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Self-assembly in chemical synthesis

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The use of molecular recognition to activate the occurrence of self-assembly has become an important principle in the template-directed syntheses of molecular assemblies and supramolecular arrays. In our early lock-and-key systems, we investigated, as the lock, crown ethers like bisparaphenylene-34-crown-10 and, as the key, the 4,4'-bipyridinium dication. Now, they have been transformed into 'permanent' inclusion complexes, *via* a post-assembly modification pathway, leading to a range of mechanically-interlocked molecules in the shape of the catenanes and rotaxanes. The knowledge and experience gained by carrying out self-assembly on these relatively simple systems in solution go a long way toward establishing the fundamental rules for the elaboration of larger polymolecular assemblies. By modifying the nature of the components that make up the molecular assemblies, we have been able to gain a fundamentally better understanding of the limitations and the opportunities available for controlling self-assembly in a structural, geometric, and electronic sense during chemical synthesis. This account deals mainly with a carefully chosen selection of different molecular components in which the principle recognition sites have been varied to provide an opportunity for a predetermined bias in the translational isomerism of the [2]catenanes and [2]rotaxanes. These systems, which have been produced recently at Birmingham, are helping toward achieving an understanding of the processes of formation of, and the dynamics associated with, the mechanically-interlocked molecular compounds.

BACKGROUND AND INTRODUCTION

The concepts of self-assembly,[1] self-organization,[2] and self-replication,[3] which are used so efficiently in the biological world to generate a wide diversity of kinetically active and thermodynamically-stable structures, are now finding an important rôle to play in synthetic chemistry. Nature does not rely upon the redundant use of protecting groups and the sophisticated complexity of reagents, after the usual manner and practice of the synthetic organic chemist. Instead, she relies on the availability of relatively simple building blocks, which contain all the information necessary to promote the formation of their own assemblies, according to the precise recognition features of the building blocks that interact physically and chemically in well-defined ways. These recognition features include weak, but specific, interactions which are reversible, allowing any necessary alteration in superstructure to occur easily under mild conditions, thus rendering the process self-checking. The efficient processes employed by nature may help to meet futuristic targets identified by enthusiastic molecular engineers in the form of functioning systems. They need to be adopted by chemists keen to develop new approaches to chemical synthesis in which highly "intelligent" components are used to construct much larger molecular assemblies and supramolecular arrays. Our objectives are (i) to show how the chemist might gain a full appreciation of the complementarity, which must exist between particular host and guest molecules, if they are to serve as efficient building blocks for catenanes and rotaxanes, and (ii) to demonstrate how this complementarity "lives on" in self-assembled molecular systems. The term self-assembly[1,4–6] relates to the construction of discrete molecular assemblies and supramolecular arrays as a result of either weak, yet specific, noncovalent bonding interactions, reversible covalent bonding, or a mixture of both. By relying upon these marshalling forces, molecular assemblies and supramolecular arrays have programmed into them a way by which their three-dimensional architectures and functions can be controlled with ease and efficiency.

The production of synthetic systems displaying molecular recognition characteristics through the processes of self-assembly is now beginning to be realized over and above the methods of crystallization.[1] One of the main driving forces behind the development of supramolecular chemistry[7] has been the urge to understand how natural systems operate to form their particular superstructures and then to extend this understanding to wholly synthetic molecular assemblies and supramolecular arrays, which have been designed to exploit the use of noncovalent bonding interactions with the emphasis on functioning systems.[8–15]

The synthetic strategy we have adopted relies upon a *template-directed* methodology as a means of achieving self-assembly. With such methodology, the formation of a molecular assembly occurs as a result of the growth of

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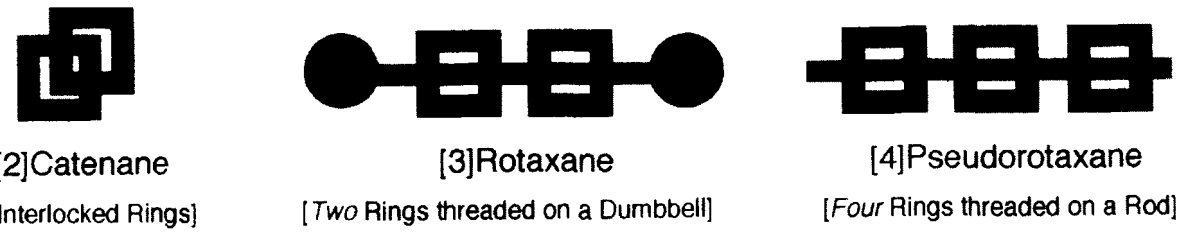


Figure 1 An assortment of schematically-drawn mechanically-interlocked and mechanically-entangled structures. (See Color Plate I.)

one component around an already preformed and complementary component. The complementarity is such that it gives rise to favourable noncovalent interactions within the developing system, thereby enhancing the formation of the molecular assembly. This strategy has led to the synthesis of a large number of mechanically-interlocked compounds and complexes (*Figure 1*) in the shape of the so-called catenanes,[8,16] rotaxanes,[8,17,18] and pseudorotaxanes[19–21] from inexpensive and readily-accessible component parts, such as the crown ethers.[22] The ultimate objective of our research program is to be able to control the construction, the form, and the function of synthetic nanometer-scale structures,[23] starting from the appropriate substrates, with the same degree of precision that is displayed in nature, without the need for reagent control or catalysis.

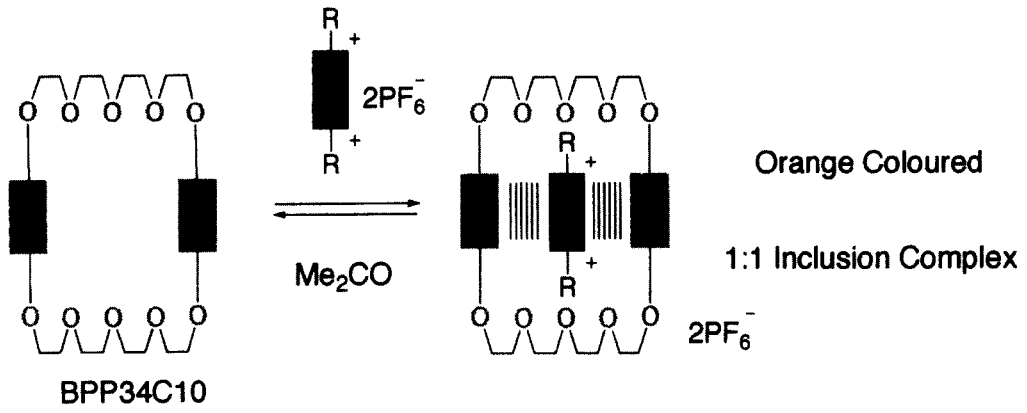
EVOLVING A SYNTHETIC STRATEGY

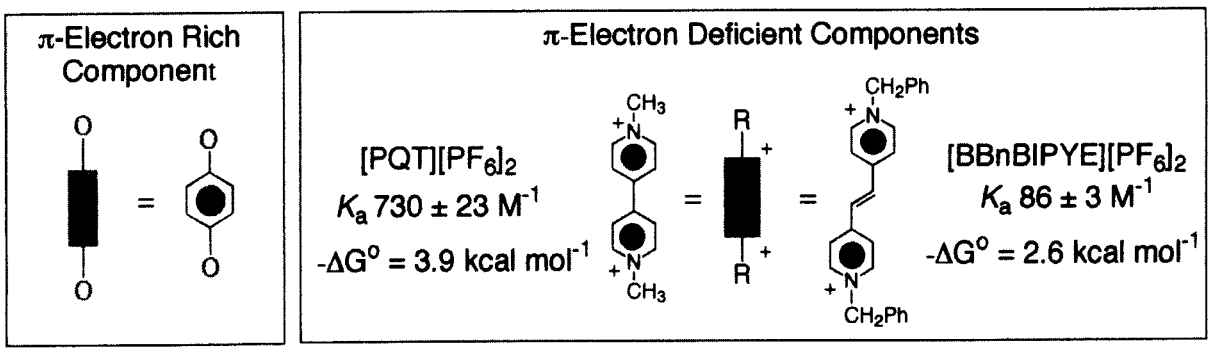
Our strategy for the self-assembly of catenanes and rotaxanes emerged from successive observations made on two complementary host-guest systems. During the early 1980s, we became interested in developing efficient, synthetic receptors for the important bipyridinium herbicides,[24] Diquat $[DQT]^{2+}$ and Paraquat $[PQT]^{2+}$ as a possible solution toward finding an antidote to their poisoning actions. The most successful receptors that emerged were dibenzo-30-crown-10[22,25,26] for $[DQT]^{2+}$ and its constitutional isomer, bisparaphenylene-34-crown-10 (BPP34C10)[27], for $[PQT]^{2+}$ (*Scheme 1*). X-Ray crystallography of the crystalline 1:1 complex, $[BPP34C10.PQT][PF_6]_2$,[§] showed that the $[PQT]^{2+}$ dication assumes a binding geometry which places it centrosymmetrically inside the BPP34C10 macrocycle, reminiscent of a key inside a lock.[8,21] The 1:1 complex formed between BPP34C10 and the $[PQT]^{2+}$ dication is stabilized by (i) electrostatic interactions, including [C-H...O] hydrogen bonding between the methyl and α-hydrogen atoms of the π-electron deficient dications and some of the polyether oxygen atoms of the crown ether, and (ii) dispersive forces—including π-π stacking[28]—which hold the mean planes of the parallelly-aligned π-donating hydroquinone rings and the π-accepting bipyridinium units in the solid state at a distance of 3.7 Å. The associated charge transfer interactions, give rise to the observed color between the π-electron deficient units in the dication and the π-electron rich hydroquinone rings in the crown ether. Indeed, π-π stacking interactions[28,29] are a major feature of the molecular assemblies discussed in this review article. The added bonus that BPP34C10 forms a deep orange-colored 1:1 inclusion complex with $[PQT][PF_6]_2$ in acetone at room temperature is another appealing feature of the systems.

