

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

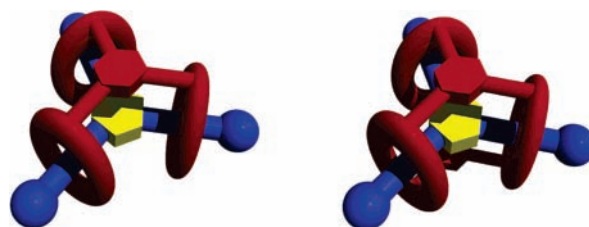
Brian H. Northrop, Fabio Aricó, Nick Tangchiavang, Jovica D. Badjić, and J. Fraser Stoddart*

Department of Chemistry and Biochemistry and the California NanoSystems Institute, University of California—Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095

stoddart@chem.ucla.edu

Received May 23, 2006

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_3NO_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 Wasserman¹ 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 rings⁵ synthesized usually by template-directed⁶ protocols depending on molecular recognition⁷ and self-assembly⁸ 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 exist⁹ beyond this first

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

(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

(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.

Dynamic covalent chemistry¹⁰ (DCC) has emerged as an efficient and versatile strategy for the synthesis of complex molecular structures. Whereas early examples of supramolecular assistance to covalent synthesis¹¹ 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 imine¹⁵ bond formation, as well as carbon–carbon bond formation during methasis¹⁶ 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

(5) (a) Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308–1312. (b) Siegel, J. S. *Science* **2004**, *304*, 1256–1258. (c) Schalley, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399–4401. (d) Chichak, K. S.; Peters, A. J.; Cantrill, S. J.; Stoddart, J. F. *J. Org. Chem.* **2005**, *70*, 7956–7962.

(6) (a) Anderson, S.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469–475. (b) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 374–384. (c) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169–2187. (d) Raymo, F. M.; Stoddart, J. F. *Pure Appl. Chem.* **1996**, *68*, 313–322. (e) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1999. (f) Stoddart, J. F.; Tseng, H.-R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4797–4800. (g) Busch, D. H. *Top. Curr. Chem.* **2005**, *249*, 1–65.

(7) (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995. (b) Lindoy, L. F.; Atkinson, I. M. *Self-Assembly in Supramolecular Systems*; Stoddart, J. F., Ed.; RSC: Cambridge, 2000. (c) Lehn, J.-M. *Science* **2002**, *295*, 2400–2403. (d) Reinhoudt, D. N.; Crego-Calama, M. *Science* **2002**, *295*, 2403–2407. (e) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.

(8) (a) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153–180. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1154–1195. (c) Fujita, M. *Acc. Chem. Res.* **1999**, *32*, 53–61. (d) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278–286. (e) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988–1011. (f) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972–983. (g) Yaghi, O. M.; O’Keeffe, M.; Ockwig, N. W.; Chae, H. K.; Eddaoudi, M.; Kim, J. *Nature* **2003**, *423*, 705–714.

(9) For a preliminary discussion of the mechanically interlocked molecules beyond catenanes and rotaxanes, see: Chang, T.; Heiss, A. M.; Cantrill, S. J.; Fyfe, M. C. T.; Pease, A. R.; Rowan, S. J.; Stoddart, J. F.; Williams, D. J. *Org. Lett.* **2000**, *2*, 2943–2946.

(10) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952.

(11) For examples of the kinetic approach, see: (a) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393–401. (b) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 129–132.

(12) (a) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4242. (b) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2005**, *127*, 13666–13671.

(13) (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438. (b) Hioki, H.; Still, W. C. *J. Org. Chem.* **1998**, *63*, 904–905. (c) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 12063–12064. (d) Ramström, O.; Lehn, J.-M. *ChemBioChem* **2000**, *1*, 41–48. (e) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590–593. (f) Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1270–1273. (g) Horikoshi, R.; Mikuriya, M. *Cryst. Growth Des.* **2005**, *5*, 223–230.

(14) (a) Brady, P. A.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3237–3253. (b) Rowan, S. J.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 1536–1546. (c) Kaiser, G.; Sanders, J. K. M. *Chem. Commun.* **2000**, 1763–1764.

(15) (a) Layer, W. R. *Chem. Rev.* **1963**, *63*, 489–510. (b) Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, 1970; pp 64–83. (c) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106–2110.

(16) (a) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600. (b) Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471. (c) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285. (d) Wang, L.; Myroslav, O. V.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312–1214. (e) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 2129–2132.

