Cyclodextrin Rotaxanes and Polyrotaxanes

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1. Introduction

Rotaxanes are molecular species consisting of one or more rings and one or more axes, where the dissociation of a ring from an axis is hindered by bulky groups (so-called stoppers) at both ends of the axis.[1] Rotaxanes are examples of mechanically interlocked molecules.[2−4] Since the pioneering work of Lüttringhaus,[5] Wasserman,[6] Harrison,[7] and Schill[1,8] more than 30 years ago, interlocked compounds, such as catenanes, rotaxanes, and knots,[9] have been of steadily increasing interest, because they allow one to construct functional molecular devices of high sophistication.[10−14] For the sake of comprehensiveness, this review was limited to rotaxanes, which are the most referenced class of interlocked compounds.

Although they contain no covalent bond between axes and rings, rotaxanes are stable entities, because a high free activation energy, $\Delta G^{\ddagger}_{diss}$, has to be overcome to withdraw a ring from the axis of a rotaxane (Figure 1). Like every other molecular entity, rotaxanes can be covalently linked together in many ways to create oligomeric or polymeric species, called polyrotaxanes. Molecular entities with covalent linkages between the axes, between the rings, and between the axes and the rings are already known. If the sum of the numbers of rings and axes in a rotaxane *n* is well-defined, this number is given in square brackets: [*n*]-rotaxane. For full nomenclature of rotaxanes, we refer the reader to recent publications.[15,16]

Threading of the axis through the ring is a necessary requirement for the synthesis of a rotaxane. Rotaxane yields are generally low in the absence of any specific interaction between axis and ring. On the other hand, host−guest interactions between axis and ring often lead to high rotaxane yields. This so-called template method[17−19] has proven to be very successful. Many complexes of organic cyclic host compounds, such as donor−acceptor complexes,[13,20,21] transi-

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Gerhard Wenz studied chemistry at the Universities of Mainz and Freiburg, Germany, and received his Ph.D. in 1984 on the topochemical polymerization of diacetylenes in the group of Professor Gerhard Wegner. He worked for another year in Freiburg on discotic liquid crystalline polymers at the Hermann-Staudinger-Institute. In 1985 he worked as a Postgraduate Research Fellow with Professor Donald J. Cram at the University of California in Los Angeles and synthesized a model for the enzyme chymotrypsin. Afterward he moved to the Max-Planck-Institute of Polymer Research in Mainz, where he finished his habilitation in 1993. From 1993 to 2000 he was Professor of Macromolecular Chemistry in Karlsruhe, Germany. In 2000, he became full Professor of Organic and Macromolecular Chemistry at Saarland University in Saarbrücken, Germany. Professor Wenz coordinated from 1996 to 1998 a European research network on "utilization of cyclodextrin", and from 1996 to 2003 a nationwide research network of the Deutsche Forschungsgemeinschaft (DFG) on cellulose chemistry together with Professor Dieter Klemm from Jena University. In the past decade, his group has mainly worked on the synthesis of hydrophilic polymers, cyclodextrin, and cellulose derivatives, and on the investigation of self-organization processes in aqueous solution and at planar surfaces.

Bao-Hang Han was born in 1967 in Jiangsu, China. He obtained his B.Sc. (1989), M.Sc. (Organic Chemistry, under the supervision of Prof. Jin-Pei Cheng, 1992), and Ph.D. (Physical Organic Chemistry/Supramolecular Chemistry, under the supervision of Prof. Yun-Ti Chen and Prof. Yu Liu, 1999) degrees at Nankai University, Tianjin, China. He has been a Lecturer and an Associate Professor at the Department of Chemistry, Nankai University. He worked as a Postdoctoral Fellow at Max-Planck Institute of Colloids and Interfaces, Germany, with Prof. Markus Antonietti (2000–2002), at the Department of Chemistry, University of Ottawa with Prof. A. Sayari (2002–2003), and at the Department of Chemistry, University of Toronto with Prof. Mitchell A. Winnik and Ian Manners (2003–2004). His research included molecular recognition of native and artificial molecular receptors, preparation of nanoporous materials templated by cyclodextrin complexes and assemblies, and the phosphorescent oxygen sensor. He joined the newly founded National Center for Nanoscience and Technology, China, as a Research Professor in 2005. His research interests are nanomaterials and supramolecular chemistry.

tion metal complexes,[22−24] crown ether complexes,[25] and hydrogen bond complexes of cyclic amides,[14,26−30] have

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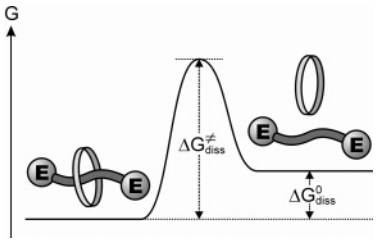

Figure 1. Energy diagram for a [2]-rotaxane and its constituents: E = end group.