With the demonstration of the existence of a successful host-guest system between BPP34C10 and $[PQT][PF_6]_2$, the next question we addressed was the reversal of the rôles of the host and the guest, *i.e.*, the formation of a receptor, incorporating bipyridinium units, which would complex with a neutral hydroquinone derivative as the substrate. To this end, the tetracationic cyclophane $[BBIPYBIXYCY][PF_6]_4$ was synthesized (*Scheme 2*) from the known[30] $[BBIPYXY][PF_6]_2$—obtained from 4,4'-bipyridine and 1,4-bis(bromomethyl)benzene (BBB) after counterion exchange (NH_4PF_6/H_2O)—and BBB. The final ring closure step afforded only a 12% yield of the desired tetracationic cyclophane.[31]

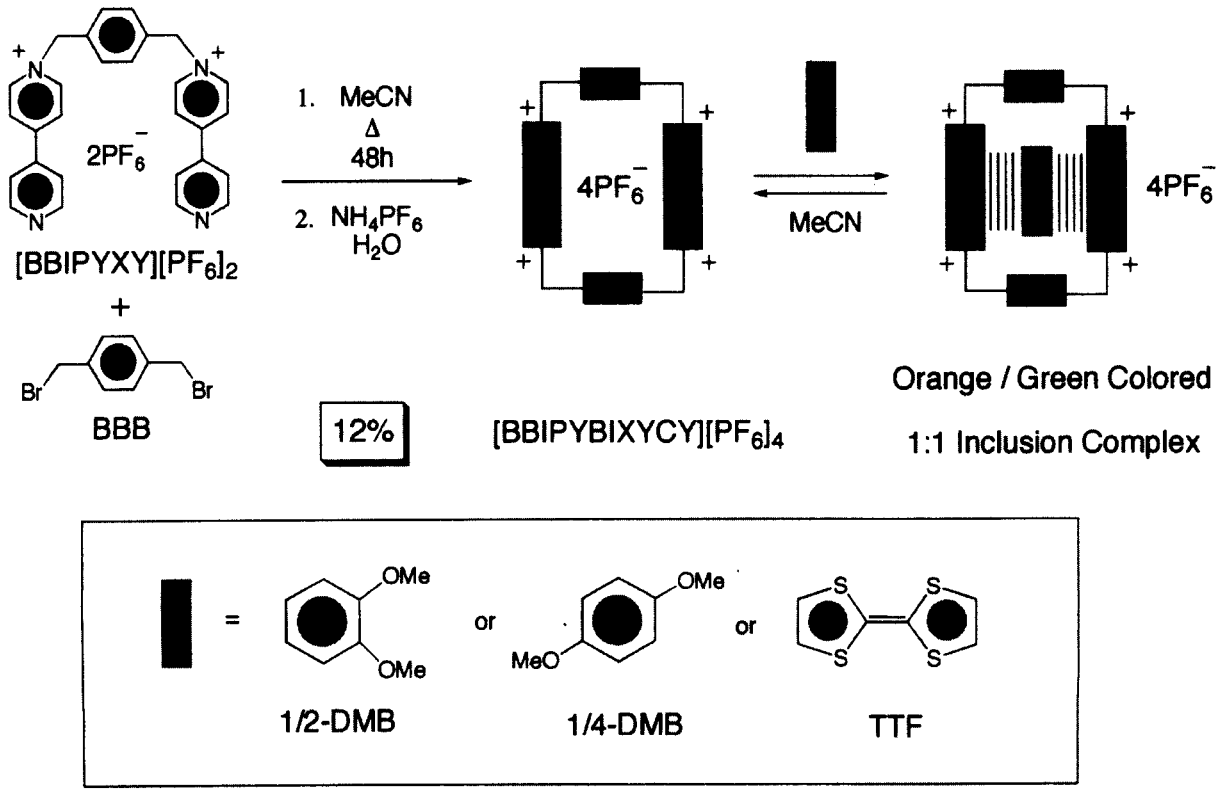
The ability of the tetracationic cyclophane[31,32] to form (*Scheme 2*) 1:1 complexes[32,33] with π-electron donating substrates—for example, with tetrathiafulvalene (TTF)[34] as well as with 1,2- and 1,4-dimethoxybenzene (DMB)[29]—with rotaxane-like[35] geometries is again a result of stabilizing dispersive forces that include (i) π-π-stacking and charge transfer interactions between the π-electron-rich substrates and the π-electron-deficient bipyridinium units in the receptor, and (ii) electrostatic "T-type" edge-to-face interactions, involving the aromatic substrates and the paraphenylene units in the

[§]It will be convenient at this point to describe the acronyms, which are composed of letters, that identify the neutral and charged compounds displayed throughout this essay. Compounds such as 1,4-dihydroxybenzene and 1,4-dimethoxybenzene are abbreviated to 1/4DHB and 1/4DMB, respectively, and bisparaphenylene-34-crown-10 to BPP34C10. The other acronyms can be deduced from the following rules: B stands for bis when at the beginning, for benzyloxy when in the middle, and benzene when at the end of the name. E, H, P, S, and T stand for ethoxy, hydroxy, phenoxy, triisopropylsilyl, and tosyloxy units, respectively. CY, TU, XY, and BIXY represent cyclophane, trioxaundecane, xylylene, and bisxylylene units, respectively. In addition, BIPY stands for a bipyridinium ring system with formal charges being indicated in the usual way. BBB stands for bis(bromomethyl)benzene. The neutral molecules are shaded in red or purple tones, while the positively charged organic species with the formal charges positioned appropriately, are shaded in blue tones.





Scheme 1 (See Color Plate II.)



Scheme 2 (See Color Plate III.)

tetracationic cyclophane. The availability of the tetracationic cyclophane has led us to examine its complexing properties toward a wide range of substrates. The edge-to-face interactions, although quite weak, play a significant organizing rôle in molecular assemblies, involving the $[BBIPYBIXYCY]^{4+}$ tetracation. The serendipitous discovery of the $[BPP34C10.PQT]^{2+}$ "lock and key" system, when married with the reciprocal $[1/4DMB.BBIPYBIXYCY]^{4+}$ "lock and key" system and combined with further covalent modifications, has led us to the production of intricate molecular assemblies of a rotaxane-like and catenane-like nature in which two or more molecular components are linked mechanically—but not covalently.

MAKING A [2] CATENANE

When $[BBIPYXY][PF_6]_2$ is mixed with an excess of BPP34C10 in acetonitrile solution, there is no visible evidence for any appreciable interaction between the $[BBIPYXY]^{2+}$ dication and the crown ether. However, the addition of BBB to this solution, followed by stirring the reaction mixture at room temperature overnight, resulted[8,36] in the deposition of a deeply colored red precipitate. After counterion exchange and recrystallization, {[2]-[BPP34C10]-[BBIPYBIXYCY]catenane}-$[PF_6]_4$ was isolated (*Scheme 3*) in the remarkable yield of 70%! Mechanistically, once the first *inter*molecular nucleophilic substitution has occurred to form the trication (*Scheme 3*), the mutual recognition—for example, by the emerging π-π stacking interactions—between the components ensures that the second *intra*molecular nucleophilic substitution, which affords the [2]catenane, proceeds rapidly *via* a favored transition state that leads to the cooperatively-assembled molecule. Indeed, this is an example of a *template-directed* synthesis,[1] wherein the template ends up being a component of the molecular assembly. The template-directed synthesis of the [2]catenane (*catena* is the Latin for chain) is a simple example[1] of (i) noncovalent self-assembly, followed by (ii) a post-assembly modification involving covalent bond formation. It gives rise to a *structure-directed*, aesthetically-pleasing and physically-intriguing molecule.[5]

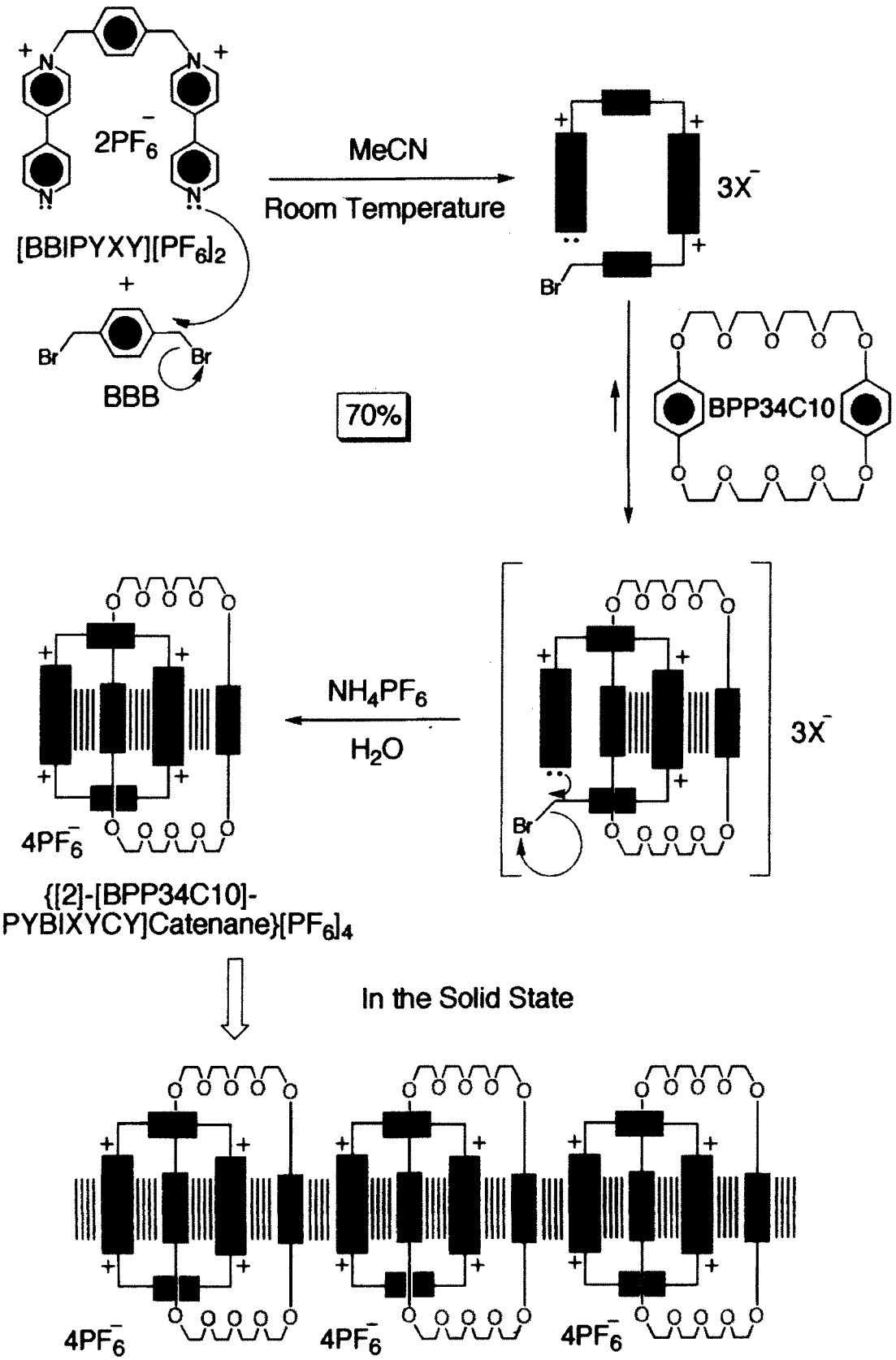
The X-ray crystal structure of the [2]catenane revealed (*Scheme 3*) a pattern of continuously stacked [2]catenane molecules aligned along one of the crystallographic axes such that the π-donors and π-acceptors alternate intermolecularly, as well as intramolecularly, at mean-plane separations[8,36,37] of 3.5Å. Variable temperature ^1H NMR spectroscopy indicated that the structural order observed in the solid state is also evident in solution.[8] In fact, the dynamics of the system in solution was illustrated by the fact that the neutral ring is circumrotating through the charged ring 300 times a second at +25 °C, while it is pirouetting around it 2000 times a second at the same temperature.[36]

