Controlling Self-Assembly**

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Abstract: As a result of cooperative noncovalent bonding interactions (namely, π–π stacking, [CH $\cdots$ O] hydrogen bonding, and [CH $\cdots$ π] interactions) *supramolecular complexes* and mechanically interlocked *molecular compounds*—in particular pseudorotaxanes (precatenanes) and catenanes—self-assemble spontaneously from appropriate complementary components under thermodynamic and kinetic control, respectively. The stereoelectronic information imprinted in the components is crucial in controlling the extent of the formation of the complexes and compounds in the first place; moreover, it has a very significant influence on the relative orientations and motions of the components. In other words, the noncovalent bonding interactions—that is, the driving forces responsible for the self-assembly processes—live on inside the final superstructures and structures, governing both their thermodynamic and kinetic behavior in solution. In an unsymmetrical [2]catenane, for example, changing the constitutions of the aromatic rings or altering the nature of substituents attached to them can drive an equilibrium associated with translational isomerism in the direction of one of two or more possible isomers both in solution and in the solid state. Generally speaking, the slower the components in mechanically interlocked compounds like catenanes and rotaxanes move with respect to each other, the easier it is for them to self-assemble.

Keywords: catenanes · molecular recognition · pseudorotaxanes · supramolecular chemistry · translational isomerism

Introduction

A lot of large and ordered molecular and supramolecular biological systems are constructed from small and simple subunits by means of self-assembly processes.[1–3] Many of the features of self-assembling biological systems are illustrated by the tobacco mosaic virus (TMV).[4] This viral particle is composed of a single strand of RNA (6400 nucleotides) encased in a protein sheath 3000 Å long and 180 Å in diameter. The protein sheath is formed from 2130 identical protein monomers, each containing 158 amino acid residues. A long time ago, it was demonstrated that the TMV can be dissociated into its component parts, and thereafter that the isolated components can be reconstituted in vitro, reforming the intact virus.[5] The assembly of TMV is an example of "strict self-assembly". This term applies to a reversible process producing a final thermodynamically stable product upon combination of the "correct" components, which contain all the necessary stereoelectronic information for their "correct" self-assembly under the appropriate conditions. The reversibility of these processes, which result from the utilization of a range of cooperative noncovalent bonding interactions, drives the self-assembly of the final superstructure (Figure 1) to a thermodynamic minimum. As a result, defective subunits are eliminated from the growing superstructure, ensuring a high degree of control. Furthermore, in some instances, identical repeating subunits are employed in building large superstructures, thus reducing greatly the amount of "genetic" information required to control the self-assembly process. A wide range of artificial systems that self-assemble under

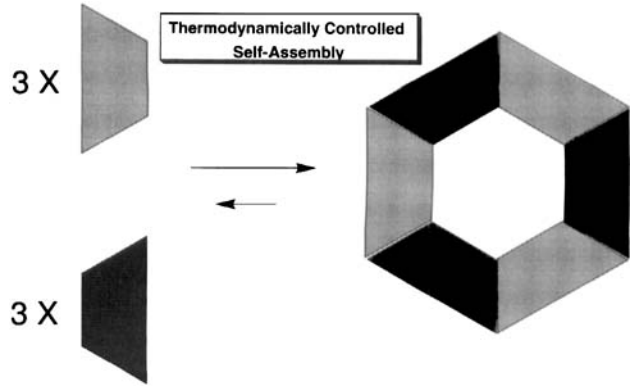

Figure 1. Schematic representation of a self-assembly process occurring under thermodynamic control.

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thermodynamic control as a result of strict self-assembly processes relying upon noncovalent bonding interactions such as hydrogen bonding[6] and metal coordination[7] have been generated.

A second category of self-assembly processes—namely, self-assembly with covalent modification—is observed in naturally occurring systems. This category is normally reserved for self-assembly processes involving the irreversible formation of covalent bonds. Such processes fall into three classes: precursor processing,[8] post-assembly processing,[9] and self-assembly with intermittent processing.[10] All three classes display four common characteristics: a) they are highly convergent; b) stable and structurally diverse superstructures can be synthesized from relatively simple subunits; c) the use of identical subunits keeps the information required to direct the formation of the final superstructure to a minimum; and d) the reversible nature of the self-assembly processes leads to a preferred pathway which is self-checking and self-correcting.

Self-assembly provides an efficient chemical means of creating interlocked structures. Since Pedersen's discovery that crown ethers form complexes with organic as well as metal cations, numerous investigations of the binding of organic guest species with macrocyclic polyethers have been reported.[6b] The complex formed by a macrocyclic component encircling a linear component has been termed a [2]pseudorotaxane, where the number in square brackets corresponds to the total number of components present in the superstructure. The noncovalent bonding interactions which drive the formation of pseudorotaxanes can be employed to synthesize [2]catenanes, where one macrocyclic component acts as the template[11] for the macrocyclization of the other, leading inexorably to the interlocking of the two rings. The self-assembly mechanism that creates these catenanes operates by intermittent processing; that is, a covalent bond is formed, followed by a molecular recognition event before a second covalent bond is formed. The selectivities associated with such a process have been found[12] to be governed not by the thermodynamics of noncovalent bonding interactions but rather by the relative rates of covalent bond formation in the final competing cyclization steps. A fascinating example of kinetic selection operating during the intermittently processed self-assembly of unnatural products can be witnessed in the five-stage two-step template-directed synthesis of a [7]catenane,[13] outlined schematically in Figure 2.

