Cyclodextrin-Based Catenanes and Rotaxanes†

Sergey A. Nepogodiev

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K.

J. Fraser Stoddart*

Department of Chemistry and Biochemistry, University of California at Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095-1569

Received November 19, 1997 (Revised Manuscript Received March 16, 1998)

Contents

I. Introduction

On account of their origins and structures, cyclodextrins (**CD**s) can be recognized immediately as carbohydrates. However, their impact[1] on the scientific community over more than a century now has been very much broader than might be implied by their mere membership of a rich class of natural products. Indeed, this unique family of cyclic oligosaccharides has been appreciated far beyond the boundaries of carbohydrate science. They are considered, with much scientific justification and with an impressive historical tradition behind them, to be one of the most important host compounds that nowadays fall under the general umbrella of supramolecular chemistry.[2] And so, in the recently published Comprehensive Supramolecular Chemistry series,[3] **CD**s merited an entire volume to themselves. The well-documented ability of the parent **CD**s to form inclusion complexes[4] with a very wide range of guest species in aqueous solutions has been exploited by many academic researchers and commercial organizations over the last half-century in particular. Moreover, **CD**s have been subjected to a large num-

† A list of the abbreviations used for cyclodextrins and their derivatives appearing in this review is given in ref 91.

Sergey A. Nepogodiev was born in the Moscow region of Russia in 1960. He graduated from the Moscow State University with an M.Sc. Degree in Chemistry in 1982 and joined the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences in Moscow where he continued to pursue research for the next 10 years. Dr. Nepogodiev received his Ph.D. in Organic Chemistry from this Institute in 1987. His research in the field of carbohydrate chemistry was associated with oligosaccharide synthesis and chemical synthesis of natural polysaccharides. In 1994, he joined the research group of Professor J. Fraser Stoddart at the University of Birmingham in the United Kingdom where he has played a key role in the development of new synthetic approaches to cyclic oligosaccharides and carbohydrate dendrimers.

J. Fraser Stoddart was born in Edinburgh, Scotland, in 1942. He received all of his degrees from the University of Edinburgh (B.Sc., 1964; Ph.D., 1966; D.Sc., 1980). After a seven year spell as the Professor of Organic Chemistry at the University of Birmingham in England, Professor Stoddart moved in 1997 to the Saul Winstein Chair of Organic Chemistry at UCLA. His current research interests are concerned with transporting well-established biological principles, such as self-assembly, from the life sciences into chemistry—with one aim being to produce molecules with devicelike characteristics. Carbohydrates, particularly cyclic oligosaccharides, have often provided building blocks for the construction of molecular receptors and machines throughout his research career.

S0009-2665(97)00049-6 CCC: $30.00
Published on Web 06/09/1998

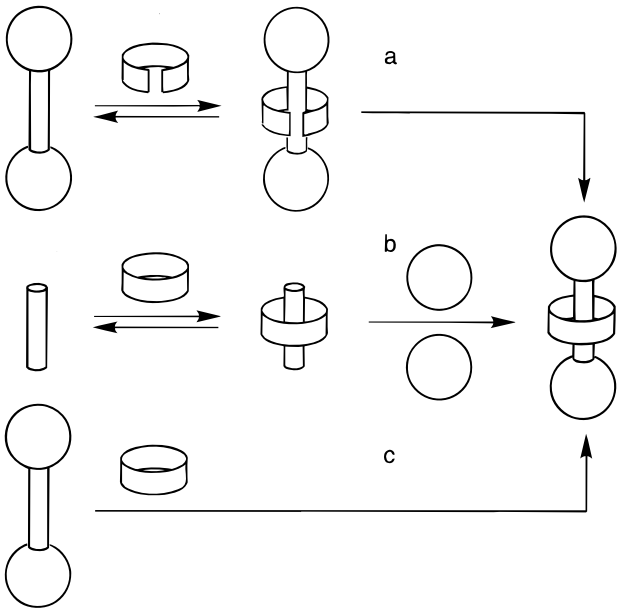


Figure 1. Three different approaches to the construction of rotaxanes: (a) "clipping"; (b) "threading"; (c) "slippage".

ber of chemical and enzymatic modifications[5] which have broadened greatly their influence upon the rapidly growing field of supramolecular chemistry.

In this review, we will summarize the research which has been carried out in recent times on mechanically interlocked compounds—namely, rotaxanes and catenanes[6]—that incorporate **CD**s as one of their (ring) components. This research represents only a small part of the intensive activity directed toward the creation of novel molecular materials,[7] based on rotaxanes and catenanes[8] during the 90s. Although the general topic has been reviewed in the literature[7,8] in the past few years, apart from some very short surveys,[9,10] no particular emphasis has been given to research carried out on **CD**-containing compounds. This article covers the literature known to us that deals with the preparation and characterization of **CD**-based catenanes and rotaxanes. Pseudorotaxanes[7,8] and polyrotaxanes incorporating **CD**s as their ring components have also been considered to lie within the scope of this review.

II. Self-Assembly of Rotaxanes Incorporating Cyclodextrins in Aqueous Solutions

At least three different mechanisms (Figure 1) for the construction of rotaxanes can be identified.[8] Although the "clipping" approach (a) is not applicable in an obviously efficient way to the self-assembly of **CD**-containing rotaxanes, both the "threading" (b) approach and "slippage" (c) approach appear to provide possible mechanisms,[11] particularly since the **CD**s possess remarkable abilities to form inclusion complexes[4] with a very wide range of guest molecules in aqueous media. The different cavity sizes of the **CD**s (ca. 5.7, 7.8, and 9.5 Å for α-**CD**, *β*-**CD**, and *γ*-**CD**, respectively) assist in this broad spectrum of guest molecular recognition. However, there are quite severe limitations that render the productions of **CD**-containing rotaxanes a rather challenging task. One is the necessity of having to carry out the self-assembly and subsequent covalent modifications in aqueous media—the environment which is by far the best when contemplating the binding of guest molecules by **CD**s. This requirement restricts considerably the scope of the chemical reactions which may be used for self-assembling rotaxanes employing the popular "threading" strategy wherein bulky "stoppers" are attached to both ends of the guests threaded through the cavities of the **CD** rings. Problems associated with the solubilities of "stoppered" components or of "half-stoppered" guest molecules in water, as well as the possibility of competition for the **CD** cavities by structural fragments of the "stoppered" molecules, have to be anticipated, and if they occur, they have to be solved.

A. Cyclodextrin-Based Pseudorotaxanes

Pseudorotaxanes are formed when threadlike molecules penetrate the cavities of cyclic molecules, forming stable complexes. Since **CD**s have cavities with depths of around 5 Å, they can be occupied rather easily by fragments of long-chain molecules. Complexes of aliphatic amphiphiles, in which the tails are believed to reside inside the cavities of **CD**s, have been claimed for a long time. Alas, the stabilities of these complexes are not high and so the characterization of pseudorotaxanes is a difficult task. Matsuo et al.[12,13] have shown that it is necessary to locate charged centers at both ends of the aliphatic chains in order to achieve sufficient dynamic stability to be able to distinguish between pseudorotaxanes and their free components. The lifetimes of the complexed species **1** and **2**, shown in Figure 2, are long enough for them to be detected separately from their uncomplexed components on the ^{1}H NMR time scale. The slow dissociation—as well as association—in these cases has been attributed to the relatively high barriers to penetration which result from increased interactions between α-**CD** and the hydrated charged "stoppers" which must have to undergo considerable dehydration prior to threading and unthreading. The thermodynamic stabilities of these pseudorotaxanes are also considerable, and their strengths increase with the chain lengths of the spacer units (Table 1). When the chain lengths are less than eight methylene groups, the charged "stoppers" are forced to enter the more hydrophobic **CD** interiors, destabilizing the pseudorotaxanes.

A similar kind of behavior has beem found[14−16] for pseudorotaxanes composed of α-**CD** and long-chain aliphatic compounds **3**−**5**, bearing a viologen unit at one of their termini and a bulky aromatic "stopper" at the other end (Figure 3). As before, eight methylene groups constitute the minimum length of spacer needed for the formation of pseudorotaxanes where complexation/decomplexation is slow on the ^{1}H NMR time scale in D_2O solution, at least for α-**CD** and *β*-**CD**. The encircling of the polymethylene spacers by the **CD** torus has been confirmed by NMR spectroscopy in D_2O as a result of COSY and NOE experiments. Dynamic NMR and UV/vis (which probes the ability of α-**CD** to inhibit the charge-transfer absorption bands between the aromatic

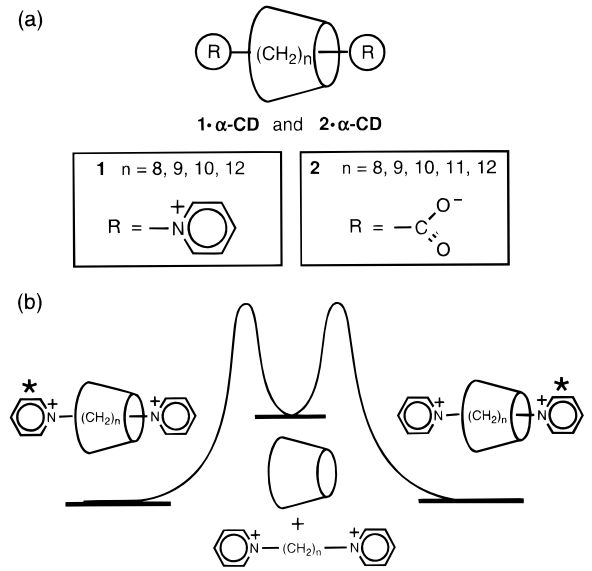
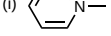
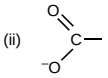


Figure 2. (a) Pseudorotaxanes built up from α-**CD** and linear guests in the form of oligomethylene chains as binding sites. (b) Schematic representation of the energy profile for the complexation/decomplexation process for **1**·α-**CD** as it relates to the NMR site exchange process observed for the "symmetrical" guest bound within the cavity of the "unsymmetrical" α-**CD** ring. Dynamic NMR spectroscopic studies in D_2O solutions that were 10 mM in the guest and 100 mM in the host revealed that the free energy of activation for the site exchange process increases with the number (n) of CH_2 groups (n = 8−12) and reaches an asymptotic value at ca. 17.2 kcal mol^{-1}.

Table 1. Stability Constants (K_a) for Pseudorotaxanes Formed between α-CD and (i) Polymethylene-bis(1-pyridinium) Dibromide and (ii) α,ω-Alkanedicarboxylates under Basic Conditions Determined by ^{1}H NMR Spectroscopy in D_2O at +5 °C[a]

terminal groups	K_a (M^{-1}) according to no. of CH_2 groups in the polymethylene spacer				
	8	9	10	11	12
(i) 	110	640	2200		4800
(ii) 	310	630	1400	1500	5400

[a] Data are taken from refs 12 and 13.

"stoppers" and the viologen units present in the free guests) spectroscopies have been used (Figure 3) to establish that it is the viologen unit that must first of all enter the cavity of the α-**CD** ring in order to achieve complexation: the relatively large activation barriers associated with the complexation/decomplexation processes were ascribed to dehydration of the viologen units prior to their passage through the α-**CD** cavity. Although the same kinds of "stable" pseudorotaxanes were formed with β-**CD**, compounds **3**−**5** do not form such stable complexes with γ-**CD**; moreover, these latter complexes undergo fast complexation/decomplexation on the ^{1}H NMR time scale in D_2O at room temperature.