So far, we have witnessed in the context of self-assembly, through the example of the [2]catenane and its crystal structure, that molecular and supramolecular structures can be constructed from the appropriate components, provided that we build into them the required geometries and complementarities to initiate and sustain the self-assembly processes. Quite remarkably, if we remove a lot of the preorganization (*Scheme 4*) *i.e.*, carry out the catenation between *five* "molecules"—*two* of BP, *two* of BBB, and *one* BPP34C10—in dimethylformamide at room temperature, then the [2]catenane can be isolated in 18% yield.[5] The yields can be improved further (to a staggering 42%!) by subjecting the same reaction mixture to ultra-high pressure (12 kbar).[5]

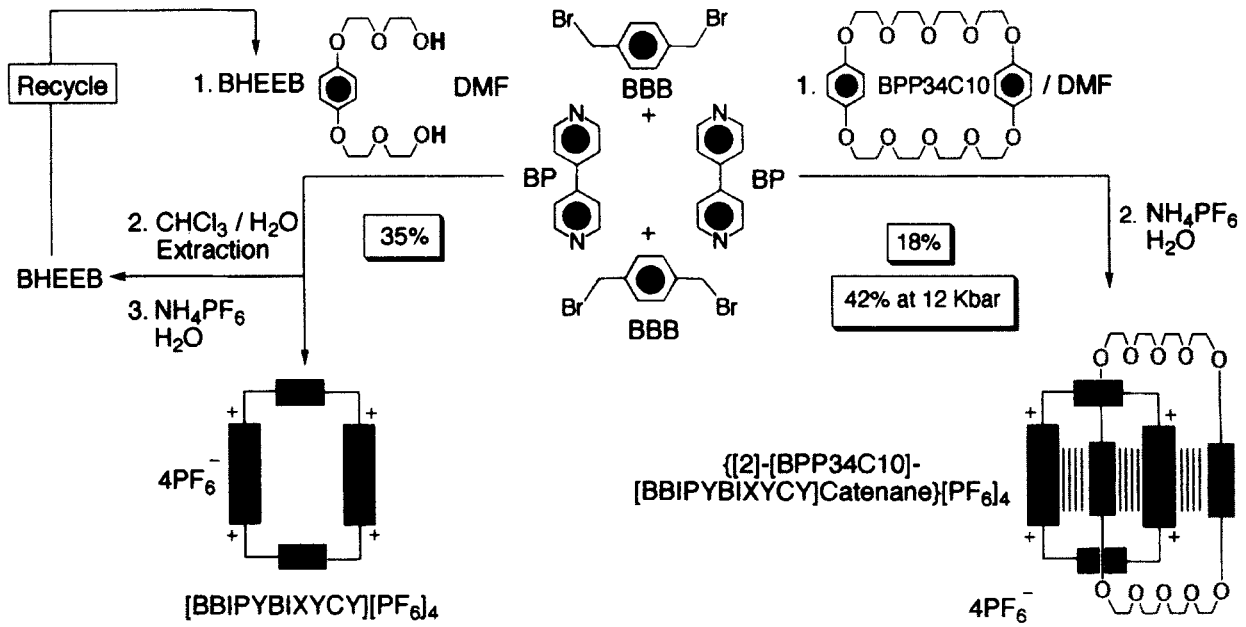
TEMPLATE-DIRECTING A SYNTHESIS

Taking into account that the primary recognition site in the [2]catenane synthesis is the included hydroquinone unit of BPP34C10, one might expect that the synthesis of the tetracationic cyclophane could itself be template-directed, provided the interlocking capability of the template is removed. Indeed, the tetracationic cyclophane $[BBIPYBIXYCY]^{4+}$ can be self-assembled (*Scheme 4*) from *two* molecules of each of BP and BBB in dimethylformamide at room temperature in the presence of the template—bis(hydroxyethoxyethoxy)-benzene (BHEEB)—in a modest 35% yield after counterion exchange.[31] This template can be thought of as "half" the macrocyclic polyether, BPP34C10.

During the syntheses shown in *Scheme 4*, either the BHEEB or the BPP34C10 *templates* organize the collection of π-electron deficient ligands around themselves, and in so doing favor *intra*molecular cyclizations over *inter*molecular reactions, *i.e.*, polymerizations. In the absence of the π-electron rich templates, and certainly at high concentrations, quaternizations of this type tend to yield polymeric materials. The increase in yield of the tetracationic cyclophane in the presence of the hydroquinone ring is a direct result of the organizing influence of this ring when it performs its role as a template. The addition of a second organizing feature in the shape of another hydroquinone ring in BPP34C10 enhances the reaction further, leading to even higher yields during the molecular assembly process. This type of *molecular imprinting*[†] is an example of a *directed* self-assembly,



Scheme 3 (See Color Plate IV.)



Scheme 4 (See Color Plate V.)

whereby either (i) a temporary template participates as a superstructural element in the assembly process but does not appear in the final assembled product, or (ii) a permanent template ends up forming a molecular assembly in which it is trapped in a mechanical sense. In the case of the BHEEB-templated reaction, we rely upon liquid-liquid extraction, which exploits the rapid equilibrium between the components of the inclusion complex, to separate the template away from the newly-formed tetracationic cyclophane.

INTRODUCING A CONSTITUTIONAL BIAS INTO [2]CATENANES

The basis for catenation is a logical extension of the formation of 1:1 inclusion complexes, except that it results in the synthesis of a permanent "inclusion complex" in the form of an interlocked ring. However, [2]catenanes also incorporate dynamic motions—pirouetting and circumrotation—which makes their molecules even more intriguing still. The recognition processes that lead to the self-assembly[1,5] of these [2]catenanes[8,36] are controlled by the information stored in the molecular components, which are constructed from preprogramed starting materials. This information[38] is trapped within the [2]catenane whose properties are quite different from those of their molecular components on their own. The dynamic behavior of [2]catenanes, such as {[2]-[BPP34-C10]-[BBIPYBIXYCY]catenane}[PF_6]$_4$, is such that both interlocked rings can pass freely through each other at ambient temperatures. When we impart some aspect of dissymmetry into this kind of [2]catenane, either by replacing *one* of the π-electron deficient units or *one* of the π-electron rich rings, or both, with different ones, then there arises the possibility (*Figure 2*) of the catenane existing as a mixture of so-called translational isomers,[39] most likely with some predetermined bias for one isomer over the other. The translational isomers differ on account of (i) which residue occupies the cavity inside the other ring component, and of (ii) which residue takes up a position alongside the other ring component.

The study of phenomena, such as translational isomerism—a structural characteristic[39] of many of these intriguing molecules—provides a direct means of gaining insight into the recognition processes that operate during their formation and subsequently characterize their molecular states. Furthermore, the control of the translational isomerism in interlocked molecular compounds is important in understanding and demonstrating their chemical properties and for predicting the applications[40] they might address. Some recent examples illustrate[41,42] the progress that has been made already toward the construction of controllable catenanes and rotaxanes. The kinetic control of this translational isomerism (*i.e.* the rate of circumrotation of one macrocycle through the other within the [2]catenane) is an important goal in understanding the dynamics of the system.[46] In all cases,

†*Molecular imprinting* occurs when the shape of the guest molecule is used as a template to sculpture the architecture of the developing host molecule. For a more detailed discussion, see Lindsey, J.S. *New J. Chem.* **1991**, *15*, 153–180.

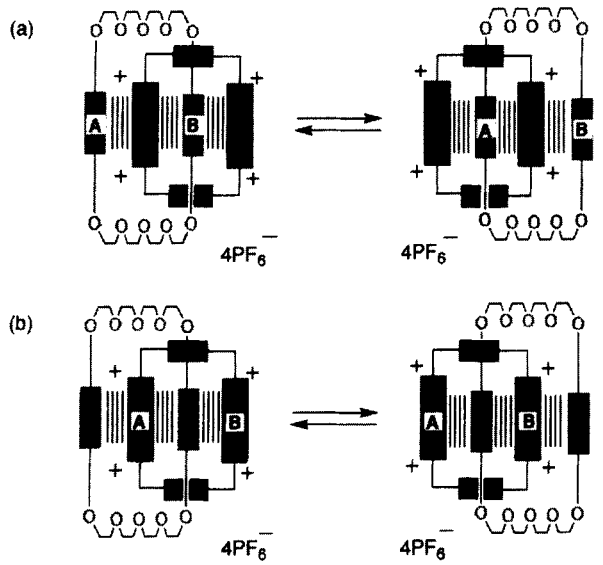


Figure 2 Illustration of the translational isomerism possible either (a) by having two different π-electron rich units in the crown ether, or (b) by having two different π-electron deficient units in the tetracationic cyclophane. Unit A differs from unit B either sterically or electronically or both. (See Color Plate VI.)

