Template-Directed Synthesis of Mechanically Interlocked Molecular Bundles Using Dynamic Covalent Chemistry
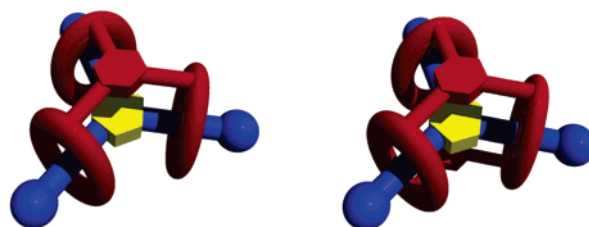
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ABSTRACT

Mixing the dipyrido[24]crown-8 derivatives carrying one or two formyl group(s) on the 4 position(s) of their pyridine ring(s) with a 3-fold symmetrical trisammonium ion template in a 3:1 ratio in CD$_3$NO$_2$ results in the formation of thermodynamically stable [4]pseudorotaxanes which, upon addition of a 1,3,5-trisaminobenzene cap, form mechanically interlocked molecular bundles with one and two caps, respectively, by virtue of dynamic imine bond formation.

Beginning with the first chemical synthesis of a catenane by Wasserman[1] in 1960, molecular compounds that exhibit exotic topologies and/or mechanical bonds have been targeted by synthetic chemists. Mechanically interlocked and knotted compounds, such as catenanes,[2] rotaxanes,[3] trefoil knots,[4] and Borromean rings[5] synthesized usually by template-directed[6] protocols depending on molecular recognition[7] and self-assembly[8] processes, represent challenging synthetic goals that have nonetheless been realized. While much progress has been made in developing synthetic strategies to make such compounds, molecules exist[9] beyond this first

crop of compounds that need to be accessed by chemical synthesis.

(1) (a) Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433–4434. (b) Frisch, H.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795.

(2) Catenanes are molecules comprised of two (or more) ring-shaped components that are interlocked like the links in a chain. See: (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971. (b) *Molecular Catenanes, Rotaxanes and Knots*; Sauvage, J.-P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, 1999.

(3) Rotaxanes are molecules comprised of ring-shaped component(s) and dumbbell-shaped component(s) that are mechanically interlocked. For recent examples, see: (a) Stainer, C. A.; Alderman, S. J.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1769–1772. (b) Andersson, M.; Linke, M.; Chambron, J.-C.; Davidson, J.; Heitz, V.; Hammarström, L.; Sauvage, J.-P. *J. Am. Chem. Soc.* **2002**, *124*, 4347–4362. (c) Asakawa, M.; Brancato, G.; Fanti, M.; Leigh, D. A.; Shimizu, T.; Slawin, A. M. Z.; Wong, J. K. Y.; Zerbetto, F.; Zhang, S. *J. Am. Chem. Soc.* **2002**, *124*, 2939–2950. (d) Nikitin, K.; Long, B.; Fitzmaurice, D. *Chem. Commun.* **2003**, 282–283. (e) Iijima, T.; Vignon, S. A.; Tseng, H.-R.; Jarrosson, T.; Sanders, J. K. M.; Marchioni, F.; Venturi, M.; Apostoli, E.; Balzani, V.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 6375–6392.

(4) For examples of synthetic trefoil knots, see: (a) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189–192. (b) Carina, R. F.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9110–9116. (c) Ashton, P. R.; Matthews, O. A.; Menzer, S.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *Liebigs Ann. Chem.* **1997**, 2485–2494. (d) Hunter, C. A.; Mayers, P. C. *Nature* **2001**, *411*, 763. (e) Lukin, O.; Kubota, T.; Okamoto, Y.; Kaufmann, A.; Vögtle, F. *Chem.—Eur. J.* **2004**, *10*, 2804–2810