Recently, Kaifer and Mirzoian[17] have investigated (Figure 4) the complexation in aqueous solutions of a series of viologen derivatives with both β-**CD** and

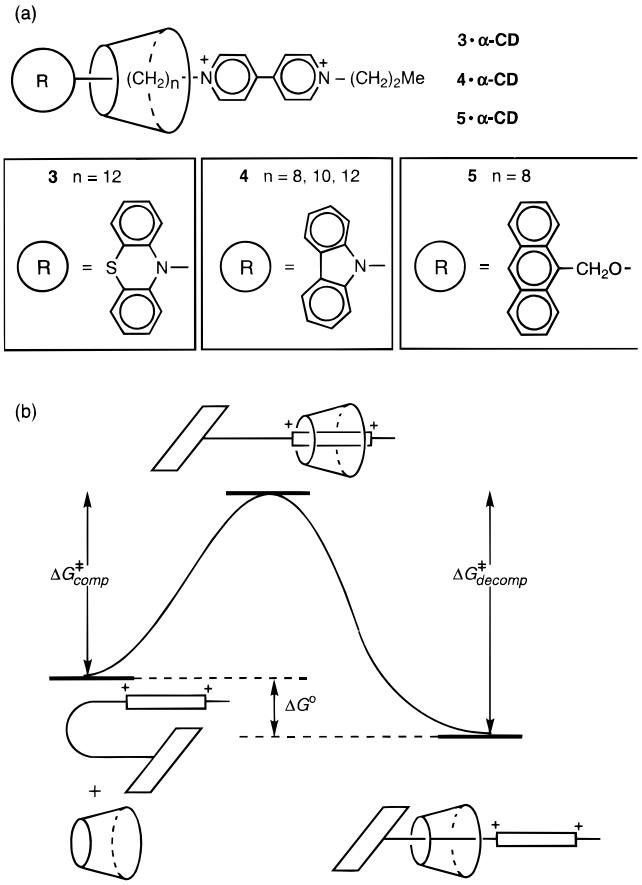


Figure 3. (a) Pseudorotaxanes obtained from complexation between α-**CD** and "unsymmetrical" guest components with large aromatic "stoppers" at one end and bipyridinium "stoppers" at the other end. (b) Schematic representation of the energy profile for the complexation (*comp*)/decomplexation (*decomp*) process for **4**·α-**CD** and **4**·β-**CD** as it relates to the NOE experiments (which establish the preferred relative orientations of the "unsymmetrical" α-**CD** and β-**CD** rings) and dynamic ^{1}H NMR spectroscopic studies in D_2O. Line shape analyses carried out on **4**·β-**CD** (n = 12) indicate that the free energies of activation at 70 °C for complexation and decomplexation are 11.6 and 17.2 kcal mol^{-1}, respectively. Activation parameters for the much more stable **4**·α-**CD** complexes were obtained from measuring the rate of disappearance of the charge-transfer absorption band (420 nm) between the carbazole ring system and the viologen unit when α-**CD** is added to **4**. In all cases (n = 8, 10, and 12), the $\Delta G^{\ddagger}_{decomp}$ was >22 kcal mol^{-1}.

DM-β-**CD**, using voltammetric techniques. It was found that the binding of these viologen-containing guests is dramatically dependent on their redox states. The dications are not bound, the cation radicals are weakly bound, and the neutral two-electron reduced guests are strongly bound by the **CD**s. In all cases, **DM**-β-**CD** forms more stable complexes than β-**CD**. These findings render the fully reduced viologens excellent candidates for constructing rotaxanes containing electrochemically controllable recognition sites. The substituents on the nitrogen atoms of the viologen units need to be chosen not only to maintain water solubility but also to prevent unthreading of the partially and fully reduced viologen derivatives. Provided that the dumbbell components of the rotaxanes are of such a nature that the **CD** rings can undergo free move-

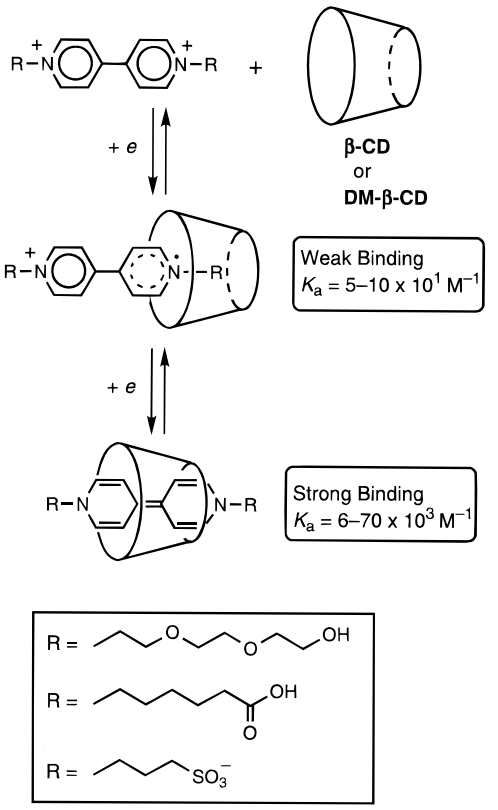


Figure 4. Redox control of the binding of guests containing viologen units with *β*-**CD** and **DM**-*β*-**CD**. The K_a values relate to measurements carried out at 25 °C in a 0.1 M phosphate buffer.

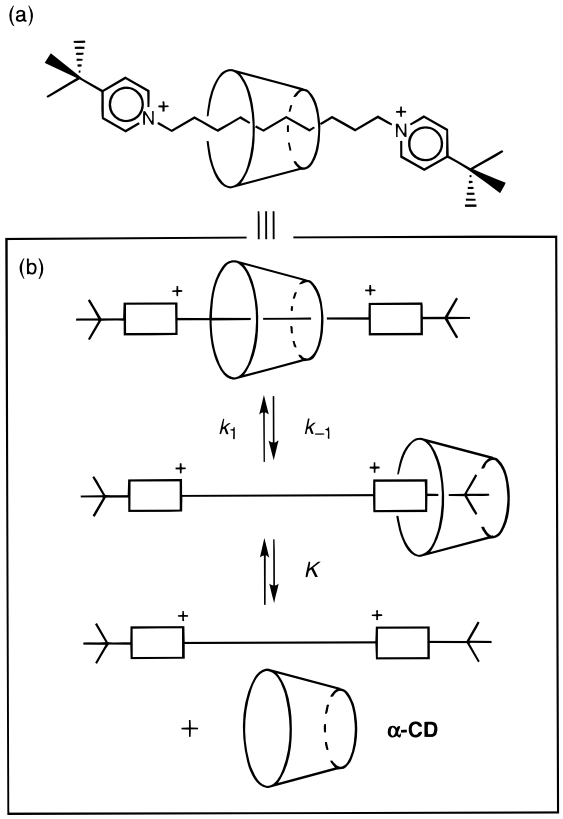


Figure 5. (a) α-**CD**-based rotoxane prepared using the "slippage" procedure. (b) Scheme proposed for the "slippage" mechanism to account for the kinetics of the formation of the [2]pseudorotaxane, shown in (a), from α-**CD** and the 1,10-bis[1-(4-*tert*-butylpyridiniumyl]decane dication. Note that the association constant $K_a = k_1K/k_{-1}$.

ments, the construction of electrochemically driven molecular shuttles[18] can be envisaged.

Extending the lifetimes of pseudorotaxanes can also be achieved by increasing the steric bulk of the "stoppers" on the dumbbell components up to sizes that match closely the diameters of the **CD** cavities. An attempt to use this so-called "slippage" mechanism to self-assemble a [2]pseudorotaxane of α-**CD** has been described recently by Macartney.[19] He chose to investigate the kinetics and thermodynamics of the threading (Figure 5) of the 1,10-bis[1-(4-*tert*-butylpyridiniumyl)] decane dication as its dibromide onto α-**CD** in D_2O containing 0.1 M NaCl by ^1H NMR spectroscopy. Weak inclusion ($K = 18 \pm 3$ M^{-1}) of the *tert*-butylpyridinium end group precedes very slow threading [$k_1 = (4.2 \pm 0.3) \times 10^{-4}$ s^{-1}] of the α-**CD** ring onto the dication. Dissociation of the [2]-pseudorotaxane thus formed occurs with a first-order rate constant of $(4.2 \pm 0.2) \times 10^{-6}$ s^{-1}, corresponding to a K_a value for pseudorotaxane formation of $(1.8 \pm 0.2) \times 10^3$ M^{-1}. When 4-isopropylpyridinium units constitute the end groups of the dicationic ligand, the corresponding [2]pseudorotaxane is formed much more rapidly with α-**CD**, indicating a very sharp discontinuity in the kinetics associated with the formation of these species. The prospect of studying chiral discrimination in the slippage process with (chiral) α-**CD** by introducing chiral "stoppers" onto the dicationic ligand has been raised by Macartney.

Superstructures with pseudorotaxane geometries can be "frozen" in the solid state. The crystallographic data, which are available for numerous **CD** inclusion complexes, make it possible to identify a number of examples among them that resemble pseudorotaxanes. The solid-state inclusion complexes[20] of α-**CD** with octanol and with valeric acid, for example, fall into this category of superstructures.

In very recent times, Mavridis et al.[21] have determined the X-ray crystal structures of 2:1 complexes, i.e. [3]pseudorotaxanes, formed between α-**CD** and (i) 1,12-diaminododecane and (ii) 12-aminododecanoic acid. The amino acid molecule lies parallel to the "dimer" axis with its carboxyl group protruding from one primary face and its amino group from the other primary face of the head-to-head α-**CD** dimer. The Athens group have also established that the α,*ω*-amino acid forms 2:1, as well as 1:1, complexes with α-**CD** in D_2O at alkaline pDs. At higher pDs (13.6), the proportion of [2]- relative to [3]pseudorotaxanes increases, possibly on account of the increased electrostatic repulsions in the 2:1 complex between the carboxylate anion in the guest and the partially ionized hydroxyl groups on the primary face of the **CD**.

A rather unique kind of superstructure (Figure 6) has been observed[22] in the solid state for a monosubstituted *β*-**CD** derivative that behaves both as a host and as a guest, such that a $-CH_2NH(CH_2)_6NH_2$ side chain on the primary face of one molecule enters into the cavity of the *β*-**CD** ring of a neighboring molecule and so on in a linear fashion. The monosubstituted *β*-**CD** derivatives are arranged spirally along a 2-fold

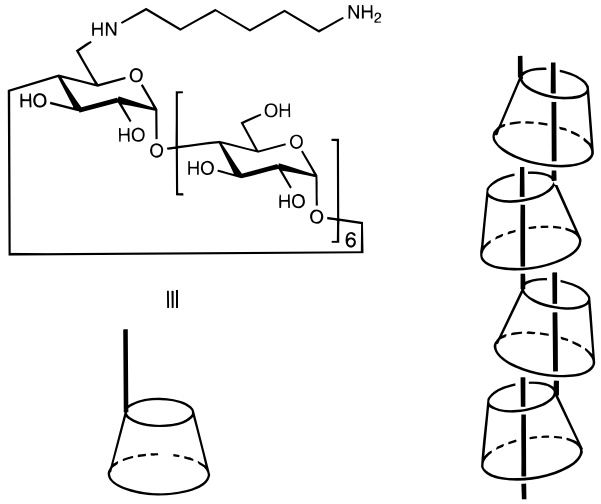


Figure 6. Structural formula of a monosubstituted β-**CD** derivative (left) that forms a continuous supramolecular polymer with a "pseudo-daisy chain" arrangement (right).

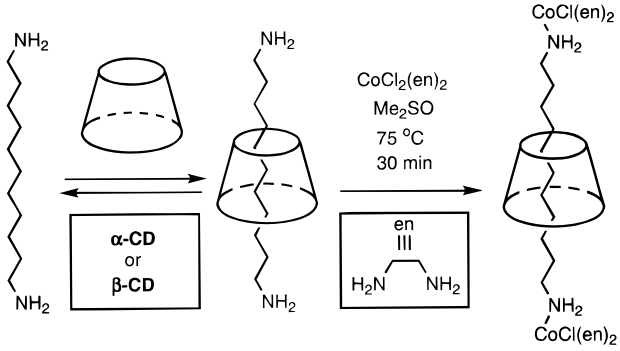


Figure 7. Self-assembly of [2]rotaxanes using the "threading" procedure.

screw axis, forming a polymer-like superstructure. This kind of supramolecular arrangement may be considered as a prototype of the so-called daisy-chain polymers,[23] which can be formed when AB-monomer units are interconnected by mechanical bonds of the rotaxane type. These AB-monomers fulfill the dual role of host and guest in a repetitive manner to give a stable polymer, provided the side chain attached to the ring (1) contains a recognition site for the ring and (2) is terminated by a "stopper" sufficiently large to prevent dissociation of the AB-monomers from each other.