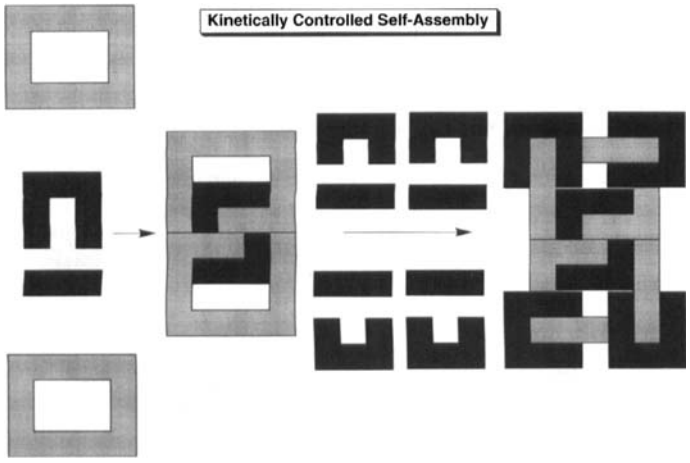

Figure 2. Schematic representation of a two-step self-assembly process occurring under kinetic control and involving the self-assembly of a [3]catenane intermediate, followed by the self-assembly of a [7]catenane.

Discussion

From [2]Pseudorotaxanes to [2]Catenanes: A wide range of synthetic methodologies for the self-assembly of catenanes has been developed in recent years by exploiting different host–guest interactions, for example, the binding of aromatic guests inside the cavities of cyclodextrins,[14] metal coordination,[15] and hydrogen-bonding interactions between amide-containing macrocycles[16] or ammonium ions and crown ethers.[6b] In particular, the recognition between π-electron-deficient and π-electron-rich components has provided the inspiration[17] for the syntheses of a large family of mechanically interlocked compounds.

The bipyridinium herbicide paraquat[18] is capable of forming strong complexes[19] with macrocyclic polyethers incorporating π-electron-rich recognition sites (Figure 3, left). The X-ray crystal structure of the 1:1 complex formed between bis-*p*-phenylene-34-crown-10 and paraquat reveals[19b] a pseudorotaxane-like geometry in which the paraquat dication is threaded through the cavity of the macrocyclic polyether. The complex is stabilized by a) [CH···O] hydrogen-bonding interactions[20] between the hydrogen atoms in the α positions with respect to the nitrogen atoms on the bipyridinium unit and the polyether oxygen atoms, and by b) π–π stacking interactions[21] between the complementary π systems. By reversing the role of the recognition sites, the π-electron-deficient bipyridinium unit can be incorporated into a host capable of binding π-electron-rich guests. Indeed, cyclobis(paraquat-*p*-phenylene) forms[22] a 1:1 complex with 1,4-bis(2-(2-methoxyethoxy)-ethoxy)benzene (Figure 3, right). The X-ray analysis reveals the complex to be stabilized by a) [CH···O] hydrogen bonding interactions between the hydrogen atoms in the α positions with

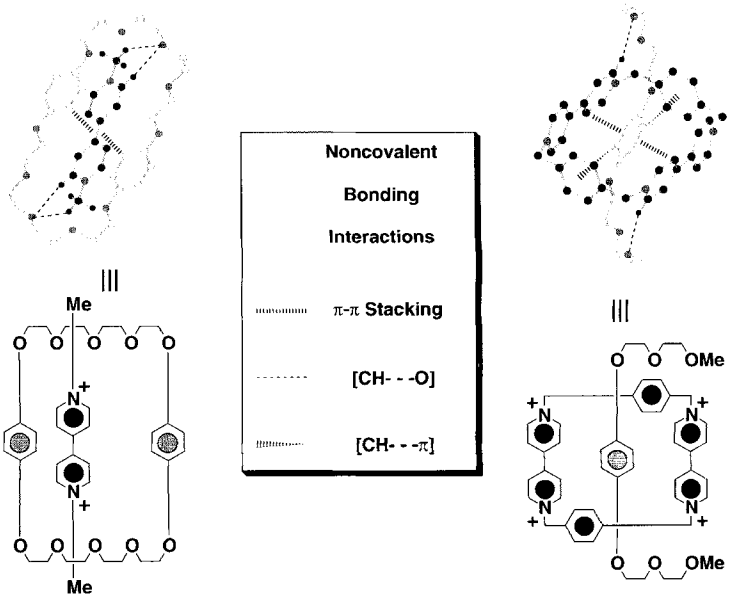

Figure 3. Noncovalent bonding interactions driving the self-assembly of two [2]pseudorotaxanes, as revealed by their single-crystal X-ray analyses.

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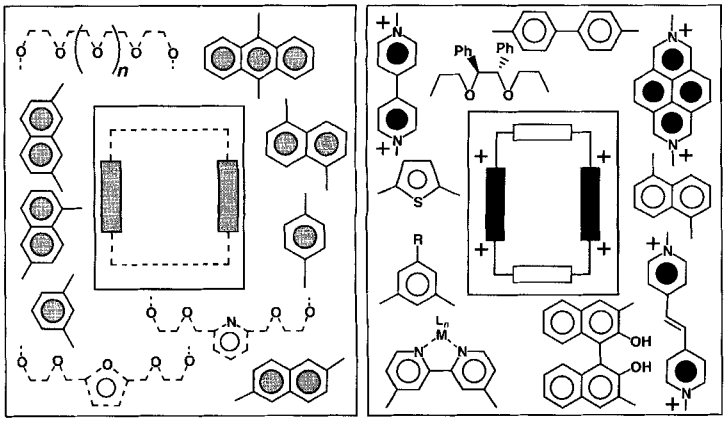

Figure 4. The "molecular meccano" set of building blocks that have been employed as recognition sites and spacers in the π-electron-deficient and π-electron-rich components of pseudorotaxanes and catenanes.

