synthetic work was led by T.H. and also involved T.M. and X.W. Characterization and data analysis was carried out by T.H. (FTIR, NMR, TGA), J.J. (NMR, PXRD), J.B. and A.S. (SCXRD). A.S. analysed the number of potential positional isomers for the catenated cages. A.T. was responsible for the modelling work. T.H., A.S. and A.C. led the writing of the paper with input from all co-authors.

Additional information

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