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Catenanes

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Chloride Anion Templated Synthesis and Crystal Structure of a Handcuff Catenane**

*Nicholas H. Evans, Christopher J. Serpell, and Paul D. Beer**

Catenanes and rotaxanes are highly attractive synthetic targets in supramolecular chemistry due, in part, to their potential uses as molecular machines[1] or as selective hosts for ionic and molecular guests.[2] The preparation of higher-order interlocked architectures provides a much greater synthetic challenge than the construction of the prototypical [2]catenanes and [2]rotaxanes, but can allow for functionality not open to simpler systems. Indeed, impressive examples of such species have been assembled using cationic[3,4] and neutral[5] templates. In contrast, the use of anion templation to generate interlocked structures, whilst having been demonstrated by us[6] and others,[7] remains in its infancy. In particular, almost all reports of anion templation of interlocked molecules involve the construction of either [2]catenane or [2]rotaxane structures.[8,9] A "handcuff" catenane is an example of a higher-order interlocked architecture where two covalently linked macrocycles have a single macrocycle passing through both rings (Figure 1). To the best of our knowledge, only two examples of such species—constructed using cationic templation—have been described in the chemical literature to date.[10,11] Here, we detail the preparation and characterization of a novel chloride anion templated handcuff catenane, along with its crystal structure—this being the first handcuff catenane crystal structure to be determined.

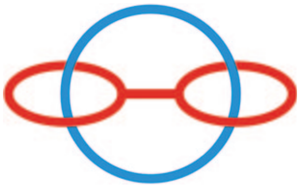

Figure 1. "Handcuff" catenane.

The synthetic strategy undertaken to prepare the target handcuff catenane is illustrated in Figure 2. Two identical *N*-methyl pyridinium molecules thread, by anion templation, through a handcuff-like bis(macrocycle), where each macrocycle contains an isophthalamide group able to hydrogen bond to the chloride anion. Pseudorotaxane formation is also supported by π–π stacking between the electron-rich hydroquinone groups of the bis(macrocycle) and electron-poor pyridinium rings of the threading components. Subsequent cyclization will lead to the formation of the desired handcuff catenane.

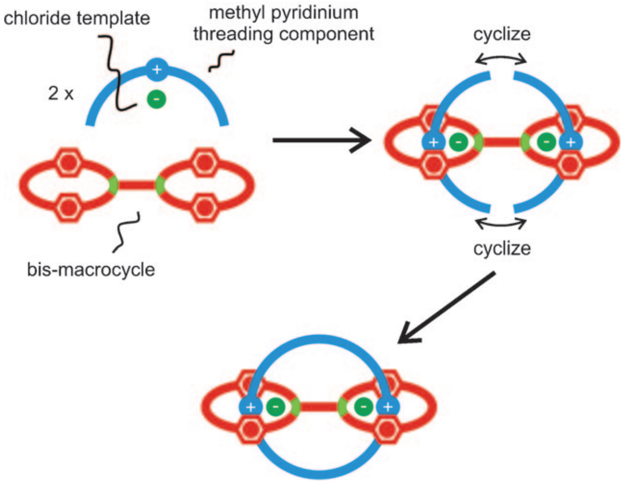

Figure 2. Synthesis of "handcuff" catenane.

The actual detail of the synthesis of novel bis(macrocycle) **4** and handcuff catenane $\mathbf{6}^{2+}(Cl^-)_2$ is shown in Schemes 1 and 2. The bis(macrocycle) was synthesized by reacting 2 equivalents of bis(amine) **1** with tetraacid chloride **2**[12] in the presence of 2 equivalents of the *N*-methyl pyridinium template $\mathbf{3}^+Cl^-$ and NEt_3 in dry CH_2Cl_2.[13] After aqueous workup and silica gel chromatography, **4** was isolated in a 15% yield.[14] Subsequently, **4** was suspended in dry CH_2Cl_2, and two equivalents of the bis(vinyl) precursor $\mathbf{5}^+Cl^-$ [6b] added, which led to the solubilization of the bis(macrocycle) indicating that the prerequisite pseudorotaxane complex was formed. Addition of 10% (by wt) Grubbs' second-generation catalyst, followed by stirring at room temperature for 16 hours under a nitrogen atmosphere allowed ring-closing metathesis (RCM) to occur. After solvent removal, preparative silica gel thin layer chromatography (TLC) was undertaken, whereupon a new yellow band was separated from the crude reaction mixture. ^{1}H NMR spectroscopy and