Dynamic covalent chemistry[10] (DCC) has emerged as an efficient and versatile strategy for the synthesis of complex molecular structures. Whereas early examples of supramolecular assistance to covalent synthesis[11] relied heavily on kinetically controlled reactions for postassembly covalent modification, DCC takes advantage of the reversible nature of acetal,[12] disulfide,[13] ester,[14] and imine[15] bond formation, as well as carbon−carbon bond formation during methasis[16] and metal−ligand coordination,[17] to allow the formation of the new covalent bonds to be thermodynamically controlled. The reversible formation of covalent bonds provides a means of proofreading and editing intermediate structures to achieve, with time, the most thermodynamically stable product. When coupled with templation, DCC has been shown

to provide a highly efficient route to mechanically interlocked molecules. Recent examples include a calix[4]arene-based [8]catenane,[16d] multiple rotaxanes,[18] interlocked dendrimers,[19] and molecular Borromean rings.[5] In some cases, the dynamic covalent structures have been fixed[5,18,19] through reduction of their imine bonds to kinetically stable amine ones. Here, we describe the use of DCC in the context of imine bond formation, along with computational modeling, in the template-directed synthesis of two mechanically interlocked molecular bundles from five and six components, respectively. The pool of structures from which these components have been drawn is shown in Figure 1, and the manner in
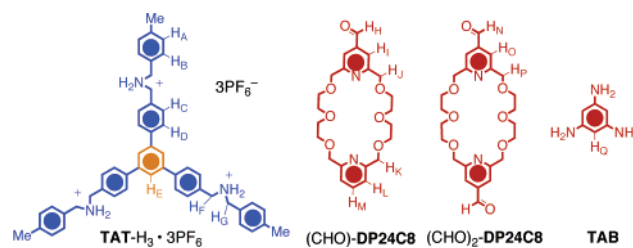

Figure 1. Structural formulas of the trisammonium ion template **TAT**-$H_3 \cdot 3PF_6$, the formyl derivatives (CHO)-**DP24C8** and (CHO)$_2$-**DP24C8** of dipyrido[24]crown-8 (**DP24C8**), and 1,3,5-trisaminobenzene (**TAB**). The proton descriptors employed in Figures 2 and 4 are defined on the four structural formulas.

which they have been employed in the two syntheses is outlined in Scheme 1. The supramolecular assistance to covalent synthesis[11] is provided by hydrogen bonding between crown ether derivatives and secondary dialkylammonium ion centers, and the DCC uses imine bond formation to link together three individually derivatized crown ethers, carrying either one or two formyl groups, singly or doubly, with a trigonal capping reagent[20] displaying the three matching amine functions.

Complexation occurs immediately upon addition of 3.0 equiv of (CHO)-**DP24C8** to **TAT**-$H_3 \cdot 3PF_6$ in CD_3NO_2, as

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Scheme 1. Addition of Either (CHO)-**DP24C8** or (CHO)$_2$-**DP24C8** to **TAT**-H$_3$·3PF$_6$ in a 3:1 Ratio Leads to the Formation of the [4]Pseudorotaxanes **MFPR**-H$_3$·3PF$_6$ and **DFPR**-H$_3$·3PF$_6$, Respectively[a]
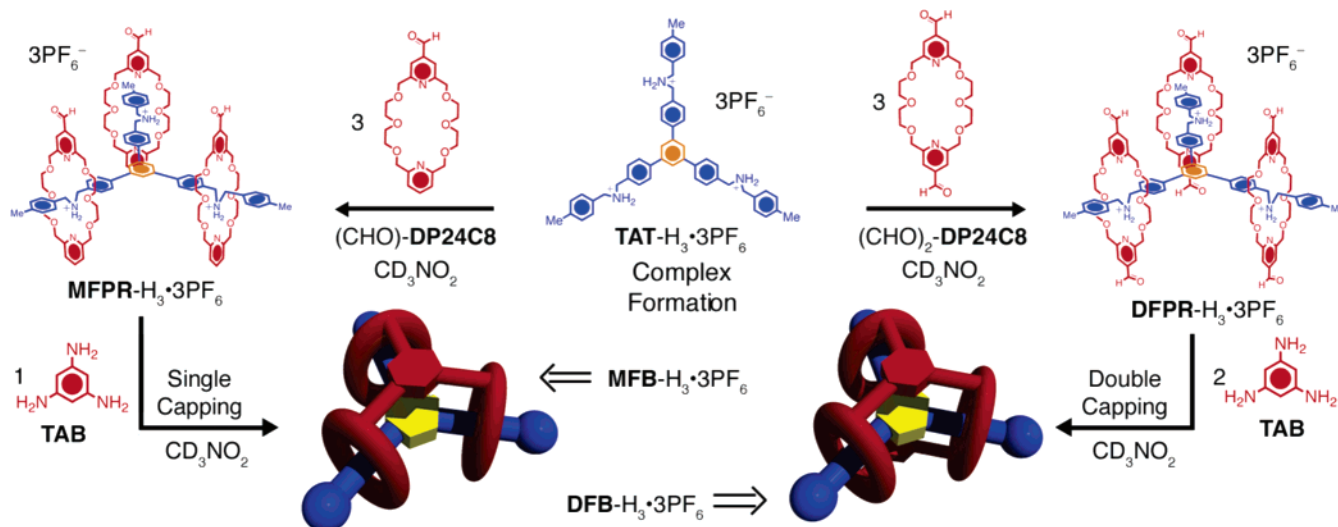
[a] Capping of these two complexes with 1.0 and 2.0 equiv, respectively, of **TAB** results in the formation of the mechanically interlocked molecular bundles **MFB**-H$_3$·3PF$_6$ and **DFB**-H$_3$·3PF$_6$, respectively.