Table 1. Association constants for the 1:1 complexes formed between the tetracationic cyclophane **1**·4PF$_6$ and the 1,4-dioxybenzene-based acyclic guests **2**–**12** in MeCN at 298 K.

Guest	R (R–⟨⟩–R)	K_a [a] M^{-1}	$-\Delta G°$ [c] kcal mol^{-1}	Ref
2	–OH	18	1.7	37b
3	–OMe	17	1.7	37a
4	–O–	28	2.0	37b
5	–O–OH	257	3.3	37b
6	–O–OMe	290	3.4	37b
7	–O–O–OH	2200	4.6	37a
8	–O–O–OMe	3800 [b]	4.9	22
9	–O–O–O–OH	2240	4.6	37a
10	–O–O–O–O–OH	2520	4.6	37a
11	–O–	22	1.8	37b
12	–O–	54	2.4	37b

[a] Determined by spectrophotometric titration at λ_{max} (between 465 and 479 nm) corresponding to the charge-transfer band of the complex. [b] Determined by ^{1}H NMR spectroscopy employing the continuous variation method. [c] Free energy of complexation calculated from the value of K_a.

respect to the nitrogen atoms on the bipyridinium units and the polyether oxygen atoms, b) [CH···π] interactions[23] between the 1,4-dioxybenzene hydrogen atoms and the π-face of the *p*-phenylene spacers in the tetracationic cyclophane, and by c) π–π stacking interactions between the complementary π systems.

A great deal of effort has gone into modifying the macrocyclic polyether and tetracationic cyclophane components of these host–guest systems and the catenanes derived from them. A small selection of the building blocks that make up a so-called "molecular meccano set" is shown in Figure 4. Two variations can be envisaged for the macrocyclic polyether component: modification of the aromatic units or modification of the polyether chains. The 1,4-dioxybenzene rings of bis-*p*-phenylene-34-crown-10 have been replaced with 1,3-dioxybenzene,[24] disubstituted naphthalene[25] and anthracene[26] units, as well as by difluoro- and tetrafluoro-substituted[27] 1,4-dioxybenzene rings. Also furan[28] and pyridine[29] rings have been incorporated symmetrically into the polyether chains. Similarly, the bipyridinium recognition sites or the aromatic spacers of cyclobis(paraquat-*p*-phenylene) can be modified. The bipyridinium units have been replaced by *trans*-1,2-bis(4-pyridinium)ethylene[30] and by 2,7-diazapyrenium units.[31] The *p*-phenylene spacer has been replaced by a *m*-phenylene,[24] a 2,5-disubstituted thiophene ring,[32] a 4,4′-biphenylene unit,[33] an (*S*,*S*)-hydrobenzoin fragment[34], and a metal-coordinated 2,2′-bipyridine ligand system, as well as binaphthol and a 1,5-disubstituted naphthalene ring system.[35] In addition, π-electron-rich and π-electron-deficient recognition sites have been located within the same molecule, creating self-complementary cyclophanes.[36]

[2]Pseudorotaxanes: The bipyridinium-based tetracationic cyclophane **1**·4PF$_6$ binds π-electron-rich guests, such as the 1,4-dioxybenzene-based derivatives listed in Table 1, with pseudorotaxane-like geometries both in solution and in the solid state. The values of the association constants (K_a's) of the corresponding complexes range from 17 to 3800 M^{-1} in MeCN at 25 °C, varying significantly with the nature of the substituents attached to the aromatic ring of the guests. Interestingly, very low association constants were obtained[37] for the compounds **2**–**4** bearing hydroxy or alkoxy substituents. On replacing the terminal methyl groups of **4** with hydroxy and methoxy groups, as in **5** and **6**, respectively, the K_a values of the corresponding complexes increase by approximately one order of magnitude.[37] Further extension of the polyether chains, as in **7** and **8**, results in an increase in the K_a values by approximately one order of magnitude more.[22, 37] By contrast, only a small increase in the K_a values is observed[37] upon addition of one and two more bismethyleneoxy units, as in **9** and **10**, respectively. These observations suggest that the [CH···O] interactions between the polyether oxygen atoms and the hydrogen atoms located in the α-positions with respect to the nitrogen atoms on the bipyridinium units, which are observed[22] (Figure 3, right) in the solid state, are maintained in solution and are responsible for the large differences in the K_a values. Furthermore, the largest contribution to the attractive [CH···O] interactions arises from the second and third oxygen atoms (counting away from the aromatic unit) along the polyether chains, while the effect of the addition of a fourth and a fifth oxygen atom in **9** and **10**, respectively, on the K_a values is significantly less pronounced. Consistently, removal of the second and third oxygen atoms from the substituent chains of **11** results[37] in a dramatic decrease of the association constant. Interestingly, when only the second oxygen atom is removed from the substituent chains of **12**, a very low value of K_a is measured,[37] suggesting that the third oxygen atom needs the second one to approach the bipyridinium units; that is, wrapping of the polyether chains around the bipyridinium units is driven by allosteric effects associated with the helicity of these chains.