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[*] N. H. Evans, Dr. C. J. Serpell, Prof. P. D. Beer
Inorganic Chemistry Laboratory, Department of Chemistry
University of Oxford, South Parks Road, Oxford, OX1 3QR (UK)
E-mail: paul.beer@chem.ox.ac.uk

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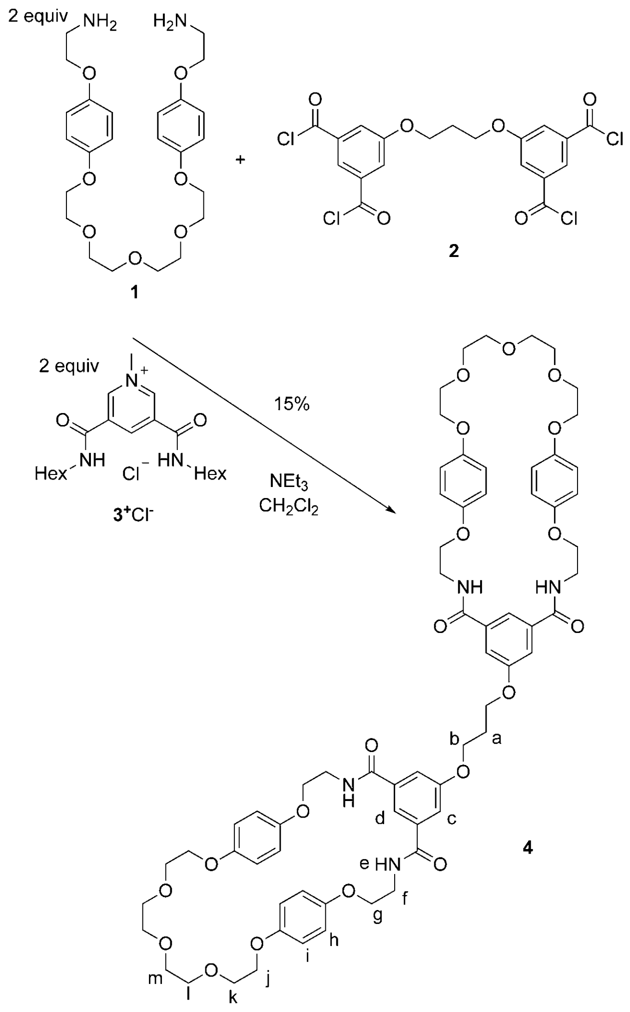
Supporting information for this article (synthetic details, along with full spectral data of all novel compounds, plus further information about the crystal structure analysis of catenane $\mathbf{6}^{2+}(Cl^-)_2$) is available on the WWW under http://dx.doi.org/10.1002/anie.201007741.