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

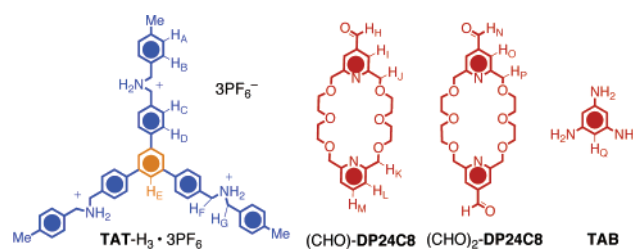


Figure 1. Structural formulas of the trisammonium ion template **TAT-H₃·3PF₆**, the formyl derivatives **(CHO)-DP24C8** and **(CHO)₂-DP24C8** of dipyrido[24]crown-8 (**DP24C8**), and 1,3,5-trisaminobenzene (**TAB**). The proton descriptors employed in Figures 2 and 4 are defined on the four structural formulas.

which they have been employed in the two syntheses is outlined in Scheme 1. The supramolecular assistance to covalent synthesis¹¹ 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 reagent²⁰ displaying the three matching amine functions.

Complexation occurs immediately upon addition of 3.0 equiv of **(CHO)-DP24C8** to **TAT-H₃·3PF₆** in **CD₃NO₂**, as

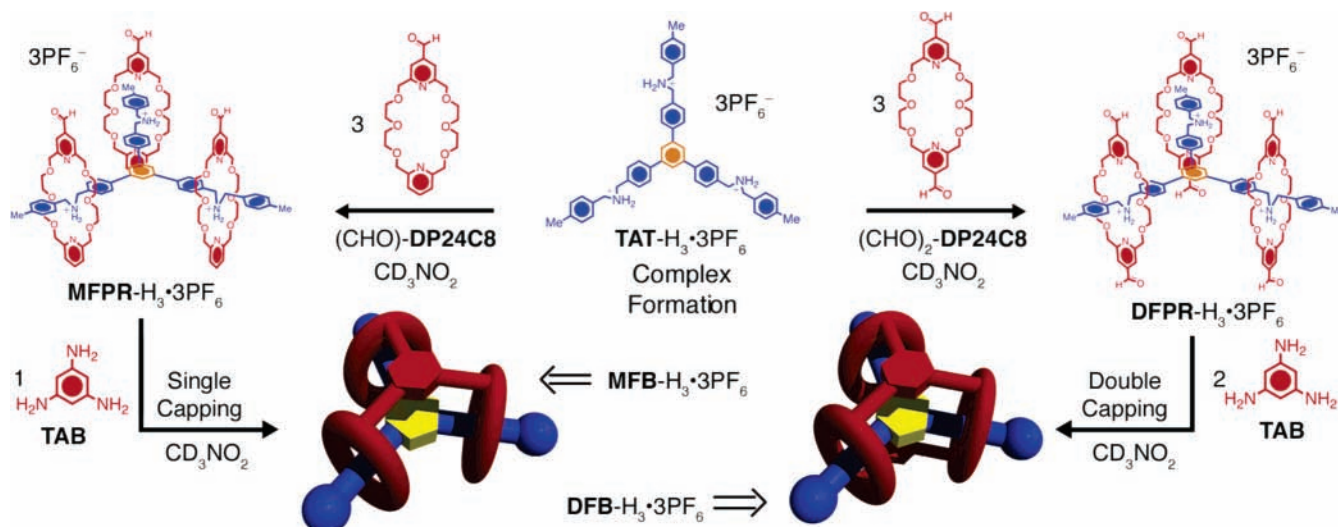
(17) (a) Fujita, M.; Ibukuro, F.; Hagaira, H.; Ogura, K. *Nature* **1994**, *367*, 720–725. (b) Baer, A. J.; Macartney, D. H. *Inorg. Chem.* **2000**, *39*, 1410–1417. (c) Chichak, K. S.; Walsh, M. C.; Branda, N. R. *Chem. Commun.* **2000**, 847–848. (d) Gunter, M. J.; Bampos, N.; Johnstone, K. D.; Sanders, J. K. M. *New J. Chem.* **2001**, *25*, 166–173. (e) Stulz, E.; Ng, Y.-F.; Scott, S. M.; Sanders, J. K. M. *Chem. Commun.* **2002**, 524–525. (f) Kubota, Y.; Sakamoto, S. S.; Yamaguchi, K.; Fujita, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4854–4856. (g) Yoshizawa, M.; Nakagawa, J.; Kurnazawa, K.; Nagao, M.; Kawano, M.; Ozeki, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1810–1813.

(18) Aricó, F.; Chang, T.; Cantrill, S. J.; Khan, S. I.; Stoddart, J. F. *Chem.–Eur. J.* **2005**, *11*, 4655–4666.

(19) Leung, K. C.-F.; Aricó, F.; Cantrill, S. J.; Stoddart, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5808–5810.