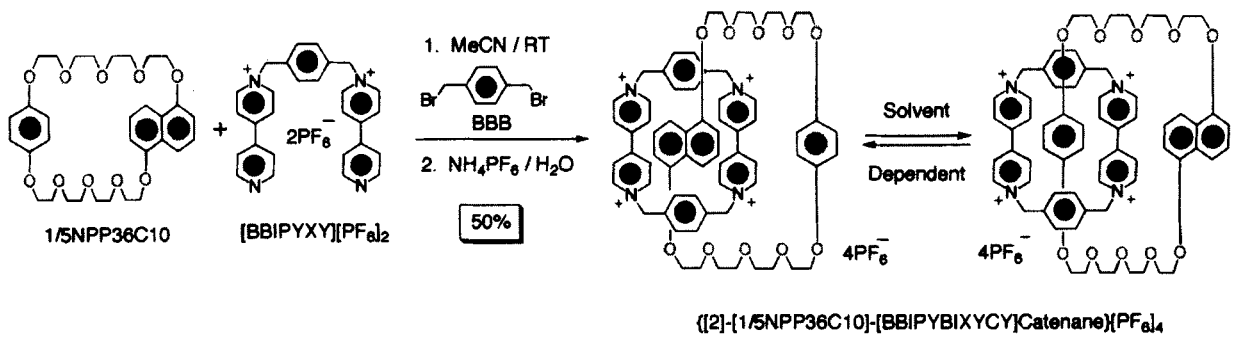
the fundamental objective of much research is to learn how to effect structural changes between the component parts of these interlocked molecules that are induced either by chemical,[43] electrochemical,[44] or photochemical[45] stimuli. The introduction of constitutional dissymmetry into catenated structures relies on the use of differentiated components that, given the choice, exhibit a preference for one translational isomer which then displays a distinctive property. The need for this dissymmetry implies a search for different building blocks for the construction of new catenanes and rotaxanes. The most obvious approach led us to identify the candidates for exhibiting translational isomerism, according to whether the dissymmetric component is located in the neutral macrocycle or in the charged cyclophane. In principle, the control of translational isomerism may be accomplished by steric[46] and/or electronic means.

Building the Constitutional Bias into the Crown Ether

The π-donating ability of the crown ether components has a large capacity not only to determine the production of the catenanes, but also to dictate the energy barriers necessary to overcome the dynamic barriers.[8,36,37] In order to shed more light on this effect, we self-assembled (*Scheme 5*) a [2]catenane containing 1/5NPP36C10 by template-directed methods[43] in the belief that the different π-donating abilities of the 1,5-dioxynaphthalene unit and the hydroquinone ring would influence strongly the relative populations of the two equilibrating translational isomers. In the event, the position of the equilibrium was found (*Scheme 5*) to be highly dependent on the dielectric constant of the solvent in which the [2]catenane was dissolved. The larger π-surface of the naphthalene ring seems to act as a solvent shield in apolar solvents and in so doing minimizes the unfavorable interactions between the solvent and the tetracationic cyclophane. This result indicates that the molecular recognition, which operates between the components of a [2]catenane, not only relies on the strengths of the binding of the fragmented components, but must also relate to the properties of the larger molecular assembly. Moreover, it illustrates how a controllable [2]catenane could acquire functions similar to those of a sensor.

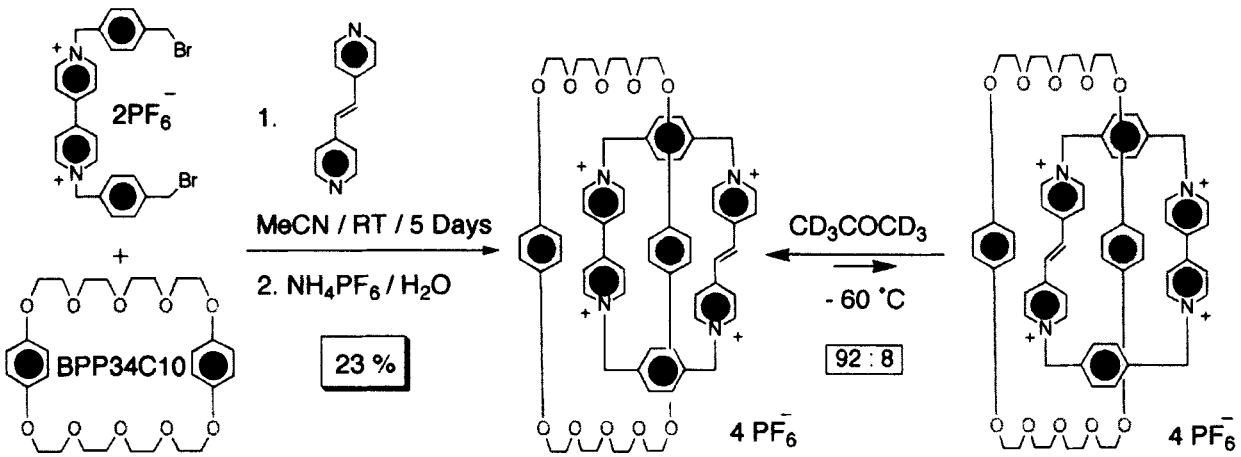
Building the Constitutional Bias into the Tetracationic Cyclophane

In the search for new building blocks for the construction of constitutionally dissymmetric [2]catenanes, we considered several π-extended viologen units as alternatives to the bipyridinium units. Eventually, we chose the bis(pyridinium)ethylene unit, not only because it displays a different binding potential toward π-electron rich units than does the bipyridinium unit, but also because it has a higher reduction potential—a feature which could lead to [2]catenanes becoming electrochemically controlled. Their photoactive properties also give them the potential to be able to respond to photochemical stimuli. For these reasons, we carried out the self-assembly,



{[2]-[1/5NPP36C10]-[BBIPYBIXYCY]Catenane}$[PF_6]_4$

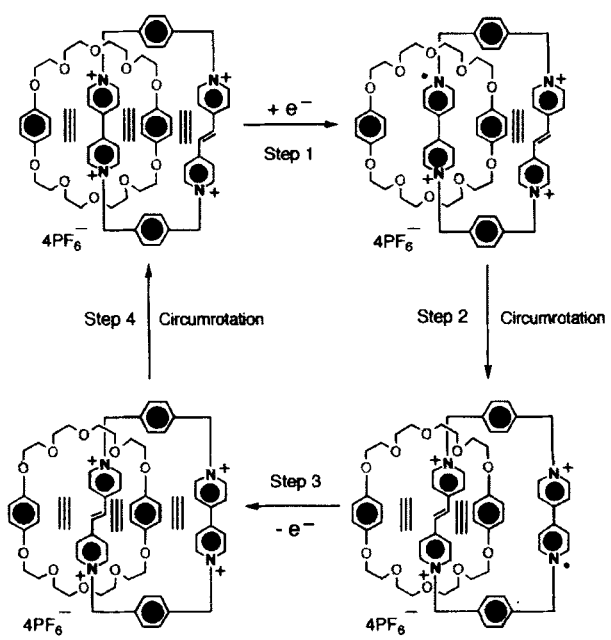
Scheme 5 (See Color Plate VII.)



Scheme 6 (See Color Plate VIII.)

characterization, and investigation of the electrochemical properties of a [2]catenane in which the macrocyclic polyether, BPP34C10, was encircled by a tetracationic cyclophane containing one bipyridinium and one bis(pyridinium)ethylene.[44] This [2]catenane was self-assembled using a template-directing methodology as shown in *Scheme 6*. The instantaneous formation of a 1:1 complex between BPP34C10 and $[BBXYBIPY][PF_6]_2$ was followed by stepwise alkylation of bis(pyridinium) ethylene (BPE) to form the [2]catenane in 23% yield. Spectroscopic studies indicated that the translational isomer, in which BPP34C10 encircles the bipyridinium unit rather than the bis(pyridinium)ethylene unit, is by far the more predominant one in CD_3COCD_3 solution at low temperatures.[44] This selectivity is a consequence of the lower binding affinity of the π-extended viologen unit with π-electron donating hydroquinone rings in BPP34C10. The much diminished strength of nonbonding interactions, including the charge-transfer interactions, modulates the dynamic properties of this [2]catenane and leads to selectivities for certain structural arrangements.

The [2]catenane can exist as two different translational isomers—with either the viologen unit or the π-extended viologen unit 'inside' the macrocyclic polyether. Furthermore, the redox properties of the molecule confer the potential to control the translational isomerism of the molecule according to the reaction sequence outlined in *Scheme 7*. The predominant isomer in solution is the one represented in the **top left-hand corner**, in which the viologen occupies the 'inside' position of the macrocyclic polyether, because this dication is a better π-acceptor than the π-extended viologen dication which occupies the 'alongside' position. However, we can switch this situation electrochemically, according to the following sequence: (1) Reduction of the [2]catenane: the first reduction occurs at the 'inside' bipyridinium unit because its reduction potential is lower than that of the 'alongside' π-extended viologen unit. The [2]catenane exists as the monoradical cation, represented in the **top right-hand corner** in *Scheme 7*. (2) After being reduced, the 'inside' bipyridinium unit loses its ability to bind the π-electron rich hydroquinone rings of the macrocyclic polyether and in so doing favors the 'alongside' π-extended viologen which is still a dication. As a consequence, the tricationic macrocycle circumrotates within the neutral macrocycle in order to locate the π-extended viologen dication unit 'inside'. The predominant translational isomer is now the one represented in the **bottom right-hand corner** (3). This process is reversible by oxidation, producing again a tetracationic compound, drawn in the **bottom left-hand corner**. In this state, the original preference obtains again and the viologen unit recovers its ability to bind the hydro-



Scheme 7 (See Color Plate IX.)

quinone rings of the macrocyclic polyether (4) and so, circumrotation takes place, returning the equilibrium in favor of the original translational isomer, shown in the **top left-hand corner**. The incorporation of a macrocyclic polyether and two π-electron deficient units can also be applied in a rotaxane sense. The control of translational isomerism, through stimuli from either an electron or photon source, using a [2]catenane assembly, can be envisaged as a way to establish a whole set of "zeros" and "ones", leading to the creation of a binary molecular device. Our research efforts are concentrating on this next step toward nanoscale molecular devices.