In order to assess the effect on the molecular recognition event of the nature and substitution pattern of the aromatic unit incorporated within the guest, the K_a values measured in MeCN at 25 °C for the complexation (Table 2 and Figure 5) of the acyclic polyethers **7** and **13**–**18** by the tetracationic cyclophane **1**·4PF$_6$ were compared. The 1,4-dioxybenzene-based compound **7** is strongly bound[37] (K_a = 2200 M^{-1}) by the tetracationic cyclophane **1**·4PF$_6$. Introducing two fluorine substituents in the aromatic unit of the guest, as in the compound **13**, results in a decrease[27] in the association constant of the

Table 2. Association constants for the 1:1 complexes formed between the tetracationic cyclophane **1**·4PF$_6$ and the acyclic guests **7** and **13**–**18** in MeCN at 298 K.

Guest	K_a [a] (M^{-1})	$-\Delta G^\circ$ (kcal mol^{-1})	Ref.
7	2200	4.6	37a
13	15	1.7	27
14	0	0	27
15	> 5000 [b]	> 5	25
16	378	3.5	25
17	177	3.1	25
18	221	3.2	25

[a] Determined by ^{1}H NMR spectroscopy employing the continuous variation method. [b] A value of 21 000 M^{-1} was obtained by ^{1}H NMR spectroscopic single-point determination in CD_3CN at 298 K for the complexation of a guest analogous to **15** but incorporating *p*-*t*-butylphenoxy groups in place of the hydroxy groups.

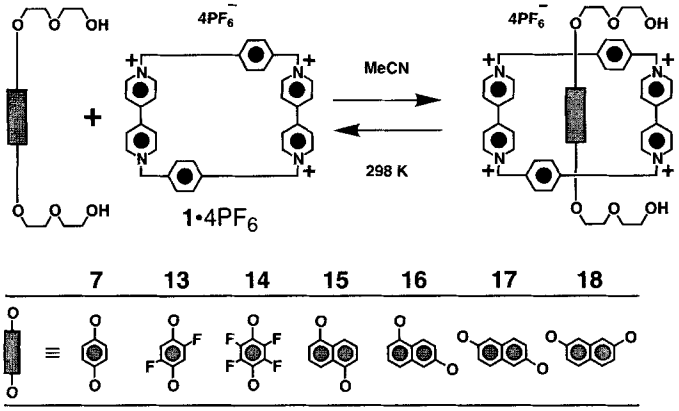

Figure 5. Complexation of the π-electron-rich acyclic polyethers **7** and **13**–**18** by the tetracationic cyclophane **1**·4PF$_6$.

Table 3. Association constants for the 1:1 complexes formed between the bis(hexafluorophosphate) salt **19**·2PF$_6$ and the macrocyclic polyethers **20**–**26** in MeCN at 298 K.

Macrocyclic polyether	K_a [a] (M^{-1})	$-\Delta G^\circ$ (kcal mol^{-1})	Ref.
20	240 [b]	3.2	31
21	[c]	–	27
22	0	0	27
23	1190	4.2	25
24	472	3.6	25
25	[c]	–	25
26	970	4.1	25

[a] Determined by UV/Vis spectroscopy employing the titration method. [b] Determined by ^{1}H NMR spectroscopy in CD_3CN at 300 K. An association constant of 730 M^{-1} was measured in Me_2CO at 298 K by UV/Vis spectroscopy. [c] The K_a value was not determined because of the low solubility of the macrocyclic polyether in MeCN.

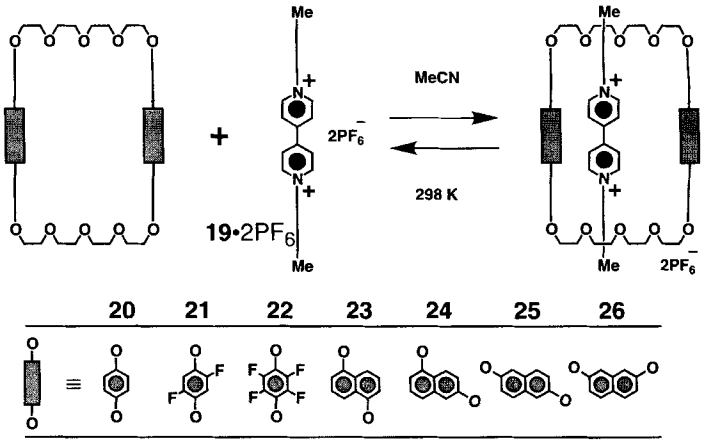

Figure 6. Complexation of the bis(hexafluorophosphate) salt **19**·2PF$_6$ by the π-electron-rich macrocyclic polyethers **20**–**26**.

corresponding complex by approximately two orders of magnitude. This "damping" effect upon the K_a value is a result of a) the electron-withdrawing effect of the fluorine atoms on the aromatic ring, as well as of b) stereoelectronic effects that force the guest **13** into a conformation unfavorable for its complexation by the tetracationic cyclophane **1**·4PF$_6$. Further introduction of two more fluorine atoms in **14** results[27] in no complex formation at all. These observations suggest that the π–π stacking interactions between the complementary aromatic units of the host and the guest are affected dramatically by the stereoelectronic nature of the substituents associated with the aromatic ring of the guest. By employing the 1,5-dioxynaphthalene-based acyclic polyether **15**, which possesses a larger π surface, a stronger complex ($K_a > 5000\,M^{-1}$) is formed.[25] By contrast, when the 1,6-, the 2,6-, and the 2,7-dioxynaphthalene-based guests are employed,[25] the K_a values are significantly lower ($K_a \leq 378\,M^{-1}$). Presumably, varying the substitution pattern alters the charge distribution on the dioxynaphthalene ring system, thus affecting the π–π stacking interactions between the complementary aromatic unit of the host and the guest and sterically disfavoring the [CH···O] interactions between the polyether oxygen atoms and the bipyridinium protons.