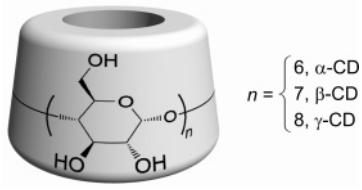

Figure 2. Schematic drawing of cyclodextrins (CDs).

indeed been used for rotaxane synthesis, but cyclodextrin inclusion compounds have been used most, because cyclodextrins are readily available and can be functionalized in well-defined ways.

Cyclodextrins (CDs) are 1 → 4 α-linked cyclic oligomers of anhydroglucopyranose.[31−33] Those CDs consisting of six, seven, or eight glucose entities are called α-, *β*-, or *γ*-CDs. CDs assume a toroidal shape with the primary hydroxyl groups at the narrow side and the secondary hydroxyl groups at the wide side (Figure 2). CDs offer several advantages compared to other ring molecules: CDs are readily available in both high purities and large quantities. Furthermore, CDs can be functionalized by a wide variety of synthetic methods.[31,34] They are water-soluble and biocompatible. CDs spontaneously incorporate guest molecules, a necessary prerequisite for rotaxane formation. CDs are good candidates for sophisticated drug delivery systems. Sensitive dye molecules or molecular wires can also be protected against decomposition by "rotaxanation" within CD cavities. As a consequence, the importance of CD rotaxanes has significantly increased within the last five years. CD rotaxanes have developed from milligram lab curiosities to readily available compounds providing very promising new applications.

This review covers both synthesis and properties of CD rotaxanes and pseudorotaxanes as published over the last seven years. Work prior to 1998, including work on CD catenanes,[35] has been summarized in the past.[36] This topic was also reviewed recently in part by Harada.[37,38] More general overviews about interlocked structures of other rings, for example, crown ethers, cucurbituril, and cyclic ureas, have been provided by Stoddart and co-workers.[39,40]

Besides synthetic aspects, this review also addresses the structural evidence for rotaxane structures. Ten years ago, it was difficult to convince the scientific community that hundreds of CD rings spontaneously thread onto a polymer chain. In the meantime, threading has been proven unambiguously by many authors using a great variety of physicochemical and theoretical methods. Rotaxane formation requires an axis to penetrate through a CD ring, leading to a so-called axial inclusion compound. General rules for the formation of axial CD inclusion compounds and their different constellations are described in the following. The word "constellation" is used here in the figurative sense for the well-defined spacial arrangement of molecules.

2. Axial Cyclodextrin Inclusion Compounds

2.1. General Considerations

The major driving forces of the formation of CD inclusion compounds are hydrophobic and van der Waals interactions between the inner surface of the CD ring and the hydrophobic sites on the guest.[41] The higher the binding constant, K_s, of a CD inclusion compound is, the better a guest fills out the CD cavity. Guests exhibiting strong dipole moments, for example, *p*-nitrophenol, are additionally bound by dipole−dipole interactions because of the strong axial dipole moment of CDs.[42] Charge-transfer interactions between CDs and certain guest molecules were also discussed.[43] It is difficult to find a universal binding theory because the constellations of CD inclusion compounds show a great variety.

The formation of axial inclusion compounds is mainly governed by the thickness of the guest compared to the internal diameter of the CD. As shown by molecular modeling studies, the guest experiences a bottleneck at the level of the H-5 hydrogens (Figure 3) invading the CD cavity.[44] The diameter of the hydrophobic part of the guest has to be less than the minimum diameter d_{min} to permit the formation of a stable axial inclusion compound. The values of d_{min} are listed in Table 1. Guests thicker than d_{min} do not penetrate the cavity. They are preferably bound between two CDs in a sandwichlike arrangement.