indicated (Figure 2) by ^{1}H NMR spectroscopy. As is characteristic of the binding of $-CH_2NH_2^+CH_2-$ centers by crown ethers, the two pairs of benzylic methylene protons in **TAT**-H$_3^{3+}$ are shifted upfield from $\delta = 4.5$ and 4.6 pm to $\delta = 3.9$ and 4.4 pm, respectively. Moreover, **MFPR**-H$_3^{3+}$ is a kinetically stable complex on the ^{1}H NMR timescale at 298 K because peaks can be identified for uncomplexed and
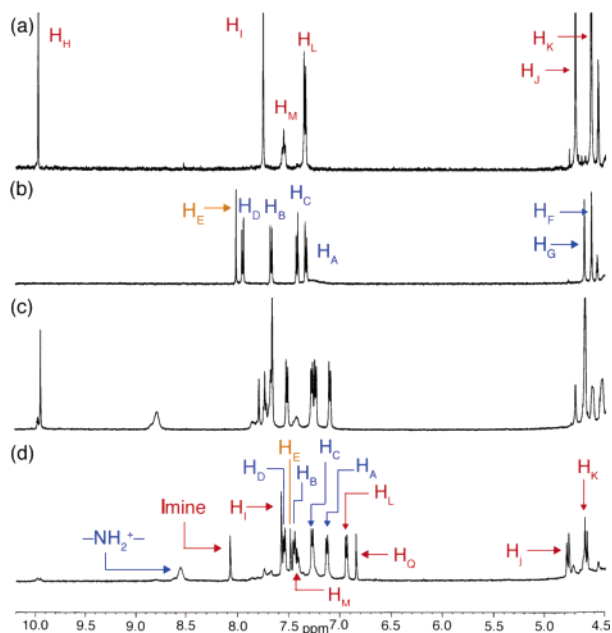

Figure 2. Partial ^{1}H NMR spectra (CD$_3$NO$_2$, 13.8 mM) of (a) (CHO)-**DP24C8**, (b) **TAT**-H$_3$·3PF$_6$, (c) **MFPR**-H$_3$·3PF$_6$, and (d) **MFB**-H$_3$·3PF$_6$. For a definition of the proton (H) descriptors, see Figure 1.

partially complexed, as well as fully complexed, species. Integration of these peaks suggests that **MFPR**-H$_3^{3+}$ accounts for >95% of the species present in solution. Isothermal titration microcalorimetry (ITC) indicates a "binding constant" per binding site of 11 800 M^{-1} ($\Delta G° = -5.5$ kcal/mol) between **TAT**-H$_3^{3+}$ and (CHO)-**DP24C8** in MeNO$_2$. Computational force-field modeling (Figure 3a) reveals that the three NH$_2$ functions in **TAB** should be capable of forming imine bonds with the CHO groups in three complexed (CHO)-**DP24C8** macrocycles. Indeed, although ^{1}H NMR spectroscopy reveals the formation of a number of products initially when 1.0 equiv of **TAB** is added to **MFPR**-H$_3$·3PF$_6$, after 2 h these kinetic intermediates converge[21] to the most stable thermodynamic product—**MFB**-H$_3$·3PF$_6$ with 3-fold (C_{3v}) symmetry—containing three imine bonds. This outcome[22] is supported (Figure 3a) by high-resolution electrospray ionization (HR-ESI) mass spectrometric analysis: m/z = 1131.52 for [M − 2PF$_6$]$^{2+}$ compared with the calculated value of 1131.28.