Similar effects have been observed for the binding of the paraquat bis(hexafluorophosphate) salt **19**·2PF$_6$ by a series of macrocyclic polyethers (Table 3 and Figure 6). The π-electron-rich macrocyclic polyether **20** binds **19**·2PF$_6$ with pseudorotaxane-like geometries both in solution and in the solid state[19] ($K_a = 240\,M^{-1}$ in MeCN at 25 °C). Decreasing the electron densities of the two aromatic units incorporated within the macrocyclic polyether by introducing four fluorine atoms as substituents on each ring results in a reduction in the strength of the molecular recognition. Indeed, no complex formation was detected at all between **22** and **19**·2PF$_6$, either by ^{1}H NMR or by absorption UV/Vis spectroscopies.[27] By contrast, when the macrocyclic polyether **23**, incorporating 1,5-dioxynaphthalene ring systems, was employed as the host, a K_a value approximately one order of magnitude higher was obtained ($K_a = 1190\,M^{-1}$ in MeCN at 25 °C).[25] However, once more, varying the substitution pattern on the dioxynaphthalene units results in a decrease in the K_a values to 472 and 970 M^{-1} (MeCN at 25 °C) for **24** and **26**, respectively.[25]

[2]Catenanes and [2]Rotaxanes: The [2]catenanes **34**·4PF$_6$–**43**·4PF$_6$ can be self-assembled[25, 27, 37a, 38] according to the synthetic route depicted in Figure 7. Reaction of the bis(hexafluorophosphate) salt **44**·2PF$_6$ with 1,4-bis(bromomethyl)-benzene **45** gives a tricationic intermediate which is bound by the preformed macrocyclic polyether—that is, the three components **44**·2PF$_6$, **45**, and the macrocyclic polyether self-assemble into an intermediate supramolecular complex. This intermediate complex is perfectly set up to undergo a second ring-closing reaction to afford the corresponding [2]catenane, that is, the

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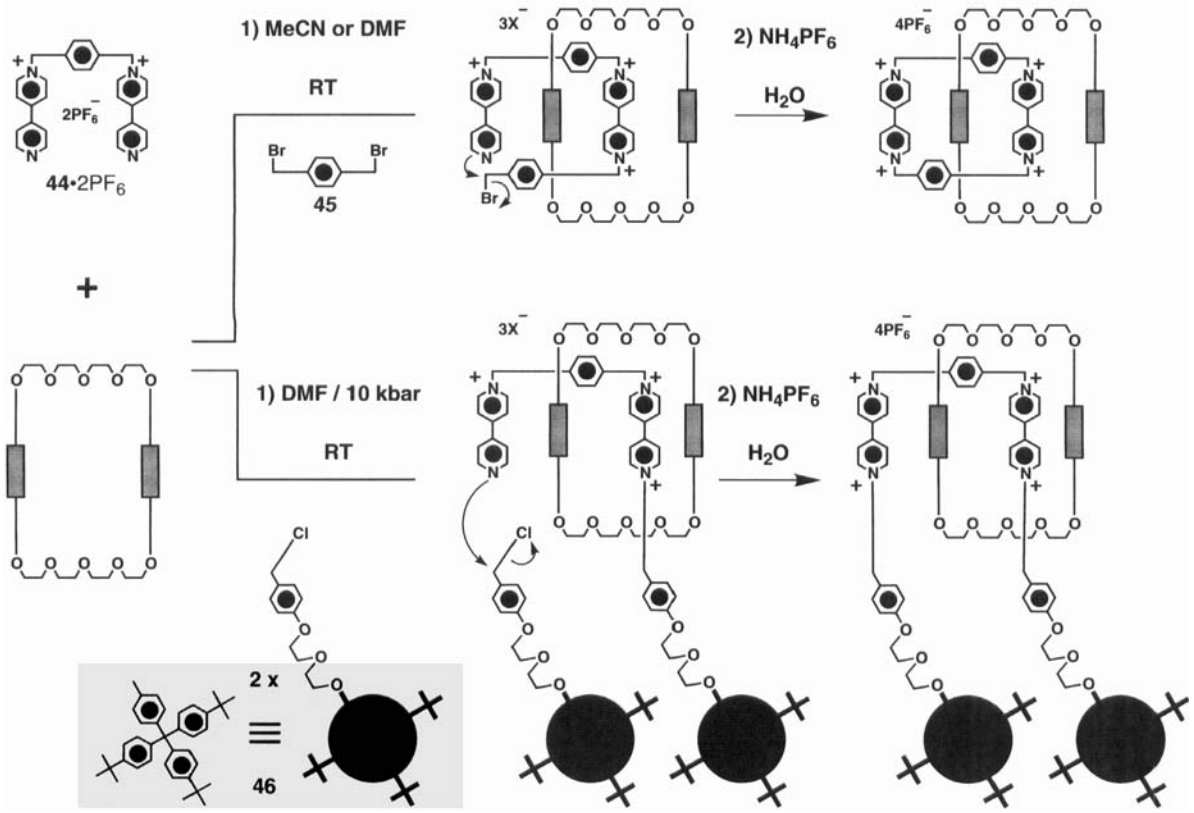

Figure 7. Kinetically controlled self-assembly of [2]catenanes (top) and of [2]rotaxanes incorporating complementary π-electron-rich and π-electron-deficient components.

self-assembled supramolecular intermediate is converted irreversibly into the final molecular compound as a result of the kinetically controlled formation of a "mechanical bond". This overall kinetically controlled self-assembly process can be extended to the synthesis of other mechanically interlocked compounds—namely, rotaxanes.[39] Thus, reaction of the bis(hexafluorophosphate) salt **44**·2PF$_6$ with the bulky tetraarylmethane-based chloride **46** again gives a tricationic intermediate that is immediately recognized and bound by the macrocyclic polyether. The self-assembled supramolecular complex is then converted into a kinetically stable molecular structure—specifically, a [2]rotaxane—after the irreversible formation of a second covalent bond.

