Templates, “Wheeled Reagents”, and a New Route to Rotaxanes by Anion Complexation: The Trapping Method

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Abstract: The topological aspects of rotaxanes are compared with those of the other families of mechanically interlocked molecules: catenanes and molecular knots. The role of the different types of templates in the well-known threading and clipping procedures often used for rotaxane synthesis are discussed. Finally the conceptually new trapping method that is based on the action of supramolecular nucleophiles formed by anionic stopper–wheel complexes is described.

Keywords: host–guest chemistry · rotaxanes · supramolecular chemistry · template synthesis

The structure of a molecule is usually defined unambiguously by its constitution and configuration; in some cases conformational aspects have to be considered, too. These properties determine the Euclidean geometry of molecules. Recently, interlocked molecules—knots, catenanes, and rotaxanes—have become a popular playground for preparative chemists; but with these species topological considerations additionally come into play.[1] A single large ring for example can exist as a simple loop or as a knot within a loop, in the simplest case a trefoil. Both, of course, have an identical constitution, that is, the same atomic connectivities; they are topological isomers. As with “conventional” structural isomers, these can be converted into each other only by the breaking of chemical bonds. However, the topology is invariant upon conceptual continuous deformation of the molecular framework. Catenanes consist of at least two large interlocked rings that are separate molecular entities. They are held together by a so-called “topological bond”—which is also a “mechanical” one—and are topologically isomeric with (the set of) their disjoint components, however unfamiliar it might be to call one molecule an isomer of a system of several others.[1a]

At first glance, rotaxanes might be less intriguing since they are not topologically isomeric to the set of their constituent components—the ring(s) and the axle(s). The reason is that in the imaginary transition from one arrangement to the other chemical bonds have only to be distorted in order to break or form the mechanical bond, which is consequently not a topological one and owes its stability to the lack of flexibility of the molecular entities. Thus one could consider “mechanical isomerism” here. Figure 1 illustrates the relation between interlocked molecules and their constituent components.

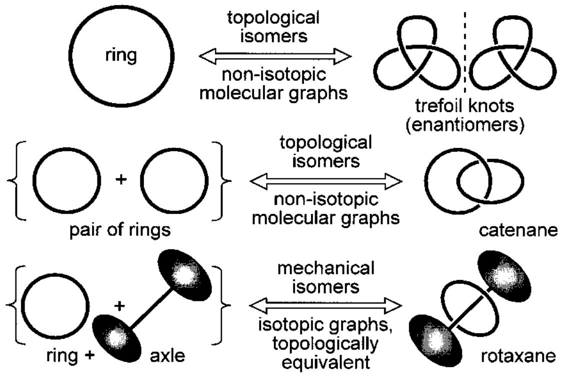

Figure 1. Pairs of isomers with identical bond connectivity (constitution) and homeomorphic molecular graphs. Knots and catenanes have extrinsically nonplanar graphs.

The threading of a string through a ring is a difficult task on the molecular scale because there are no mechanical instruments to grasp, fix, or maneuver the components. Instead, the threading has to be preprogrammed by giving the molecules appropriate chemical and physical properties. Not least because of the seemingly impossible task to synthesize preparative amounts, mechanically interlocked molecules were mere laboratory curiosities until about the late 1980s and did not get the attention of a larger scientific audience—undeservedly so. Early pioneers in the field were Schill and Lüttringhaus who relied on a multistep directed strategy via di- and triansa prerotaxanes and precatenanes.[2] However elegant, it was an extremely tedious approach considering the rather primitive—from today’s viewpoint—analytical and chromatographic techniques of the late 1960s. At about the same time Harrison alternatively used purely statistical low-

