Pure Appl. Chem., Vol. 80, No. 3, pp. 485–506, 2008.
doi:10.1351/pac200880030485

Template-directed synthesis of donor/acceptor [2]catenanes and [2]rotaxanes*

Kirsten E. Griffiths and J. Fraser Stoddart‡

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

Abstract: The synthesis of mechanically interlocked molecular compounds has advanced by leaps and bounds since the early days of statistical methods and covalent-directing strategies. Template-directed synthesis has emerged as the method of choice for the construction of increasingly complex and functional [2]catenanes and [2]rotaxanes. In particular, mechanically interlocked molecules employing π-donating and π-accepting recognition units have been produced with remarkable efficiencies and show great promise in technologies as diverse as molecular electronics and drug delivery.

Keywords: [2]rotaxanes; [2]catenanes; template-directed synthesis; pseudorotaxanes; donor/acceptor recognition; mechanically interlocked molecules; mechanical bonds; molecular machines; molecular motors; molecular electronics.

INTRODUCTION

For more than 50 years, chemists have been intrigued by the challenge of making mechanically interlocked molecules. However, the development of molecules containing a mechanical bond was hampered in its early years by poor yields from traditional synthetic methods [1–4]. Beginning in the 1980s and continuing throughout the 1990s, the synthesis of mechanically interlocked molecular compounds has advanced by leaps and bounds as a consequence of developments in template-directed synthesis [5] and an increased understanding of self-assembly processes as they relate to the formation of key supramolecular intermediates [6]. Despite some early synthetic difficulties, the design and production of molecules containing mechanical bonds has matured into a rich and rewarding field of research as different mechanically interlocked molecules are continually being produced (Fig. 1). Today these compounds are being studied for their unique static and dynamic properties, including their topological behavior and switching characteristics. Recent advances in the synthesis of mechanically interlocked molecules, including the introduction of "click chemistry" [7–9] and thermodynamic clipping methods [10], are making these complex structures even more synthetically accessible in better yields and by robust synthetic pathways.

From pseudorotaxanes to rotaxanes and catenanes

While topologically distinct, catenanes and rotaxanes may be considered molecular siblings as both may be synthesized from a common intermediate known [15] as a pseudorotaxane (Fig. 2), a supra-

*Paper based on a presentation at the 12th International Symposium on Novel Aromatic Compounds (ISNA-12), 22–27 July 2007, Awaji Island, Japan. Other presentations are published in this issue, pp. 411–667.

‡Corresponding author

molecular species in which a thread is encircled by one or more macrocycles. Generally, the threading of a linear component through the macrocycle is driven thermodynamically by noncovalent bonding interactions to create the most stable species in solution. Noncovalent bonding interactions including (i) donor/acceptor forces, (ii) metal/ligand coordination, (iii) hydrogen bonding, (iv) π–π stacking, (v) solvophobic repulsion, and/or (vi) electrostatic forces have all been employed [6] to create supramolecular assemblies. While chemically interesting in their own right, pseudorotaxanes are dynamic species and may decomplex when subjected to changes in solvent, temperature, or competitive guests. However, it is possible to fix a pseudorotaxane kinetically either (i) by stoppering or (ii) by macrocyclization of the ends of the thread to produce, by what is in essence supramolecular assistance to covalent synthesis [16], a rotaxane or catenane, respectively.

The name "rotaxane" [11] is derived from the Latin word for a wheel (*rota*) and an axle (*axis*). Rotaxanes are molecules comprised of a linear dumbbell-shaped component encircled by one or more macrocycles. The stoppers attached to the ends of the dumbbell must be large enough to trap the macrocycle(s) mechanically and prevent them from dethreading. A standard piece of nomenclature has been established wherein the number of components that comprise the rotaxane appears in square brackets before the term. Thus, an [*n*]rotaxane is a molecule comprised of a dumbbell and $n - 1$ macrocyclic components.

Catenanes [11] are comprised of two or more interlocked rings, and their name is derived from the Latin word *catena*, meaning "chain". In the same way as for rotaxanes, catenanes utilize a naming convention wherein the number of macrocycles that comprise a catenane appears in square brackets before the term. Thus, an [*n*]catenane is a molecule comprised of *n* macrocycles.

Despite their conceptual similarity, catenanes are considered to be topologically nontrivial, whereas rotaxanes are simply considered to be topologically trivial [17]. This difference exists since a catenane's topology cannot be altered, no matter how the rings are distorted, and the structure will remain mechanically interlocked unless a covalent bond is broken. In a rotaxane, by comparison, if the macrocycle is stretched it may dethread over one of the bulky stoppers, resulting in two topologically trivial components. Thus, a rotaxane is topologically identical to its equivalent free dumbbell and macrocycle(s), while a catenane and its equivalent macrocycles are topologically isomeric.

Historical perspective

The field of mechanically interlocked molecules is considered by many to have begun in 1960 when Wasserman [1] described in the literature what is commonly known as the first wholly synthetic [2]catenane. To obtain this catenane, he utilized a statistical synthetic methodology in which macrocyclizations of alkyl chains containing 34 carbon atoms in length were performed. In his synthesis, statistically less than 1 % of the starting material reacts in a mechanically interlocked co-conformation, creating only a small quantity of catenane (Fig. 3). Wasserman and Frisch [2] followed this initial work with a landmark paper in 1961 entitled "Chemical topology," which captured the imagination of many synthetic chemists. In this treatise, the authors explored the possibility of statistical knotting and/or linking during macrocyclizations of long alkyl chains to create molecules such as trefoil knots and catenanes. Most importantly, Frisch and Wasserman firmly established mechanically interlocked species as being molecules rather than assemblies of separate entities, and so gave substance to the concept of the mechanical bond [18]. While mechanically interlocked molecules contain two or more sets of atoms which fulfill the classical definition of a molecule individually, the mechanically interlocked structure fulfills the definition of a molecule as it requires the breaking of at least one covalent bond to allow the entities to separate. Thus, in a [2]rotaxane or [2]catenane, the union between the two components equates with the same strength as the weakest covalent bond, and therefore it may be argued that a "mechanical bond" exists between the two entities, creating a single molecule. Also, mechanically interlocked compounds have structural and functional properties that differ significantly from those of their individual components.

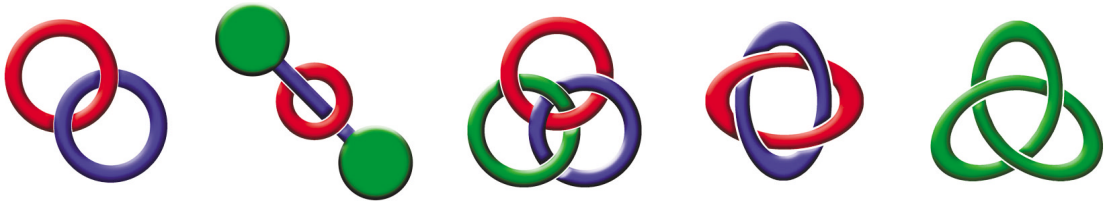


Fig. 1 Five types of interlocked molecules (from left to right) which have been synthesized by chemists—a [2]catenane [11], a [2]rotaxane [11], Borromean rings [12], Solomon links [13], and a trefoil knot [14].

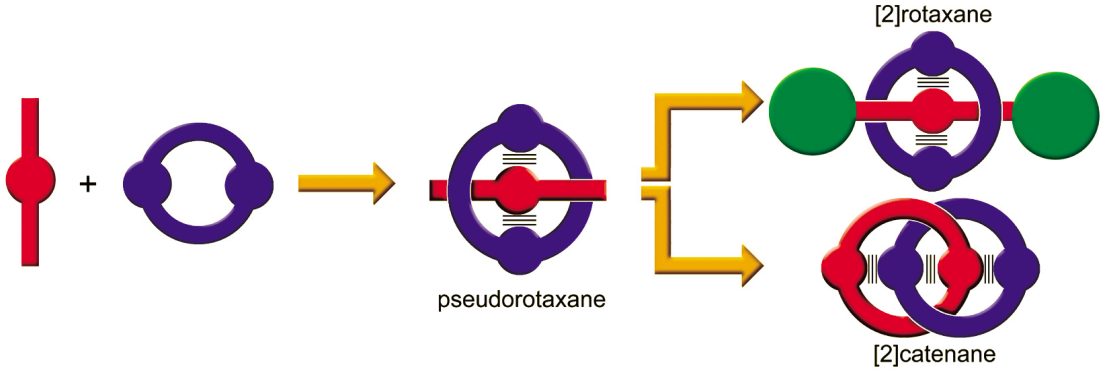


Fig. 2 Formation of a pseudorotaxane as a precursor to either a [2]rotaxane or [2]catenane.

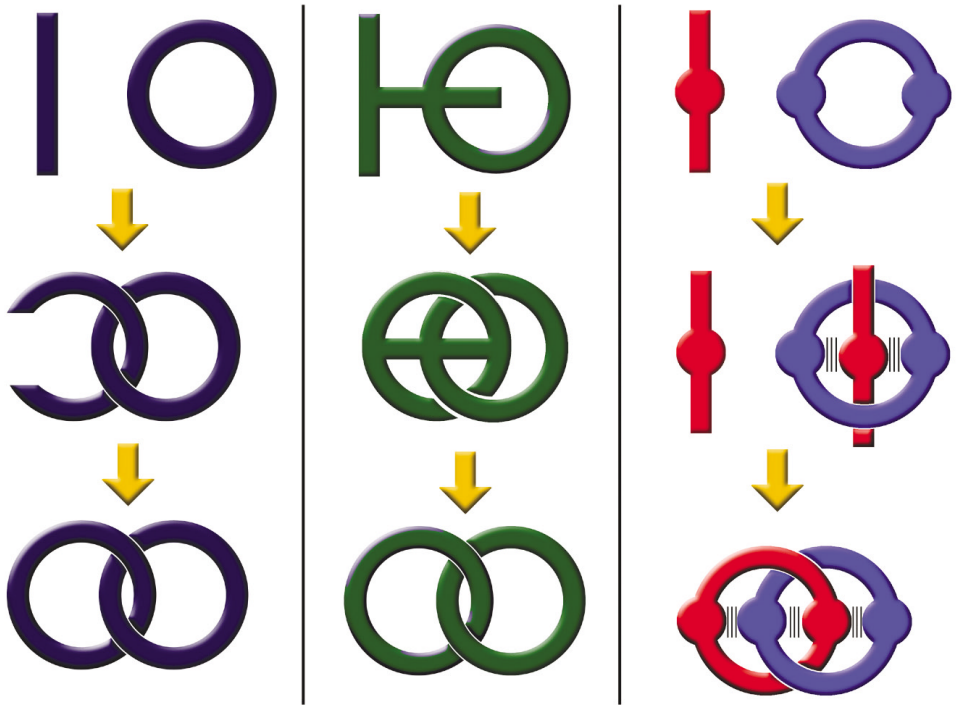


Fig. 3 (left) Statistical catenation, (center) covalent-directed catenation, (right) template-directed catenation.

By 1964, Lüttringhaus and Schill [4] had recognized the limitations of the statistical synthesis of catenanes and strove to prepare appreciable quantities of catenanes through the use of covalent bonds to direct the formation of a catenane. In this strategy, the authors were able to use steric control, provided by well-designed covalent bonds, to prevent the extra-annular ring closures which plagued the statistical method of catenation, increasing the yield of the desired pre-catenane (Fig. 3). The desired [2]catenane was then formed by breaking the directing covalent bonds such that the two rings were no longer connected covalently. Despite its elegance, this approach requires lengthy synthetic pathways, resulting in only small yields overall. In recent years, more succinct covalent-directing pathways have been developed [19] to synthesize [2]rotaxanes. However, there is also the issue that after the directing covalent bonds are broken the strong communication between the components is lost.