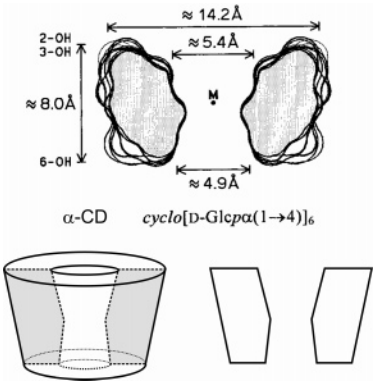

Figure 3. Schematic drawings of the shape of the CD torus, with cuts along the C_n axis: top, as calculated by Lichtenthaler et al. (Reprinted with permission from ref 44. Copyright 1994 Elsevier Ltd.); bottom, idealized drawings.

Table 1. Minimum Internal Diameters d_{min} and Cross-Sectional Areas A_{min} of CDs[45]

CD	d_{min}/Å	A_{min}/Å^2
α-CD	4.4	15
β-CD	5.8	26
γ-CD	7.4	43

The spacial arrangements of CD inclusion compounds strongly depend on the polarity pattern of the guest. Guests can be classified into three major groups: (A) channel inclusion compounds of nonpolar guests, (B) inclusion compounds of amphiphilic guests, and (C) axial inclusion compounds of bola-amphiphiles.

2.2. Channel Inclusion Compounds

In CD channel inclusion compounds CD rings are piled up to columns in a way that CD cavities are interconnected (Figure 4a).[46] These columns are parallelly packed to form crystals that are generally almost insoluble in water. CD channel structures are formed, when guests are totally hydrophobic or able to associate in one dimension, for example by hydrogen bonds. CD channel inclusion compounds are stabilized by intermolecular hydrogen bonds between CD hydroxyl groups. As primary hydroxyl groups fit best to primary ones and secondary hydroxyl groups fit best to secondary ones, a head-to-head and tail-to-tail orientation of the CDs within a column (Figure 4a) should be favored over a head-to-tail orientation. This is indeed the case for channel inclusion compounds of *β*-CD, but for those of α-CD, both orientations exist.[46] These inclusion compounds only dissolve in strongly polar organic solvents, such as dimethyl sulfoxide, leading to dissociation into the free components. Therefore, solution spectroscopic methods such as NMR spectroscopy only provide the stoichiometry of the inclusion compound. The structure of channel inclusion compounds has to be investigated by solid-state methods such as wide-angle X-ray scattering (WAXS), IR, or solid-state NMR spectroscopy, CP-MAS-NMR. X-ray structure analysis was applied in those cases where single crystals could be grown.[46]

α-CD forms head-to-head channel inclusion compounds with linear alkanes, for example, *n*-pentane and *n*-hexane,[47] in which the guests are packed within the channel in *all-trans* conformations showing limited mobility.[48] Valeric acid also forms a channel inclusion compound with α-CD where the guests dimerize via the carboxy groups by strong hydrogen bonds.[49] On the other hand, thicker guests such as *p*-fluorophenol and hydroquinone form head-to-tail channel inclusion compounds.[46]

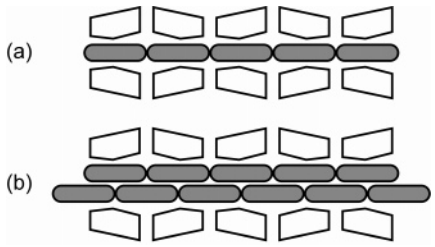

Figure 4. Schematic drawings of different constellations of CD channel inclusion compounds: (a) simple head-to-head channel inclusion compound; (b) double-stranded head-to-head channel inclusion compound.

β-CD is much better suited to accommodate benzene derivatives than α-CD. Hydrophobic monosubstituted and *p*- or *m*-disubstituted benzene derivatives generally form channel inclusion compounds. The X-ray structure of the 1:1 inclusion compound of *tert*-butyltoluene in β-CD shows a head-to-head channel packing. Likewise, tridecanoic acid forms a channel inclusion compound with β-CD in which the alkyl chains are contorted to fill the β-CD cavity while the carboxy groups are dimerized via hydrogen bonds.[50,51]

γ-CD is able to incorporate rather big guests such as 12-crown-4 within a channel structure.[46] Furthermore, γ-CD is already large enough to accommodate two rodlike guests, e.g., diphenyl hexatriene, resulting in a double-stranded channel inclusion compound (Figure 4b). Within these channel structures, guests often show a brick pattern. These special channel structures, called "nanotubes", are more stable than regular channel structures. Even in solution (solvent: water/DMF mixtures), the channel structure remains intact in the form of columnar aggregates of approximately 30 CD rings filled by the guests. These columnar aggregates were investigated by STM[52] and dynamic fluorescence spectroscopy.[53,54] Slightly different γ-CD nanotubes were formed by double-stranded inclusion of 2,5-diphenyloxazole[55,56] and polyconjugated Schiff bases, respectively.[57] As these guests are partially hydrophilic, the packing of CD rings is more flexible and less dense within the one-dimensional array. Consequently, these nanotubes are more soluble in water.