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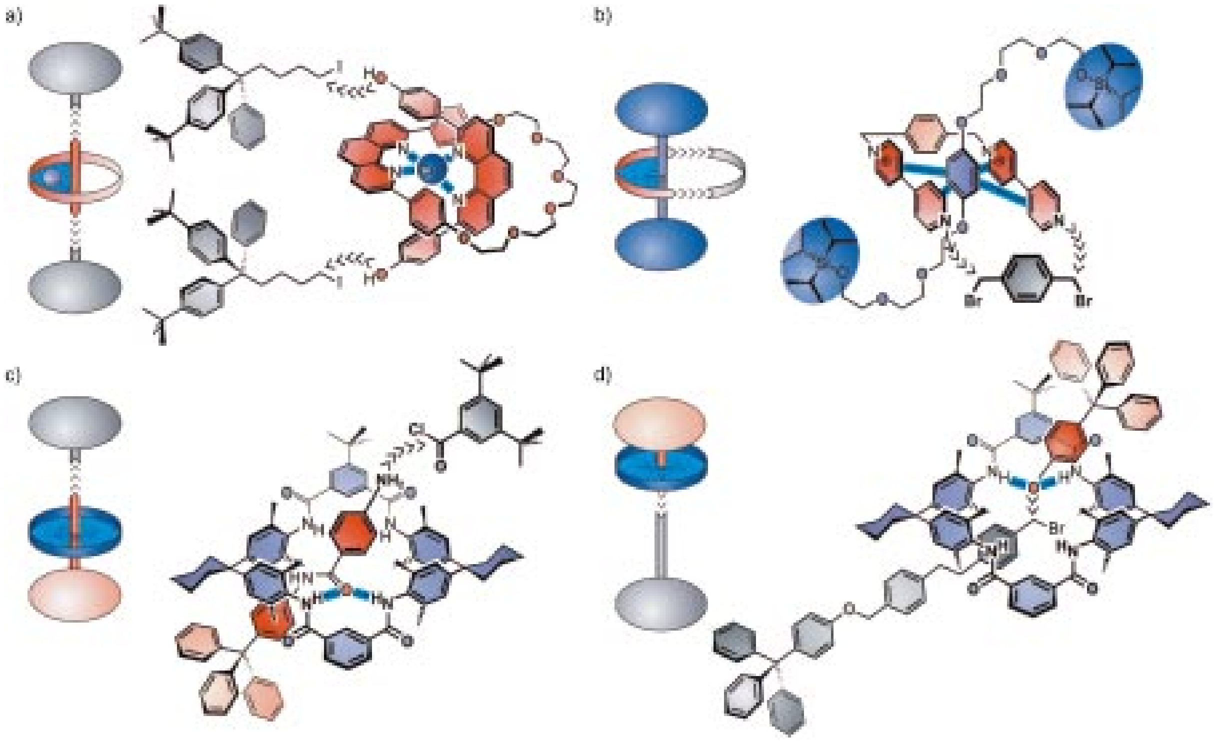

Figure 2. Template syntheses of rotaxanes. a) Threading method using the coordinative assembly of ligand building blocks by a metal cation template. b) Clipping synthesis driven by electron donor–acceptor attractions with the axle as the template. c) Threading through hydrogen bonding between the semiaxle and the templating wheel. d) Trapping: The complex between the phenolate stopper and the templating wheel causes the noncoordinated semiaxle to react through the cavity. Unlike in a) and c) the threading here does not happen prior to the bond formation. Note that in a) and b) the template is the guest and in c) and d) the host of the respective supramolecular complexes. Color coding: templates blue, ligands coordinated by the templates: red; attractive interactions: cyan; noncoordinated species: grey.

yielding slipping methods.[3] The latter term refers to the sliding of a wheel onto a stopper-bearing axle at elevated temperatures.

Only in the course of the increasing importance of supramolecular chemistry and with the better understanding of the processes of molecular recognition has it become possible to use intermolecular attractive forces in a methodical way for synthetic means. Thus versatile template-assisted interlocking methods have now been developed that are routinely applied to yield at least adequate amounts of a variety of these intriguing compounds of ever increasing complexity. The role of a chemical template, while generally not being one of the reacting partners itself, is to organize an assembly of participating molecules geometrically in order to enable the reaction to proceed in a way it would not pursue (or at least less efficiently) in its absence. The control of intermolecular forces, be they hydrogen bonds, electrostatic attractions, van der Waals forces, or others, is an indispensable prerequesite, and the consideration of geometry, size, functional complementarity, and the balance of flexibility and rigidity an imperative necessity for the development of template-directed syntheses,[4] which thus might be seen as applied supramolecular chemistry at its best.