Despite the introduction of covalent-directed synthesis in the early 1960s, the simplicity of statistical methods prevailed again in 1967 with the synthesis of the first wholly synthetic rotaxane by Harrison and Harrison [3]. In order to produce a rotaxane in appreciable quantities, the authors cleverly attached a 30-carbon macrocycle to a resin and then passed a pyridine/dimethylformamide solution containing decane-1,10-diol (thread) and triphenylmethyl chloride (stopper) over the resin 70 times. As the solution was passing over the resin, statistically some of the threads would react with the stoppers while threaded through the fixed macrocycles, creating a rotaxane. After cleaving the rotaxanes from the resin and further purification, the authors reported only a 6 % yield, despite having run the reaction 70 times. While exceptionally clever and groundbreaking in their time, statistical synthetic methods have been almost entirely surpassed and replaced by directed-synthetic methods. The synthesis by Harrison and Harrison was soon followed by a covalent-directed [2]rotaxane synthesis by Schill and coworkers [20].

In subsequent years, chemists [5] have discovered several ways to circumvent the poor yields of traditional synthetic methods by using template-directed synthetic strategies (Fig. 3). In these strategies, a template will complex with another component, usually a macrocycle, by means of coordinative or noncovalent bonding interactions. This supramolecular species can then be used as a reactive intermediate such that further covalent reactions can be carried out to produce the desired mechanically interlocked molecule. This strategy has real advantages in that it is possible to synthesize complex mechanically interlocked molecular compounds in high yields with fewer synthetic steps than by the comparable covalent-directed synthetic methods. The first demonstration of the template-directed synthesis of a catenane was reported by Sauvage and coworkers [21] in 1983. In this seminal piece of research, a 1,10-phenanthroline-based thread and a 1,10-phenanthroline-containing macrocycle were complexed by a Cu(I) ion to construct the desired pseudorotaxane, prior to the ends of the thread being cyclized to form the desired catenate, i.e., a catenane that is a ligand coordinated to a transition metal [22]. Since this report, many other noncovalent bonding interactions (e.g., hydrogen-bonding, π–π stacking, and donor/acceptor interactions) have been employed successfully to make mechanically interlocked molecular compounds in high yields.

DONOR/ACCEPTOR-BASED PSEUDOROTAXANES

Donor/acceptor-based template-directed synthesis began with the pairing of π-electron-rich macrocycles with π-electron-deficient rod-shaped molecules in anticipation that the rod would thread through the macrocycle forming a pseudorotaxane. We reported an early example of this type of complexation (Fig. 4) in 1987 [23].

In this case, the electron-rich macrocyclic polyether host, bis-*p*-phenylene[34]crown-10 (BPP34C10), binds a paraquat dication, an electron-deficient guest. The complex is held together by (i) π–π stacking interactions between the complementary aromatic units and (ii) [C-H···O] interactions between the hydrogen atoms—[CH_3-N] and [CH-N]—in the α-positions with respect to the nitrogen atoms in the bipyridinium unit and the crown ether oxygen atoms. The assembly of the BPP34C10/paraquat pseudorotaxane can be extrapolated to an inverse recognition system, where the macrocycle is constructed from paraquat units and the guest species is a hydroquinone unit carrying eth-

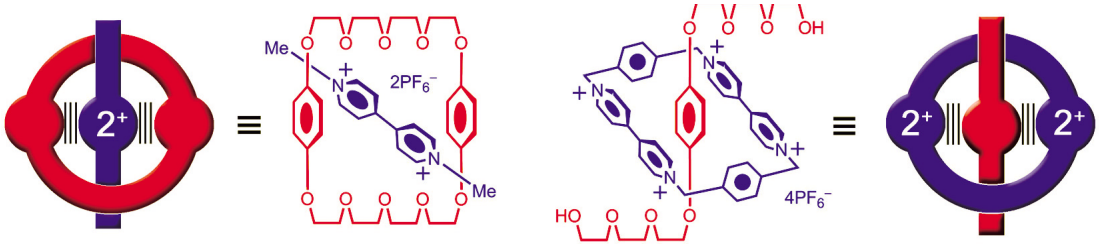


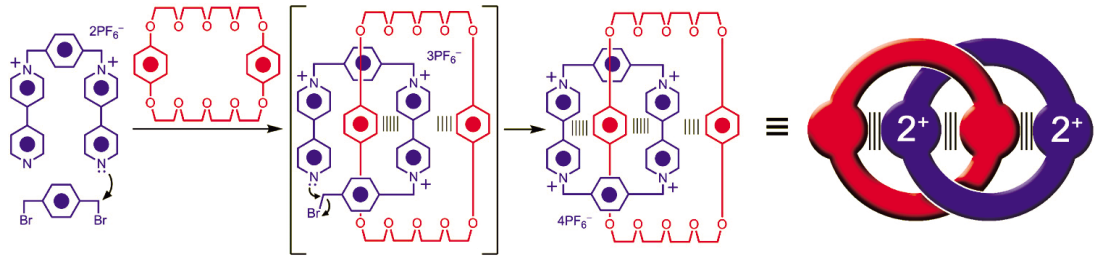
Fig. 4 Donor/acceptor-based pseudorotaxanes.

ylene glycol chains. Indeed, this system was reported by us [24] in 1988, with the isolation and characterization of cyclobis(paraquat-*p*-phenylene) cyclophane ($CBPQT^{4+}$), (Fig. 4, right) a promiscuous π-electron-deficient receptor. In this reverse recognition system, the host is able to bind a variety of linear acyclic oligoether substituted aromatic moieties effectively [25]. Both types of pseudorotaxanes have been described and have been elaborated subsequently, either by cyclization or stoppering, to yield [2]catenanes or [2]rotaxanes, in high yield.

DONOR/ACCEPTOR [2]CATENANES

Following the introduction of the concept of template-directed synthesis on the back of the immense progress in the field of host/guest chemistry, much research was directed into the development of efficient syntheses of donor/acceptor catenanes with variations in their structures. In order to understand the mechanism of formation and physical properties which govern catenation and the dynamic properties of catenanes, it was necessary to vary [26] the sizes, component geometries, and electron-donating abilities of both macrocycles systematically. Additionally, it is possible to communicate between the two macrocyclic components in a donor/acceptor [2]catenane because of the π–π stacking interactions between π-donors and π-acceptors.

The most simplistic and elegant method of synthesizing a donor/acceptor-based [2]catenane involves [27] mixing an acetonitrile solution of BPP34C10 with 1,4-bis(bromomethyl)benzene and a bipyridinium dication as shown in Scheme 1. The proposed mechanism for this reaction involves the bipyridinium dication reacting first of all with the bis(bromomethyl)benzene, since the dication has not been shown to associate with BPP34C10. However, once a full bipyridinium unit on the thread is formed, this intermediate trication threads through the BPP34C10 to form a pseudorotaxane, which is a more thermodynamically stable species than the components individually. Once this 1:1 complex is formed, the hydroquinone units are then aligned so as to template the final bond formation leading to the cyclization of the $CBPQT^{4+}$ cyclophane. This final step yields the catenane in an astounding 70 %

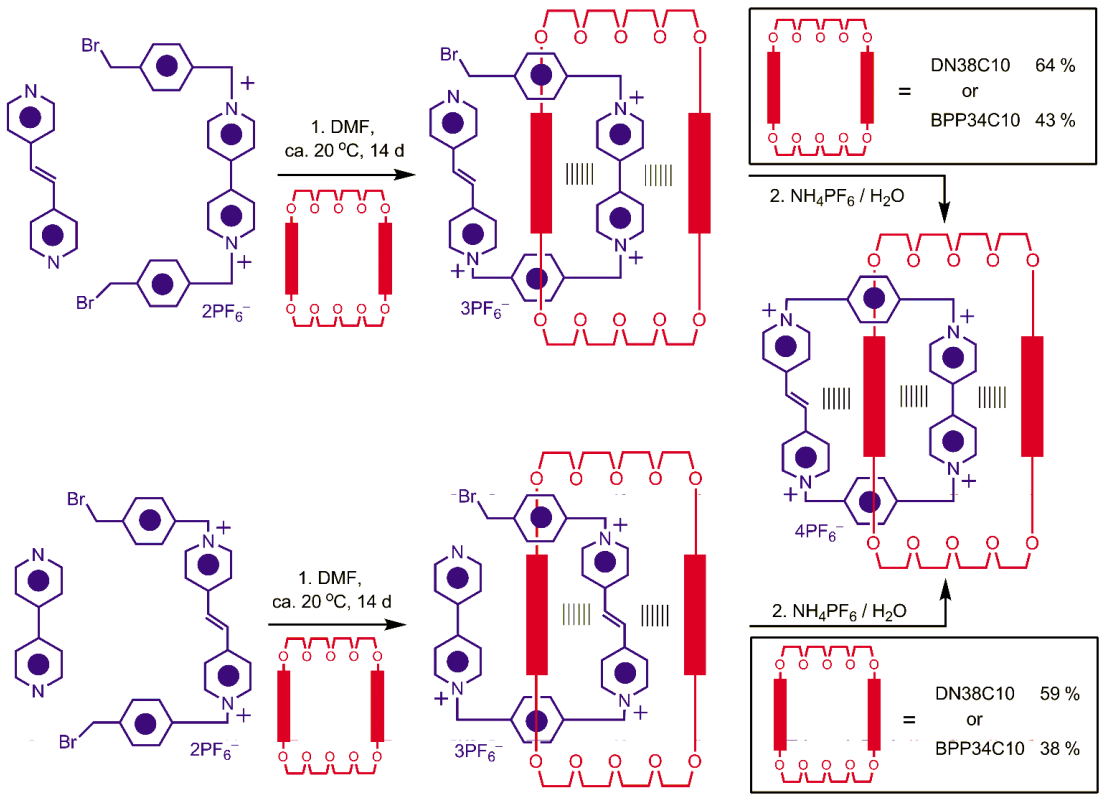


Scheme 1 Proposed mechanism for the kinetically controlled template-directed synthesis of a [2]catenane incorporating a BPP34C10 ring and a $CBPQT^{4+}$ cyclophane. The desired [2]catenane was isolated from the reaction mixture by counterion exchange with an aqueous solution of NH_4PF_6.

yield with its built-in π-acceptor/π-donor/π-acceptor/π-donor stack. This type of π–π sandwiching allows the [2]catenane to be formed in a highly efficient manner. The alignment by stacking of the π-acceptor and π-donor units has been demonstrated by ^{1}H NMR spectroscopy and in the solid state by X-ray crystallography, both within a single catenane molecule and between stacks of catenane molecules. [28]

As a demonstration of the power of template-directed synthesis, the same [2]catenane was made simply by mixing the basic $CBPQT^{4+}$ components, namely, 1,4-bis(bromomethyl)benzene and 4,4'-bipyridine with BPP34C10. Despite the lack of preorganization in this system and its propensity to form polymeric side products, it was possible to isolate the desired [2]catenane in 18 % yield, effectively demonstrating the power of molecular recognition and self-assembly using donor/acceptor recognition systems.

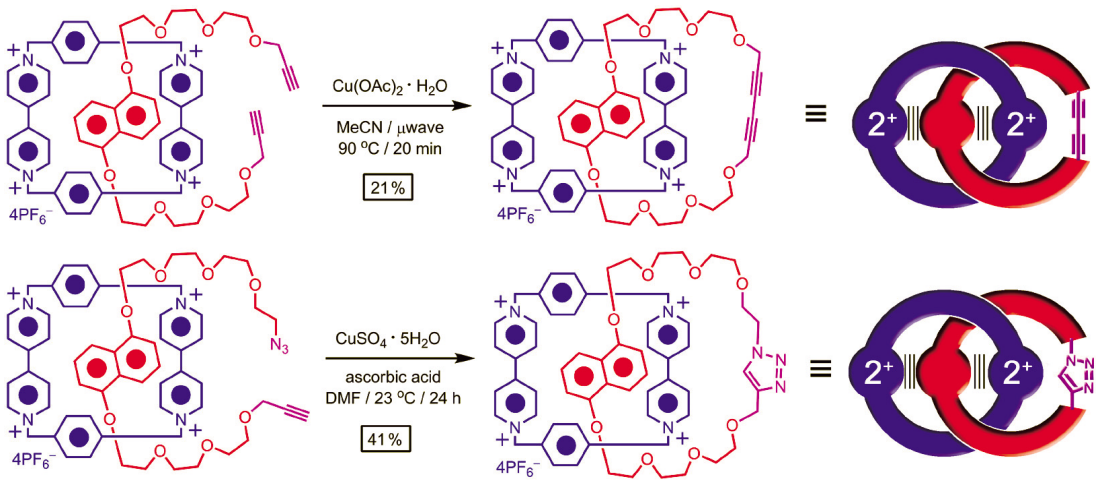
In order to gain a better understanding of the mechanism and physical properties which govern the assembly of donor/acceptor [2]catenanes, several experiments were performed in which components were varied in their size, electron donating/withdrawing abilities, and shapes. A competition experiment was devised wherein a "mixed" 4,4'-bipyridium/bis(4-pyridinium)ethylene tetracationic cyclophane was clipped around either a BPP34C10 or a 1,5-dinaphtho[38]crown-10 (DN38C10) macrocycle [29]. In this experiment, it was shown that when the clipping reaction was carried out in the presence of equimolar amounts of BPP34C10 and DN38C10, 99 % of the catenane formed contained the DN38C10 ring and only 1 % incorporated the BPP34C10 ring. In a complementary experiment, the percent yield of formation of a [2]catenane incorporating either a DN38C10 or a BPP34C10 was monitored by the two different reaction pathways shown in Scheme 2. Despite this strong preference and



Scheme 2 The competitive self-assembly experiments of four [2]catenanes and the ratio of products formed.