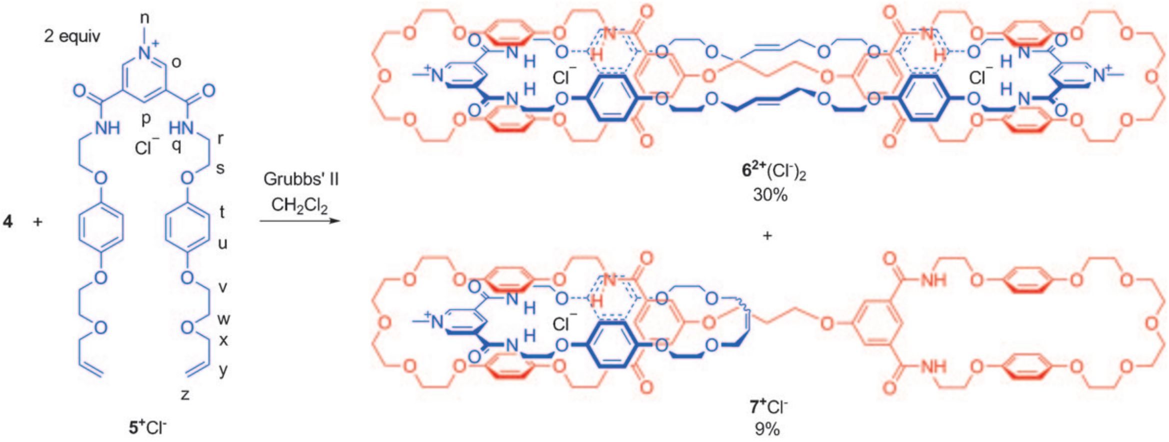
Scheme 1. Synthesis of bis(macrocycle) **4**.

electrospray MS revealed this band contained two catenane species: the desired handcuff catenane $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$ and the by-product [2]catenane $\mathbf{7}^+\mathrm{Cl}^-$. Yields of formation of these two species were calculated by integration of non-coincidental peaks in the ^{1}H NMR spectrum and were found to be 30 % for the handcuff catenane $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$ and 9 % for the by-product [2]catenane $\mathbf{7}^+\mathrm{Cl}^-$. Further purification by preparative TLC methods on silica gel enabled isolation of analytically pure samples of both species for characterization.

Both catenanes were characterized by ^{1}H and ^{13}C NMR spectroscopy and electrospray HRMS. The ^{1}H NMR spectrum of handcuff catenane $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$, along with those of bis(macrocycle) **4** and the *N*-methyl pyridinium chloride RCM precursor $\mathbf{5}^+\mathrm{Cl}^-$ for comparison, are shown in Figure 3. Cyclization is implied by the loss of the vinylic multiplet *z*, and multiplet *y* becoming a pseudosinglet in the catenane spectrum. The upfield shifts of *p* and *q* and the downfield shifts of *d* and *e*, are indicative of competitive hydrogen bonding to the chloride anion template. The splitting and upfield shifts of signals for the hydroquinone protons *h* and *i* are attributed to the expected π–π stacking between the bis(macrocycle) hydroquinone and pyridinium rings. Hydrogen bonding of the *N*-methyl pyridinium group to the polyether oxygen atoms of the bis(macrocycle) can be inferred by the downfield shift of resonance *n*. The interlocked nature of the catenane was further supported by the appearance of multiple through-space correlations between signals arising from protons in the two ring components as observed in a ^{1}H ROESY NMR spectrum. In addition, the dicationic molecular ion peak is readily identifiable at *m*/*z* 1222.53 in the electrospray HRMS.[15]

The importance of the chloride anion template was highlighted by repeating the reaction with the hexafluorophosphate salt of the RCM precursor $\mathbf{5}^+\mathrm{PF}_6^-$. While a dicationic peak was just visible in a low-resolution electrospray MS of the reaction mixture at *m*/*z* 1223, no handcuff catenane was detected by ^{1}H NMR spectroscopy or MS in the various fractions of the reaction mixture that were partially separated by preparative TLC methods on silica gel, thus implying that it was formed in only trace amounts.[16] This supports the theory that chloride is essential for the formation of the handcuff catenane.

Considering the isolation of the [2]catenane by-product $\mathbf{7}^+\mathrm{Cl}^-$, the formation of an alternative isomer—that of two covalently linked [2]catenanes—is a distinct possibility. Despite being encouraged by the highly symmetric nature of the one-dimensional ^{1}H NMR spectrum of $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$ compared to that of the by-product [2]catenane $\mathbf{7}^+\mathrm{Cl}^-$, we



Scheme 2. Synthesis of catenanes $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$ and $\mathbf{7}^+\mathrm{Cl}^-$.