Abstract in German: *Die topologischen Gesichtspunkte von Rotaxanen werden mit denen der anderen Typen mechanisch verknüpfter Moleküle, den Catenanen und molekularen Knoten, verglichen. Die Rolle der verschiedenen Arten von Schablonenmolekülen (Templaten) in den wohlbekannten Einfädelungs- (threading) und Clippingtechniken, die häufig für Rotaxansynthesen eingesetzt werden, wird erörtert. Schließlich wird das neue Konzept der Trappingmethode beschrieben, das auf der Reaktion supramolekularer Nukleophile basiert, die aus Komplexen von Stopper- und Reifmolekülen bestehen.*

The simplest application of a chemical template in synthesis—and also the first one conceived and originally termed “reaction of coordinated ligands” (Busch, 1962)[5]—is probably the formation of macrocyclic rings instead of polymeric compounds by wrapping a linear molecule around the template “to make ends meet” for cyclization. Surely the most widely known examples for this are the syntheses of phthalocyanines and crown ethers in the presence of templating metal cations (first examples 1927 and 1967, respectively).[6, 7]

It was also through the assembling and templating properties of (transition) metal cations that catenanes, rotaxanes, and molecular knots became available in preparative amounts by the seminal work of the group of Sauvage.[1c, 8] Figure 2a depicts how a 2,9-difunctionalized phenanthroline has to thread through a phenanthroline crown in order to provide the tetrahedral ligand sphere (red) required by a copper(I) cation (blue). Thus the protruding phenolic functional groups are positioned adequately for the condensation reaction with the stopper units.[9] This is a prototypical example for a threading synthesis via a pseudorotaxane as the crucial precursor.

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Stoddart et al. conceived a versatile strategy for the interlocking of molecules, which is based on the donor–acceptor interactions between π-electron-deficient and π-electron-rich aromatic building blocks (paraquat-like bipyridinium and phenylene diether units, respectively).[10] Additional attractive forces here are (edge-to-face) T-stacking and hydrogen bonding between ether oxygens and CH-acidic pyridinium hydrogens.[11] Both types of arenes, be it as macrocycles or open-chain compounds, have been used as molecular templating agents in the syntheses, that is, as the component that does not undergo chemical reaction. An example of the so-called clipping route towards rotaxanes is shown in Figure 2b where a hydroquinone ether axle as the template (blue) causes a hereby U-shaped bis(bipyridinium) cation (red) to wrap around it prior to the cyclization reaction with a dibromide.[12] Hydrophobic interactions have also been used in threading syntheses with the same[12] as well as with other types of host–guest systems such as inclusion complexes of cyclodextrins[13] and of water-soluble cyclophanes.[14]

Figure 2c describes a templating method towards rotaxanes that employs hydrogen bonds as directing forces, which cause the amide axle building block (red) to thread through the cavity of the tetralactam macrocycle (blue) under assembly of a semirotaxane precursor.[15] Note that here the wheel acts as the template, which thus becomes one of the components of the rotaxane. In contrast, in the above case (Figure 2a) the wheel is one of the ligands of the template and the latter, the copper(I) cation, does not become an integral part of the rotaxane framework. The lactam/amide recognition motif as shown in Figure 2c was originally applied to catenane synthesis independently and in a slightly different way by the groups of Hunter[16] and Vögtle[17] and then modified by the latter for rotaxanes.[18] Hydrogen bonding of this type has likewise been employed for clipping syntheses.[19] Furthermore, comparable threading approaches are based on the hydrogen bond driven association of crown ethers and linear secondary ammonium componds[20] or 1,2-bis(pyridinium)-ethanes.[21]