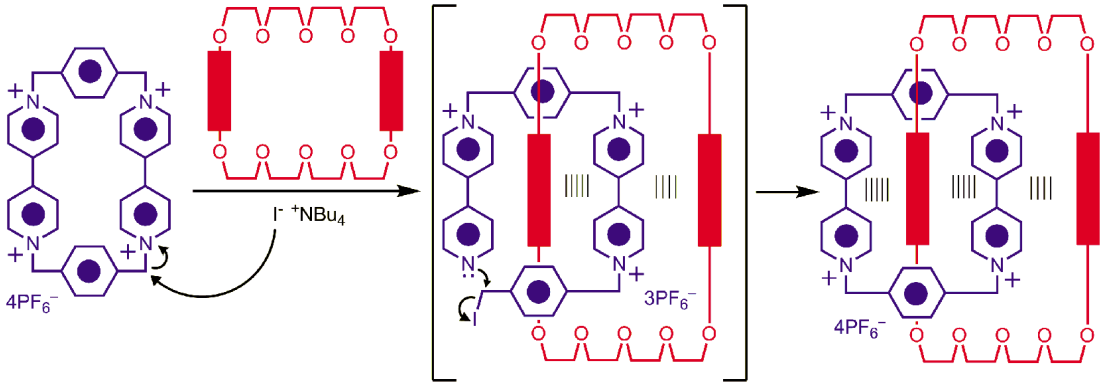
the much lower association constants for the complexation of the ethylene-substituted bipyridinium dications with BPP34C10 relative to those for the bipyridinium dications, only a modest difference in chemical yields was observed, irrespective of the templating macrocycle. This observation tells us that the factors governing the relative efficiencies of the self-assembly processes are predominately kinetic ones.

While historically the first method of choice for the preparation of donor/acceptor [2]catenanes involved [27] clipping $CBPQT^{4+}$ (or a derivative thereof) around a crown ether, it has been shown recently that, it is also possible to trap a pseudorotaxane kinetically, constructed from a glycol-appended naphthalene thread encircled by a $CBPQT^{4+}$ cyclophane using high-yielding reactions, such as the Cu(II)-mediated Eglinton coupling, or Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition [7,9]. These particular reactions are attractive because they are typically high-yielding and efficient, and additionally they proceed under neutral, oxidative, and non-nucleophilic conditions at room temperature. It was found that when the di-alkyne-appended naphthalene glycol was subjected to $Cu(OAc)_2$ for four days, the alkynes underwent (Scheme 3, top) oxidative coupling and the resulting [2]catenane could be isolated in 14 % yield. The yield from the reaction was improved by using microwave irradiation for 20 min in order to form the same [2]catenane in 21 % yield. In a similar fashion, it was found that the alkyne/azide-terminated naphthalene glycol assembles efficiently with $CBPQT^{4+}$ to form a pseudorotaxane which can then be cyclized when it is exposed to $CuSO_4$ for 24 h at room temperature, affording a [2]catenane in 41 % yield (Scheme 3, bottom). While neither of these reactions surpass the yields attained by clipping $CBPQT^{4+}$ around the equivalent π-electron-rich macrocycle, these methods are attractive because of their brevity and simplicity and will undoubtedly prove to be highly useful in the synthesis of more complex mechanically interlocked compounds.



Scheme 3 Synthesis of [2]catenanes via Eglinton coupling and click chemistry.

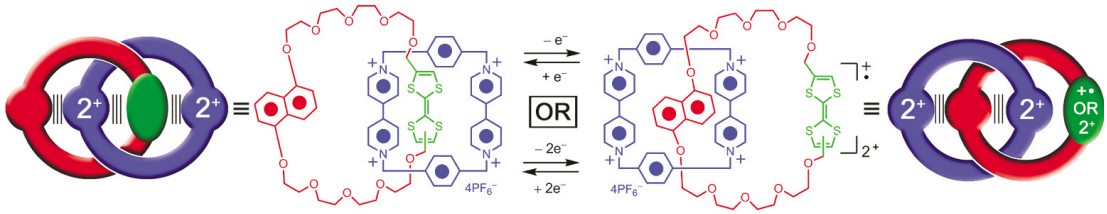
Recently, a thermodynamic method has been developed to make the "original" degenerate catenanes—$CBPQT^{4+}$ encircling either BPP34C10 or DN38C10—in high yields by utilizing a set of error-checking and proofreading processes (Scheme 4) to provide ultimately the energetically most favorable species [10]. The proposed mechanism of equilibration involves the nucleophilic attack by iodide (I^-) anion on the $CBPQT^{4+}$ cyclophane at one of its four benzylic methylene centers, displacing one of the positively charged bipyridinium groups, opening the cyclophane and relieving a considerable amount of ring strain in so doing. This linear thread is then able to complex a free crown ether, forming a pseudorotaxane in solution, followed by a reverse nucleophilic attack by the pyridyl nitrogen lone pair



Scheme 4 Proposed mechanism for the thermodynamic formation of a [2]catenane where the π-electron-rich ring is either BPP34C10 or DN38C10.

to displace the leaving group (I^-) and hence generate the degenerate [2]catenane. This method has been coined a "magic ring" approach, as the synthesis begins with two closed macrocycles and yet results in a [2]catenane in the presence of a small amount of the catalyst (NBu_4I). It was found that the $CBPQT^{4+}$/BPP34C10 catenane could be isolated in 46 % yield from a 1:1 solution of the starting materials. The equilibrium, however, was much more favorable for the formation of the $CBPQT^{4+}$/DN38C10 catenane, which was formed in a 93 % yield.

With the development of facile template-directed protocols, it became possible to construct more complex and sophisticated [2]catenanes [30]. In particular, it was of interest to be able to vary the translational isomerism of a [2]catenane by, for example, making one unit in the π-donating ring of the catenane electrochemically active [31]. This objective was achieved most successfully by substituting a tetrathiafulvalene (TTF) unit for one of the 1,5-dioxynaphthalene (DNP) units in DN38C10, followed by clipping this crown ether with 1,4-bis(bromomethyl)benzene and the appropriate bispyridinium dication to form the $CBPQT^{4+}$ cyclophane and, thus, a nondegenerate [2]catenane [32]. This catenane is bistable, which is to say that, in its ground state, the lowest energy isomer has the $CBPQT^{4+}$ ring encircling the TTF unit (Scheme 5). However, when the TTF is oxidized to its radical cation or dication, the charged $CBPQT^{4+}$ ring is repelled and the crown ether circumrotates such that the DNP unit is encircled by the cyclophane. After reduction of the TTF moiety back to its neutral state, the crown ether slowly relaxes back to its ground state co-conformation, where the $CBPQT^{4+}$ cyclophane encircles the TTF unit.



Scheme 5 A TTF/DNP bistable [2]catenane undergoing circumrotation as a result of oxidation and subsequent reduction of the electroactive TTF unit.

In summary, as a result of advances in template-directed protocols and the modularity of the synthetic routes employed, it was possible to build up a wide variety of [2]catenanes to gain a better understanding of the molecular dynamics associated with mechanically interlocked molecules [26].

DONOR/ACCEPTOR [2]ROTAXANES

The synthesis of template-directed donor/acceptor [2]rotaxanes [11] has closely paralleled that of [2]catenanes, since advances with respect to one compound type have spurred advances in the case of the other. Since rotaxanes possess a different geometry, however, their assembly is subject to a much wider variety of synthetic approaches, leading to an extensive range of methodologies and structures. Additionally, while donor/acceptor [2]catenanes are always composed of one π-donating and one π-accepting ring, it is possible to differentiate "normal" recognition-based [2]rotaxanes from "reverse" recognition-based [2]rotaxanes as the dumbbell of a rotaxane is constitutionally different from the ring encircling it. It transpires that [2]rotaxane syntheses have benefited equally from advances in host/guest chemistry and self-assembly, as these concepts are fundamental to understanding the processes involved in the templation of donor/acceptor-based rotaxanes [33]. Applications that rely upon [2]rotaxanes have taken advantage of their linear nature, a situation which makes it possible to harness translational motion of the ring along the axle of a [2]rotaxane.

The three most common methods of rotaxane formation are summarized in Fig. 5. The first method involves the formation of a pseudorotaxane, where a thread is complexed within a macrocycle, and then the ends of the thread are reacted with bulky stoppers to form the desired [2]rotaxane. While this method is a common and useful one, its challenges lie in finding reaction conditions so that ends of the thread and stopper will react efficiently, while not interfering with the supramolecular assembly that constitutes the pseudorotaxane. In another method, the stoppers of a rotaxane are matched closely in size with the size of the macrocycle, such that when a solution containing both the macrocycle and dumbbell is heated, the macrocycle has the necessary energy to pass over the stopper to form the thermodynamically more stable species. While this thermodynamically controlled method may appear simple, it is challenging to find a macrocycle-stopper pair which only allows dethreading at higher temperatures yet does not lead to decomposition—but is such that the stoppers resist dethreading at room temperature. In addition, [2]rotaxanes formed using this method are not thermally stable, limiting their future investigations and uses [34]. The final method of rotaxane formation shown in Fig. 5 is known as clipping. It involves a linear fragment containing functionality which will interact noncovalently with a dumbbell such that the ends of the linear fragment are most likely to react while encircling the dumbbell template, thus forming the desired [2]rotaxane. The clipping strategy of rotaxane formation has proven to be very effective and can be accelerated at high pressures when the ring being formed is $CBPQT^{4+}$.

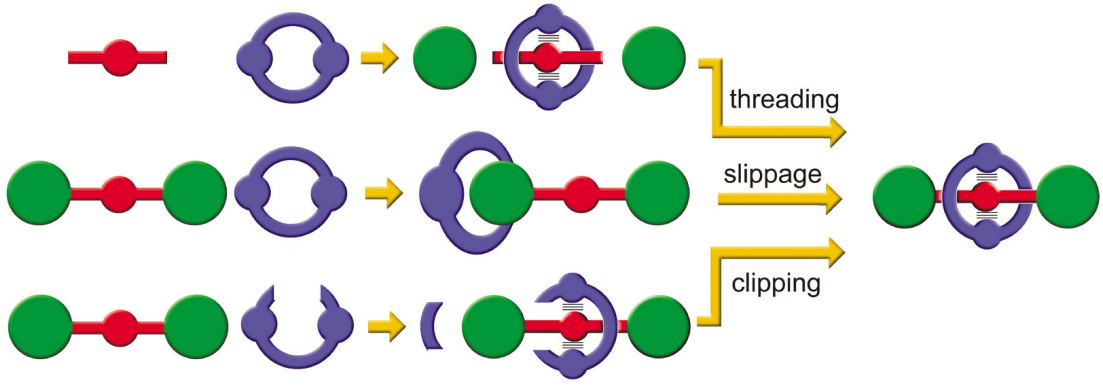
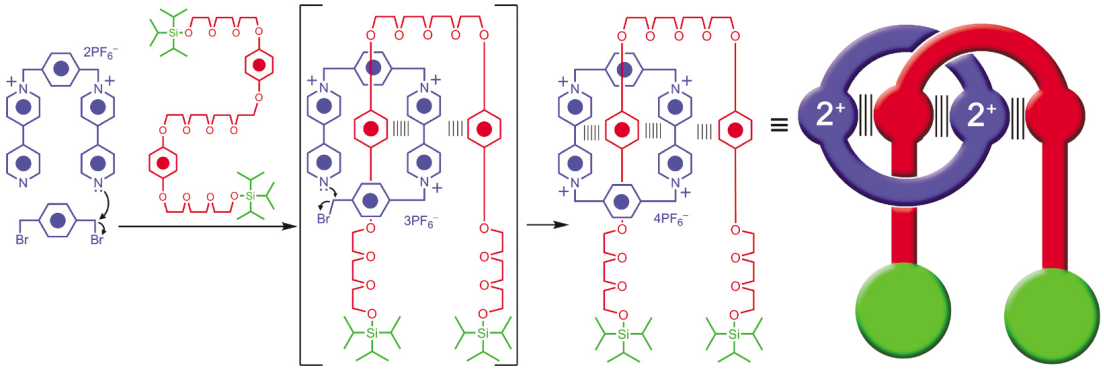


Fig. 5 A graphical representation of three methods of rotaxane formation—threading-followed-by-stoppering, slippage of the macrocycle over the stoppers at elevated temperatures, and clipping of the macrocycle around the dumbbell.