B. Rotaxanes with "Stoppers" Linked by Coordinative or Ionic Bonds

The idea of self-assembling [2]rotaxanes, incorporating **CD**s as the ring components, was achieved for the first time by using transition metal complexes to constitute the "stoppers" at the ends of bisfunctionalized threadlike guests encircled by the **CD**s. In 1981, Ogino[24] reported the use of the reaction between *cis*-$[CoCl_2(en)_2]Cl$ (en denotes ethylenediamine) and α,ω-diaminoalkanes (Figure 7) as a way to construct the dumbbell components of rotaxanes incorporating either α-**CD** or β-**CD**. The best yield (19%) was obtained[24] when equimolar amounts of α-**CD** and 1,12-diaminododecane were reacted with 2 molar equiv of *cis*-$[CoCl_2(en)_2]Cl$ in Me_2SO solution.

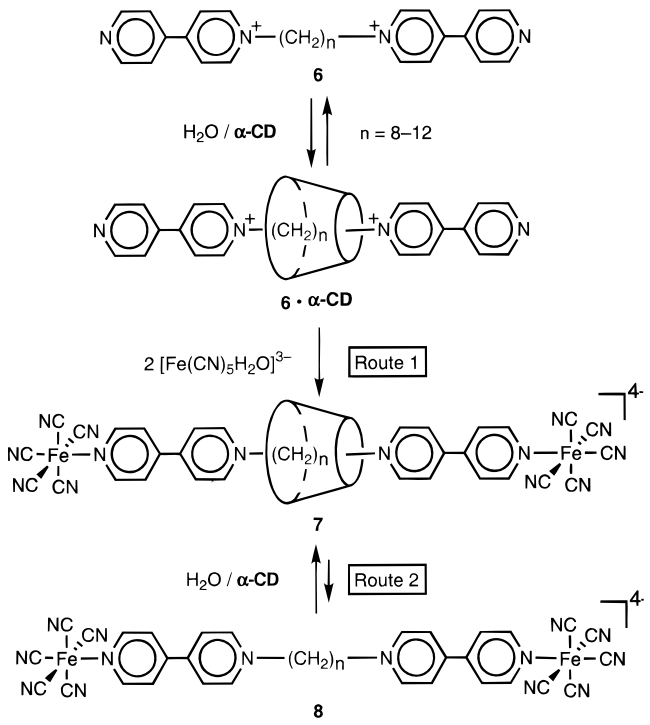


Figure 8. Self-assembly of an α-**CD**-containing "[2]rotaxane" capped with metallo-organic "stoppers".

When the ring component is β-**CD** or the diaminoalkanes have 10 and 14 methylene groups, the yields of [2]rotaxanes are low (≤6%). These low yields obtained in this early procedure for making **CD** rotaxanes were probably caused, not only by the formation of many Co(III)-containing products, but also by the unfavorable complexation between the **CD** rings and the threadlike guests in Me_2SO solution. A very similar approach to the formation of rotaxanes containing **CD** rings and dumbbell components, based on bifunctionalized polymethylene chains terminated by Co(III) complexes serving as the "stoppers", has been described by Yamanari and Shimura.[25]

Much more recently, the construction of a series of α-**CD**-based "[2]rotaxanes", by an approach which involves metal complexation as the key reaction for the attachment of the "stoppers" to polymethylene threads terminated by pyridylpyridinium units, has been achieved by Macartney et al.[26−29] In a typical experiment, pseudorotaxanes of the type **6**·α-**CD** formed in H_2O between α-**CD** and dicationic ligands **6** are allowed to react (Figure 8) with labile $[Fe(CN)_5H_2O]^{3-}$ ions, resulting in the rapid formation (route 1) of the "rotaxane" **7**. Essentially, the same outcome was noted when α-**CD** was added to aqueous solutions of the preformed dumbbell compound **8**. The existence of route 2 can be explained by the slow dissociation of one of the $[Fe(CN)_5]^{3-}$ "stoppers" from **8**, leading to "semirotaxane" formation and subsequent recomplexation of a $[Fe(CN)_5H_2O]^{3-}$ ion producing "rotaxanes". Kinetic studies,[28] performed on the spontaneous self-assembly of "[2]rotaxanes" by route 2, revealed that the rate-determining step in the process is the cleavage of the Fe−N coordination bond. These "[2]rotaxanes", which have been investigated by Macartney et al.[26−28] in great detail, are

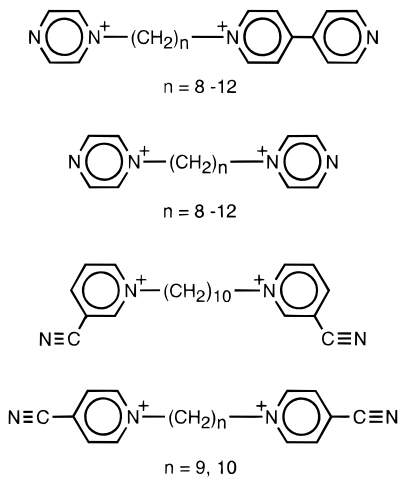


Figure 9. Guests used as threading ligands in the self-assembly of α-**CD**-based "[2]rotaxanes" capped with metallo-organic "stoppers".

definitely stable on the ^{1}H NMR time scale as indicated by spectra recorded in D_2O (0.10 M NaCl).

In addition to the ligands **6** bearing pyridylpyridinium terminal groups, a range of very similar compounds (Figure 9) containing pyridyl nitrogen atoms capable of coordinating bulky $[Fe(CN)_5]^{3-}$ "stoppers" have been employed successfully in the construction of "**CD**-[2]rotaxanes". These systems have been the subject of very careful kinetic investigations.[29] It has been suggested that, by replacing the $[pyz(CH_2)_n bpy]^{2+}$ ligands with $[pyz(CH_2)_n bpy(CH_2)_n pyz]^{4+}$ ligands, a series of "[3]rotaxanes" composed of two α-**CD** rings and one dumbbell component should become realistic targets for synthesis. Preliminary results indicate the formation of a non-statistical distribution of orientational isomers, as far as the relative orientations of two α-**CD** rings on a "symmetrical" dumbbell component are concerned.

A similar approach, that is believed to rely upon ionic interactions for the stabilization of **CD**-containing pseudorotaxanes, has been developed by Lawrence et al.[30] If the thread component carries ammonium centers at both its termini, the resulting water soluble pseudorotaxane can be precipitated by counterion exchange of the bis(ammonium) dihalide salt with bulky hydrophobic anions—e.g. tetraphenylborates. Thus, treatment of the complex formed between **9** and **DM**-*β*-**CD** with $NaBPh_4$ in water results (Figure 10) in the instantaneous formation of an insoluble [2]rotaxane **10**. The compound, which was stable in an acetone solution that was used for its TLC, was isolated in 71% yield. Proof of its rotaxane structure comes from ^{1}H and ^{13}C NMR spectra measured in CD_3SOCD_3 solutions. However, the biphenyl-containing thread dissociates from the **CD** loop in the presence of Et_3N. It has been suggested that it is solvation of the ammonium centers by acetone, rather than electrostatic "mechanical" capping, which is responsible for the primary stabilization of the [2]rotaxane **10** in this solvent, provided it is not heated under reflux.

The same type of "threading" process has been applied[31] to the self-assembly (Figure 11) of the [3]-rotaxane **14** which may be regarded as a mimic of

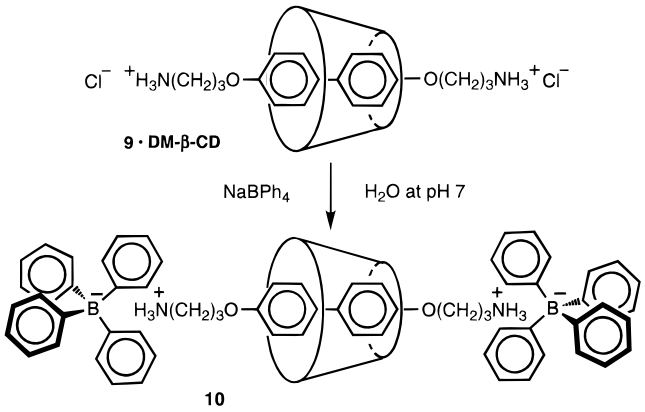


Figure 10. Template-directed self-assembly of a [2]rotaxane in aqueous media.

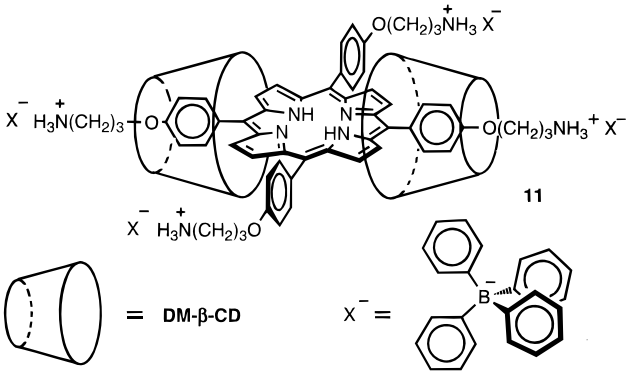


Figure 11. A [3]rotaxane formed between two **DM**-α-**CD** rings and a porphyrin derivative.

heme-containing proteins. Indeed, replacement of the apoprotein with the **CD**-based protective sheaths in **14** means that this [3]rotaxane exhibits many of the characteristics of the natural analogues.

C. Cyclodextrin-Containing [2]Rotaxanes with Covalently Bound "Stoppers"

One's first impression, in view of the amount of attention that has surrounded the construction of rotaxanes in recent years, is that it is surprising to find so few examples of **CD**-based rotaxanes incorporating dumbbell components with "stoppers" covalently linked to the threads. Obviously, rotaxanes with dumbbells of this kind could be considered to be the ultimate molecular structures in view of their unquestionably higher stabilities. However, since the covalent bond-forming reactions have to be carried out in aqueous solutions, the efficient attachment of "stoppers" to "threads" when they are complexed by **CD** rings is quite a challenge. Employing functional groups with relatively high nucleophilicities—such as NH_2 or S^-—at the termini of the "threads" is one possible solution to this problem. In this vein, Isnin and Kaifer[32] have used the water-soluble condensing agent $Et_3N^+(CH_2)_3N{=}C{=}NEt$ (EDC) to create an amide bond in a dumbbell component, starting from (1) a long-chain aliphatic carboxylic acid derivative, terminated by a large positively charged group, and (2) a bulky aromatic amine carrying a negatively charged function (Figure 12). In one of the reactants—the carboxylic acid **12**—a polymethylene chain,

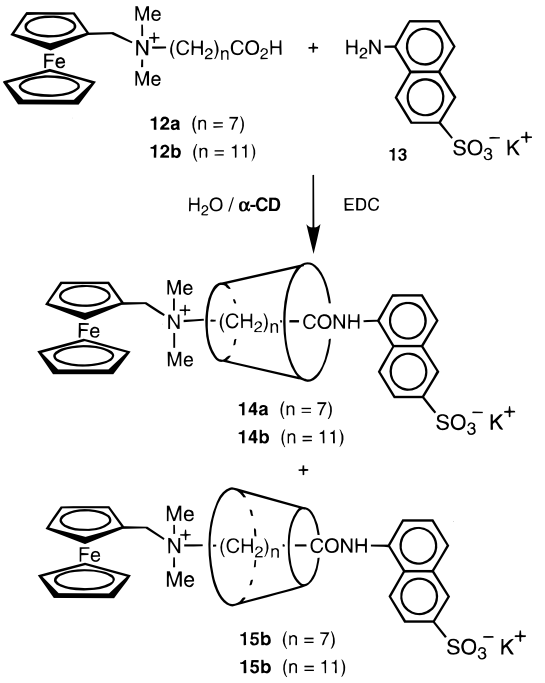


Figure 12. Self-assembly of two pairs of orientationally isomeric zwitterionic [2]rotaxanes in aqueous media using the "threading" procedure.

which is responsible for the recognition of the **CD** ring, is attached via a tetrasubstituted ammonium site to a ferrocenyl methyl unit which ultimately serves as one of the "stoppers" in the rotaxanes. The other "stopper" is derived from potassium 5-amino-2-naphthalensulfonate (**13**). Amide bond-forming reactions were carried out in water with carboxylic acids **12a**,**b** having 7 and 11 carbon atoms, respectively, in their polymethylene chains. In each case, they afforded the orientationally isomeric [2]rotaxanes **14** and **15** in 15% yields overall. The isomerism is a direct consequence of the end-to-end "asymmetries" of both the ring and dumbbell components. Using reversed phase preparative TLC, it was possible to separate the two pairs of isomeric rotaxanes and assign structures to them as shown in Figure 12. An intriguing property of the two different sets of orientational isomers is that the **a** isomers undergo slow unthreading by a mechanism that is highly solvent dependent, whereas the **b** isomers are completely stable and do not unthread.