Table 4. Yields of catenations and free energy barriers for the dynamic processes associated with the [2]catenanes **27**·4PF$_6$–**33**·4PF$_6$.

[2]Catenane	Yield [a] (%)	Process I		Process II		Ref.
		$-\Delta G_c^{\ddagger}$ (kcal mol^{-1})	T_c (K)	$-\Delta G_c^{\ddagger}$ (kcal mol^{-1})	T_c (K)	
27·4PF$_6$	70 [b]	15.6 [e]	354	12.2 [f]	247	37a
28·4PF$_6$	3 [b]	12.4 [f]	279	11.6 [f]	240	27
29·4PF$_6$	0	–	–	–	–	27
30·4PF$_6$	51 [c]	17.2 [e]	361	12.7 [e]	257	25
31·4PF$_6$	35 [c]	13.5 [e]	278	9.8 [e]	208	25
32·4PF$_6$	0 [d]	14.4 [e]	305	11.4 [e]	226	25
33·4PF$_6$	0 [d]	13.9 [f]	302	8.9 [f]	182	25

[a] *Yield of the [2]catenane after column chromatography and counterion exchange.* [b] Reaction performed employing an excess (2.5 equiv) of the macrocyclic polyether with respect to the bis(hexafluorophosphate) salt **44**·2PF$_6$ in MeCN for **27**·4PF$_6$ and in DMF for **28**·4PF$_6$ at ambient temperature and pressure. [c] Reaction performed employing an excess (6.0 equiv) of the bis(hexafluorophosphate) salt **44**·2PF$_6$ with respect to the macrocyclic polyether in DMF at ambient temperature and pressure. [d] No catenated products were obtained at ambient pressure and so ultrahigh pressure (12 kbar) was employed to obtain the [2]catenane. [e] In CD_3CN. [f] In CD_3COCD_3.

The yields of the catenations after counterion exchange range from 3 to 89% (Tables 4 and 5). This range is a semiquantitative measure of the efficiency of the molecular recognition event. Thus, for example, when the macrocyclic polyether **22** incorporating 1,4-dioxytetrafluorobenzene rings is employed, no catenane is detected.[27] This result is consistent with the observations that a) the same macrocycle **22** does not bind the bipyridinium-based guest **19**·2PF$_6$ (Table 3), and b) the tetracationic cyclophane **1**·4PF$_6$ does not bind the 1,4-dioxytetrafluorobenzene-based guest **14** (Table 2). By contrast, when the macrocyclic polyether **20** incorporating two 1,4-dioxybenzene rings is employed, the corresponding [2]catenane **27**·4PF$_6$ is obtained in a yield as high as 70%.[37] This result is consistent a) with the ability of this same macrocycle **20** to bind the bipyridinium-based guest **19**·2PF$_6$ (Table 3) and b) with the high association constant measured (Table 2) for the complexation of the 1,4-dioxybenzene-based guest **8** by the tetracationic cyclophane **1**·4PF$_6$.

The dynamic processes illustrated in Figure 8 characterize the [2]catenanes in solution. Process I involves the circumrotation of the macrocyclic polyether through the cavity of tetracationic cylophane component: it exchanges the "inside" and "alongside" aromatic units incorporated within the π-electron-

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Table 5. Yields of catenation reactions and ratios between the translational isomers associated with the [2]catenanes **34**·4PF$_6$–**43**·4PF$_6$.

[2]Catenane	Yield [a] (%)	**A**:**B** [b]	K_{eq} [c]	$-\Delta G_c^{\neq}$ (kcal mol^{-1})	Ref.
34·4PF$_6$	57 [d]	>95:<5	>19	>1.7	27
35·4PF$_6$	60 [d]	≈100:0		–	27
36·4PF$_6$	50 [e]	65:35 [f]	1.9	0.4	38
		35:65 [g]	0.5	−0.4	
37·4PF$_6$	82	≈100:0	–	–	25
38·4PF$_6$	89	≈100:0	–	–	25
39·4PF$_6$	74	≈100:0	–	–	25
40·4PF$_6$	74	≈100:0	–	–	25
41·4PF$_6$	25	≈100:0	–		25
42·4PF$_6$	84	≈100:0	–		25
43·4PF$_6$	25	≈100:0	–	–	25

[a] Yield of the [2]catenane after column chromatography and counterion exchange. The reactions were performed employing an excess (2.0 molar equivalents) of the bis(hexafluorophosphate) salt **44**·2PF$_6$ with respect to the macrocyclic polyether in DMF at ambient temperature and pressure. [b] Ratio of translational isomer **A** to translational isomer **B** (Figure 6) both above (CD_3CN) and below (CD_3COCD_3) room temperature. [c] K_{eq} = [A]/[B]. [d] Reaction performed employing an excess (2.5 equiv) of the macrocyclic polyether with respect to the bis(hexafluorophosphate) salt **44**·2PF$_6$ in DMF for **34**·4PF$_6$ and in MeCN for **35**·4PF$_6$ at ambient temperature and pressure. [e] Reaction performed employing an excess (1.1 equiv) of the macrocyclic polyether with respect to the bis(hexafluorophosphate) salt **44**·2PF$_6$ in MeCN at ambient temperature and pressure. [f] In CD_3COCD_3 at 243 K. [g] In CD_3SOCD_3 at 243 K.