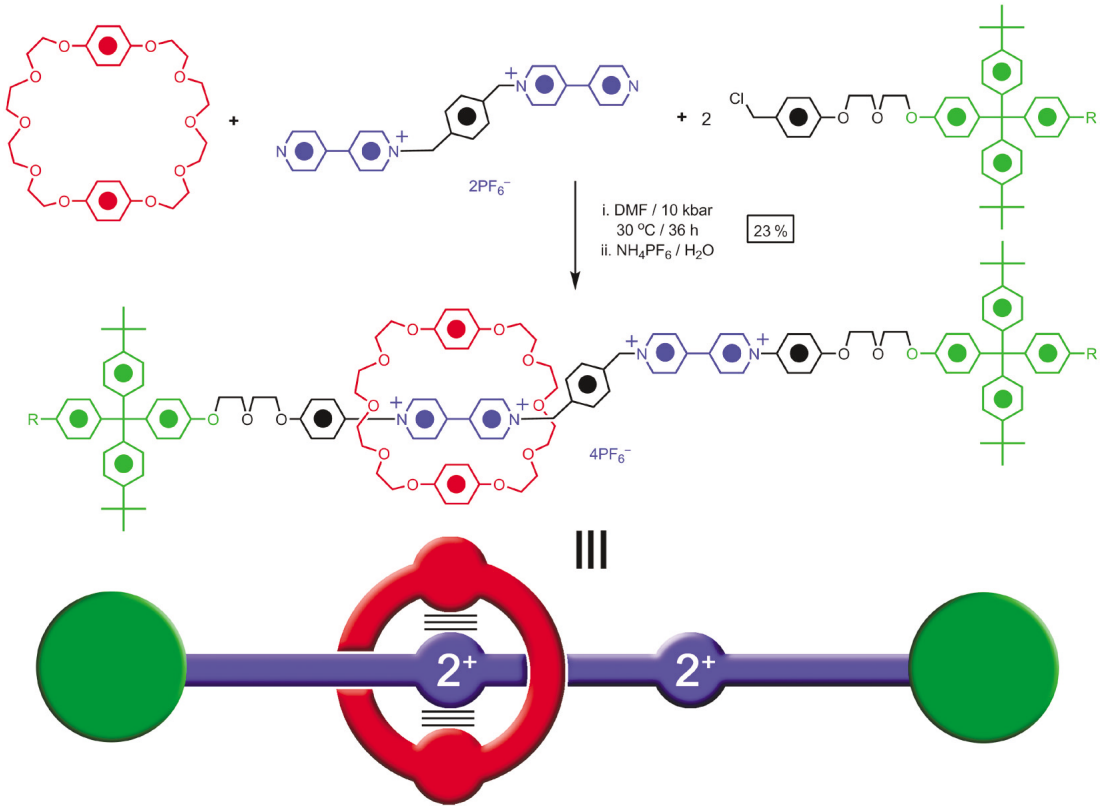
While the synthesis of the first degenerate donor/acceptor catenane was published in 1989, it was two more years before the analogous [2]rotaxane was reported in the literature. The protocol for the synthesis of a molecular shuttle is summarized in Scheme 6 [35]. For the template-directed synthesis of the [2]rotaxane, the proposed mechanism involves the reaction of a bispyridinium dication, first of all, with 1,4-bis(bromomethyl)benzene to form a bipyridinium unit which then associates strongly with the two hydroquinone stations on the dumbbell component of the molecular shuttle. This thermodynamically stable complex templates the final bond formation in the cyclization of the $CBPQT^{4+}$ ring to form the desired [2]rotaxane in 32 % yield. This lower yield can be attributed to a less pre-organized template than in the case of the [2]catenane where the BPP34C10 is held in a complexing conformation as a consequence of being a macrocycle, while in the case of the template-directed synthesis of the [2]rotaxane, the dumbbell will exist in many different conformations in solution until it is confronted with a tetracationic precursor to $CBPQT^{4+}$, which induces folding. ^1H and extended spectroscopic NMR studies on this system have shown that the tetracationic ring moves back and forth between the two binding stations ca. 500 times per second, reflecting an activation barrier for shuttling of 13 kcal mol^{-1} in CD_3COCD_3.



Scheme 6 Proposed mechanism for the synthesis of a donor/acceptor [2]rotaxane, also known as a molecular shuttle. The desired [2]rotaxane was isolated from the reaction mixture by counterion exchange with an aqueous solution of NH_4PF_6.

It is also possible to synthesize a rotaxane utilizing the "reverse" recognition motif in which the macrocycle is π-electron-rich and the dumbbell is π-electron-deficient. This objective was accomplished using a threading-followed-by-stoppering approach. Once one stopper (R = *t*-Bu) undergoes substitution with a pyridine nitrogen atom as the nucleophile, a bipyridinium station is formed which complexes a BPP34C10 ring to form a pseudorotaxane (Scheme 7) [36]. Upon a final reaction with a second stopper, a [2]rotaxane or "reverse" molecular shuttle is formed. This selective complexation of only the dicationic bipyridinium unit within the tricationic thread ensures that only one BPP34C10 is incorporated into the [2]rotaxane. A molecular shuttle can be synthesized by slippage when a slightly smaller stopper (R = H) is used. The thermodynamically controlled self-assembly occurs in a dimethylformamide (DMF) solution of the dumbbell when four molar equivalents of BPP34C10 are heated to 55 °C for 10 days [37]. When using the slippage approach to rotaxane formation with this dumbbell and BPP34C10, a second bipyridinium station is available for binding and, as such, 8 % of a [3]rotaxane incorporating an addition BPP34C10 ring was isolated. This ratio can be manipulated by using even more of the crown ether: it was shown that, when 10 molar equivalents of BPP34C10 are used, a 20 % yield of the [2]rotaxane and 55 % yield of the [3]rotaxane could be isolated.

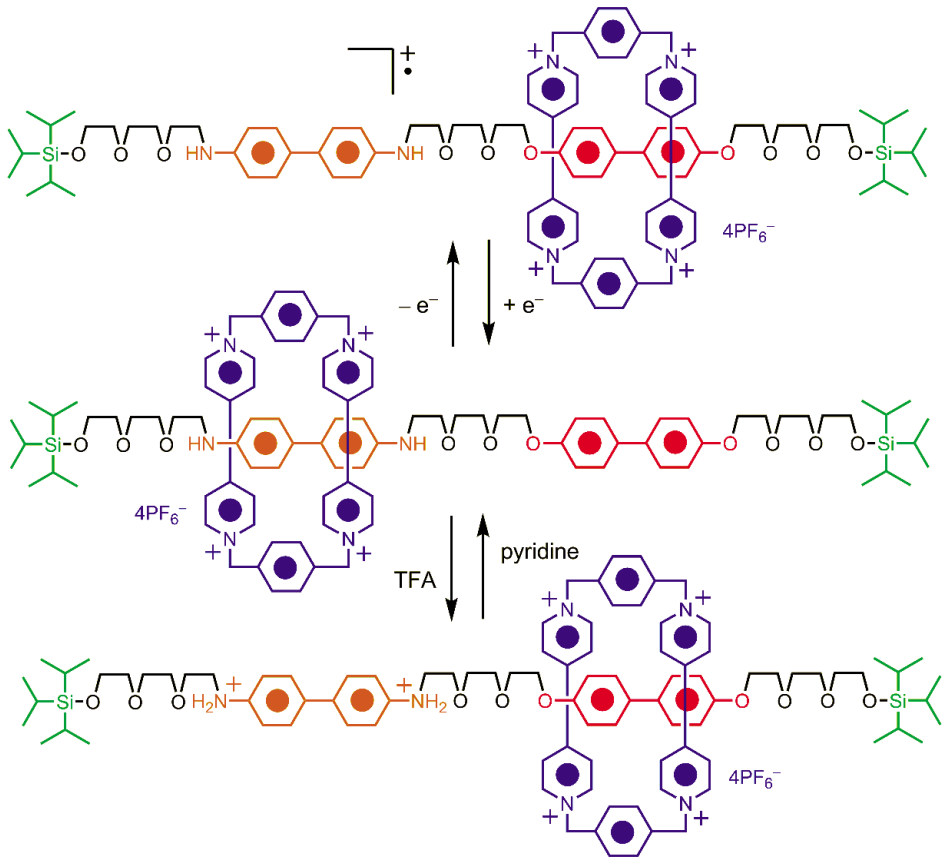
Having observed the shuttling of the $CBPQT^{4+}$ cyclophane between the two recognition stations on the dumbbell component of the degenerate [2]rotaxane, efforts were made to control this motion



Scheme 7 Synthesis of a [2]rotaxane with two bipyridinium stations from BPP34C10 and a tris(4-*tert*-butylphenyl)methyl stopper (R = *t*-Bu) using the threading-followed-by-stoppering approach.

using both electrochemical and chemical inputs. This goal was accomplished in the construction of a donor/acceptor-based [2]rotaxane where one station is a much better π-electron-donating station for the π-electron-accepting $CBPQT^{4+}$ ring than the other station. The cyclophane sits preferentially on only the better of the two stations in the ground state. Ideally, the ring should occupy the better donating station most of the time. This situation is not always the case in practice, however, since it depends on the ratio of the π-electron-donating abilities of the stations. In the first three reported attempts at electrochemically controlling the translational isomerism in donor/acceptor [2]rotaxanes, the affinities of the $CBPQT^{4+}$ cyclophane for the stations—a hydroquinone unit paired with either a *p*-xylyl unit, a 2,3,5-trisubstituted indole unit, or a bis(2-oxypropylenedithio)TTF unit—were not all that different and so electrochemical switching was partial at best [38].