SELF-ASSEMBLING [n]CATENANES

In the past 10 years or so, since the advent of supramolecular chemistry[7] and the consequent development of a new kind of chemistry, which relies upon noncovalent bonding interactions to form stable structures, chemists have begun to realize their dreams of making chain-like molecules. Polycatenanes are themselves interesting compounds in a topological sense. In essence, their architecture resembles chains, where, for example, alternating macrocyclic polyethers and tetracationic cyclophanes form a linked combination (*Figure 3*). Obviously, to make polycatenanes, we need to increase the size of both the tetracationic cyclophane and macrocyclic polyether components described so far in this review in order to allow more than one ring to occupy a position within the cavity of its neighbouring ring. [3]Catenanes provide a good starting point toward a template-directed approach to polycatenanes. Extending the methodology, however, was not as straightforward as one might have expected. This next section highlights some of the limitations we have encountered and the rewards we have experienced in trying to self-assemble [n]catenanes.

Expanding the Tetracationic Cyclophane Component

Early in the quest for [n]catenanes, we targetted a larger cyclophane, such that the two bipyridinium units could each be encircled simultaneously by two neutral macrocyclic polyether rings. The tetracation, [BBIPYBIBTCY]$^{4+}$, where the bridging *p*-xylyl spacers units in [BBIPYBIXYCY]$^{4+}$ have been replaced by bitolyl ones, was identified as a hopeful target. While the synthesis of the tetracationic receptor could not be achieved by itself using the familiar template-directed methodology, its conversion into (*Scheme 8*) the corresponding [3]catenanes, with either BPP34C10 or 1/5DN38C10 as the permanent templates, was easily accomplished.[47] When the salt [BBIPYBT][PF_6]$_2$, bis(bromomethyl)biphenyl (BBBP), and either BPP34C10 or 1/5DN38C10 were mixed in a 1:1:3 molar ratio in acetonitrile for 9 days, the corresponding [3]catenanes were isolated after counterion exchange in 20% and 31% yields, respectively.[47] The cavity of [BBIPYBIBTCY]$^{4+}$ was found to be almost square with inner dimensions of approximately 11.0 × 10.5 Å. The cavity was fortunately just the right size required for the incorporation of two aromatic residues stacked face-to-face. Our failure to make the tetracationic cyclophane stems from being unable to identify suitable templates. It will surely be self-assembled when a suitable template is identified. *The take-home message is that it is sometimes easier to make the self-assembled structure than it is to make the molecular components by themselves*!

Expanding the Neutral Crown Ether Component

Once [3]catenanes were realized, and in order to produce chain-like assemblies, it was necessary to form larger π-electron rich ring components. While the crown tetrakisparaphenylene-68-crown-20 (TPP68C20), which was twice the size of BPP34C10, could be used in the self-assembly (*Scheme 9*) of the [2]catenane— {[2]-[BBIPYBIXYCY]-[TPP68C20]catenane}[PF_6]$_4$— at ambient pressure, and the [3]catenane— {[3]-[BBIPYBIXYCY] - [TPP68C20] - [BBIPYBIXYCY]catenane}[PF_6]$_8$— under ultra-high pressure conditions, using the familiar tetracationic cyclophane [BBIPYBIXYCY][PF_6]$_4$, the reduced preorganization of the TPP68C20 compared with BPP34C10, meant that no catenanted materials were produced when [BBIPYBT][PF_6]$_2$ and BBBP were added to solutions of TPP68C20. We attribute this lack of catenation to the

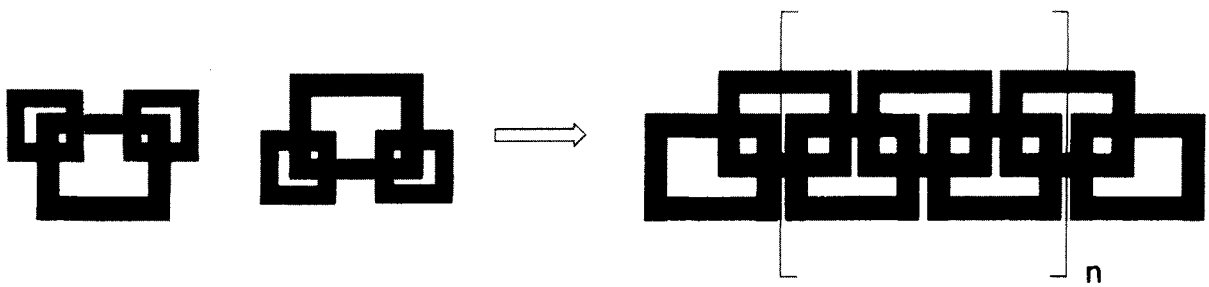
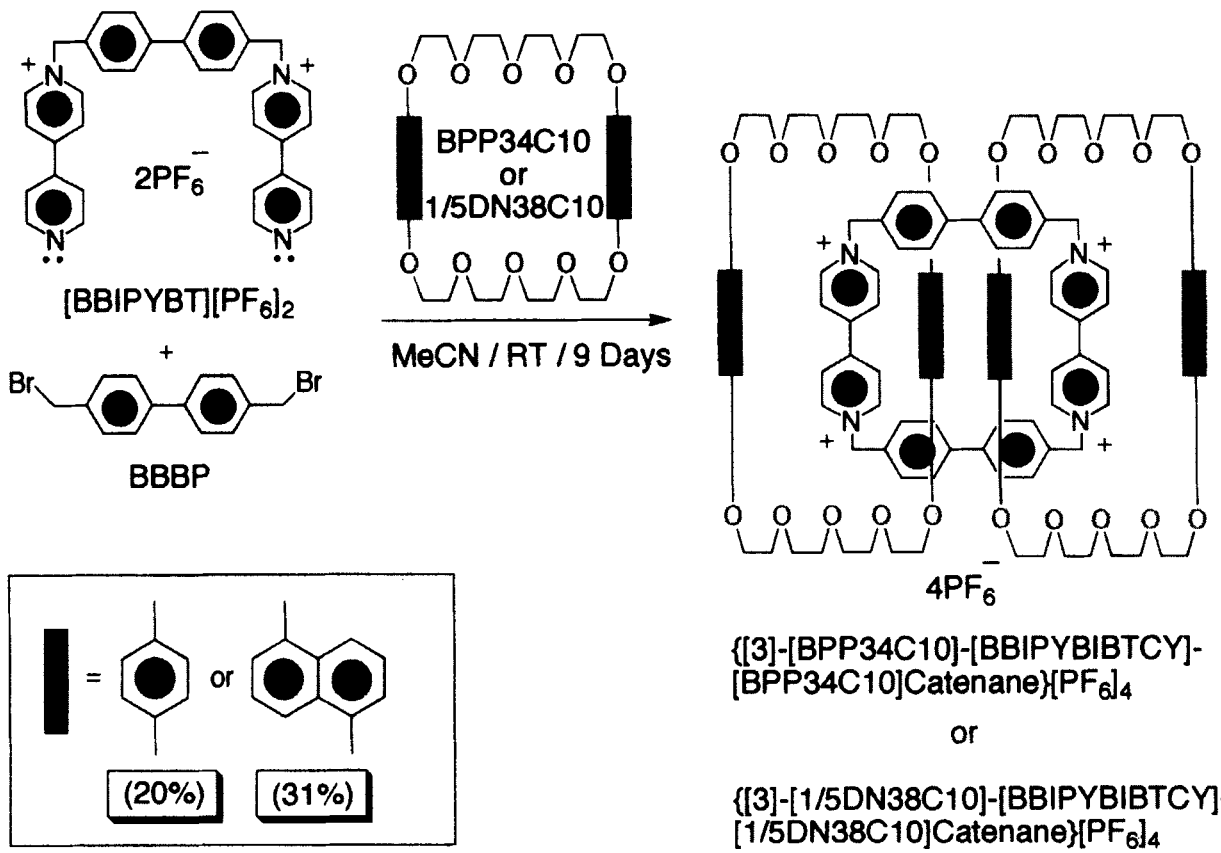


Figure 3 The formal amalgamation of two [3]catenanes to form polycatenanes. (See Color Plate X.)