Formation of **DFPR**-H$_3$·3PF$_6$ was observed (Figure 4) by ^{1}H NMR spectroscopy to occur spontaneously upon mixing of (CHO)$_2$-**DP24C8** and **TAT**-H$_3$·3PF$_6$ in CD$_3$NO$_2$ in a 3:1 ratio. ITC measurements indicate a binding constant per binding site[23] of 3520 M^{-1} ($\Delta G° = -4.8$ kcal/mol) between **TAT**-H$_3^{3+}$ and (CHO)$_2$-**DP24C8** in MeNO$_2$. Computational force-field modeling (Figure 3b) reveals that 2.0 equiv of **TAB** is capable of linking all six formyl functions of the

(21) Within 10 min of the addition, one witnesses a decrease in the intensity of the peak at $\delta = 9.95$ ppm for formyl protons as the intensity of the singlet at $\delta = 8.10$ ppm for imine protons increases simultaneously.

(22) All attempts to obtain X-ray quality single crystals of **MFB**-H$_3$·3PF$_6$ and **DFB**-H$_3$·3PF$_6$ or to reduce (e.g., with BH$_3$-THF and BH$_3$-lutidine) the three and six imine bonds, respectively, have been unsuccessful to date. Hence, the evidence for the formation of these two mechanically interlocked compounds rests primarily on ^{1}H NMR spectroscopy and mass spectrometry for the present.
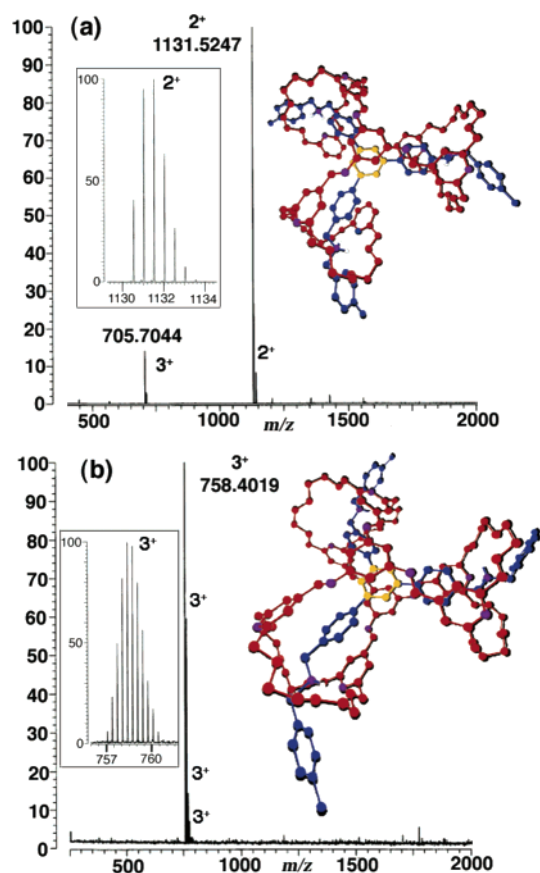
Figure 3. HR-ESI mass spectra showing the $[M - 2PF_6]^{2+}$ and $[M - 3PF_6]^{3+}$ peaks at $m/z = 1131.52$ and 705.70 for (a) **MFB**-$H_3 \cdot 3PF_6$ as well as the $[M - 3PF_6]^{3+}$ peak at $m/z = 758.40$ for (b) **DFB**-$H_3 \cdot 3PF_6$ along with the computed lowest-energy structures displayed alongside and the isotopic patterns inset within each spectra.