With the aim of constructing a [2]rotaxane incorporating an aromatic chromophore in the recognition site of the dumbbell component, Nakashima et al.[33] have used *β*-**CD** as the ring component. Their approach relied upon the complexation (Figure 13) of 4,4′-diaminostilbene by *β*-**CD** in aqueous bicarbonate solution and the subsequent reactions of the terminal amino functions of the aromatic guest with the capping reagent **17**. The reactivity of this reagent resides in its 4,6-dichlorotriazinyl residue in which one of the chlorine atoms can be substituted in aqueous solution by the amino functions in **16**·*β*-**CD**. Treatment of this complex with **17** at room temperature in aqueous bicarbonate solution, followed by addition of aniline to displace the residual chlorine atoms on the putative "stoppers", afforded the [2]-rotaxane **18** in 28% yield. Its rotaxane structure was

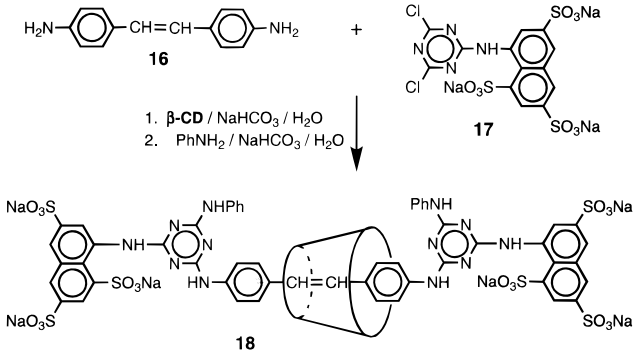


Figure 13. Supramolecular-assisted synthesis of a [2]-rotaxane involving successive covalent bond-forming reactions

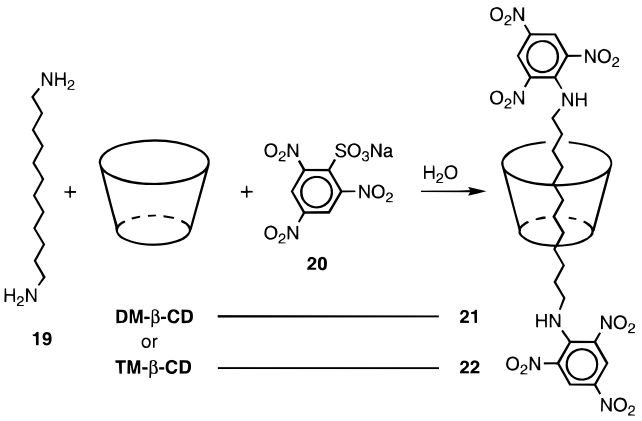


Figure 14. Self-assembly of two [2]rotaxanes incorporating **DM**-*β*-**CD** and **TM**-*β*-**CD** in aqueous solution.

established by UV/vis spectroscopy and also by the observation of induced circular dichroism spectra.

Another approach to capping the amino functions of appropriate **CD** complexes in water has been described by Harada et al.[34] for the preparation of [2]rotaxanes incorporating **DM**-α-**CD** and **TM**-α-**CD**. Complexes of 1,12-diaminododecane (**19**) with the methylated **CD**s were allowed to react (Figure 14) with sodium 2,4,6-trinitrobenzenesulfonate (**20**) in water. The [2]rotaxanes **21** and **22** were isolated as precipitates from the aqueous solutions in 42 and 48% yields, respectively.

The 2,4-dinitrophenyl group is also sufficiently bulky to serve as "stoppers" in rotaxanes incorporating α-**CD** rings. It can be introduced easily onto the primary amino termini of appropriate diamines threaded through an α-**CD** ring using the well-known amino-labeling reagent 2,4-dinitrofluorobenzene. Very recently, Nakashima et al.[35] have employed (Figure 15) this reagent to prepare a photoswitchable [2]-rotaxane **23**. Irradiation of an aqueous solution of **23** with UV light (360 nm) causes isomerization of the azobenzene moiety from the trans to the cis configuration: the isomerization can be reversed when the solution is irradiated with visible light (430 nm). These configurational changes are reflected in a dramatic alteration of the geometry of the primary recognition site within the dumbbell component, causing the ring component to adopt different positions with respect to the latter. When the azobenzene unit has the trans configuration, both NOE

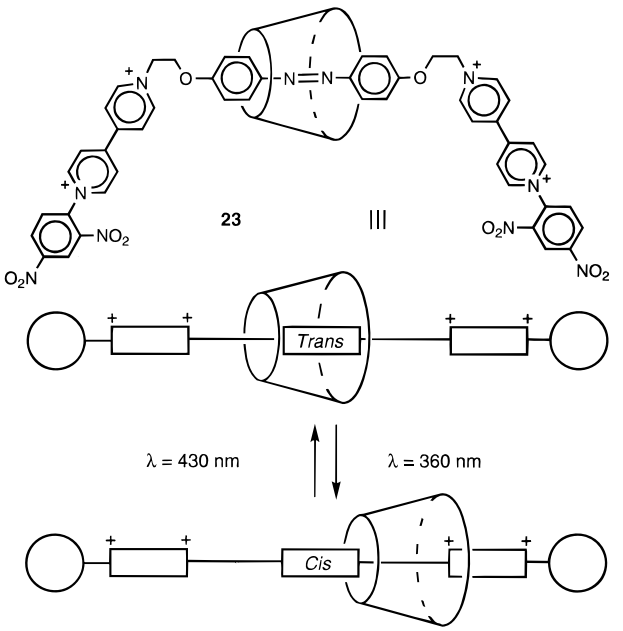


Figure 15. A light-driven molecular shuttle.

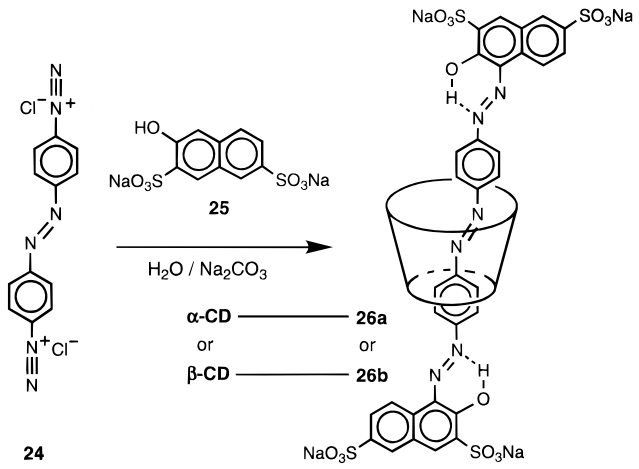


Figure 16. Self-assembly of water-soluble azo-dye rotaxanes incorporating α-**CD** and *β*-**CD**.

experiments and circular dichroism measurements indicate that the α-**CD** ring resides around the recognition site. When the azobenzene unit adopts the cis configuration, the α-**CD** ring migrates onto one of the bis(methylene) spacers linking the recognition site to the two bipyridinium units. The photoswitching process is reversible and has been taken through six cyclic responses. This [2]rotaxane is a beautiful example of a light-driven molecular shuttle.[36]

Inclusion complex formation by **CD**s has long been recognized as a method by which photosensitive molecules can be protected from decomposition. Stabilizing these complexes by converting them into rotaxanes provides a means of improving upon this protection. A range of azo dyes mechanically interlocked within the cavities of either α-**CD** or *β*-**CD** have been described by Anderson et al.[37] The [2]-rotaxanes **26a**,**b** are formed in 12 and 15% yields, respectively, when the preparation of the azo dye from the bis(diazonium) salt **24** and the *β*-naphthol derivative **25** is carried out (Figure 16) in aqueous sodium carbonate solution in the presence of α-**CD** and *β*-**CD**, respectively. Water soluble azo-dye rotaxanes offer an elegant means of controlling the stability, solubility, and aggregation of these commercially important synthetic colorants.

It might be anticipated that the conformational behavior of particular molecules will be influenced by their complexation inside the cavities of **CD**s. An opportunity to make a direct comparison is provided by a dumbbell component of a rotaxane when it is compared with the free dumbbell compound **27**. Kraüter *et al.*[38] have synthesized (Figure 17) [2]-rotaxane **28** incorporating unnatural B_{12} derivatives as very large organometallic "stoppers". The lipophilic dodecamethylene chain of the dumbbell compound **27** is relatively small compared with the hydrophilic cob(III)alamin "stoppers" and provides a "hydrophobic gap" within the molecule. Detailed examination of the ^{13}C NMR spectra of **27** and **28** in D_2O solutions revealed that the dodecamethylene chain is contracted as a result of gauche conformations being present in the free dumbbell compound **27**, whereas, in the [2]rotaxane **28**, the dodecamethylene chain is extended on account of it being shielded by the **CD** torus.

III. Cyclodextrin-Containing Polyrotaxanes

Polymers which incorporate **CD** rings as covalently bound monomers within linear and cross-linked macromolecules are well-known.[39] Another way of creating new polymeric materials containing **CD** rings is to exploit their supramolecular properties. An obvious extension of **CD**-based [2]rotaxanes is in the direction of [*n*]rotaxanes or polyrotaxanes. A discussion of the potential properties of polymers with such novel primary structures is tempting, but it would be largely speculative at this time. Accordingly, in this section, we will concentrate our attention on the different approaches that have been described in recent years for the construction of **CD**-based polyrotaxanes. So far, most of these novel polymers have been assembled as a result of modifying known polymers rather than by polymerizing monomeric smaller rotaxanes such as **CD**-based [2]-rotaxanes.