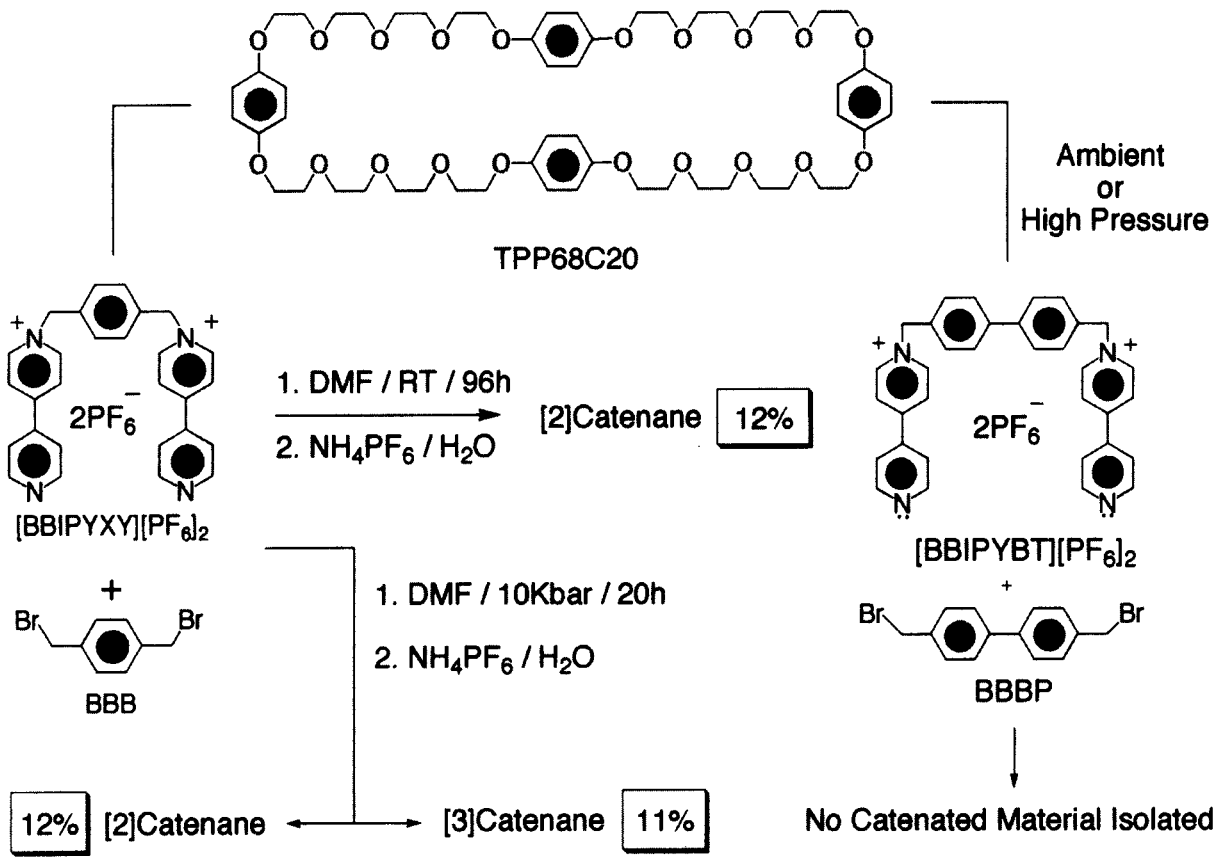


Scheme 8 (See Color Plate XI.)

large dimensions of the two components, and, in the case of TPP68C20, to its high flexibility.

Toward [n]Catenanes *via* [4]- and [5]-Catenanes

While our initial approaches toward self-assembling higher catenanes proved unrewarding, the macrocyclic polyether TPP51C15 (*Scheme 10*), which is intermediate in constitution between the "failed" TPP68C20 and "successful" BPP34C10, was expected to be sufficiently large in order to allow the formation of higher catenanes, provided it was not too flexible.[48] As before, both the [2]catenane (in 48% yield) and the [3]catenane (in 15% yield) could be isolated under ambient and high pressure conditions, respectively. This result infers that the smaller crown ether (TPP51C15) contains the necessary molecular recognition information to self-assemble with the usual components of the tetracationic cyclophane to form catenated species. Small amounts of a [3]catenane were also produced when TPP51C15 was mixed with $[BBIPYBT][PF_6]_2$ and BBBP, under ambient conditions and after counterion exchange. We then experimented with the idea of converting the [3]catenane into the corresponding [5]catenane by reacting it with an excess of $[BBIPYXY][PF_6]_2$ and BBB, again, under ambient conditions. The template-directed methodology meant that the new cyclophanes would form around one of the "free" hydroquinone receptors in either of the TPP51C15 macrocycles. Our results indicated that the molecular assembly could not be taken successfully past the [4]catenane stage (22% yield), while only ever yielding trace amounts of the [5]catenane, even at high pressure.[49] A different situation prevails when the hydroquinone rings are replaced by the more π-donating 1,5-dioxynaphthalene units. Under the same reaction conditions, after fourteen days at ambient pressure, the reaction mixture contained[50] the starting [3]catenane (45%), the intermediate [4]catenane (31%), and the ultimate [5]catenane (5%). A possible explanation for why the self-assembly falters at the [4]catenane, when using hydroquinone rings, might be the fact that some complementarity exists between the three hydroquinone rings and the large tetracationic cyclophane as a result of π–π stacking. Hence, by programming sufficient structural and electronic information into the constituent recognition components of both the macrocyclic polyether and tetracationic cyclophanes, the makings of a template-directed route to polycatenanes are fast beginning to emerge.

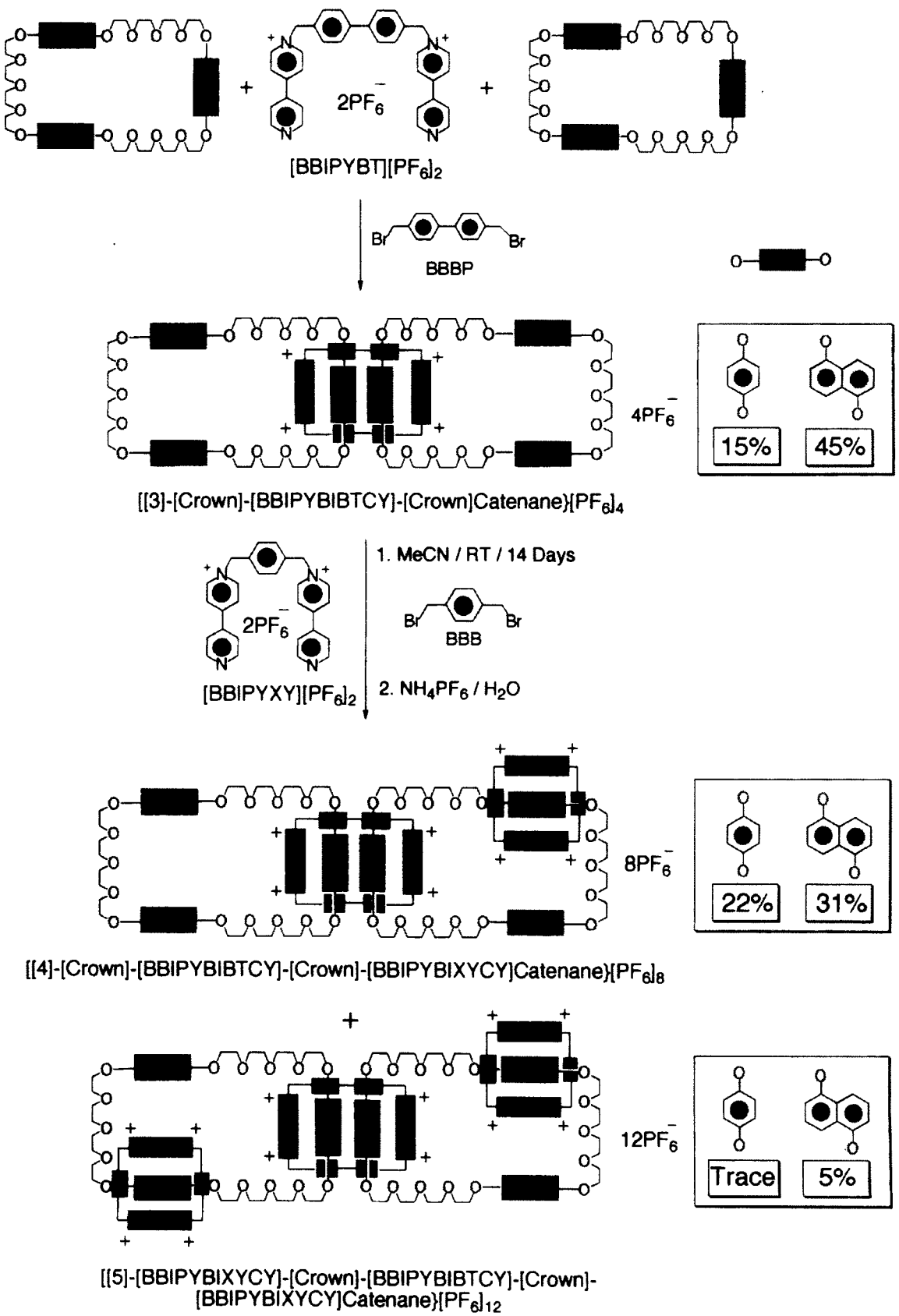


Scheme 9 (See Color Plate XII.)

MAKING ROTAXANES

It would be remiss in the context of a general review not to include some mention of rotaxanes related to the catenanes we have just been discussing. Rotaxanes[35] that contain more than one recognition site in the dumbbell component provide potentially useful synthetic targets. A major objective is to be able to control their molecular structures in order to create nanoscale devices by influencing somehow the interactions between the ring and the dumbbell components, analogous to the manner in which the translational isomerism in the [2]catenanes can be controlled (*vide supra*). In chemical terms, a [2]rotaxane contains a linear component (*axis* is the Latin for axle) encircled by a macrocyclic component (*rota* is the Latin for wheel). In order to prevent the wheel from leaving the axle *readily*, the linear component must be terminated at both ends by large stoppers, *i.e.*, blocking groups. The blocking groups mainly take the form of inert-structures (dumb stoppers!) or they may be addressable by some means. The mechanically-interlocked nature of the complementary molecular components provides, not only an aesthetically-pleasing form, but also a resulting molecular structure which can have the ability to function in response to external stimuli, such as a flux of protons, photons, or electrons. The ability of the supramolecular chemist to take control of the self-assembly processes available—namely clipping, threading and slipping (*Figure 4*)—provides straightforward entries into nanometer-scale architectures. Clipping and slipping both require the prefabrication of the dumbbell component by some traditional synthetic approach (*Figure 4*).

The choice of either a π-electron deficient or a π-electron rich dumbbell is one that is in the hands of the molecular engineer, since both systems are readily assembled by our methodology. Once the rotaxane has been characterized, variable temperature ^{1}H NMR spectroscopy can be employed to reveal that the dynamic properties of the [2]rotaxane are such that, in both scenarios, the bead component "shuttles" readily between the two receptors, or "stations", incorporated within the dumbbell component. This kind of dynamic process ultimately led to a new direction in the research—the construction of controllable molecular shuttles.[41] Such dynamic processes are crucial for the successful self-assembly of nanostructures capable of exhibiting device-like functions at the molecular level. In each of the examples shown in *Figure 5*, there is the



Scheme 10 (See Color Plate XIII.)