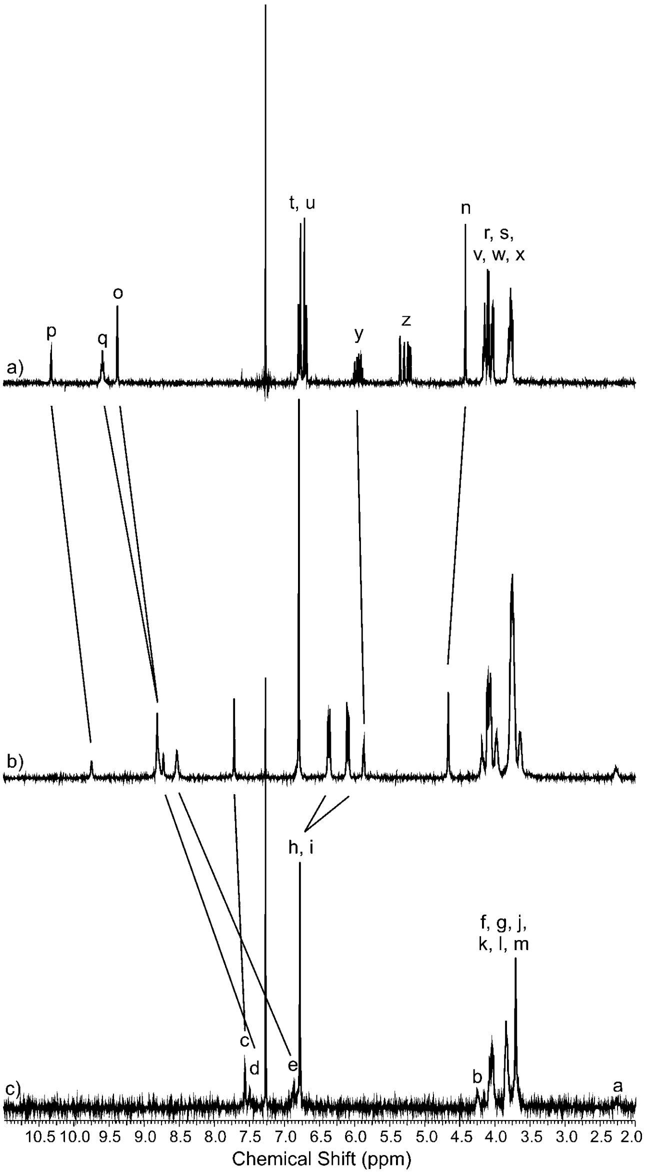


Figure 3. ^{1}H NMR spectra of a) methyl pyridinium chloride RCM precursor **5**$^+$Cl$^-$, b) handcuff catenane **6**$^{2+}$(Cl$^-$)$_2$ and c) bis(macrocycle) **4** (Solvent: CDCl$_3$, $T = 293$ K). For atom labels see Schemes 1 and 2.

sought to establish conclusively that we had isolated the desired catenane isomer. This was first demonstrated by a fragmentation MS experiment. By raising the collision voltage, a new dicationic peak appeared in the mass spectrum at m/z 592.26 thus arising from the doubly charged macrocyclic component of the handcuff catenane.

Incontrovertible proof of isolation of the handcuff catenane was obtained by the elucidation of a crystal structure (Figure 4). A crystal suitable for X-ray diffraction structural determination was grown by slow diffusion of diisopropyl ether into a chloroform solution of **6**$^{2+}$(Cl$^-$)$_2$, and the diffraction data was collected using synchrotron radiation at Diamond Light Source beamline I19.[17] The entire molecular structure was revealed by structure solution using charge flipping, confirming the topology of the handcuff catenane. The importance of the chloride anion templation strategy is illustrated by the orthogonal arrangement of the two pyridinium bis(amide) and isophthalamide pairs (supplemented by charge-assisted π–π stacking) about the chlorides, an artifact of the [3]pseudorotaxane precursor which brought together two of the **5**$^+$Cl$^-$ threading components to form the unusually large [1+1] macrocyclic component. Only *trans* olefins were observed as a product of the ring-closing metathesis—consistent with the single peak for the olefinic proton *y* in the ^{1}H NMR spectrum of **6**$^{2+}$(Cl$^-$)$_2$.