The development of host–guest chemistry started with the discovery of cyclodextrins and crown ethers and was in the beginning mainly focused on the complexation of metal cations. The attention shifted towards the molecular recognition of organic molecules when the synthetic means became more sophisticated and the understanding and control of the weak intermolecular forces that determine the recognition processes improved. The complexation of anionic species on the other hand was for a long time and still is to some extent a rather neglected field of research—even if early on attempts were made to use protonated azacrowns as ligands.[22] This was at least in part due to the higher solvation energy of anions (as compared to cations) that has to be overcome prior to binding as well as to the larger size and lower charge density and the variety of shapes and geometries of anions. Most anion ligands feature cationic groups as docking sites such as ammonium or guanidinium groups.[22] Incorporation of Lewis acids such as Sn^{IV} and Hg^{II} into organic or inorganic molecular scaffolds has also been employed.[22] However, some neutral and purely organic molecules have also been shown to strongly bind anions in organic solution or in the solid state, most of which contain multiple, cooperatively acting amide, sulfonamide, or urea groups as hydrogen bond donors to associate with the anions.[22]

Similar to their role in the evolution of host–guest chemistry, anionic species were the last to be employed as participants in the template-directed synthesis of mechanically interlocked molecules. We recently reported that macrocyclic isophtalamides like the ones used in the threading synthesis portrayed above (Figure 2c) bind inorganic and organic anions such as halides (Cl^-, Br^-) or acetate strongly in nonpolar media such as dichloromethane with association constants in the order of about $10^5\,\text{M}^{-1}$.[23] This observation led to the conception of a modified threading route towards rotaxanes (Figure 2d), in which the key feature is the binding of a voluminous phenolate by a tetralactam wheel through hydrogen bonding.[23] In the resulting complex the stopper unit sits on top of the wheel, blocking one face of it. Thus the reactive group, the phenolate oxygen, is sterically shielded from attack from this direction. Consequently the approach of the electrophilic semiaxle, which is not coordinated to the stopper/wheel complex, is only possible from the other side and through the cavity. Hence, the wheel again acts as the template while the stopper is the guest. The complex formed then functions as a "wheeled" supramolecular nucleophile, while the semiaxle is a "mere" reaction partner that gets trapped inside the wheel. In other words, the threading of the string coincides with the bond formation and does not happen in an earlier step through an assembling process as in the threading methods of Figures 2a and 2c. This is also the only type of rotaxane synthesis where a reactive group (the phenolate oxygen) is actively involved in the prereaction assembly process (H-bonding) and where the reaction happens inside the wheel cavity. To differentiate it, we call this new synthetic strategy trapping; after all, in the macroscopic analogue there is likewise no attractive force between the trap itself and the prey: The "binding" is purely mechanical as between wheel and axle; and the cheese gets consumed as does the phenolate in the reaction. Yields of up to 95% have been obtained in the synthesis of rotaxanes with phenyl ether axles.[23] Simiarly, other nucleophilic substitution reactions that lead to ester, thioester, phosphoric acid ester, acetal, sulfide, or sulfonamide axles have been succesfully applied for rotaxane synthesis.[24] A conceptually similar approach was used by the group of Gibson for the synthesis of a series of polydisperse polyrotaxanes.[25] Here the binding motif is the hydrogen bonding of OH groups by crown ethers. The nucleophilic attack of the resulting supramolecular nucleophilic comonomers on diisocanates—to give just one example—leads to polyurethanes that are mechanically crosslinked by rotaxane subunits.[25a]

The different template-assisted reactions described here, be they based on transition metal coordination, electron donor–acceptor and hydrophobic interactions, or multiple hydrogen bonding of neutral or ionic molecules are of course not restricted to rotaxane syntheses. In recent years a great number of appealing interlocked molecules has been presented by groups worldwide. There are polyrotaxanes, multicatenanes of diverse shape, doubly interlocked [2]catenanes, trefoil knots, pretzelanes, dendritic rotaxanes, topologically chiral molecules, and more that imaginative minds only two decades ago could merely dream of.[26, 27] It will be interesting to observe what this fascinating field of supramolecular chemistry has to offer in the near future.