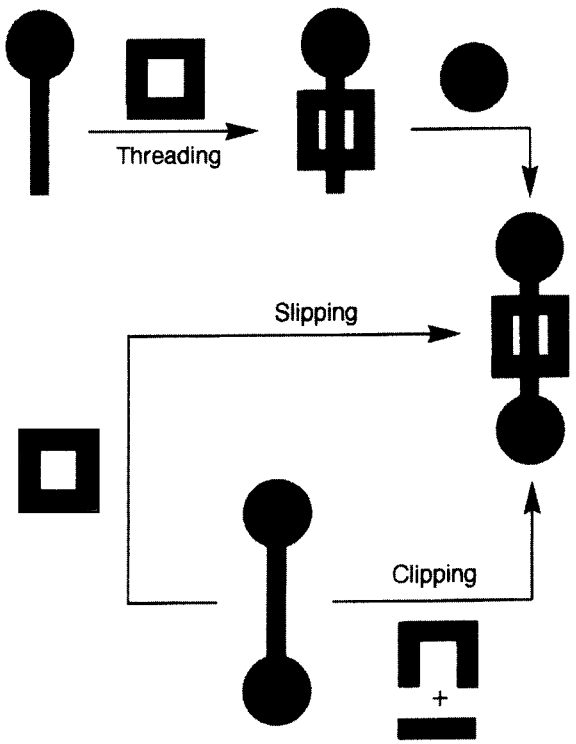


Figure 4 The three self-assembly processes which have been used for synthesizing rotaxanes. (See Color Plate XIV.)

possibility for translational isomerism to occur and in nearly all cases it can be observed by dynamic ^{1}H NMR spectroscopy.

Controlling the Shuttling

The strategy for the construction of an electrochemically-addressable molecular switch requires that both π-electron rich stations in a constitutionally dissymmetric dumbbell component recognize the tetracationic cyclophane component, but that the station which has the lower oxidation potential is also the better receptor, *i.e.* the tetracationic cyclophane should reside on it preferentially. Perturbation by an external stimulus, *e.g.*, from an electrode, should cause the tetracationic cyclophane to move between stations. There are two ways to tackle the problem of controlling the translational isomerism. They are to (i) replace one hydroquinone station by a π-electron donor whose affinity for the cyclophane is less than that of a hydroquinone ring—our previous experience at the time led us to the use of a *p*-xylyl unit—or (ii) replace the hydroquinone station by a π-electron donor with a greater affinity for the tetracationic cyclophane.

The first model compound we undertook to study incorporated a *p*-xylyl residue as the second station.[41] Since dispersive interactions between the tetracationic cyclophane and the π-electron rich site account for a sizeable fraction of the binding energy between them, we predicted that the tetracationic cyclophane would occupy preferentially the hydroquinone station. The low temperature ^{1}H NMR spectrum of the corresponding [2]rotaxane in CD_3CN did reveal some skewness in relation to site occupancies. However, only 70% of the tetracationic cyclophane populates the hydroquinone ring (*Figure 6*).[41] The indecisive mechanical behavior of this [2]rotaxane led to an inversion of the design logic. The necessary modification was achieved by replacing the *p*-xylyl residue with a 2,3,5-trisubstituted indole unit, an aromatic system which is more π-electron rich than the hydroquinone ring but has a much lower oxidation potential.[41] On this basis, we predicted that the tetracationic cyclophane should reside on the indole ring in preference to the hydroquinone one, at least until the former is oxidized to the radical cation, at which point the tetracationic cyclophane should be repelled electrostatically and so would return to the hydroquinone station—the next lower energy situation. Variable temperature ^{1}H NMR spectroscopy on the resulting [2]rotaxane in CD_3CN showed that, in fact, the hydroquinone ring is occupied completely by the tetracationic cyclophane! This outcome is probably a consequence of steric outweighing electronic factors, leaving the larger indole unit to "solvate" the exterior of the tetracationic cyclophane. The pronounced preference for this [2]rotaxane to adopt the "incorrect" translational isomer meant that this system was not suited to our immediate needs, *i.e.* it was not going to be possible to control its molecular shuttling.

The breadth of investigations we undertook in the early research, involving different substrates for the tetracationic cyclophane, left us in the position to be able to choose from a broad selection of π-electron rich stations. One such substrate, which has a high affinity for the tetracationic cyclophane, is tetrathiafulvene (TTF).[34] The [2]pseudorotaxane nature of the inclusion complex formed between the tetracationic cyclophane and TTF made its introduction into the dumbbell component of a [2]rotaxane an extremely attractive proposition. The targeted TTF derivative (*Scheme 5*) was expected to fulfil the same criteria that were set for the indole unit (*i.e.* high affinity for a receptor containing π-electron deficient units and a low oxidation state) while being less sterically demanding. The ^{1}H NMR spectrum in CD_3SOCD_3 of the [2]rotaxane incorporating the TTF unit revealed the desired complete occupancy of the tetracationic cyclophane around the TTF moiety, a result which was confirmed by UV/VIS spectroscopy (the charge transfer band is located at 752 nm, compared with the more normal band at 450 nm observed with hydroquinone rings).[41] The solvent dependency (*Figure 6*) of the translational isomerism exhibited by the [2]rotaxane in CD_3SOCD_3 and CD_3COCD_3 was quite an unexpected result. The use of CD_3COCD_3 for dynamic ^{1}H NMR

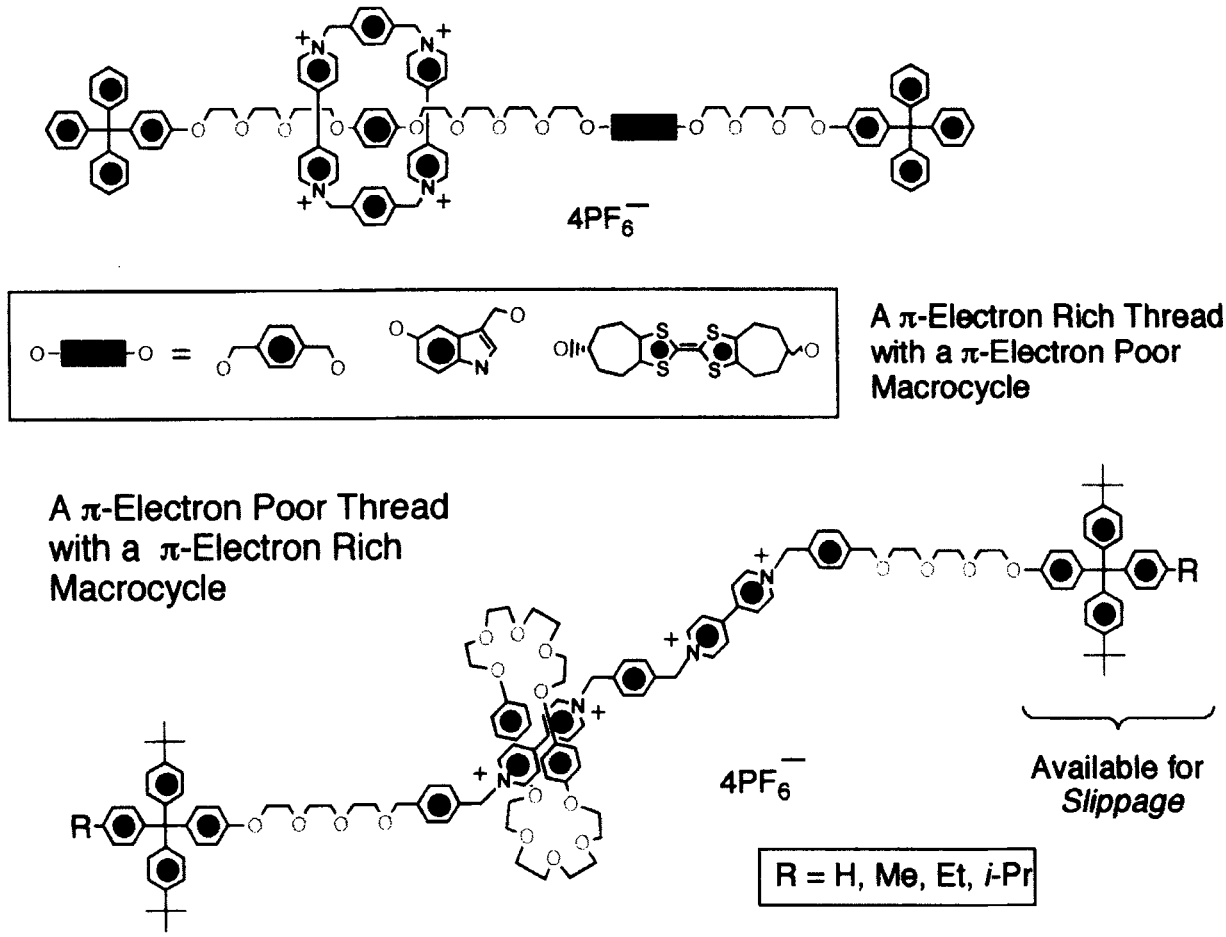


Figure 5 Some of the potentially functioning [2]rotaxanes that have been made to order. Note that the dumbbell component may incorporate either π-electron rich or π-electron deficient recognition stations, with the appropriate complementarity being expressed in the ring component. (See Color Plate XV.)

spectroscopy revealed this solvent dependent behavior. The preferred translational isomer in CD_3COCD_3 involves equal population of the two equivalent hydroquinone rings by the tetracationic cyclophane with it experiencing no residence on the TTF unit. This kind of behavior creates the possibility of developing a solvent dependent switch. Unfortunately, while an ideal occupancy situation was found to pertain in CD_3SOCD_3, the possibility of exploiting this system for electrochemical studies was not possible because of the lack of reversibility in a redox sense shown by this compound in this solvent.