A. Inclusion Complexes of Polymers with Cyclodextrins

Although the inclusion of low molecular weight compounds by **CD**s has been the subject of numerous investigations over several decades, there were a limited number of observations[40,41] involving the threading of polymers and polyelectrolytes with **CD**s before the independent studies of Harada and Kamachi[42,43] and Wenz and Keller.[44] Both these research groups have proved unequivocally that **CD** rings can be strung along the chains of water-soluble polymers. Harada and Kamachi[45] have investigated thoroughly the crystalline inclusion complexes that α-**CD** forms with poly(ethylene glycol)s (**PEG**s). The complexation, which occurs when either an aqueous solution of **PEG** or the bulk polymer is added to a concentrated aqueous solution of α-**CD**, results in the precipitation of products that are close to insoluble

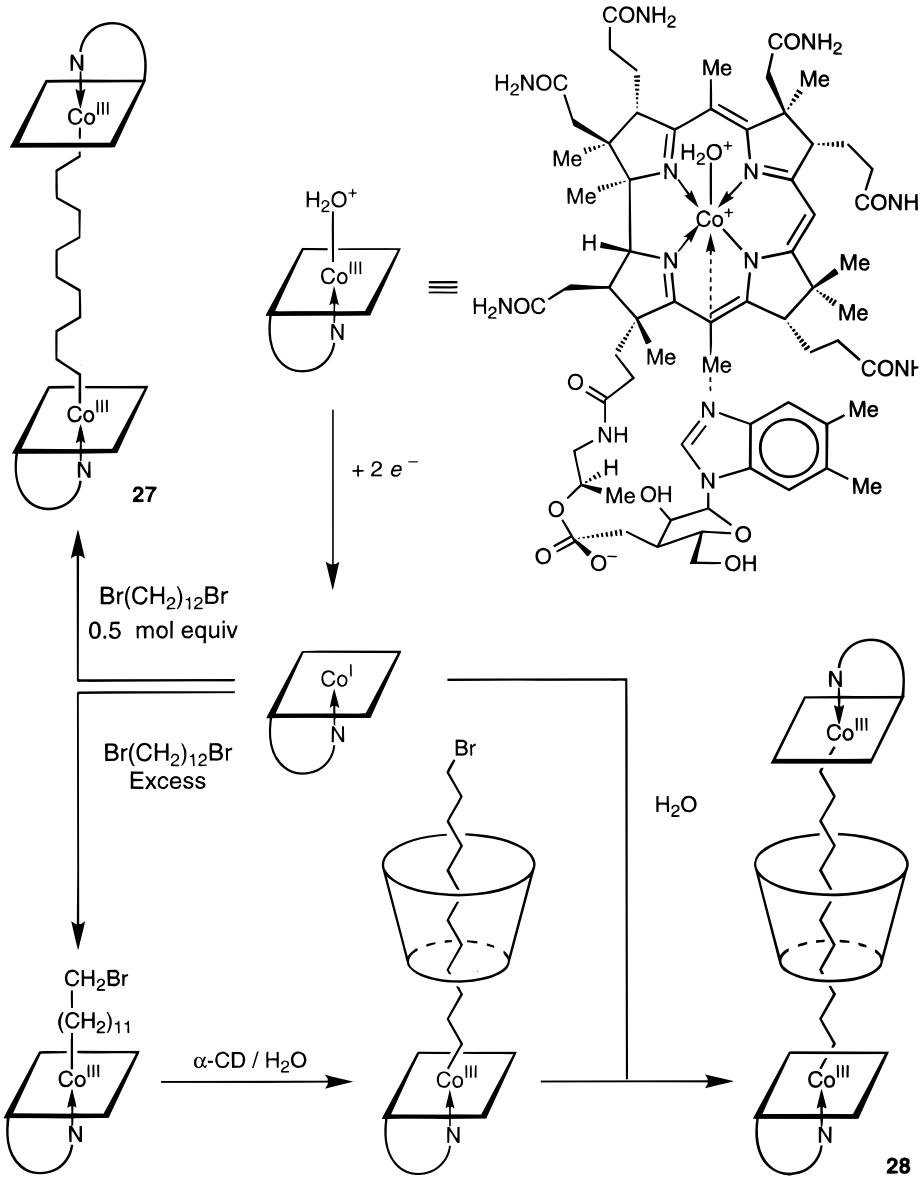


Figure 17. Organometallic B_{12}-rotaxane and B_{12}-dimer: relaxed and loaded forms of a molecular spring.

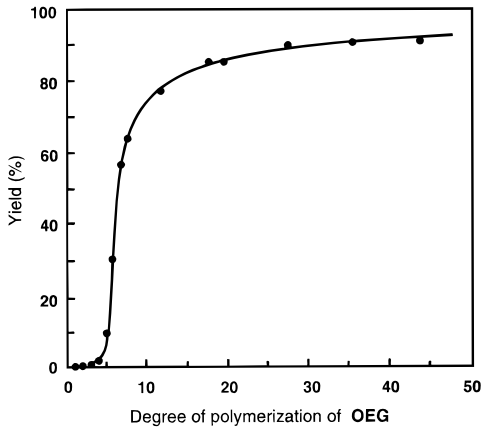


Figure 18. Yields of the complexes of α-**CD** with oligo(ethylene glycol)s (**OEG**) as a function of the degree of polymerization **OEG**. (The plot is taken from ref 46.)

in water. The process only takes place (Figure 18) when the degree of polymerization is higher than three and reaches[46] its most efficient for **PEG** with a molecular weight of 1000 Da. The yields of the

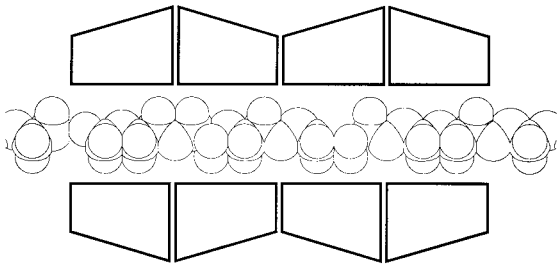


Figure 19. Proposed superstructure for α-**CD**·**PEG** complexes.

complexes increase with an increase in the degree of polymerization. ^{1}H NMR spectra of the complexes show their stoichiometries are 2:1 (two ethylene glycol units to one α-**CD**) when the degree of polymerization is higher than six. Since the length of two ethylene glycol units corresponds exactly to the depth of the α-**CD** cavity, the **CD** rings must be strung very tightly onto the **PEG** chain (Figure 19). This hypothesis is supported by X-ray powder patterns and ^{13}C CP/MAS NMR spectra which suggest that α-**CD** forms channels which are accommodated by **PEG** in

Table 2. Inclusion Complexes of CDs with Polymers

		yields[a] (%) and stoichiometries (monomer unit: **CD**)			
no.	polymer (MW)	**α-CD**	***β*-CD**	***γ*-CD**	ref
1	poly(ethylene glycol) (1000)	91 (2:1)	0	trace	45
2	poly(propylene glycol) (1000)	0	96 (2:1)	80 (2:1)	47
3	poly(methyl vinyl ether) (20 000)	0	0	67 (3:1)	48
4	poly(oligoethylene) (702)	67 (3:1)	0	0	49
5	polyisobutylene[b]	0	67	96 (3:1)	50
6	poly(oxytrimethylene) (1200)	90 (1.5−2:1)	67 (2−2.5:1)		51
7	poly(oxytetramethylene)[c]	82 (1.5:1)		100 (2.8:1)	52
8	poly(ϵ-capralactone) (530)	82 (1:1)			53

[a] The yields of complexes are usually dependent on the molecular weights of the included polymers. Only data for the complexes prepared in the most efficient manner from a given polymer are quoted. [b] MW = 500 in the case *β*-**CD** whereas MW = 1350 in the case of *γ*-**CD**. [c] MW = 250 in the case α-**CD** whereas MW = 1000 in the case of *γ*-**CD**.

the α-**CD·PEG** complexes. The polypseudorotaxane channel superstructure is thought to be stabilized by hydrogen bonding between adjacent **CD** rings which are believed to be arranged in a head-to-head/tail-to-tail fashion. Nonetheless, the formation of α-**CD·PEG** complexes is reversible. Suspensions of these complexes in aqueous solutions can be solubilized by the addition of an excess of a low molecular weight guest, e.g. benzoic acid, which has a high affinity for the cavity of α-**CD**. *β*-**CD** does not form complexes with any **PEG**s.

The higher members of the **CD** family are also capable of forming inclusion complexes with water-soluble polymers over a broad molecular weight range. This fact has been demonstrated (Table 2) convincingly by the preparation and characterization of many stoichiometric (monomer unit:**CD**) complexes by Harada and Kamachi[47−53] following their pioneering investigations[42,43,45] of the α-**CD·PEG** complexes. Selectivity of binding toward different polymers is dependent upon the sizes of the **CD** rings. Thus, a crucial factor in these complexations is the match of the dimensions of the **CD** cavity to the monomer unit. Table 2 also includes some examples (entries 4, 5, and 8) of the complexation of polymers that are insoluble in water. Many of the properties of these particular crystalline complexes are very similar in their characteristics to those that water-soluble polymers form with **CD**s. Harada[54] has reviewed his research on the preparation and properties of supramolecular architectures consisting of cyclodextrins and polymers.

Topchieva et al.[55] have studied the interactions of **CD**s with amphiphilic triblock copolymers of poly(ethylene oxide) and poly(propylene oxide) and found that *β*-**CD** forms stable inclusion complexes with these polymers. Most of them are insoluble in water and crystalline. It was shown that only the propylene oxide regions of the polymer chains are involved in complexation in such a manner that each *β*-**CD** ring accommodates two propylene oxide units.

The introduction of specific functions onto the end groups of polymer chains does not normally affect their abilities to form complexes with **CD**s, provided that these end groups can penetrate the cavity of the corresponding **CD** ring. However, a remarkable effect upon complexation is observed[56] in the case of the interaction of *γ*-**CD** with **PEG** which carries naphthylacetyl residues as end groups. First of all, in contrast with "native" **PEG**, the bis(1- or 2-naphthylacetyl)-**PEG**s do form complexes with *γ*-**CD**. ^{1}H NMR spectroscopy indicated that these complexes have 4:1 stoichiometries as regards the ratio of ethylene glycol repeating units to **CD** rings. On the basis of fluorescence studies, it was concluded that these complexes possess double-stranded superstructures with the characteristics illustrated by the schematic description present in Figure 20.

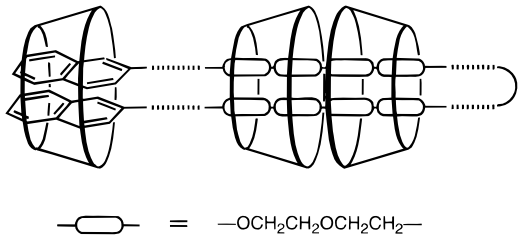


Figure 20. Probable superstructure of the double-stranded inclusion complex of *γ*-**CD** with bis(naphthyl)poly(ethylene glycol).

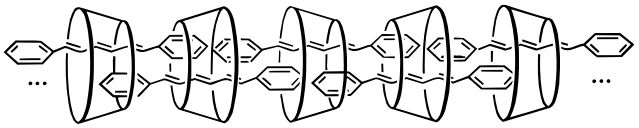


Figure 21. Proposed superstructure of the linear nanotubular aggregates of *β*-**CD** rings with 1,6-diphenyl-1,3,5-hexatriene.

Nanotube aggregates, containing as many as 20 *β*-**CD** and 20−35 *γ*-**CD** rings have been detected[57] in aqueous solution (as indicated by fluorescence anisotropy and light scattering measurements) and in the solid state (from the results of imaging by STM) for complexes of these **CD**s with *all-trans*-1,6-diphenyl-1,3,5-hexatriene. The linking of the **CD** rings into a tubular arrangement is suggested to be a consequence of the side-by-side self-assembling of the rodlike guest, included within the **CD** cavities, such that they form (Figure 21) double linear arrays in which the diphenylhexatriene molecules are staggered with respect to each other along the axes of the nanotubes.

All the polymeric pseudorotaxanes discussed so far in this section exhibit very low or even "zero" aqueous solubility, quite independently of the solubility characteristics of the "native" polymer. Water-soluble complexes can be prepared from **CD**s and polyelectrolytes (Figure 22), such as ionized poly(iminooligomethylenes) **29**—which were first investigated by Wenz and Keller[44,58,59]—or polyionens **30**[58,60] and poly-

Table 3. Polyrotaxanes Composed of Bisamino Poly(ethylene glycol) and α-CD with Two 2,4-dinitrophenyl "Stoppers"[a]

MW		yield of	no. of ethylene	no. of **α-CD**	molar ratio between ethylene
"native" **PEG**	rotaxane	polyrotaxane (%)	glycol units	rings included	glycol units and **α-CD** rings
3350	23 500	60	77	20	3.9
2000	20 000	30	45	18	2.5
1450	16 500	27	35	15	2.3
2918[b]	12 600	16	28	12	2.3

[a] Data are taken from refs 65 and 66. [b] Monodisperse 28-mer of α,ω-diamino-**PEG**.