However, with the synthesis of the compound shown in Scheme 8, according to ^{1}H NMR spectroscopic studies, the $CBPQT^{4+}$ ring prefers to occupy the benzidine unit as opposed to the biphenol unit at a ratio of 5.25:1 in the ground state at 229 K [39]. It was then possible to switch the recognition such that the stronger π-donating unit becomes weaker than the second station. In this case, the benzidine unit can either be oxidized or protonated with an acid such as trifluoroacetic acid (TFA) to form the radical cation or dication, respectively. The positively charged benzidine unit repels the $CBPQT^{4+}$ cyclophane, and it moves to 100 % occupation of the biphenol π-donating station. Once the benzidine station is reduced or deprotanated, the $CBPQT^{4+}$ ring will return to encircling the benzidine unit primarily as it is once again the stronger π-electron-donating unit. The molecular shuttle illustrated in

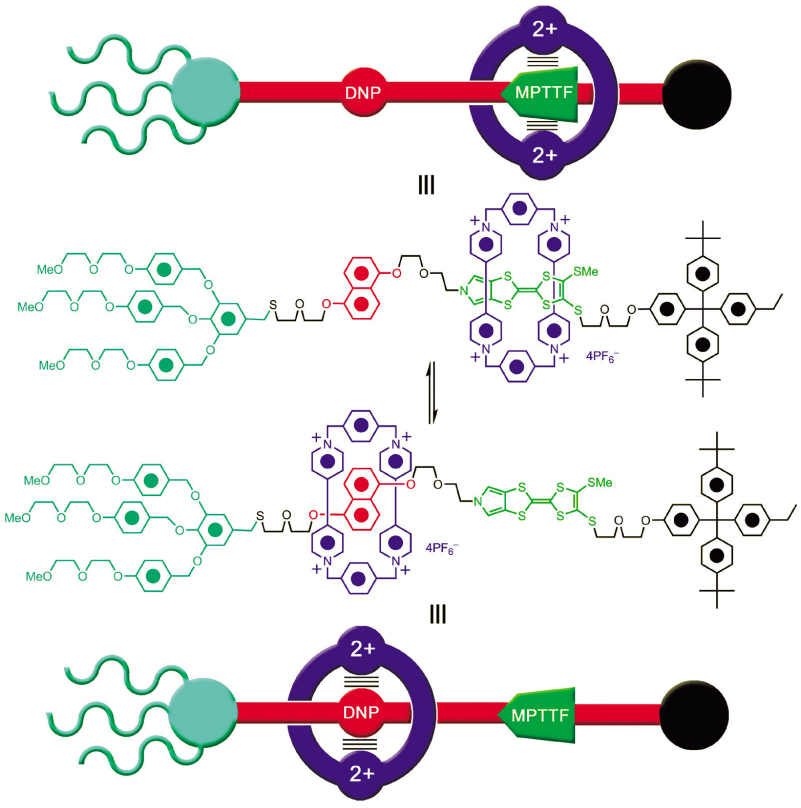


Scheme 8 Electrochemical or acid/base switching of a bistable [2]rotaxane composed of a π-electron-deficient $CBPQT^{4+}$ encircling benzidine and biphenol π-electron-donating stations.

Scheme 8 was synthesized by first assembling the dumbbell and then clipping the components that comprise the $CBPQT^{4+}$ cyclophane around the dumbbell.

While the benzidine/biphenol rotaxane generally accomplished the desired switching behavior upon electrochemical or chemical stimulation, the shuttle needed to be operated at low temperatures (229 K) and the occupancy of the $CBPQT^{4+}$ ring in the desired translational isomer was not as selective as desired since only 84 % of the rotaxane molecules were available for switching in any given cycle. The populations of the ring on the two binding stations reflect the relative free energies as determined primarily by the strengths of the two different sets of noncovalent bonding interactions present in the co-conformations of the [2]rotaxane molecules. Thus, it was desirable to design a system which could be switched at room temperature and in which the $CBPQT^{4+}$ ring would have much better selectivity for the more π-electron-donating station.

With this aim, a new amphiphilic [2]rotaxane was synthesized using DNP and pyrrolo[3,4-*d*]tetrathiafulvalene (MPTTF) stations on the dumbbell component and $CBPQT^{4+}$ as the ring (Scheme 9) [40]. It will be recalled that a bistable [2]catenane incorporating the parent TTF unit and a DNP unit had already been reported and incorporated into electronic devices. We opted to utilize amphiphilic stoppers in the hope that it would be possible to fabricate single-molecule-thick electrochemical junctions in electronic devices. However, upon ^1H NMR spectroscopic investigations and electrochemical solution studies, it was found that the $CBPQT^{4+}$ ring does not have a preference for either of the two stations, i.e., both translational isomers exist in a 1:1 ratio at 300 K in CD_3CN in the

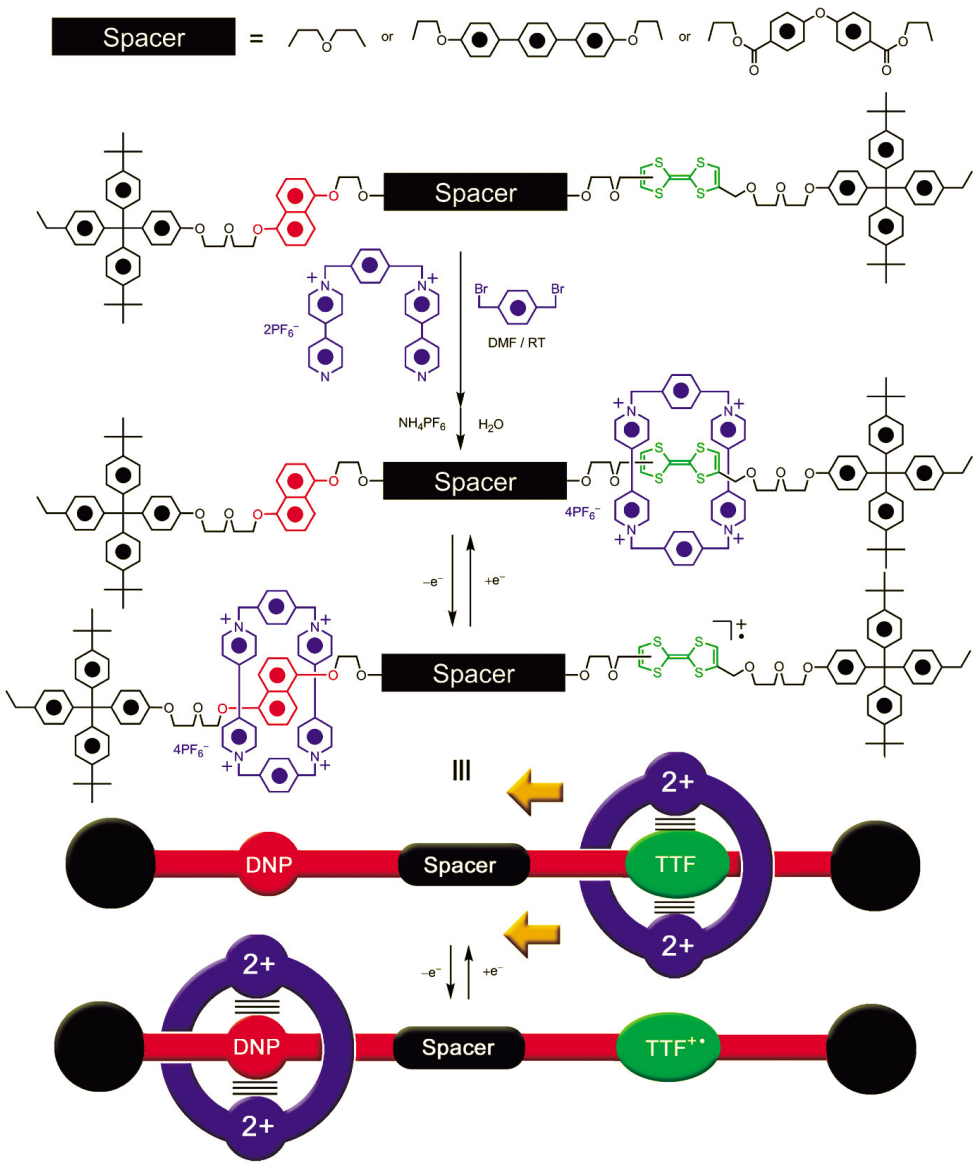


Scheme 9 An amphiphilic MPTTF/DNP [2]rotaxane in which the $CBPQT^{4+}$ macrocycle does not show a remarkable preference for either of the two recognition sites.

ground state. Consequently, this particular [2]rotaxane was proven to be less than ideal for incorporation into devices since only 50 % of the rotaxane molecules are available for switching during a given redox cycle.

Undeterred, we set about synthesizing a series of two-station [2]rotaxanes incorporating a simple disubstituted TTF unit in competition with a DNP moiety and a variety of spacer units between the two stations, such that the switching behavior in the potentially bistable molecules could be better understood [41]. The parent TTF unit was chosen to be in competition with the DNP unit since TTF had already been shown to form a strong, green 1:1 complex with $CBPQT^{4+}$ with a $K_a = 10\,000\ M^{-1}$ in MeCN, while DNP forms a much weaker, red 1:1 complex with a $K_a = 770\ M^{-1}$ in MeCN. The synthesis of this family of bistable [2]rotaxanes was accomplished by clipping each dumbbell component with 1,4-bis(bromomethyl)benzene and the appropriate bispyridinium dication to form the $CBPQT^{4+}$ ring with yields of approximately 25–57 %, which vary as a consequence of the efficiency of the clipping reaction which has been shown to be highly dependent on the length of the ethylene glycol chains appended to the π-donating stations since the oxygen atoms in these chains participate actively in hydrogen-bonding interactions with the $CBPQT^{4+}$ ring (Scheme 10) [42].

The rotaxane illustrated in Scheme 10 was then shown to possess bistability—which is to say that, in its ground state, the lower-energy isomer has the $CBPQT^{4+}$ ring encircling the TTF unit in excess of 97 % of the time [41]. When the TTF is oxidized to its radical cation or dication, the tetracationically charged $CBPQT^{4+}$ ring is repelled and undergoes rapid translational motion encircling the DNP unit. After reduction of the TTF moiety back to its neutral state, the $CBPQT^{4+}$ ring relaxes back to the ground state of the bistable rotaxane where it encircles the TTF unit.



Scheme 10 Electrochemical switching of a bistable [2]rotaxane. Note that the TTF in the [2]rotaxane backbone exists as a mixture of both *cis*- and *trans*-isomers, complicating NMR spectroscopic interpretation.

The affect of the spacer unit separating the two binding stations was accessed by the synthesis, not only of the bistable rotaxane, but also of the degenerate [2]rotaxanes incorporating either TTF or DNP at both recognition sites [43]. Variable-temperature ^{1}H NMR spectroscopic studies revealed that the barrier for shuttling between two DNP station is ~15 kcal mol^{-1}, while the barrier increases to ~17–18 kcal mol^{-1} in the case of two TTF units regardless of the spacer units investigated. Closer examination of the experimental data revealed that, despite the similar energetic barriers for shuttling, there are significant differences in the entropic and enthalpic contributions to these barriers. Of the three spacer units studied, the enthalpic penalty for shuttling over the pentaethylene glycol spacer was the smallest, presumably because of the favorable electrostatic interactions between the partially negative

oxygen atoms and $CBPQT^{4+}$ ring, while the entropic barrier was the highest as a consequence of the greater flexibility of the chain. While the terphenyl and diphenyl ether spacers display similar entropic penalties on account of their more rigid structures, the largest enthalpic penalty was found to be for the diphenyl ether-containing spacer, perhaps because of its "bent" shape.

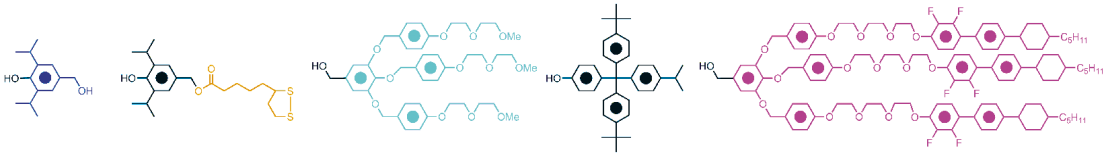
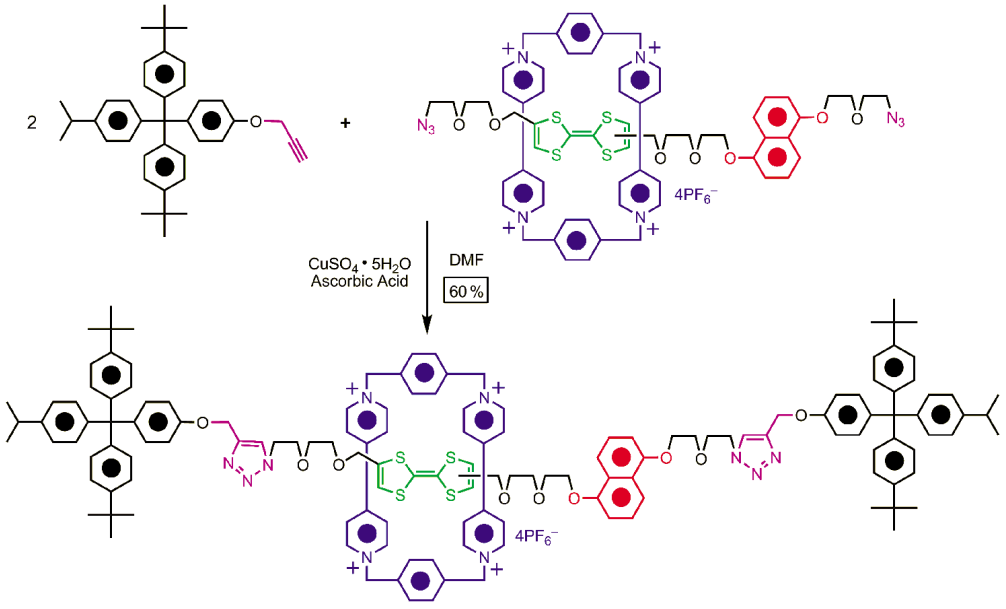


Fig. 6 An assortment of stoppers used in TTF/DNP/$CBPQT^{4+}$ [2]rotaxanes—a benzylic alcohol for attachment to silica [44], a thioctic acid appended stopper for attachment to gold surfaces [45], a hydrophilic stopper, a hydrophobic stopper [40], a dendritic mesogenic stopper [46] (left to right).