[1] a) H. L. Frisch, E. Wassermann, *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795; b) D. M. Walba, *Tetrahedron* **1985**, *41*, 3161–3212; c) J.-C. Chambron, C. Dietrich-Buchecker, J.-P. Sauvage, *Top. Curr. Chem.* **1993**, *165*, 131–162; d) D. K. Mitchell, J.-C. Chambron, *J. Chem. Educ.* **1995**, *72*, 1059–1064; e) K. Mislow, *Top. Stereochem.* **1997**, *22*, 1–82.

[2] G. Schill, A. Lüttringhaus, *Angew. Chem.* **1964**, *76*, 567–568; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 546–547; G. Schill, *Chem. Ber.* **1967**, *100*, 2021–2037; G. Schill, H. Zollenkopf, *Liebigs. Ann. Chem.* **1969**, *721*, 53–74.

[3] I. T. Harrison, S. Harrison, *J. Am. Chem. Soc.* **1967**, *89*, 5723–5724; I. T. Harrison, *J. Chem. Soc. Perkin Trans. 1* **1974**, 301–304.

[4] a) D. H. Busch, N. A. Stephenson, *Coord. Chem. Rev.* **1990**, *100*, 119–154; b) S. Anderson, H. L. Anderson, J. K. M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469–475; c) R. Hoss, F. Vögtle, *Angew. Chem.* **1994**, *106*, 389–398; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1956–1959; d) *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-P. Sauvage, M. W. Hosseini), Pergamon, Oxford, **1996**; e) *Template Synthesis* (Eds.: N. V. Gerbeleu, V. B. Arion, J. Burgess), Wiley, Chichester, **1999**; f) *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1999**; g) T. J. Hubin, A. G. Kolchinski, A. L. Vance, D. H. Busch in *Advances in Supramolecular Chemistry, vol. 5* (Ed.: G. W. Gokel), JAI Press, London, **1999**, pp. 237–357.

[5] M. C. Thompson, D. H. Busch, *J. Am. Chem. Soc.* **1962**, *84*, 1762–1763.

[6] H. de Diesbach, E. von der Weid, *Helv. Chim. Acta* **1927**, *10*, 886–888.

[7] C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496.

[8] J.-C. Chambron, J.-P. Sauvage, *Chem. Eur. J.* **1998**, *4*, 1362–1366, and references therein.

[9] C. Wu, P. R. Lecavalier, Y. X. Shen, H. W. Gibson, *Chem. Mater.* **1991**, *3*, 569–572; J.-C. Chambron, V. Heitz, J.-P. Sauvage, *J. Chem. Soc. Chem. Commun.* **1992**, 1131–1133.

[10] D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725–2828. For a neutral π-assembled system, see: D. G. Hamilton, J. E. Davies, L. Prodi, J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 608–620.

[11] K. N. Houk, S. Menzer, S. P. Newton, F. M. Raymo, J. F. Stoddart, D. J. Williams, *J. Am. Chem. Soc.* **1999**, *121*, 1479–1487.

[12] P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent, D. J. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 193–218.

[13] First example: H. Ogino, *J. Am. Chem. Soc.* **1981**, *103*, 1303–1304.

[14] S. Anderson, H. L. Anderson, *Angew. Chem.* **1996**, *108*, 2075–2078; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1956–1959.

[15] For the molecules depicted, see: C. Seel, A. H. Parham, O. Safarowsky, G. M. Hübner, F. Vögtle, *J. Org. Chem.* **1999**, *64*, 7236–7242.

[16] C. A. Hunter, *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311.

[17] F. Vögtle, S. Meier, R. Hoss, *Angew. Chem.* **1992**, *104*, 1628–1631; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1619–1622.

[18] First example: F. Vögtle, M. Händel, S. Meier, S. Ottens-Hildebrandt, F. Ott, T. Schmidt, *Liebigs Ann.* **1995**, 739–743.

[19] A. G. Johnston, D. A. Leigh, A. Murphy, J. P. Smart, M. D. Deegan, *J. Am. Chem. Soc.* **1996**, *118*, 10662–10663; D. A. Leigh, A. Murphy, J. P. Smart, A. M. Z. Slawin, *Angew. Chem.* **1997**, *109*, 752–756; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 752–756.