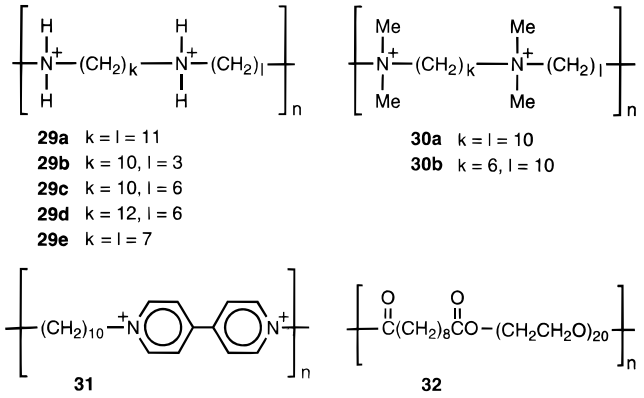


Figure 22. Polyelectrolytes employed as guests for complexation with **α-CD**.

(oligomethylenebipyridinium dibromide)s.[31,61,62] The threading of **α-CD** rings onto these polymers is driven by the gain in hydrophobic bonding and van der Waals interactions between oligomethylene segments of the polymeric guests and the interior of the host, **α-CD**. The bulky ammonium centers and bipyridinium units probably act as activation barriers to the free movement of **CD** rings along the polymer chains, making the inclusion processes very slow and resulting thereafter in very stable complexes. Thus, equilibrium dialysis into its separate components of the complex formed between poly(((iminotrimethylene)imino)decamethylene) (**29b**) and **α-CD** is far from complete after 2 weeks.[44] And, for example, the complex of polyionene-6,10 (**30b**) with **α-CD** containing about 65 rings on the polymer chain is so stable that it can be subjected to GPC as well as to dialysis.[59] Indeed, the complex can only be prepared on a reasonable time scale by a thermally induced threading process: inclusion of **30b** by **α-CD** at 80 °C in aqueous solution gives the same (55%) yield as would ensue if the process was allowed to happen at 25 °C for 2 years! In yet another fascinating experiment, the existence of a "molecular necklace" formed by **30b** and fluoresceinyl-labeled *β*-**CD** could be visualized[63] by electrophoresis; while the free fluoresceinyl-modified *β*-**CD** moves toward the anode, its complex with **30b** migrates to the cathode on account of the excess of positive charge on the polymer chain. Very recently, Wenz et al.[64] have demonstrated that water-soluble polymeric pseudorotaxanes can also be prepared from **CD**s and neutral polymers. The polyester **32** (M_n = 11 700) incorporating 20 oxyethylene units and an octamethylene segment was synthesized from dimethyl 1,8-dicarboxylic and **PEG** (M_n = 900). This polymer forms inclusion complexes with **α-CD**, *β*-**CD**, and hydroxypropyl-**α-CD** in aqueous solutions, whereas **PEG**s are known to produce

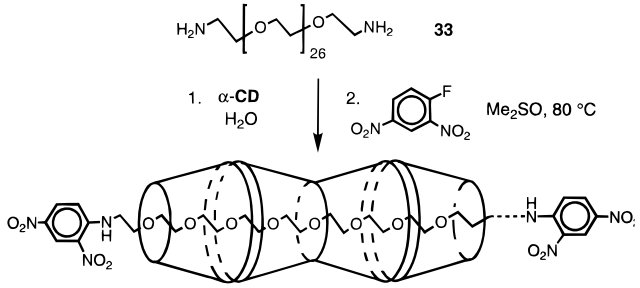


Figure 23. Polyrotaxane obtained by self-assembly of **α-CD** rings onto a monodisperse bis(amino)-**PEG** followed by "stoppering".

insoluble complexes and only in the case of **α-CD**. The solubility of the polyester complexes has been attributed to the partial coverage of the polymeric guest with **CD** rings which, according to ^{1}H NMR spectroscopic data, occupy preferentially the alkyl segments rather than the hydrophilic **PEG** ones.

B. Linear-Chain Cyclodextrin-Based Polyrotaxanes

In the knowledge that a **PEG** chain threads **α-CD** beads such as a necklace and that threading does not happen when the **PEG** chain has large substituents at both its ends, Harada et al.[65] have succeeded in self-assembling "genuine" polyrotaxanes by capping the reactive polymer chain ends with bulky "stoppers". The complexes between **PEG**-bis(amines) and **α-CD** were prepared first of all; they were dried thoroughly before being treated with an excess of 2,4-dinitrofluorobenzene in a DMF solution at 80 °C. After extensive purification, polyrotaxanes which are soluble in Me_2SO or 0.1 N NaOH solution were isolated (Table 3) in 27−60% yields, depending upon the molecular weights of the starting **PEG**s. The number of **CD** rings trapped on the polymeric chains were estimated from spectroscopic data: it was found, not surprisingly, to depend on the **PEG** chain length. More precise characterization has been performed[66] on the polyrotaxane **33** (Figure 23), prepared from the monodisperse diamino-**PEG**. In this case, 12 **α-CD** rings were found on each polymer chain, demonstrating that the rings are close-packed from one end of the macromolecule to the other. This close packing of **α-CD** rings threaded onto **PEG** chains has lent[67] itself to the efficient coupling of vicinal **CD** rings in polydisperse **α-CD**/**PEG** polyrotaxanes using epichlorihydrin as the cross-linking reagent. Following removal of the "stoppers" and release of the original **PEG**, a fascinating new type of **CD** polymer with a nanoscale tubular structure is released. In recent times, the structural features of

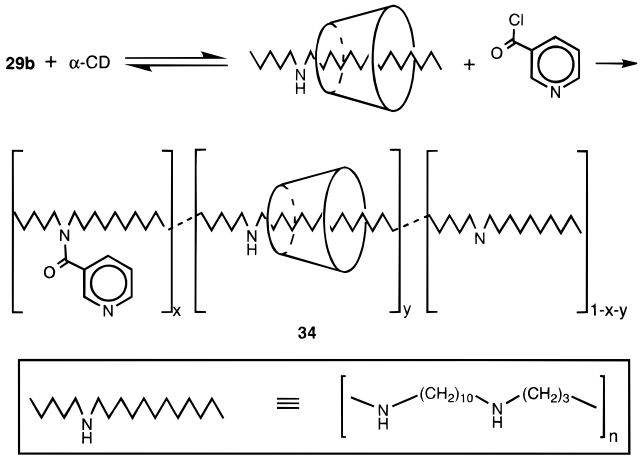


Figure 24. Self-assembly of a **CD**-polyrotaxane by trapping α-**CD** rings onto a polymer chain as a result of attaching "blocking" groups at arbitary positions along the chain.

α-**CD**/**PEG** polyrotaxanes have been investigated[68] by molecular dynamics simulations: the calculations suggest that the **PEG** chain in the complex is more extended than the "free" chain and "captures" as many **CD** rings as it possibly can along its whole length.

It is, however, not always necessary to attach "stoppers" to the termini of a polymer to prevent **CD** rings unthreading from a polymer chain. Wenz and Keller[44] have employed another approach which involves the attachment of at least two "blocking groups" at arbitrary positions along the polymer chain. Obviously, these positions must represent some reactive functionalities, such as secondary amines, along the polymer chain, as in **29b**. Treatment of the complex α-**CD**·**29b** with nicotinyl chloride in water leads (Figure 24) to the isolation of 43% of a product which exhibits water solubility. This product was identified as the polyrotaxane **34** incorporating about 37 α-**CD** rings permanently threaded on the polymer chain and randomly covering 67% of all the monomer units.

A similar kind of polyrotaxane with **CD** rings randomly clipped between "blocking groups" positioned along a polymer chain has been isolated by Osakado et al.[69] However, their synthetic strategy is quite different from that of Wenz and Keller. It involves the polymerization of a monomer with a well-defined binding site in the presence of host, α-**CD**. In principle, this approach has been around since the studies of Ogata et al.[70] and Maciejewsky[71] in the 70s: they carried out polymerizations of what they assumed to be encapsulated monomers and probably obtained some of the first **CD**-based polyrotaxanes. In their paper, Osakado et al. describe a dramatic improvement on this approach which involves using reactive monomer units incorporating recognition sites and "blocking groups". These two functions were divided between the two different components—**35** and **36** in Figure 25—of the polycondensation which was carried out in the presence of α-**CD** (molar ratio **35**:**36**:α-**CD** = 1:3:0.5) and a catalyst. During this catalyzed reaction, two types of covalent bonds are formed, giving rise to imidazole

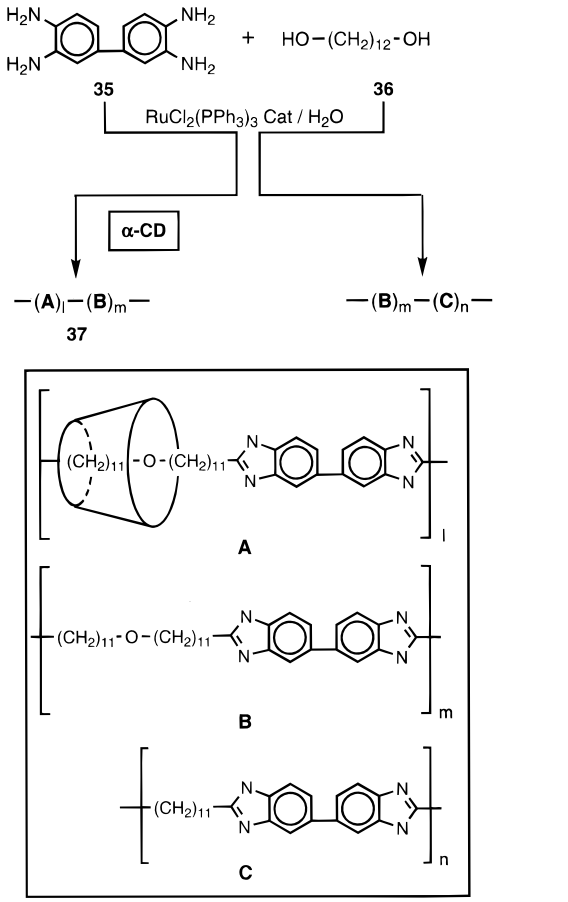


Figure 25. Self-assembly of poly(alkylenebenzimidazole) incorporating "blocking" groups in every structural unit and the corresponding polyrotaxane with threaded α-**CD** rings.

rings and ether linkages in an irregular copolymer **37** built up of blocks containing structural units A and B in a ratio of 16:84. Interestingly, no structural units of the type C were formed in this polymerization whereas, in the absence of α-**CD**, the same polycondensation afforded a polymer containing 20% of these units.

In summary, linear-chain cyclodexrin-based polyrotaxanes can be prepared either (i) by "threading" of **CD** rings onto polymer chains or (ii) by the polymerization of monomer units included within **CD** rings. Although the latter process is more laborious, it has the advantage of leading to the creation of water-soluble **CD** inclusion compounds with polymers insoluble in water. Apparently, high coverage of the polymer chains with **CD**s is a necessary condition for aqueous solubility. This high coverage is unlikely to be achieved when the polymerization of a complexed monomer is carried out in aqueous solution; both dissociation and lowering of the monomer reactivity by inclusion are likely outcomes. In an attempt to overcome these problems, Wenz et al.[72] have investigated solid-state polymerizations in host crystals, clathrates, with **CD**s as part of the matrixes. Microcrystalline inclusion compounds of α,ω-amino acids with α-**CD**, which were obtained from water, were heated in a vacuum at 190−240 °C to produce polyamides that are completely covered by **CD** rings and are highly soluble in water.

Table 4. Association Constants (K_a) of the Complexes Formed between CDs and Alkyl Units of Water-Soluble Copolymers of Acrylamide with Alkyl Methacrylates[a]

	K_a (M^{-1})					
	n-butyl	*tert*-butyl	isobutyl	*n*-hexyl	isooctyl	dodecyl
α-CD	55		36	290	303	990
β-CD		340		110	294	660
γ-CD		57			51	245

[a] Data are taken from ref 73.

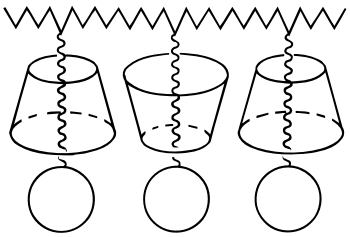


Figure 26. Schematic representation of a side-chain polyrotaxane.