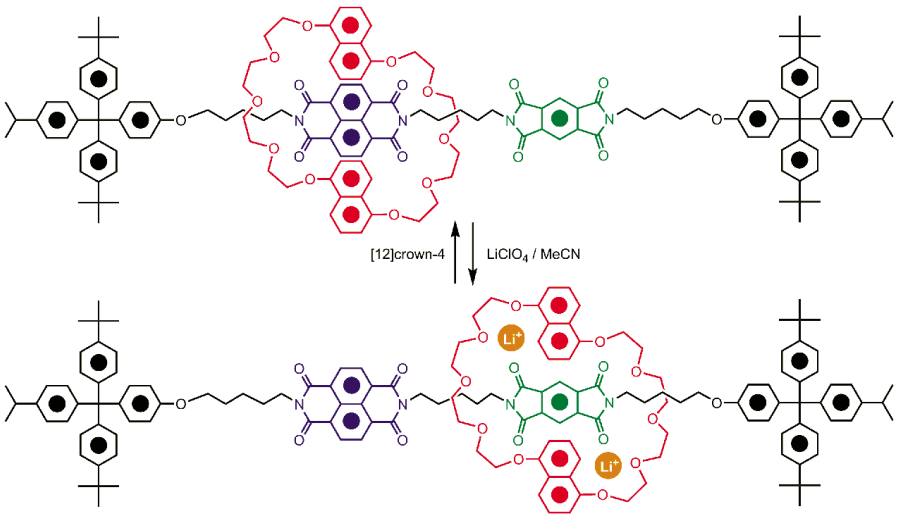
This class of bistable [2]rotaxane has be studied in great depth, at least in part, as a consequence of the modularity of the synthesis which allows for the introduction of structural diversity with relative ease. For example, a wide variety of different stoppers have been utilized to impart functionality into the termini of the rotaxanes (Fig. 6). In particular, a benzylic alcohol was used to couple a bistable [2]rotaxane to the surface of silica nanoparticles [44], thioctic acid functionalized stoppers were used to form self-assembled monolayers on a gold electrode [45], a combination of a hydrophobic and a hydrophilic stopper has been shown to render a bistable [2]rotaxane amphiphilic in order to form Langmuir–Blodgett (LB) monolayers [40], and the attachment of liquid-crystalline mesogens allows for the formation of aligned liquid-crystalline bistable [2]rotaxane phases [46].



Scheme 11 Synthesis of an electrochemically switchable [2]rotaxane synthesized in high yield using click chemistry.

Recently, the synthesis of TTF/DNP rotaxanes was further developed by the introduction of Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition—an extremely high-yielding and robust kinetically controlled reaction which has garnered the name "click chemistry" as a result [8,9]. This reaction has been used to react stoppers appended with terminal alkynes to a pseudorotaxane terminated by azide groups in the presence of $CuSO_4 \cdot 5H_2O$ and ascorbic acid (Scheme 11). This example of the threading-followed-by-stoppering approach to a bistable [2]rotaxane, illustrated in the scheme, led to the desired product in an impressive 60 % yield. This method benefits from the full thermodynamic binding of the $CBPQT^{4+}$ ring to the pseudorotaxane of interest, as it is fully formed at the outset of the reaction. In addition, the reaction can be performed at –10 °C to increase the concentration of pseudorotaxane as opposed to free thread and free $CBPQT^{4+}$ present in solution.

While TTF/DNP rotaxanes have certainly been explored in considerable depth and used in the most applications of any donor/acceptor [2]rotaxanes synthesized to date, it is also of interest to make and study neutral, bistable [2]rotaxanes as a means of assessing the influence of bulky PF_6^- counterions on the electromechanical switching processes. Thus, a reverse recognition-based bistable [2]rotaxane was designed where the dumbbell contains two π-electron-withdrawing stations, a pyromellitic diimide (PmI) one, and a naphthodiimide (NpI) one [47]. The stoppers for the dumbbell were carefully chosen such that a DN38C10 was able to slip onto the axle only at elevated temperatures to form the [2]rotaxane. When the dumbbell and macrocycle were heated to 60 °C in the presence of lithium ions, which enhance binding of the π-electron-donating macrocycle with the dumbbell, the bistable [2]rotaxane was isolated in 60 % yield. This compound has been shown to undergo switching both electrochemically and chemically (Scheme 12). In the ground state, the DN38C10 resides exclusively, for all intents and purposes, on the NpI unit as determined by variable-temperature ^1H NMR spectroscopy. The chemical switching process involves the addition of a source of lithium cations, in this case from LiBr or $LiClO_4$, such that they form a strong 2:1 co-complex with the PmI unit and DN38C10 macrocycle. To reverse the switching, an excess of [12]crown-4 is added to the solution to sequester Li^+ ions and return the [2]rotaxane to its ground-state translational isomer. It is also possible to switch the rotaxane electrochemically such that the NpI unit undergoes a one-electron reduction and is deactivated so that the DN38C10 ring is obliged to move to the PmI station. It is then possible to oxidize the system back to its ground state and switch through multiple cycles. In addition, it is possible to turn off all recognition between the dumbbell and the ring by reducing both the NpI and PmI stations to their radical anions,



Scheme 12 Switching of a neutral [2]rotaxane via binding of Li^+ ions.

such that both the stations and DN38C10 are π-electron-rich and, thus, no longer involved in any donor/acceptor interactions with the ring.

APPLICATIONS

As a consequence of the progress in the template-directed synthesis of mechanically interlocked compounds, these intriguing molecules can be synthesized in appreciable quantities for use in a variety of applications. In addition, the modularity of synthesis allows for the facile introduction of functionality necessary for specific applications. While a variety of uses for these molecules has been explored—including the introduction of [2]rotaxanes into liquid crystals [46] and the investigation of a three-station [2]catenane for RGB display applications [48]—arguably the two most successful applications to date for these molecules have been in the field of molecular electronics [49] and in the construction of molecular valves [44].

Two-terminal crossbar devices have been constructed around both bistable [2]catenanes and amphiphilic bistable [2]rotaxanes, making use of their ability to display binary switching behavior [49]. In order to construct such devices, an LB monolayer of closely packed molecular switches is deposited onto a highly doped polysilicon (*p*-Si) electrode. A top electrode of Ti, followed by Al, is subsequently vapor-deposited on top of the monolayer. It is then possible to apply a "write" voltage, *V*, and record the "read" current, *I*, at each crossbar junction in the device. These molecular devices display switching between high and low conductance states. The ON state is accessed at net oxidizing conditions (+2V), whereas the OFF state is triggered at net reducing conditions (–2 V). The data reveals that, in addition to the reversible voltage-gated switching of the device ON and OFF more than 30 times, the ON state displays a temperature-dependent resetting of the device back to the OFF state over time.

The nanoelectromechanical switching mechanism for these bistable mechanically interlocked molecules has been proposed to account for the crossbar device's observed experimental behavior. The proposed switching mechanism, while based on the molecule's known mechanical movements in solution, is supported experimentally by comparison with control devices. The OFF state corresponds to the translational isomer or co-confirmation, with the cyclophane encircling the TTF unit, which is commonly referred to as the "ground state" of the molecule. In the device, application of a +2 V bias generates an oxidized form of the TTF unit in the rotaxane or the catenane. The resulting charge–charge repulsive force drives the translational movement of the cyclophane component to a position encircling the DNP binding station, just as is observed in the solution state. When the applied bias is lowered to +0.1 V, for the purpose of reading the device, the charge on the TTF unit is neutralized, and yet the cyclophane remains around the DNP ring system as a consequence of the noncovalent bonding interactions between the cyclophane and the bound DNP station. This new metastable translational isomer is responsible for the high-conductance ON state. This metastable state of the device is observed to decay to the OFF state as a result of the thermally activated linear movement of the cyclophane back to the TTF station. Alternatively, applying a reverse bias of –2 V causes the electrochemical reduction of the tetracationic cyclophane, turning off the binding between the cyclophane and DNP unit, leading to the facile formation of the most stable translational isomer. This proposed mechanism has been shown to be consistent [50] between studies in the solution state [41,43], in a half-device assembled on an electrode [45], in a polymeric matrix [50], in LB films [51], and in molecular-switch tunnel junctions (MSTJs) [49].

While applications in molecular electronics take advantage of changes in the conductance of bistable rotaxanes and catenanes upon switching, it is also possible to take advantage of the mechanical energy produced by the shuttling of the $CBPQT^{4+}$ ring along the backbone of a bistable [2]rotaxane. In nanovalves, the ring in bistable [2]rotaxanes can act as gatekeepers regulating the movement of small organic molecules into and out of nanopores when the bistable [2]rotaxane is tethered to the surface of mesoscopic porous silica particles [45]. Guest molecules are loaded by diffusion into the open nanopores, which act as nanoreservoirs, when the $CBPQT^{4+}$ ring is located on the distant TTF station.

The nanovalves can then be closed by oxidation of the TTF units to their dications, causing the $CBPQT^{4+}$ rings to move to the DNP stations, which are located much closer to the openings of the pores. The bistable rotaxane is attached to the silica particle such that the openings of the cylindrical pores on the silica are blocked by the $CBPQT^{4+}$ ring when the macrocycle is bound to the DNP station. Then, the nanovalves can be opened by adding ascorbic acid to reduce the TTF dications back to their neutral state, whereupon the $CBPQT^{4+}$ rings move from the DNP stations to encircle the much more π-electron-rich TTF stations, releasing the guest molecules. The nanovalves are then ready for recharging and may put through many cycles. With such successful proof-of-concept experiments, it is possible to imagine future applications for bistable [2]rotaxane-based nanovalves in the areas of drug delivery and other functional materials.

PROSPECTUS

Mechanically interlocked molecules have captured the imagination of a generation of chemists with their exotic structures and aesthetic features. However, these exotic structures were historically very difficult to make in the beginning. Despite being addressed by Wasserman, Schill, and others using laborious synthetic methods, only very small quantities of the desired [2]catenanes and [2]rotaxanes could be attained. In recent years, the on-going development of molecular recognition and self-assembly processes and, consequently, our greater understanding of template-directed protocols in synthesis have made it possible for these molecules to be attained, not only in high yields, but with more and more functionality. This functionality has been harnessed such that it is now possible to control translational isomerism in bistable [2]catenanes and [2]rotaxanes for use in a wide range of applications in such diverse fields as molecular electronics, drug delivery, liquid crystals, and RGB display technologies. While these applications are impressive in their breadth and promise, the power of template-directed synthesis has only begun to be realized and the future holds promise for many sophisticated materials and nano-driven functionalities that are yet to be discovered.