[20] First example: A. G. Kolchinsky, D. H. Busch, N. W. Alcock, *J. Chem. Soc. Chem. Commun.* **1995**, 1289–1291. For related pseudorotaxanes, see: P. R. Ashton, E. J. T. Chrystal, P. T. Glink, S. Menzer, C. Schiavo, J. F. Stoddart, P. A. Tasker, D. J. Williams, *Angew. Chem.* **1995**, *107*, 2001–2004; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1869–1872.

[21] S. J. Loeb, J. A. Wisner, *Chem. Commun.* **1998**, 2757–2758.

[22] For general reviews on anion binding, see: B. Dietrich, *Pure Appl. Chem.* **1993**, *65*, 1457–1464; C. Seel, A. Galán, J. de Mendoza, *Top. Curr. Chem.* **1995**, *175*, 101–132; C. Seel, J. de Mendoza in *Comprehensive Supramolecular Chemistry*, *Vol. 2* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**, pp. 519–552; K. T. Holman, J. L. Atwood, J. W. Steed in *Advances in Supramolecular Chemistry, Vol 4* (Ed.: G. W. Gokel), JAI Press, London, **1997**, pp. 287–330; F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646; *The Supramolecular Chemistry of Anions* (Ed.: A. Bianchi, K. Bowman-James, E. García-España), Wiley, Chichester, **1997**.

[23] G. M. Hübner, J. Gläser, C. Seel, F. Vögtle, *Angew. Chem.* **1999**, *111*, 395–398; *Angew. Chem. Int. Ed.* **1999**, *38*, 383–386.

[24] C. Reuter, W. Wienand, G. M. Hübner, C. Seel, F. Vögtle, *Chem. Eur. J.* **1999**, *5*, 2692–2697; G. M. Hübner, C. Reuter, C. Steel, F. Vögtle, *Synthesis* **1999**, in press.

[25] Selected papers: a) C. Gong, H. W. Gibson *J. Am. Chem. Soc.* **1997**, *119*, 8585–8591; b) H. W. Gibson, D. S. Nagvekar, J. Powell, C. Gong, W. S. Bryant, *Tetrahedron* **1997**, *53*, 15197–15208; c) C. Gong, T. E. Glass, H. W. Gibson *Macromolecules* **1998**, *31*, 308–313.

[26] For recent reviews, see: References [1c], [4d], [10]; H. W. Gibson in *Large Ring Molecules* (Ed.: J. A. Semlyen), Wiley, Chichester, **1996**, pp. 191–262; R. Jäger, F. Vögtle, *Angew. Chem.* **1997**, *109*, 966–980; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930–944; *Catenanes, Rotaxanes, Knots* (Ed.: J.-P. Sauvage), VCH-Wiley, Weinheim; in press.

[27] Not all of the reported syntheses are template-directed, see, for example: References [2] and [3]; G. Agam, D. Graiver, A. Zilkha, *J. Am. Chem. Soc.* **1976**, *98*, 5206–5214; D. M. Walba, R. M. Richards, R. C. Haltiwanger, *J. Am. Chem. Soc.* **1982**, *104*, 3219; M. Händel, M. Plevoets, S. Gestermann, F. Vögtle, *Angew. Chem.* **1997**, *109*, 1248–1250; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1199–1201; D. B. Amabilino, M. Asakawa, P. R. Ashton, R. Ballardini, V. Balzani, M. Belohradsky, A. Credi, M. Higuchi, F. M. Raymo, T. Shimizu, J. F. Stoddart, M. Venturi, K. Yase, *New J. Chem.* **1998**, 959–972. For a catenane synthesized from preformed metallamacrocycles under thermodynamic template assistance, see: M. Fujita, M. Aoyagi, F. Ibukuro, K. Ogura, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120,* 611–612; N. Takeda, K. Umemoto, K. Yamaguchi, M. Fujita, *Nature* **1999**, *398*, 794–796.

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