(20) While the templating effect of $-\text{CH}_2\text{NH}_2^+\text{CH}_2-$ centers located in dumbbell components have been used to activate the formation of two imine bonds in macrocyclic polyethers to form rotaxanes in a process known as clipping (Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870–1875. Horn, H.; Ihringer, I.; Glink, P. T.; Stoddart, J. F. *Chem.–Eur. J.* **2003**, *9*, 4040–4054.), the capping process described in this letter is more reminiscent of forming rotaxanes under thermodynamic control by imine exchange (Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916. Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366).

Scheme 1. Addition of Either (CHO)-DP24C8 or (CHO)₂-DP24C8 to TAT-H₃·3PF₆ in a 3:1 Ratio Leads to the Formation of the [4]Pseudorotaxanes MFPR-H₃·3PF₆ and DFPR-H₃·3PF₆, 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-H₃·3PF₆ and DFB-H₃·3PF₆, respectively.

indicated (Figure 2) by ¹H NMR spectroscopy. As is characteristic of the binding of -CH₂NH₂⁺CH₂- centers by crown ethers, the two pairs of benzylic methylene protons in TAT-H₃³⁺ are shifted upfield from δ = 4.5 and 4.6 ppm to δ = 3.9 and 4.4 ppm, respectively. Moreover, MFPR-H₃³⁺ is a kinetically stable complex on the ¹H NMR timescale at 298 K because peaks can be identified for uncomplexed and

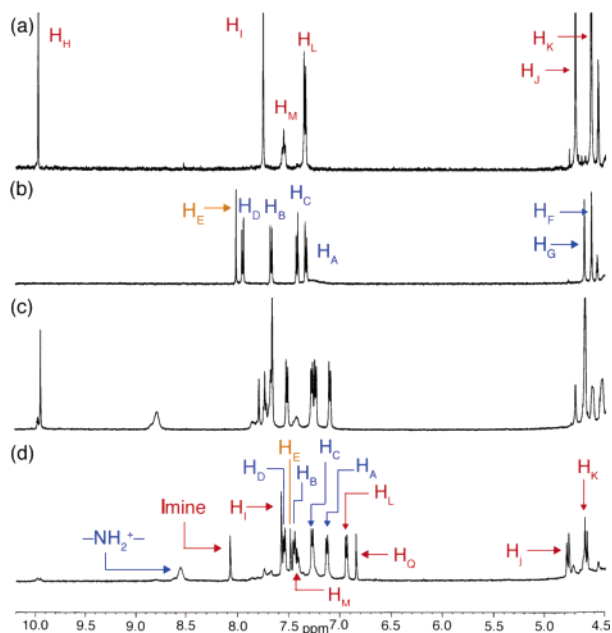


Figure 2. Partial ¹H NMR spectra (CD₃NO₂, 13.8 mM) of (a) (CHO)-DP24C8, (b) TAT-H₃·3PF₆, (c) MFPR-H₃·3PF₆, and (d) MFB-H₃·3PF₆. For a definition of the proton (H) descriptors, see Figure 1.

partially complexed, as well as fully complexed, species. Integration of these peaks suggests that MFPR-H₃³⁺ 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 (ΔG° = -5.5 kcal/mol) between TAT-H₃³⁺ and (CHO)-DP24C8 in MeNO₂. Computational force-field modeling (Figure 3a) reveals that the three NH₂ functions in TAB should be capable of forming imine bonds with the CHO groups in three complexed (CHO)-DP24C8 macrocycles. Indeed, although ¹H NMR spectroscopy reveals the formation of a number of products initially when 1.0 equiv of TAB is added to MFPR-H₃·3PF₆, after 2 h these kinetic intermediates converge²¹ to the most stable thermodynamic product—MFB-H₃·3PF₆ with 3-fold (C_{3v}) symmetry—containing three imine bonds. This outcome²² is supported (Figure 3a) by high-resolution electrospray ionization (HR-ESI) mass spectrometric analysis: m/z = 1131.52 for [M - 2PF₆]²⁺ compared with the calculated value of 1131.28.

Formation of DFPR-H₃·3PF₆ was observed (Figure 4) by ¹H NMR spectroscopy to occur spontaneously upon mixing of (CHO)₂-DP24C8 and TAT-H₃·3PF₆ in CD₃NO₂ in a 3:1 ratio. ITC measurements indicate a binding constant per binding site²³ of 3520 M⁻¹ (ΔG° = -4.8 kcal/mol) between TAT-H₃³⁺ and (CHO)₂-DP24C8 in MeNO₂. 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 δ = 9.95 ppm for formyl protons as the intensity of the singlet at δ = 8.10 ppm for imine protons increases simultaneously.