three $(CHO)_2$-**DP24C8** macrocycles in such a way that each equivalent of **TAB** reacts with the three formyl groups positioned on either side of **TAT**-H_3^{3+}. Double capping of **DFPR**-H_3^{3+} was achieved by adding 2.0 equiv of **TAB** to the reaction mixture containing the [4]pseudorotaxane. While capping of **MFPR**-H_3^{3+} requires only 2 h, double capping of **DFPR**-H_3^{3+} requires a lot longer. Although ^1H NMR spectra (Figure 4) obtained 5 h after addition of **TAB** showed some initial sharpening of peaks corresponding to the high-symmetry (D_{3h}) product **DFB**-H_3^{3+}, a peak at $\delta = 9.84$ ppm for aldehydic protons could still be observed after 48 h. In the event, it took 8 days for the mechanically interlocked molecular bundle **DFB**-H_3^{3+} to become (Figure 4d) the dominant product in the ^1H NMR spectrum. Its formation

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(23) The additional formyl group in $(CHO)_2$-**DP24C8**, compared to (CHO)-**DP24C8**, appears to have a disruptive effect upon its binding to the **TAT**-H_3^{3+} trication, possibly as a result of the increased electron-withdrawing influence of the additional formyl group upon the electron-donating ability of the heteroatoms in the **DP24C8** macrocycles.
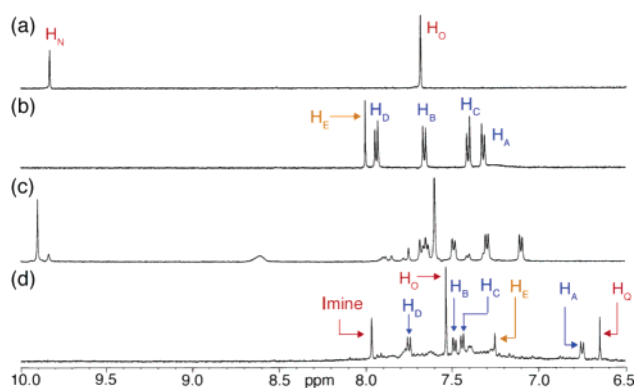

Figure 4. Partial ^1H NMR spectra (CD_3NO_2, 8.8 mM) of (a) $(CHO)_2$-**DP24C8**, (b) **TAT**-$H_3 \cdot 3PF_6$, (c) **DFPR**-$H_3 \cdot 3PF_6$, and (d) **DFB**-$H_3 \cdot 3PF_6$ and other unidentified minor products. For a definition of the proton (H) descriptors, see Figure 1.

was confirmed (Figure 3b) by HR-ESI mass spectrometric analysis: $m/z = 758.40$ for $[M - 3PF_6]^{3+}$, compared with the calculated value of 756.91.

The mechanically interlocked molecular bundles are distinguishable[9] from regular rotaxanes. Once either the singly capped **MFB**-H_3^{3+} or doubly capped **DFB**-H_3^{3+} has been formed, it is the mutual linking together, by a combination of supramolecular and dynamic covalent chemistry, of either five or six components, respectively, that results in the mechanically interlocking—not the addition of large stoppers to rods to constrain the movement of rings trapped thereupon. This alternative mode of construction[24] of mechanically interlocked compounds represents another way of exploiting the mechanical bond at the molecular level in chemistry.

Supporting Information Available: Synthesis of compounds, ITC, HR-ESI, and computational modeling procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Mechanically interlocked molecular bundles have been synthesized previously by kinetically controlled postassembly modification from triply threaded, two-component superbundles with a trifurcated trication wherein three dibenzylammonium ions are linked to a central benzenoid core. See: (a) Fyfe, M. C. T.; Lowe, J. N.; Stoddart, J. F.; Williams, D. J. *Org. Lett.* **2000**, *2*, 1221−1224. (b) Balzani, V.; Clemente-Leon, M.; Credi, A.; Lowe, J. N.; Badjić, J. D.; Stoddart, J. F.; Williams, D. J. *Chem.−Eur. J.* **2003**, *9*, 5348−5360. (c) Badjić, J. D.; Balzani, V.; Credi, A.; Lowe, J. N.; Silvi, S.; Stoddart, J. F. *Chem.−Eur. J.* **2004**, *10*, 1926−1935. This particular synthetic approach expressed itself ultimately in the making of molecular elevators. See: (d) Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. *Science* **2004**, *303*, 1845−1849. (e) Badjić, J. D.; Ronconi, C. M.; Stoddart, J. F.; Balzani, V.; Silvi, S.; Credi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1489−1499.