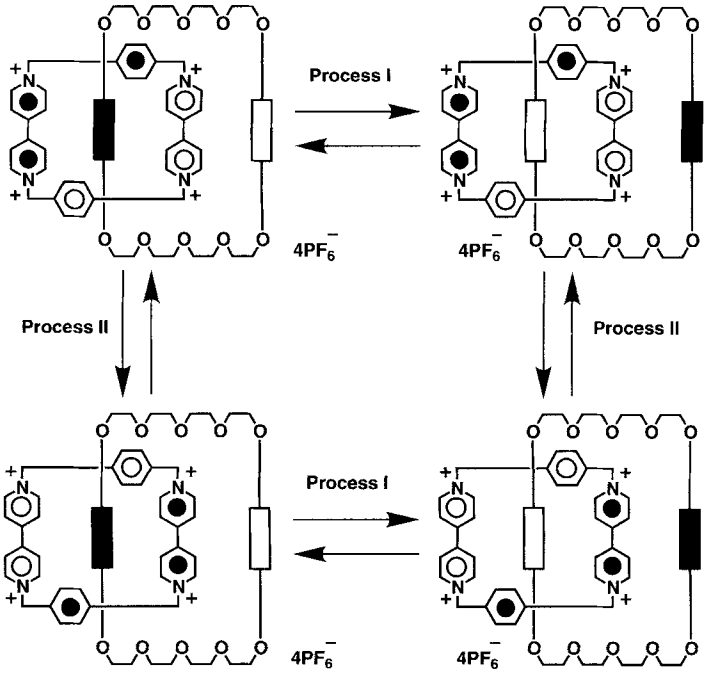

Figure 8. Dynamic processes associated with the [2]catenanes in solution.

rich macrocyclic component. Process II involves the circumrotation of the tetracationic cyclophane through the cavity of the macrocyclic polyether component: it exchanges the "inside" and "alongside" bipyridinium units. In the case of the [2]catenanes **27**·4PF$_6$–**33**·4PF$_6$, which incorporate symmetrical macrocyclic polyether components, the free energy barriers associated with the dynamic processes have been determined by variable temperature ^{1}H NMR spectroscopy (Table 4).[25, 27, 37a] Interestingly, significant differences in the values of the coalescence temperatures and of the corresponding free energy barriers were observed, suggesting that varying the nature and the substitution pattern of one and/or both of the dioxyarene units incorporated within the macrocyclic polyether components affects significantly the dynamic properties of the [2]catenanes in solution.

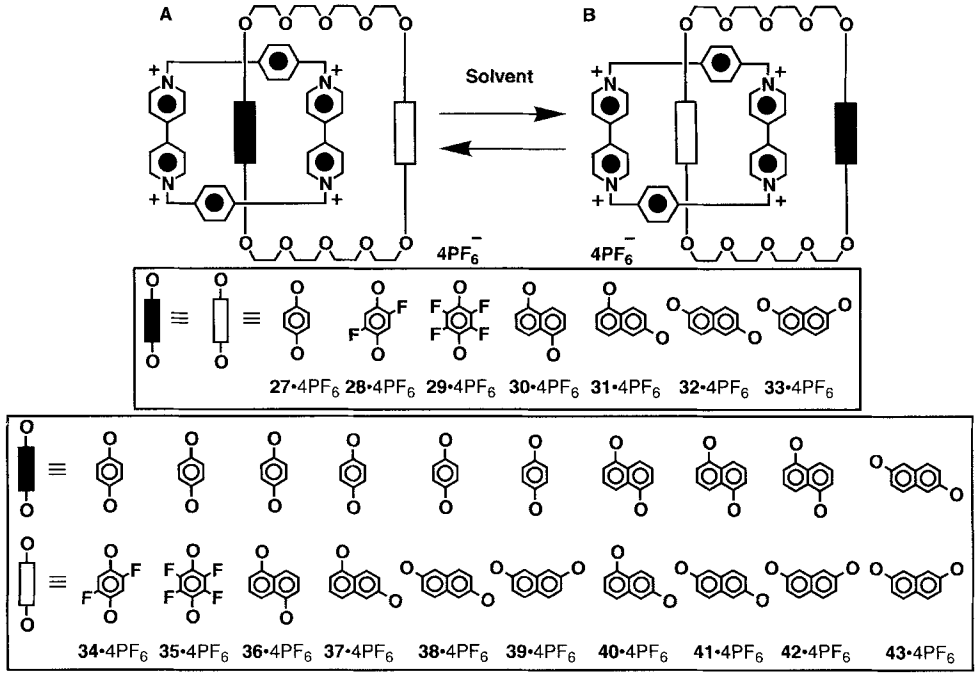

Figure 9. Translational isomers **A** and **B** associated with the [2]catenanes **27**·4PF$_6$–**43**·4PF$_6$.