A redesign of the dumbbell component, in which the hydroquinone ring was also replaced, led to the desired breakthrough. Preliminary studies on benzidine and biphenol derivatives showed that they are both bound inside the cavity of the tetracationic cyclophane with the benzidine unit being included preferentially.[41] The analysis of model [2]rotaxanes incorporating these units showed that the anticipated control by external stimuli was possible (*Figure 7*). The control of a system incorporating both these units in the dumbbell component was actually found to be possible by two means—chemically (through protonation of the benzidine nitrogen atoms) and electrochemically (on account of the low oxidation potential of the benzidene unit). The position of the tetracationic cyclophane can be switched from the benzidine station (which corresponds to the major translational isomer with 84% occupancy in CD_3CN at 229 K) to the biphenol station by either protonation of the basic nitrogen atoms, yielding the [2]rotaxane $\mathbf{14}^{6+}$ (as a result of charge repulsion) or by electrochemical oxidation, yielding the [2]rotaxane $\mathbf{13}^{5+}$ (as a consequence of destroying the dispersive interactions) (*Figure 7*). Although this model represents the state-of-the-art version of a controllable molecular shuttle, there is plenty of room left for improvement.

CONCLUSIONS AND REFLECTIONS

It has now been demonstrated beyond any doubt that it is possible to use self-assembly processes, in particular template-directed syntheses, to construct molecular assemblies and in the case of their crystal structures—

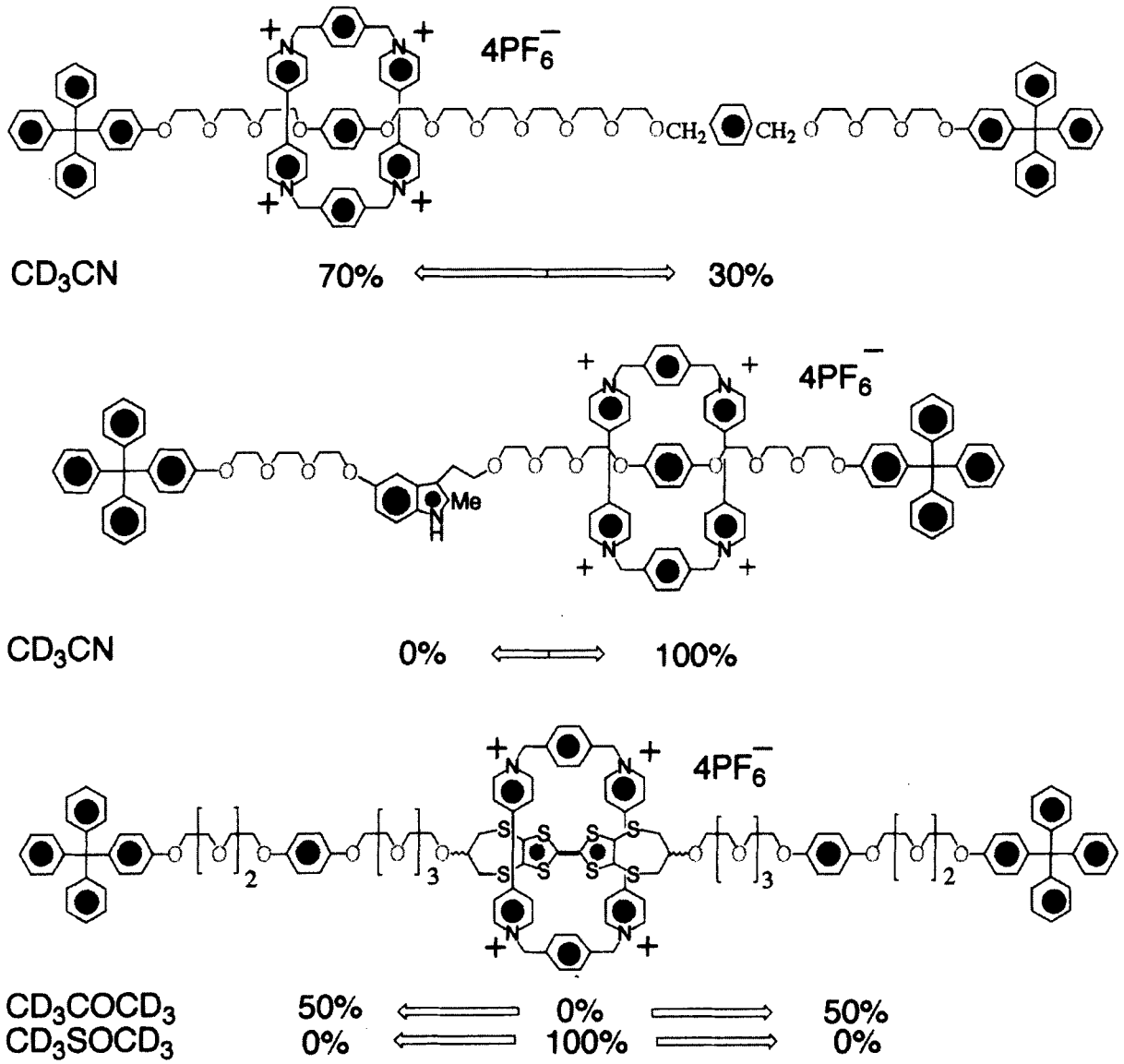


Figure 6 Low temperature ^{1}H NMR spectroscopic studies reveal that each of the three [2]rotaxanes is biased toward one translational isomer. (See Color Plate XVI.)

supramolecular arrays, which are of nanometer-scale with a high degree of control and precision from molecular components comprised of relatively simple and inexpensive building blocks. Furthermore, it is often easier to make the molecular assemblies than it is to make some of the components on their own. The molecular components are encoded in such a way that they hold all of the information necessary for the construction of the precisely assembled structures and superstructures without the need for external reagent control or catalysis. It is becoming increasingly obvious, however, that self-assembly occurs under very precise constitutional and stereochemical control. The viability of self-assembly as a concept for the synthesis of novel molecular architectures on the nanometer-scale is surely vindicated by now. We continue, in our own research laboratory, to be amazed by the extent and efficiency of self-assembly processes in chemical synthesis. There is an enormous potential for the construction of a diverse range of molecular structures and supramolecular architectures. Now that the foundations have been laid, our explorations into just how far structurally we can take the *form* of these systems begins. Furthermore, the addition of photoactive and/or electrochemically-active components could very well open up the means of controlling the *function* of these systems. One of the messages that has been noted throughout this account is that it is often very much easier to make the molecular assemblies than it is to prepare the molecular components on their own. There could hardly be a stronger recommendation for the applicability of self-assembly as a powerful concept and tool in chemical synthesis.

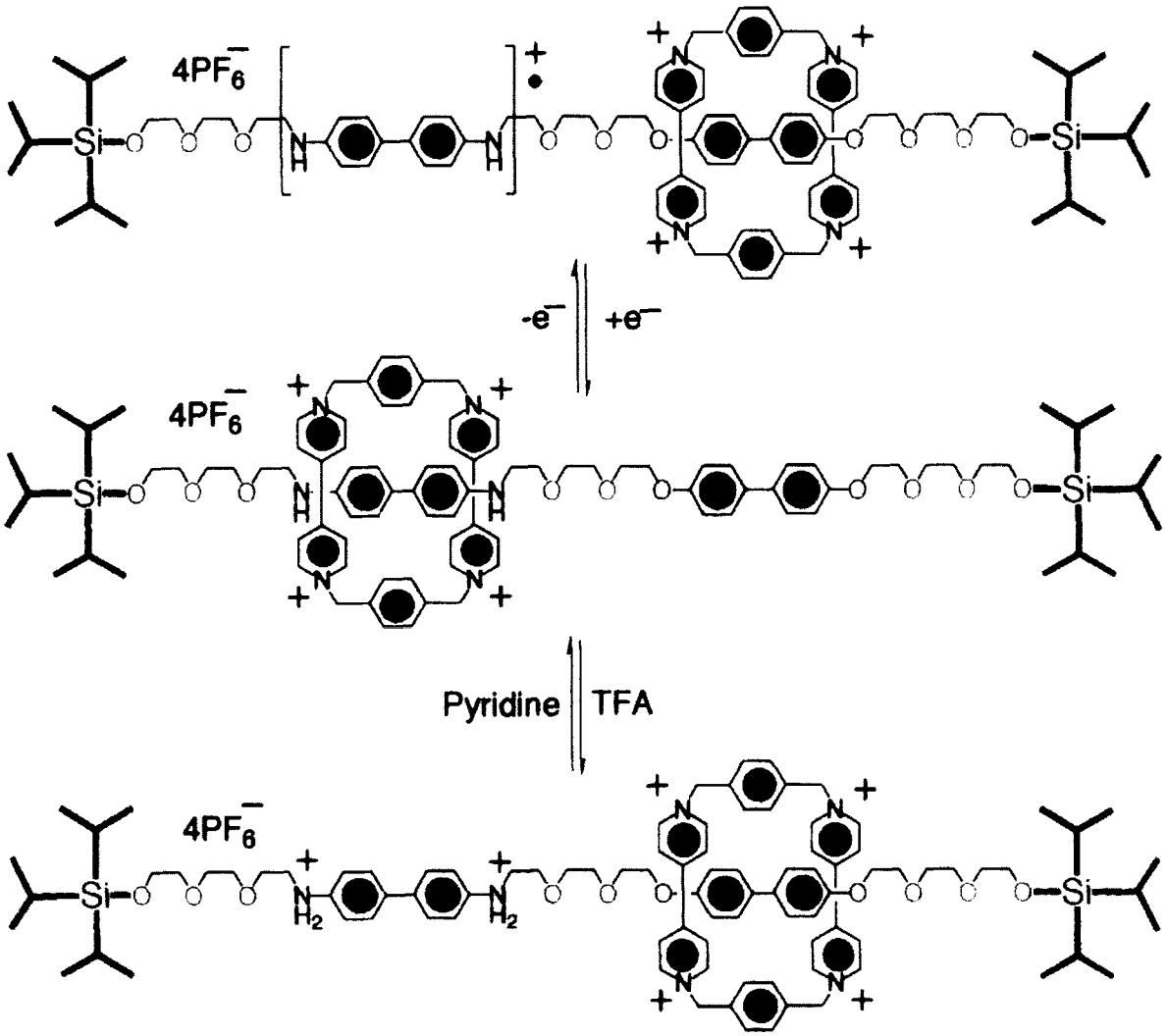


Figure 7 An electrochemically and chemically controlled [2]rotaxane. In each case, control is accomplished either by protonation of the benzidine nitrogen atoms or by oxidation of the benzidine unit.

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