There is a degree of bunching in both the polyether portions of the large macrocycle and the link between the smaller macrocycles. This is partly due to the requirements of packing efficiency, but the large loops of the [1+1] macrocycle indicate that it is not stretched tight by the handcuffs, but possesses a degree of slack. This looseness could be beneficial for future application of analogous systems in switchable molecular machines, by minimizing kinetic barriers to rotation. The splayed polyether portions of the large macrocycle, in combination with the tether of the handcuff, create a cryptand-like cavity in which a disordered chloroform molecule was found. The presence of twelve ethereal and carbonyl oxygen atoms bordering this volume suggest that the void could be used for binding cations, hinting at the potential as an ion-pair receptor.

In summary, we have prepared and isolated a chloride templated handcuff catenane. We have also structurally

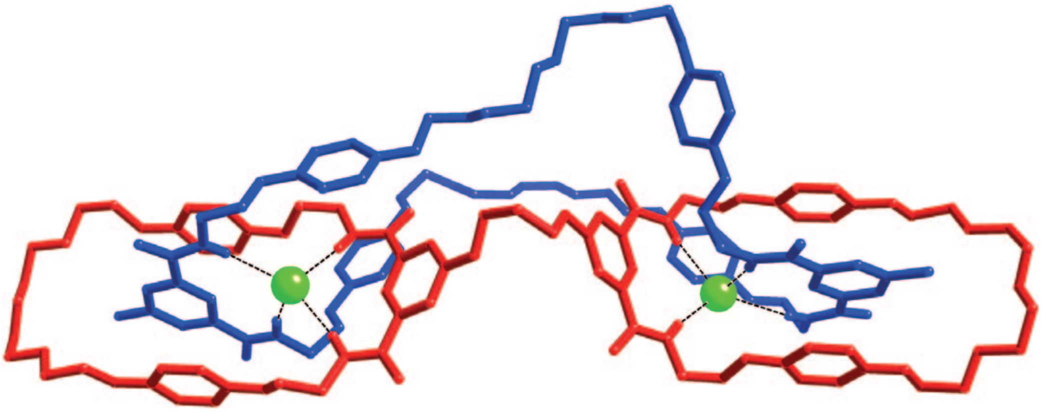


Figure 4. Crystal structure of handcuff catenane **6**$^{2+}$(Cl$^-$)$_2$.

determined the first crystal structure of a handcuff catenane, thus verifying the isolation of the target isomer. Efforts to construct further higher-order interlocked architectures by anion templation are continuing in our laboratories.