In the case of the [2]catenanes **34**·4PF$_6$–**43**·4PF$_6$ incorporating unsymmetrical macrocyclic polyether components, the two translational isomers **A** and **B** (Figure 9) are different. In solution, the ratios between the translational isomers **A** and **B** (Table 5) range from 100:0 to 35:65, while, in the solid state, only one of the expected two translational isomers has been observed in all cases where single-crystal X-ray analyses have been performed.[25, 27] Furthermore, the major isomer observed in solution is always the one which is present exclusively in the solid state, translational isomer **A**. Interestingly, with the exception of the [2]catenanes **36**·4PF$_6$ and **43**·4PF$_6$, the selectivity observed for the translational isomerism can be related back to the association constant measured for the binding of the acyclic polyethers **7** and **13**–**18** (Table 2 and Figure 5) by the tetracationic cyclophane **1**·4PF$_6$. As an example, the more abundant translational isomer **A** of the [2]catenane **34**·4PF$_6$ is the one bearing the 1,4-dioxybenzene ring "inside" and the 2,5-difluoro-1,4-dioxybenzene unit "alongside" the cavity of the tetracationic cyclophane.[27] Thus, it is not surprising that the K_a value associated with the binding of the 1,4-dioxybenzene-based guest

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7 by the tetracationic cyclophane **1**·4PF_6 is approximately two orders of magnitude higher than that measured for the 2,5-difluoro-1,4-dioxybenzene-based guest. Interestingly, the [2]catenane **36**·4PF_6 shows[38] solvent dependence of the equilibrium ratio between the two translational isomers. By increasing the dielectric constant of the medium, the inclusion of the 1,5-dioxynaphthalene ring system inside the cavity of the tetracationic cyclophane is favored with respect to the inclusion of the 1,4-dioxybenzene ring. As a result, the ratio between the translational isomers **A** and **B** can be inverted by the use of CD_3SOCD_3 instead of CD_3COCD_3. Hence, the [2]catenane **36**·4PF_6 can be regarded as a chemically controllable molecular switch. In the case of the [2]catenane **43**·4PF_6, the ratio between the translational isomers is 100:0 in favor of the translational isomer **A**, which incorporates the 2,6-dioxynaphthalene ring system inside the cavity of the tetracationic cyclophane component. This result apparently contrasts with the values of the association constant measured for the binding of the acyclic polyethers **17** and **18** incorporating 2,6- and 2,7-dioxynaphthalene ring systems, respectively, by the tetracationic cyclophane **1**·4PF_6 (Table 2). Presumably, the selectivity observed for the translational isomerism associated with the [2]catenane **43**·4PF_6 is a result of steric effects which govern the conformation of the polyether chains in such a way as to favor the exclusive location of the 2,6-dioxynaphthalene ring system inside the cavity of the tetracationic cyclophane component.

Reflections: The *self-assembly* of pseudorotaxanes (precatenanes) and catenanes incorporating bipyridinium-based polycationic and dioxyarene-based polyether components relies upon *a series of cooperative noncovalent bonding interactions*—namely, a) $\pi-\pi$ stacking between the π-electron-rich and the π-electron-deficient complementary aromatic units, b) [CH···O] hydrogen bonding between the polyether oxygen atoms and the bipyridinium hydrogen atoms, and c) [CH···π] interactions between the dioxyarene hydrogen atoms and the π surfaces of suitably located *p*-phenylene spacers.

Furthermore, *the noncovalent bonding interactions which drive the self-assembly processes are maintained in the final self-assembled structures and superstructures*, thus controlling their dynamic processes in solution—namely, the relative motions of the interlocked components—as well as their solid-state geometries. As a result, *the stereoelectronic information imprinted in the free modular components is responsible for* a) *the efficiencies of the self-assembly processes* (reflected in the association constants for pseudorotaxane formations and in the yields associated with the catenations) and b) *the structural features of the final molecular assemblies* (namely, the selectivities associated with translational isomerism observed in [2]catenanes incorporating unsymmetrical macrocyclic polyether components).

Subtle chemical modification of the stereoelectronic properties of the simple separate components, which can be achieved by design and synthesis, *may dramatically affect the strengths of the noncovalent bonding interactions* and, as a result, *the efficiencies of the self-assembly processes and the structural properties of the final interlocked molecular compounds*. In particular, *the $\pi-\pi$ stacking interactions can be weakened by reducing the electron density on the dioxyarene recognition sites* (e.g., by introducing fluorine atoms instead of hydrogen atoms) or *strengthened by increasing the degree of π overlap* (e.g., by employing the larger naphthalene instead of benzene rings). Similarly, the strength and cooperativity of the [CH···O] hydrogen-bonding interactions can be varied by changing the number and dispositions of the oxygen atoms along the two polyether chains attached to the dioxyarene recognition sites.

In conclusion: a) *the association constants and the yields associated with the self-assembly processes leading to [2]pseudorotaxanes and [2]catenanes*, b) *the rates of the dynamic processes involving the relative motions of the macrocyclic components of [2]catenanes*, and c) *the equilibrium ratios between the two translational isomers associated with [2]catenanes incorporating unsymmetrical macrocyclic polyether components can all be finely tuned by introducing subtle stereoelectronic perturbations into the π-electron-rich and/or the π-electron-deficient parts*. Since the nature of the mechanical bond is so strong yet so weak, it can be harnessed to remarkable effect in the production of molecular switches and machines.[40, 41]

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[41] **Note added in proof:** In a very recent *Note* in the *Journal of Organic Chemistry* (ref. [42]), the groups of Ercolani and Mencarelli in Rome have managed to isolate and characterize the tricationic intermediate—as its tris(hexafluorophosphate) salt—proposed in the template-directed reaction scheme for the formation of the [2]catenanes described in Figure 7. The availability of this key intermediate about a decade after it was first proposed by us [43] should, to quote the Italian authors, "open up new fronts regarding the study of template effects in the formation of more exotic systems such as the rotaxanes and catenanes already synthesized by Stoddart and coworkers". This is a statement with which we can empathize! For the present, the reader is advised to read the Note by the Rome groups on a quantitative evaluation of the template effect in the formation of cyclobis(paraquat-*p*-phenylene).
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