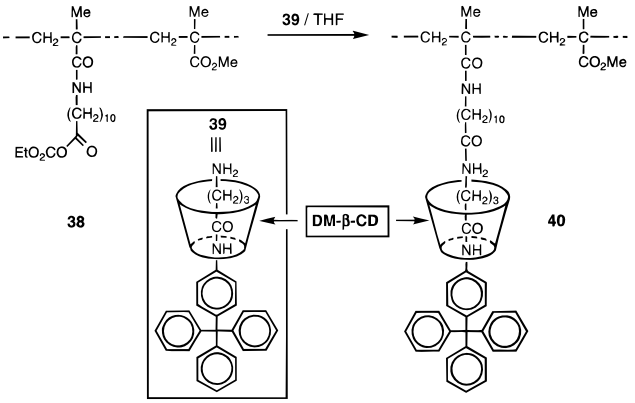


Figure 27. Synthesis of a comblike polyrotaxane incorporating **DM-β-CD** rings threaded onto side chains.

C. Side-Chain Cyclodextrin-Based Polyrotaxanes

The noncovalent bonding interactions of **CD**s with the side chains of comb-shaped polymers represent another interesting kind of macromolecular recognition. The measurement of the association constants between **CD**s and a range of copolymers of acrylamide with alkyl methacrylates[73] reveals (Table 4) that **CD**s are capable of interacting selectively with polymer side chains, affording polymeric "semirotaxanes".

The construction of comblike polyrotaxanes (Figure 26) requires the presence of rather long side chains on the starting polymers in order to permit the accommodation of **CD** rings without introducing serious steric congestion. For this reason, the starting polymers are unlikely to be soluble in water. This fact explains the choice of organic solvents for the construction of side-chain polyrotaxanes by Ritter et al.[74] and by Yamamoto et al.[75] In the first example, the crucial step in the synthesis (Figure 27) involves the coupling of the preformed "semirotaxane" complex to the activated side chains of the polymer **38**, affording a new kind of **CD**-containing rotaxane **40**. A similar strategy was employed[76−78] by the German researchers in their syntheses of a series of different side-chain polyrotaxanes incorporating **DM-β-CD**. It has also been found that chemical modification of the noncovalently bound **CD** residues can be carried out within this type of **CD**-polyrotaxane. Yamamoto et al.[79] have produced (Figure 28) the side-chain polyrotaxanes **41a**−**c** by alkylation of the NH group of the poly(benzimidazoles) with $Br(CH_2)_{12}O(CO)CH_2$-CPh_3 in the presence of **TM-β-CD**. The degree of *N*-alkylation and the proportion of included macrocycles was strongly influenced by the length of the spacer between the benzimidazole units.

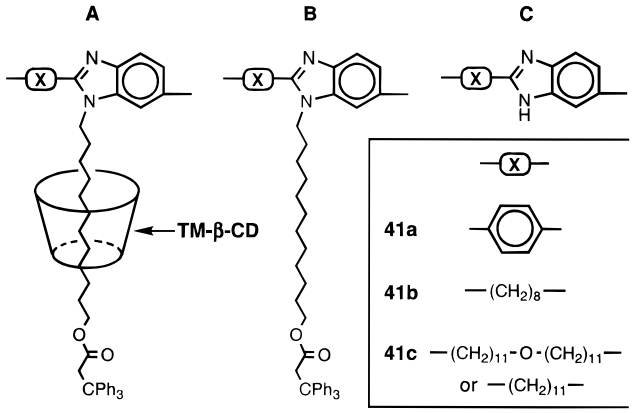


Figure 28. Structural units of the side-chain polyrotaxanes **41a**−**c**, prepared by *N*-alkylation of poly(benzimidazole)s in the presence of **TM-β-CD**.

IV. Rotaxanes and Polyrotaxanes Derived from Lipophilic Cyclodextrin Derivatives

Most of the investigations on the binding properties of **CD**s, as well as on their water-soluble derivatives, have been carried out in aqueous media where their ability to act as host molecules is expressed in a dramatic manner. This complexing ability is lost completely, however, for most of the lipophilic **CD** derivatives in organic solvents where the **CD** interior shows no preferences as a result of a special relationship with the solvent itself. Therefore, to explore the macrocyclic character of **CD** derivatives in the creation of supramolecular species in nonaqueous media, it has to be another driving force—other than the hydrophobic interactions—which directs the formation of **CD** inclusion complexes in water. Wenz et al.[80] have discovered that **CD** derivatives carrying 3-*O*-acetyl groups can complex with cationic species such as bipyridinium units on account of the high donor strength of the ester carbonyl group. This finding has been used in the construction of the first well-documented **CD**-based [2]rotaxane in an organic solvent.[81] Detailed studies of the formation and properties of rotaxanes incorporating lipophilic **CD**s have been carried out[82] in the case of the preparation (Figure 29) of the [2]rotaxane **47**. The initial stage of this template-directed synthesis involves the recognition of the guest, the substituted pyridylpyridinium monocation **42**, by the host, the *β*-**CD** derivative **43**. Complexation between these two components was, as usual for **CD** complexes, associated with orientational isomerism. The so-called exo complex **44** and the endo complex **45** have been identified

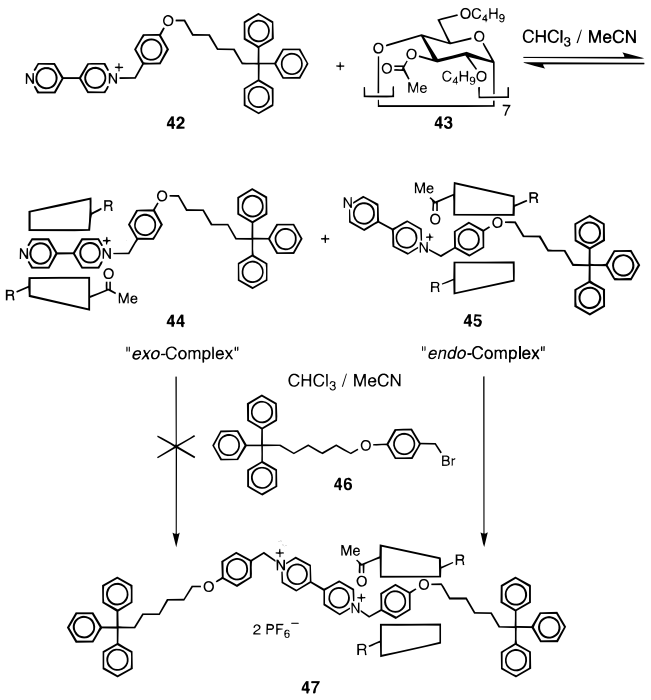


Figure 29. Self-assembly of a [2]rotaxane **47** incorporating the lipophilic **CD 43** in an apolar medium.

unequivocally by ^{1}H NMR spectroscopy. The more stable (K_a = 157 M^{-1}) is the exo complex **44**, and it is characterized by very fast exchange of the complexed and free state of the guest on the ^{1}H NMR time scale. The isomeric complex **45**, with a K_a value of 75 M^{-1}, is exchanging slowly under the same conditions, and it is indeed this species that undergoes quaternization with the bromomethyl derivative **46**, as confirmed by experiments with deutero-labeled **46**. The [2]rotaxane **47** was formed in an excellent 50% yield of which 30% was isolated. It was established by NOE experiments that the **CD** ring in **47** is located almost exclusively on only one side of the [2]rotaxane, as shown schematically in Figure 29. Reaction of **42** and **46** in the presence of the derivative of α-**CD**, with the same substitution pattern as **43**, afforded the [2]rotaxane in 15% yield. However, no rotaxane formation was observed after an attempt to carry out this reaction with the derivative of γ-**CD**, analogous to **43**.

Lipophilic **CD**s have been used for constructing polyrotaxanes. Specifically, Born and Ritter[83] have succeeded in modifying the side chain of the functionalized poly(ether−sulfone) with fully acetylated **CD**s. The **CD**s are located uniformly on the side chains with the secondary faces oriented toward aromatic anilide functions in the "stoppers".

V. Cyclodextrin-Based Catenanes

Until rather recently, the syntheses of molecular compounds containing two or more mechanically interlocked macrocycles—the so-called catenanes—was an extremely challenging task for synthetic chemists. Nowadays, a wide range of catenanes have become available with the development of template-directed methodologies[8,84] which rely upon the self-assembly of components as a result of different and often highly

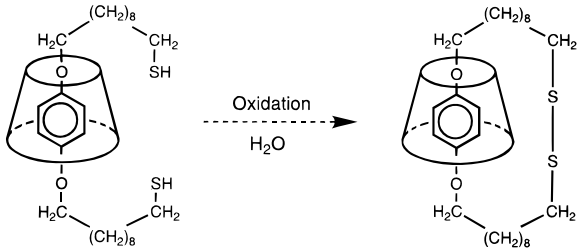


Figure 30. Attempted self-assembly of a catenated **CD** by Lüttringhaus, Cramer, Printzbach, and Henglein in 1958.

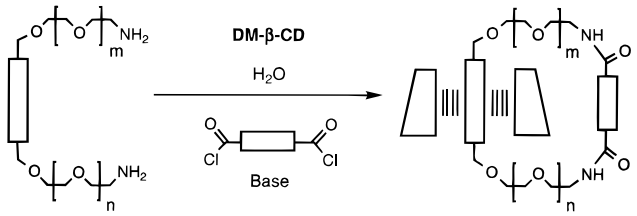


Figure 31. General strategy for making catenated **CD**s.

cooperative interactions. When it comes to constructing catenated **CD**s, the template-direction strategy is based on the same principles which have already been exploited in the preparation of **CD**-containing rotaxanes. On one hand, macrocyclization of a guest molecule which is, in part at least, incorporated inside a **CD** cavity could be favorable on steric grounds. On the other hand, since no third component, such as a blocking group, is needed in the process leading to the formation of a **CD**-catenane, one might expect that catenations would proceed smoothly in comparison with the formation of analogous [2]rotaxanes.

The first attempt to harness the binding properties of **CD**s in the synthesis of a catenane was made away back in 1958 by Lüttringhaus, Cramer, Prinzbach, and Henglein.[85] To marshall the weak noncovalent bonding forces that exist in water between α-**CD** and aromatic substrates, they prepared a series of paraphenylene and biphenyl derivatives bearing two flexible side chains. The end groups of these chains were thiol functions which were expected to form a disulfide bond on oxidation, resulting in the ring closure and, in the presence of α-**CD** or β-**CD**, the formation of a catenane (Figure 30). Unfortunately, no cyclic products, either free or catenated, were isolated following these attempted syntheses and the approach was abandoned. Nevertheless, all the essential design elements that have to be incorporated into a **CD** guest molecule in order to produce a catenated **CD** were recognized in this early work by the Freiburg group. As far as we are aware, their 1958 paper described the first reported attempt to make a catenane. Carbohydrates have attracted the attention of many highly creative chemists, and numerous "firsts" have been recorded[1] using compounds belonging to this class of natural product. With hindsight, what one cay say now is that the first catenanes were close to being carbohydrate in part: it was a "near miss".