REFERENCES

1. E. Wasserman. *J. Am. Chem. Soc.* **82**, 4433 (1960).
2. H. L. Frisch, E. Wasserman. *J. Am. Chem. Soc.* **81**, 3789 (1961).
3. (a) I. T. Harrison, S. Harrison. *J. Am. Chem. Soc.* **89**, 5723 (1967); (b) I. T. Harrison. *J. Chem. Soc., Perkin Trans. 1* 301 (1974); (c) I. T. Harrison. *J. Chem. Soc., Chem. Comm.* 231 (1972).
4. G. Schill, A. Lüttringhaus. *Angew. Chem., Int. Ed. Engl.* **3**, 546 (1964).
5. (a) F. Diederich, P. J. Stang (Eds.). *Templated Organic Synthesis*, Wiley-VCH, Weinhem (2000); (b) D. H. Busch, N. A. Stephenson. *Coord. Chem. Rev.* **100**, 119 (1990); (c) S. Anderson, H. L. Anderson, J. K. M. Sanders. *Acc. Chem. Res.* **26**, 469 (1993); (d) T. J. Hubin, D. H. Busch. *Coord. Chem. Rev.* **200**, 5 (2000); (e) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart. *Angew. Chem., Int. Ed.* **41**, 898 (2002); (f) D. H. Busch. *Top. Curr. Chem.* **249**, 1 (2005).
6. (a) J.-M. Lehn. *Supramolecular Chemistry*, VCH, Weinheim (1995); (b) J.-M. Lehn, J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle (Eds.). *Comprehensive Supramolecular Chemistry*, Pergamon, Oxford (1996); (c) D. Philp, J. F. Stoddart. *Angew. Chem., Int. Ed. Engl.* **35**, 1154 (1996); (d) H.-J. Schneider, A. Yatsimirsky. *Principles and Methods in Supramolecular Chemistry*, Wiley-VCH, Weinheim (2000); (e) J. W. Steed, J. L. Atwood. *Supramolecular Chemistry*, Wiley-VCH, Weinheim (2000); for a selection of articles on supramolecular chemistry and self-assembly, see: (f) Special issue on "Supramolecular Chemistry and Self-Assembly": *Science* **295**, 2400–2421 (2002); (g) Y. K. Agrawal, C. R. Sharma. *Rev. Anal. Chem.* **24**, 35 (2005).

7. (a) O. Š. Miljanić, W. R. Dichtel, S. I. Khan, S. Mortezaei, J. R. Heath, J. F. Stoddart. *J. Am. Chem. Soc.* **129**, 8236 (2007); (b) O. Š. Miljanić, W. R. Dichtel, S. Mortezaei, J. F. Stoddart. *Org. Lett.* **8**, 4835 (2006).
8. (a) W. R. Dichtel, O. Š. Miljanić, J. M. Spruell, J. R. Heath, J. F. Stoddart. *J. Am. Chem. Soc.* **128**, 10388 (2006); (b) I. Aprahamian, W. R. Dichtel, T. Ikeda, J. R. Heath, J. F. Stoddart. *Org. Lett.* **9**, 1287 (2007).
9. (a) A. B. Braunschweig, W. R. Dichtel, O. Š. Miljanić, M. A. Olson, J. M. Spruell, S. I. Khan, J. R. Heath, J. F. Stoddart. *Chem. Asian J.* **2**, 634 (2007); (b) I. Aprahamian, O. Š. Miljanić, W. R. Dichtel, K. Isoda, T. Yasuda, T. Kato, J. F. Stoddart. *Bull. Chem. Soc. Jpn.* **80**, 1856 (2007).
10. O. Š. Miljanić, J. F. Stoddart. *Proc. Natl. Acad. Sci. USA* **104**, 12966 (2007).
11. (a) J.-P. Sauvage, C. Dietrich-Buchecker (Eds.). *Molecular Catenanes, Rotaxanes, and Knots: A Journey Through the World of Molecular Topology*, Wiley-VCH, Weinheim (1999); (b) D. B. Amabilino, J. F. Stoddart. *Chem. Rev.* **95**, 2725 (1995); (c) T. J. Hubin, A. G. Kolchinski, A. L. Vance, D. H. Busch. *Adv. Supramol. Chem.* **6**, 237 (1999); (d) S. J. Cantrill, A. R. Pease, J. F. Stoddart. *J. Chem. Soc., Dalton Trans.* 3715 (2000); (e) L. Raehm, D. G. Hamilton, J. K. M. Sanders. *Synlett* 1742 (2002); (f) M. Bělohradský, F. M. Raymo. J. F. Stoddart. *Collect. Czech. Chem. Commun.* **62**, 527 (1997).
12. (a) K. S. Chichak, S. J. Cantrill, A. R. Pease, S.-H. Chiu, G. W. V. Cave, J. L. Atwood, J. F. Stoddart. *Science* **304**, 1308 (2004); (b) K. S. Chichak, A. J. Peters, S. J. Cantrill, J. F. Stoddart. *J. Org. Chem.* **70**, 7956 (2005); (c) C. D. Pentecost, A. J. Peters, K. S. Chichak, G. V. W. Cave, S. J. Cantrill, J. F. Stoddart. *Angew. Chem., Int. Ed.* **45**, 4099 (2006); (d) J. S. Siegel. *Science* **304**, 1256 (2004); (e) C. A. Schalley. *Angew. Chem., Int. Ed.* **43**, 4399 (2004); (f) S. J. Cantrill, K. S. Chichak, A. J. Peters, J. F. Stoddart. *Acc. Chem. Res.* **38**, 1 (2005).
13. (a) J.-F. Niergarten, C. O. Dietrich-Buchecker, J.-P. Sauvage. *J. Am. Chem. Soc.* **116**, 375 (1994); (b) F. Ibukuro, M. Fujita, K. Yamaguchi, J.-P. Sauvage. *J. Am. Chem. Soc.* **121**, 11014 (1999); (c) C. P. McArdle, J. J. Vittal, R. J. Puddephatt. *Angew. Chem., Int. Ed.* **39**, 3819 (2000); (d) C. D. Pentecost, K. S. Chichak, A. J. Peters, G. W. V. Cave, S. J. Cantrill, J. F. Stoddart. *Angew. Chem., Int. Ed.* **46**, 218 (2007).
14. (a) G. Schill. *Catenanes, Rotaxanes, and Knots*, Academic Press, New York (1971); (b) C. O. Dietrich-Buchecker, J.-P. Sauvage. *Angew. Chem., Int. Ed. Engl.* **28**, 189 (1989); (c) C. O. Dietrich-Buchecker, J. F. Nierengarten, J.-P. Sauvage, N. Armaroli, V. Balzani, L. De Cola. *J. Am. Chem. Soc.* **115**, 11234 (1993); (d) C. O. Dietrich-Buchecker, G. Rapenne, J.-P. Sauvage. *Chem. Commun.* 2053 (1997); (e) P. R. Ashton, O. A. Matthews, S. Menzer, F. M. Raymo, N. Spencer, J. F. Stoddart, D. J. Williams. *Liebigs Ann./Recl.* 2485 (1997); (f) O. Safarowsky, M. Nieger, R. Fröhlich, F. Vögtle. *Angew. Chem., Int. Ed.* **39**, 1616 (2000); (g) H. Adams, E. Ashworth, G. A. Breault, J. Guo, C. A. Hunter, P. C. Mayers. *Nature* **411**, 763 (2001); (h) O. Lukin, F. Vögtle. *Angew. Chem., Int. Ed.* **44**, 1456 (2005); (i) C. Dietrich-Buchecker, B. X. Colasson, J.-P. Sauvage. *Top. Curr. Chem.* **249**, 261 (2005); (j) M. Feigel, R. Ladberg, S. Engels, R. Herbst-Irmer, R. Fröhlich. *Angew. Chem., Int. Ed.* **45**, 5698 (2006).
15. P. R. Ashton, D. Philp, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 1680 (1991).
16. M. C. T. Fyfe, J. F. Stoddart. *Acc. Chem. Res.* **30**, 393 (1997).
17. G. A. Breault, C. A. Hunter, D. C. Mayers. *Tetrahedron* **55**, 5265 (1999).
18. H. Frisch, I. Martin, H. Mark. *Monatsh. Chem.* **84**, 250 (1953).
19. (a) K. Hiratani, J. Suga, Y. Nagawa, H. Houjou, H. Tokuhisa, M. Numata, K. Watanabe. *Tetrahedron Lett.* **43**, 5747 (2002); (b) K. Hirose, K. Nishihara, N. Harada, Y. Nakamura, D. Masuda, M. Araki, Y. Tobe. *Org. Lett.* **9**, 2969 (2007).
20. (a) G. Schill, H. Zollenkopf. *Liebigs. Ann. Chem.* **721**, 53 (1969); (b) G. Schill, R. Henschel. *Liebigs Ann. Chem.* **731**, 113 (1970).
21. C. O. Dietrich-Buchecker, J. P. Sauvage. *Tetrahedron Lett.* **24**, 5095 (1983).

22. (a) C. O. Dietrich-Buchecker, J.-P. Sauvage. *Chem. Rev.* **87**, 795 (1987); (b) J.-P. Sauvage. *Acc. Chem. Res.* **23**, 319 (1990); (c) C. O. Dietrich-Buchecker, J.-P. Sauvage. *Bioorg. Chem. Front.* **2**, 195 (1991); (d) J.-C. Chambron, C. O. Dietrich-Buchecker, J.-P. Sauvage. *Top. Curr. Chem.* **165**, 131 (1993).
23. (a) B. L. Allwood, N. Spencer, H. Shahriari-Zavareh, J. F. Stoddart, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 1061 (1987); (b) P. R. Ashton, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 1066 (1987).
24. B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams. *Angew. Chem., Int. Ed. Engl.* **27**, 1547 (1988).
25. B. L. Allwood, N. Spencer, H. Sharhriari-Zavareh, J. F. Stoddart, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 1064 (1987).
26. (a) D. B. Amabilino, P. R. Ashton, M. S. Tolley, J. F. Stoddart, D. J. Williams. *Angew. Chem., Int. Ed. Engl.* **32**, 1297 (1993); (b) D. B. Amabilino, P. R. Ashton, G. R. Brown, W. Hayes, J. F. Stoddart, M. S. Tolley, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 2479 (1994); (c) P. R. Ashton, M. A. Blower, S. Iqbal, C. H. McLean, J. F. Stoddart, M. S. Tolley, D. J. Williams. *Synlett* 1056 (1994); (d) P. R. Ashton, J. A. Preece, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams. *Synthesis* 1344 (1994); (e) P. R. Ashton, M. A. Blower, C. H. McLean, J. F. Stoddart, M. S. Tolley. *Synlett* 1063 (1994); (f) D. B. Amabilino, P.-L. Anelli, P. R. Ashton, G. R. Brown, E. Córdova, L. A. Godínez, W. Hayes, A. E. Kaifer, D. Philp, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, M. S. Tolley, D. J. Williams. *J. Am. Chem. Soc.* **117**, 11142 (1995); (g) P.-L. Anelli, M. Asakawa, P. R. Ashton, G. R. Brown, W. Hayes, O. Kocian, S. R. Pastor, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams. *J. Chem. Soc., Chem. Commun.* 2541 (1995); (h) M. Asakawa, C. L. Brown, S. Menzer, F. M. Raymo, J. F. Stoddart, D. J. Williams. *J. Am. Chem. Soc.* **119**, 2614 (1997); (i) M. Asakawa, P. R. Ashton, S. E. Boyd, C. L. Brown, R. E. Gillard, O. Kocian, F. M. Raymo, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams. *J. Org. Chem.* **62**, 26 (1997); (j) R. Ballardini, V. Balzani, A. Credi, C. L. Brown, R. E. Gillard, M. Montalti, D. Philp, J. F. Stoddart, M. Venturi, A. J. P. White, B. J. Williams, D. J. Williams. *J. Am. Chem. Soc.* **119**, 12503 (1997); (k) R. Ballardini, V. Balzani, A. Credi, M. T. Gandolfi, D. Marquis, L. Pérez-García, J. F. Stoddart. *Eur. J. Org. Chem.* 81 (1998); (l) S. Menzer, A. J. P. White, D. J. Williams, M. Bělohradský, C. Hamers, F. M. Raymo, A. N. Shipway, J. F. Stoddart. *Macromolecules* **31**, 295 (1998); (m) P. R. Ashton, S. E. Boyd, S. Menzer, D. Pasini, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, P. G. Wyatt. *Chem.—Eur. J.* **4**, 299 (1998); (n) R. Ballardini, V. Balzani, M. T. Gandolfi, R. E. Gillard, J. F. Stoddart, E. Taellini. *Chem.—Eur. J.* **4**, 449 (1998); (o) P. R. Ashton, V. Balzani, A. Credi, O. Kocian, D. Pasini, L. Prodi, N. Spencer, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams. *Chem.—Eur. J.* **4**, 590 (1998); (p) M. Asakawa, P. R. Ashton, V. Balzani, C. L. Brown, A. Credi, O. A. Matthews, S. P. Newton, F. M. Raymo, A. N. Shipway, N. Spencer, A. Quick, J. F. Stoddart, A. J. P. White, D. J. Williams. *Chem.—Eur. J.* **5**, 860 (1999); (q) P. R. Ashton, A. M. Heiss, D. Pasini, F. M. Raymo, A. N. Shipway, J. F. Stoddart, N. Spencer. *Eur. J. Org. Chem.* 995 (1999); (r) P. R. Ashton, V. Baldoni, V. Balzani, C. G. Claessens, A. Credi, H. D. A. Hoffmann, F. M. Raymo, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams. *Eur. J. Org. Chem.* 1121 (2000); (s) E. Alcalde, L. Pérez-García, S. Ramos, J. F. Stoddart, S. A. Vignon, A. J. P. White, D. J. Williams. *Mendeleev Commun.* **13**, 1 (2003); (t) E. Alcalde, L. Pérez-García, S. Ramos, J. F. Stoddart, A. J. P. White, D. J. Williams. *Mendeleev Commun.* **14**, 233 (2004).
27. P. R. Ashton, T. T. Goodnow, A. E. Kaifer, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent, D. J. Williams. *Angew. Chem., Int. Ed. Engl.* **28**, 1396 (1989).
28. F. M. Raymo, K. N. Houk, J. F. Stoddart. *J. Org. Chem.* **63**, 6523 (1998).