Experimental Section

Experimental procedure for the preparation of handcuff catenane $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$: Grubbs' 2nd generation catalyst (5.2 mg, 10% by wt) was added to a solution of bis(macrocycle) **4** (50 mg, 0.039 mmol) and precursor $\mathbf{5}^+\mathrm{Cl}^-$ (52 mg, 0.078 mmol) in dry CH_2Cl_2 (20 mL). The reaction was stirred under a N_2 atmosphere for 16 h, the solvent removed and the crude reaction mixture separated by preparative TLC methods on silica gel (CH_2Cl_2:CH_3OH 96:4) to give a yellow solid (37 mg, of which 30 mg, 30% yield of formation, was calculated to be $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$ as determined by integration of the peaks in the ^{1}H NMR spectrum of the crude mixture). An analytically pure sample was obtained after repeated runs of the preparative TLC separation (CH_2Cl_2/CH_3OH 96:4 then 97:3) as a yellow solid (10 mg, 10% yield of isolated product). M.p. = 262 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 9.75 (s, 2H, *para*-pyridinium Ar*H*), 8.80 (app. s, 8H, *ortho*-pyridinium Ar*H* and pyridinium amide N*H*), 8.72 (s, 2H, *para*-isophthalamide, Ar*H*), 8.53 (br. s, 4H, isophthalamide amide N*H*), 7.72 (s, 4H, *ortho*-isophthalamide Ar*H*), 6.79 (s, 16H, pyridinium hydroquinone Ar*H*), 6.36 (d, $^3J = 8.8$ Hz, 8H, isophthalamide hydroquinone Ar*H*), 6.09 (d, $^3J = 8.8$ Hz, 8H, isophthalamide hydroquinone Ar*H*), 5.87 (br. s, 4H, C*H*=C*H*), 4.66 (s, 6H, N^+CH_3), 4.18 (t, 4H, $^3J = 5.6$ Hz, $OCH_2CH_2CH_2O$), 4.05–4.10 (m, 24H, 3 × CH_2), 3.98 (br s. 8H, CH_2), 3.74–3.78 (m, 48H, 6 × CH_2), 3.64 (br s. 8H, CH_2) 2.26–2.29 ppm (m, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 166.4$, 160.0, 159.3, 154.0, 153.1, 152.6, 151.6, 144.5, 136.5, 134.9, 133.2, 129.7, 117.7, 116.4, 115.6, 115.2, 114.6, 114.4, 71.2, 70.6, 70.1, 68.4, 68.4 (sic), 68.0, 66.0, 65.1, 64.7, 49.8, 41.2, 40.1, 29.7, 29.0 ppm; HRMS (ES +ve) *m*/*z*: 1222.5346 ($[M-2\,\mathrm{Cl}]^{2+}$, $C_{131}H_{156}N_{10}O_{36}$ requires 1222.5336).

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[14] Low yield of bis(macrocycle) **4** is attributed to a combination of very difficult separation of the desired product from impurities on a silica column, thus requiring recrystallization, all of which were hampered by the low solubility of bis(macrocycle) **4**.

[15] See the Supporting Information for the ^{1}H ROESY, ^{13}C NMR, and electrospray HR mass spectra of the handcuff catenane $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$, as well as the characterization of the by-product [2]catenane $\mathbf{7}^+\mathrm{Cl}^-$.

[16] The hexafluorophosphate analogue of the by-product [2]catenane, $\mathbf{7}^+\mathrm{PF}_6^-$, was formed, as detected by ^{1}H NMR spectroscopy and low-resolution mass spectrometry, but it could not be isolated in a pure form by silica gel chromatographic methods.

[17] Crystal data for $\mathbf{6}^{2+}(\mathrm{Cl}^-)_2$: $C_{132}H_{157}Cl_5N_{10}O_{36}$, $M_r = 2637.02$, crystal dimensions $8 \times 23 \times 64$ µm, triclinic, $P\bar{1}$, $a = 13.491(5)$, $b = 14.852(6)$, $c = 35.517(14)$ Å, $\alpha = 80.862(9)°$, $\beta = 87.507(12)°$, $\gamma = 84.089(16)°$, $V = 6986(5)$ Å^3, $Z = 2$, $\rho_{\mathrm{calcd}} = 1.254$ Mg m^{-3}, $\mu = 0.182$ mm^{-1}, synchrotron radiation, $\lambda = 0.69980$ Å, $T = 150(2)$ K, $2\theta_{\max} = 63.4$, 42217 reflections measured, 42217 independent reflections ($R_{\mathrm{int}} = 0.103$), $R_1 = 0.0927$, $wR(F^2) = 0.2079$ ($I > 2\sigma(I)$), maximum residual electron density = 0.88 e Å^{-1}. A half-sphere of data were collected at beamline I19, Diamond Light Source, Harwell, UK using a custom-built Rigaku diffractometer, and processed using the CrystalClear package. Full details about the data collection, solution and refinement of the structure may be found in the supporting information. CCDC 804095 contains 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.