(22) All attempts to obtain X-ray quality single crystals of MFB-H₃·3PF₆ and DFB-H₃·3PF₆ or to reduce (e.g., with BH₃-THF and BH₃-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 ¹H NMR spectroscopy and mass spectrometry for the present.

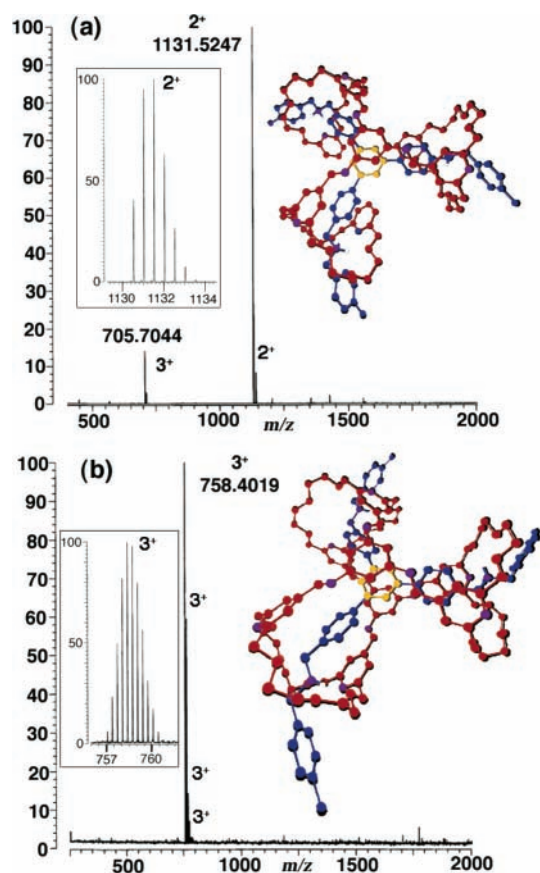


Figure 3. HR-ESI mass spectra showing the $[M - 2PF_6]^{2+}$ and $[M - 3PF_6]^{3+}$ peaks at $m/z = 1131.52$ and 705.70 for (a) **MFB-H₃·3PF₆** as well as the $[M - 3PF_6]^{3+}$ peak at $m/z = 758.40$ for (b) **DFB-H₃·3PF₆** along with the computed lowest-energy structures displayed alongside and the 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-H₃³⁺**. Double capping of **DFPR-H₃³⁺** was achieved by adding 2.0 equiv of **TAB** to the reaction mixture containing the [4]pseudorotaxane. While capping of **MFPR-H₃³⁺** requires only 2 h, double capping of **DFPR-H₃³⁺** 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-H₃³⁺**, 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-H₃³⁺** to become (Figure 4d) the dominant product in the ¹H NMR spectrum. Its formation

(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-H₃³⁺** 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.

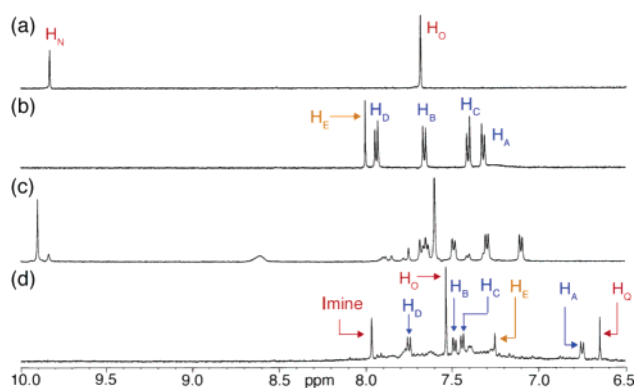


Figure 4. Partial ¹H NMR spectra (CD_3NO_2 , 8.8 mM) of (a) **(CHO)₂-DP24C8**, (b) **TAT-H₃·3PF₆**, (c) **DFPR-H₃·3PF₆**, and (d) **DFB-H₃·3PF₆** and other unidentified minor products. For a definition of the proton (H) descriptors, see Figure 1.

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 distinguishable⁹ from regular rotaxanes. Once either the singly capped **MFB-H₃³⁺** or doubly capped **DFB-H₃³⁺** 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 construction²⁴ of mechanically interlocked compounds represents another way of exploiting the mechanical bond at the molecular level in chemistry.

Acknowledgment. One (B.H.N.) of us thanks the ACS Division of Organic Chemistry for a graduate fellowship, sponsored by the Nelson J. Leonard ACS DOC Fellowship, sponsored by Organic Synthesis, Inc.

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>.

OL061262U

(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.