29. (a) D. B. Amabilino, P. R. Ashton, L. Pérez-García, J. F. Stoddart. *Angew. Chem., Int. Ed. Engl.* **34**, 2378 (1995); (b) P. R. Ashton, R. Ballardini, V. Balzani, A. Credi, M. T. Gandolfi, S. Menzer, L. Pérez-García, L. Prodi, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams. *J. Am. Chem. Soc.* **117**, 11171 (1995).
30. (a) P. R. Ashton, L. Pérez-García, J. F. Stoddart, A. J. P. White, D. J. Williams. *Angew. Chem., Int. Ed. Engl.* **34**, 571 (1995); (b) P. R. Ashton, S. E. Boyd, A. Brindle, S. J. Langford, S. Menzer, L. Pérez-García, J. A. Preece, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams. *New J. Chem.* **23**, 587 (1999); (c) V. Balzani, A. Credi, S. J. Langford, F. M. Raymo, J. F. Stoddart, M. Venturi. *J. Am. Chem. Soc.* **122**, 3542 (2000).
31. (a) M. Asakawa, P. R. Ashton, V. Balzani, S. E. Boyd, A. Credi, G. Mattersteig, S. Menzer, M. Montalti, F. M. Raymo, C. Ruffilli, J. F. Stoddart, M. Venturi, D. J. Williams. *Eur. J. Org. Chem.* 985 (1999); (b) R. Ballardini, V. Balzani, A. Di Fabio, M. T. Gandolfi, J. Belcher, J. Lau, M. Brøndsted Nielsen, J. F. Stoddart. *New J. Chem.* **25**, 293 (2001).
32. (a) M. Asakawa, P. R. Ashton, V. Balzani, A. Credi, C. Hamers, G. Mattersteig, M. Montalti, A. N. Shipway, N. Spencer, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams. *Angew. Chem., Int. Ed.* **37**, 333 (1998); (b) V. Balzani, A. Credi, G. Mattersteig, O. A. Matthews, F. M. Raymo, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams. *J. Org. Chem.* **65**, 1924 (2000).
33. M. Bělohradský, F. M. Raymo, J. F. Stoddart. *Collect. Czech. Chem. Commun.* **61**, 1 (1996).
34. (a) F. M. Raymo, K. N. Houk, J. F. Stoddart. *J. Am. Chem. Soc.* **120**, 9318 (1998); (b) P. R. Ashton, M. C. T. Fyfe, C. Schiavo, J. F. Stoddart, A. J. P. White, D. J. Williams. *Tetrahedron Lett.* **39**, 5455 (1998); (c) F. M. Raymo, J. F. Stoddart. *Pure Appl. Chem.* **69**, 1987 (1997); (d) P. R. Ashton, M. Bělohradský, D. Philp, N. Spencer, J. F. Stoddart. *J. Chem. Soc., Chem. Commun.* 1274 (1993).
35. P.-L. Anelli, N. Spencer, J. F. Stoddart. *J. Am. Chem. Soc.* **113**, 5131 (1991).
36. (a) P. R. Ashton, D. Philp, N. Spencer, J. F. Stoddart. *J. Chem. Soc., Chem. Commun.* 1124 (1992); (b) A. B. Braunschweig, C. M. Ronconi, J.-Y. Han, F. Aricó, S. J. Cantrill, J. F. Stoddart, S. I. Khan, A. J. P. White, D. J. Williams. *Eur. J. Org. Chem.* 1857 (2006).
37. (a) P. R. Ashton, R. Ballardini, V. Balzani, M. Bělohradský, M. T. Gandolfi, D. Philp, L. Prodi, F. M. Raymo, M. V. Reddington, N. Spencer, J. F. Stoddart, M. Venturi, D. J. Williams. *J. Am. Chem. Soc.* **118**, 4931 (1996); (b) P. R. Ashton, M. Bělohradský, D. Philp, J. F. Stoddart. *J. Chem. Soc., Chem. Commun.* 1269 (1993); (c) M. Asakawa, P. R. Ashton, R. Ballardini, V. Balzani, M. Bělohradský, M. T. Gandolfi, O. Kocian, L. Prodi, F. M. Raymo, J. F. Stoddart, M. Venturi. *J. Am. Chem. Soc.* **119**, 302 (1997).
38. (a) P. R. Ashton, R. A. Bissell, N. Spencer, J. F. Stoddart, M. S. Tolley. *Synlett* 914 (1992); (b) P. R. Ashton, R. A. Bissell, N. Spencer, J. F. Stoddart, M. S. Tolley. *Synlett* 919 (1992); (c) P. R. Ashton, R. A. Bissell, N. Spencer, J. F. Stoddart, M. S. Tolley. *Synlett* 923 (1992).
39. (a) R. A. Bissell, E. Córdova, A. E. Kaifer, J. F. Stoddart. *Nature* **369**, 133 (1994); (b) E. Córdova, R. A. Bissell, N. Spencer, P. R. Ashton, J. F. Stoddart, A. E. Kaifer. *J. Org. Chem.* **58**, 6550 (1993).
40. (a) J. O. Jeppesen, J. Perkins, J. Becher, J. F. Stoddart. *Org. Lett.* **2**, 3547 (2000); (b) J. O. Jeppesen, J. Perkins, J. Becher, J. F. Stoddart. *Angew. Chem., Int. Ed.* **40**, 1216 (2001); (c) J. O. Jeppesen, K. A. Nielsen, J. Perkins, S. A. Vignon, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. Becher, J. F. Stoddart. *Chem.—Eur. J.* **9**, 2982 (2003).
41. H.-R. Tseng, S. A. Vignon, P. C. Celestre, J. Perkins, J. O. Jeppesen, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. F. Stoddart. *Chem.—Eur. J.* **10**, 155 (2004).
42. S. Nygaard, B. W. Laursen, T. S. Hansen, A. D. Bond, A. H. Flood, J. O. Jeppesen. *Angew. Chem., Int. Ed.* **46**, 6093 (2007).
43. S. Kang, S. A. Vignon, H.-R. Tseng, J. F. Stoddart. *Chem.—Eur. J.* **10**, 2555 (2004).

44. (a) T. D. Nguyen, H.-R. Tseng, P. C. Celestre, A. H. Flood, Y. Liu, J. F. Stoddart, J. I. Zink. *Proc. Acad. Natl. Sci. USA* **102**, 10029 (2005); (b) T. D. Nguyen, Y. Liu, S. Saha, K. C.-F. Leung, J. F. Stoddart, J. I. Zink. *J. Am. Chem. Soc.* **129**, 626 (2007); (c) S. Saha, K. C.-F. Leung, T. D. Nguyen, J. F. Stoddart, J. I. Zink. *Adv. Funct. Mater.* **17**, 685 (2007).
45. H.-R. Tseng, D. Wu, N. X. Fang, X. Zhang, J. F. Stoddart. *ChemPhysChem* **5**, 111 (2004).
46. I. Aprahamian, T. Yasuda, T. Ikeda, S. Saha, W. R. Dichtel, K. Isoda, T. Kato, J. F. Stoddart. *Angew. Chem., Int. Ed.* **46**, 4675 (2007).
47. (a) T. Iijima, S. A. Vignon, H.-R. Tseng, T. Jarrosson, J. K. M. Sanders, F. Marchioni, M. Venturi, E. Apostoli, V. Balzani, J. F. Stoddart. *Chem.—Eur. J.* **10**, 6375 (2004); (b) S. A. Vignon, T. Jarrosson, T. Iijima, H.-R. Tseng, J. K. M. Sanders, J. F. Stoddart. *J. Am. Chem. Soc.* **126**, 9884 (2004).
48. (a) T. Ikeda, S. Saha, I. Aprahamian, K. C.-F. Leung, A. Williams, W.-Q. Deng, A. H. Flood, W. A. Goddard III, J. F. Stoddart. *Chem. Asian J.* **2**, 76 (2007); (b) W.-Q. Deng, A. H. Flood, J. F. Stoddard, W. A. Goddard III. *J. Am. Chem. Soc.* **127**, 15994 (2005); (c) T. Ikeda, I. Aprahamian, J. F. Stoddart. *Org. Lett.* **9**, 1481 (2007).
49. (a) C. P. Collier, G. Mattersteig, E. W. Wong, Y. Luo, K. Beverly, J. Sampaio, F. M. Raymo, J. F. Stoddart, J. R. Heath. *Science* **289**, 1172 (2000); (b) M. Asakawa, M. Higuchi, G. Mattersteig, T. Nakamura, A. R. Pease, F. M. Raymo, T. Shimizu, J. F. Stoddart. *Adv. Mater.* **12**, 1099 (2000); (c) C. P. Collier, J. O. Jeppesen, Y. Luo, J. Perkins, E. W. Wong, J. R. Heath, J. F. Stoddart. *J. Am. Chem. Soc.* **123**, 12623 (2001); (d) Y. Luo, C. P. Collier, J. O. Jeppesen, K. A. Nielsen, E. De Ionno, G. Ho, J. Perkins, H.-R. Tseng, T. Yamamoto, J. F. Stoddart, J. R. Heath. *ChemPhysChem* **3**, 519 (2002); (e) M. R. Diehl, D. W. Steuerman, H.-R. Tseng, S. A. Vignon, A. Star, P. C. Celestre, J. F. Stoddart, J. R. Heath. *ChemPhysChem* **4**, 1335 (2003); (f) J. E. Green, J. W. Choi, A. Boukai, Y. Bunimovich, E. Johnston-Halperin, E. Delono, Y. Luo, B. A. Sheriff, K. Xe, Y. S. Shin, H.-R. Tseng, J. F. Stoddart, J. R. Heath. *Nature* **445**, 414 (2007).
50. (a) D. W. Steuerman, H.-R. Tseng, A. J. Peters, A. H. Flood, J. O. Jeppesen, K. A. Nielsen, J. F. Stoddart, J. R. Heath. *Angew. Chem., Int. Ed.* **43**, 6486 (2004); (b) A. H. Flood, A. J. Peters, S. A. Vignon, D. W. Steuerman, H.-R. Tseng, S. Kang, J. R. Heath, J. F. Stoddart. *Chem.—Eur. J.* **10**, 6558 (2004).
51. (a) I. C. Lee, C. W. Frank, T. Yamamoto, H.-R. Tseng, A. H. Flood, J. F. Stoddart, J. O. Jeppesen. *Langmuir* **20**, 5809 (2004); (b) T. J. Huang, H.-R. Tseng, J. Sha, W. Lu, B. Brough, A. H. Flood, B.-D. Yu, P. C. Celestre, J. P. Chang, J. F. Stoddart, C.-M. Ho. *Nano Lett.* **4**, 2065 (2004).