In any event, the first successful syntheses of a **CD**-catenanes were realized in 1992 in our own research laboratories[86,87] in Birmingham, U.K. The general

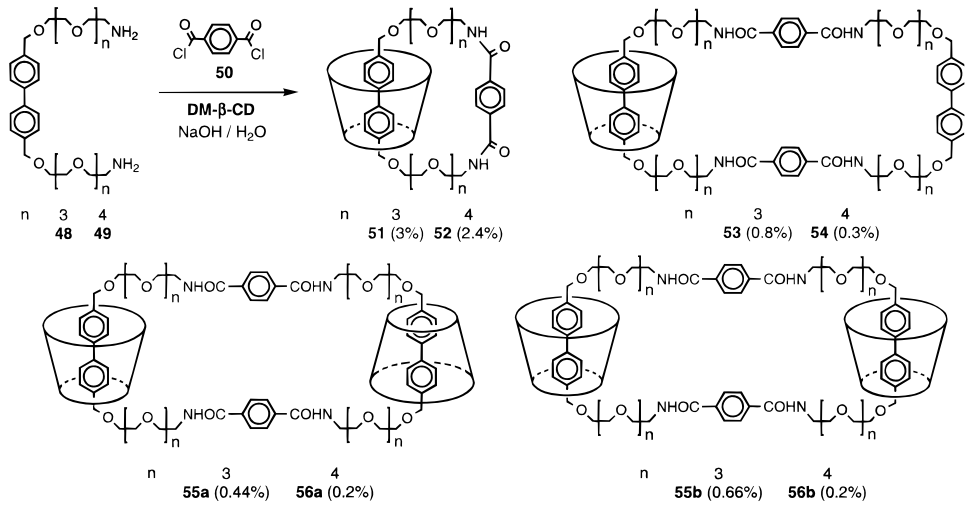


Figure 32. Catenation of **DM-*β*-CD** employing Schotten−Baumann reaction conditions.

strategy used in our approach, which bears some resemblance to the original of Cramer et al.,[85] is outlined in Figure 31. It involves threading of a **CD** by a molecular "string" containing a hydrophilic aromatic core and two hydrophilic polyether-based side chains terminated by amino groups. The rigid aromatic core entices the guest into the **CD** cavity in aqueous solution, whereas the poly(ethylene glycol) chains act as flexible water-soluble spacers predisposed toward macrocyclization and contributing positively to the solubility of the complexes. Both the primary amino groups at the termini of the bound substrate can react with the relatively water-insensitive aromatic dichlorides in a basic aqueous solution of **DM-*β*-CD**, leading to cyclization and the isolation of a [2]catenane.

Inspection of the binding of a broad range of potential molecular "strings" with various different cores and side chains by ***β*-CD**, **DM-*β*-CD**, and **TM-*β*-CD** revealed that the best binding partners were represented by 4,4′-biphenylene compounds and **DM-*β*-CD**. Thus, for the complex between the diamine **48** and **DM-*β*-CD**, a K_a value of 3.3×10^4 M^{-1} was obtained in 0.1 N NaOD/D_2O at 25 °C. With this information in mind and considering the fact that **DM-*β*-CD** has the advantage of exhibiting good solubility both in water and in organic solvents, a series of cyclizations-come-catenations were carried out (Figure 32). All the cyclic and catenated products obtained in the reaction of the diamine **48** and its homologue **49** with terephthaloyl dichloride **50** in the presence of **DM-*β*-CD** could be separated by chromatographic means. Typically, four different catenanes were found in the reaction mixtures—two [2]catenanes incorporating either a monomeric or a dimeric macrocycle and a couple of isomeric [3]-catenanes based on the macrocyclic tetralactam. In addition to these four different catenanes, free macrocycles and polyamides were invariably identified as major side products of the reactions. The relative yields of the "free" macrocycles (not shown in Figure 32) and the catenated products indicate that, somewhat disappointingly, the macrocyclizations, leading to catenane formations, seem to be inhibited by the bound **DM-*β*-CD** components. Not only do these ring components not seem to act as templates for cyclizations, but it is also likely that the cyclization processes leading to the "free" macrocycles are templated by intramolecular stacking interactions between the aromatic residues present in the uncomplexed intermediates.

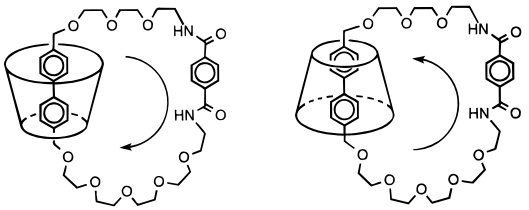


Figure 33. Two orientationally isomeric [2]catenanes **57** and **58**.

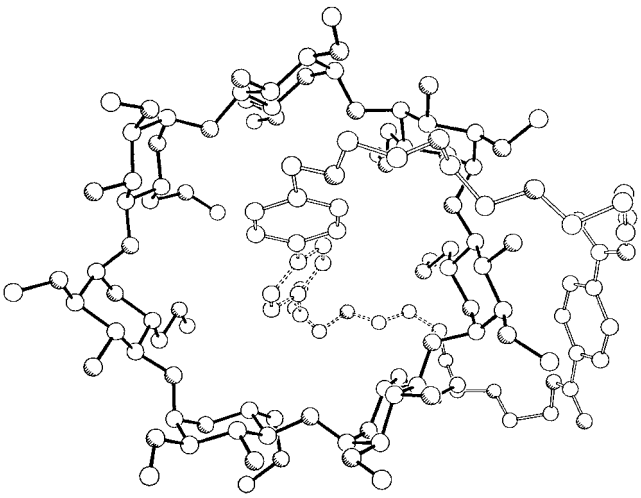


Figure 34. Ball-and-stick representation of the X-ray crystal structure of the [2]catenane **51** in a planar view. Broken bonds correspond to a disordered region of the macrocyclic bis(lactam) component.

The [3]catenanes **55** and **56** represent pairs of head-to-tail/head-to-tail and head-to-head/tail-to-tail isomers that possess different averaged symmetries (C_2 and D_2, respectively) which can be employed in the interpretation of two different sets of NMR spectra. The outcome of these experiments is the unambiguous identification of both isomers. When

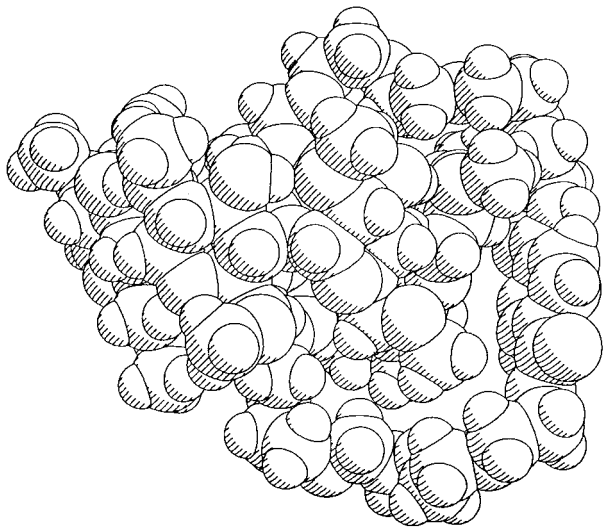


Figure 35. Space-filling representation of the X-ray crystal structure of the [2]catenane **51** viewed in a side-on manner.

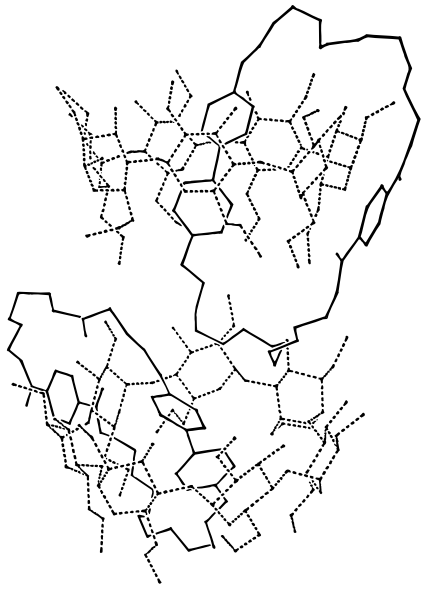


Figure 36. Pseudo-cone-in-cone packing arrangement of the [2]catenane molecules of **51** in the solid state. The **DM-**β**-CD** ring is shown with broken lines, whereas the macrocyclic bis(lactam) is traced out with solid lines.

a constitutionally asymmetrical diamine was used in the catenations with **DM-**β**-CD**, orientational isomers **57** and **58** of a [2]catenane were obtained (Figure 33).

One of the [2]catenanes—indeed compound **51**—afforded good single crystals (following vapor diffusion of diisopropyl ether into an ethanolic solution of **51**) that were suitable for X-ray structural determination. This analysis in the solid state revealed (Figures 34 and 35) that the bitolyl unit of the macrocylic bis(lactam) component is located inside the torus of the **DM-**β**-CD** ring. Surprisingly, there is no hydrogen bonding between the polyether oxygen atoms and the "free" OH groups on the secondary face of the CD. The bis(lactam) group lies against the outer surface of the torus.

The molecules of the [2]catenane **51** pack (Figure 36) in a pseudo-cone-in-cone arrangement such that the lower polyether strand of one [2]catenane molecule is inserted partially into the upper orifice of another molecule and so on throughout the crystal.

The catenated cyclodextrins are quite remarkable compounds insofar as they are soluble in halogenated and aromatic hydrocarbons as well as in hydroxylic solvents. It has been suggested by us that the existence of these particular compounds could give us a unique insight into the nature of the noncovalent bonding interactions that cyclodextrins employ in binding substrate molecules in aqueous solutions.

VI. Concluding Remarks

CD chemistry is notoriously demanding of technique when it comes to chemical synthesis. Many so-called chemically modified **CD**s reported in the literature these last few decades have not been at all well characterized, and surely numerous compounds, assumed to be pure, are indeed highly complex mixtures. It is therefore hardly surprising in a situation, where either a mechanical bond is formed or it is not, that the overall number of **CD**-based rotaxanes, compared with the vast number of well-studied **CD** inclusion complexes including pseudorotaxanes, is still really quite small. The situation is brought even further into focus when it is considered that only one full paper[87] has so far been published describing the synthesis of **CD**-based catenanes. The research described in this paper was undertaken 35 years after the first unsuccessful attempt to catenate a **CD** had been reported[85] back in 1958. Moreover, a good and efficient **CD**-catenane synthesis has still to be announced in the literature. It is clear that the interlocking of the torus-shaped **CD**s with dumbbell and ring components is a pursuit that we are only just beginning to understand and hence know how to tackle. As our knowledge base increases and more and more examples of **CD**-based rotaxanes and catenanes, at both a molecular and macromolecular level, are authenticated, then our ability to involve **CD**s and their derivatives in interlocked compounds will become much more highly developed. The incentives are, as always, with **CD**s, their cheapness, their aqueous solubilities, and their environmentally acceptable forms. The vehicle will be the development of better and better template-directed procedures applicable in aqueous solution that will ensure much improved self-assembly processes leading to many **CD** derivatives of an interlocked nature. The result of this kind of chemistry will be to provide compounds not only with fascinating and exotic forms but also with functions that could find applications in a nanotechnological context if we should ever learn how to address the microscopic world of molecular machines[88,89] from the macroscopic world in which we live.

This review article describes seminal contributions to a relatively new area of research in cyclodextrin chemistry by a very few pioneers. Take away the contributions over the last 5 years by Born and Ritter, by Harada and Kamachi, by Kaifer, by Macartney, by Matsuo, by Nakashima, and by Wenz and there would be little left to write about in the form of a detailed review. This article is a tribute to their

innovation and invention. We thank Dr. Gerhard Wenz for sharing some of his most recent results with us in the form of preprints of manuscripts recently submitted for publication. It is fitting to end this review with mention of the latest piece of elegant chemistry announced in a communication[90] from the Karlsruhe laboratories. In it, Wenz et al.[90] describe the photochemical synthesis of polyrotaxanes from stilbene polymers and a mixture of β- and γ-**CD** in an aqueous solution. In addition to stilbene units, the polymer contains quaternary ammonium centers, as well as hexa- and decamethylene chains. When the supramolecular complex with the **CD**s is irradiated at 312 nm for 30 h, a polyrotaxane, from which unthreading of the **CD** rings is prevented by the formation of bulky tetraphenylcyclobutane groups, was isolated. The authors claim that this experiment represents "the first demonstration of the supramolecular catalysis of a polymer-analogous conversion; that is, a conversion of the repeating units without changing the length of the polymer chain."

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(91) Abbreviations: **CD**, cyclodextrin; α-**CD**, α-cyclodextrin; *β*-**CD**, *β*-cyclodextrin; *γ*-**CD**, *γ*-cyclodextrin; **DM**-*β*-**CD**, per(2,6-di-*O*-methyl-*β*-cyclodextrin); **TM**-*β*-**CD**, per(2,3,6-tri-*O*-methyl-*β*-cyclodextrin).

CR970049W