Interestingly, empty native CDs do not crystallize in channel structures but in a herringbone type of packing. Therefore, CD channel inclusion compounds can easily be distinguished from native CDs by wide-angle X-ray diffraction. Volatile guests such as pentane were removed from the channel inclusion compounds by heating to obtain metastable empty CD channel structures.[47] Recently, empty CD channels could also be obtained by simple precipitation of CDs, but experimental conditions seem to be rather delicate.[58]

2.3. Inclusion of Amphiphiles

Most publications about CD inclusion compounds are dealing with the inclusion of amphiphilic guests. In general, these inclusion compounds are water-soluble. While the hydrophilic head group prefers to stay in an aqueous environment, the hydrophobic tail is included in the CD cavity (Figure 5). Repulsive forces between head groups prevent further aggregation of the inclusion compounds to columnar assemblies.

The water solubility of these inclusion compounds enables detection of complex formation in solution by spectroscopic methods, such as NMR,[59] UV, fluorescence, or circular dichroism spectroscopy, as well as by thermodynamic methods, e.g., microcalorimetry[60] or density,[61,62] or by solubility measurements. Likewise, mass spectrometry was used.[63] The kinetics of complex formation are generally ultrafast, as no steric barrier has to be overcome.[64] The fast orientational dynamics within CD inclusion compounds were measured by time-resolved polarization spectroscopy.[65]

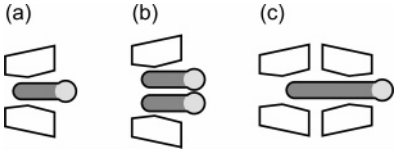

Figure 5. Schematic drawings of possible inclusion compound constellations of amphiphilic guests (hydrophobic parts of the guests are marked in dark gray, and hydrophilic parts, in light gray): (a) 1:1; (b) 1:2; (c) 2:1 stoichiometry of CD/guest.

Binding constants, K_s, as well as binding enthalpies and entropies are obtainable from the concentration and temperature dependence of the degree of inclusion. The most reliable and accurate method is isothermal microcalorimetric titration (ITC), which provides not only the binding constant, K_s, but also the binding enthalpy and entropy. Binding data have already been extensively reviewed.[66,67] The better the hydrophobic part of a guest fills the hydrophobic CD cavity, the higher is the value of K_s.[68] Binding constants in water usually range between 10^2 and 10^4 M^{-1}. Sometimes even higher values up to 10^5 M^{-1} have been observed, for instance, for adamantane derivatives in β-CD.[67] Hydrophilic substituents at the guest diminish the binding constant, whereas hydrophobic ones increase it, showing that hydrophobic and van der Waals interactions are the major driving forces for inclusion compound formation.[60] In the case of oppositely charged hosts and guests, binding constants were additionally enhanced by Coulomb interactions.[69,70]

Only for guest molecules with long hydrophobic chains was convincing evidence provided for a complete penetration of a CD cavity. These inclusion compounds showed a 2:1 stoichiometry (Figure 5c).[59,71]

As already described for channel inclusion compounds, α-CD includes linear alkyl derivatives,[59] while β-CD accommodates benzene derivatives (Figure 5a). γ-CD is able to incorporate two guests (Figure 5b), for example, naphthalene,[69,70] phenothiazine,[72] or pyrene[73] derivatives. These 2:1 inclusion compounds exhibit strong excimer fluorescence signals because of the tight neighborship of the chromophores.

2.4. Inclusion of Bola-Amphiphiles

Amphiphiles with two hydrophilic end groups are commonly called bola-amphiphiles.[74] In fact, bola-amphiphiles can form 1:1, 2:1, and 1:2 inclusion compounds (Figure 6) like other guests. On the other hand, bola-amphiphiles show inclusion dynamics significantly different from those of regular amphiphiles. Inclusion of bola-amphiphiles occurs much slower than inclusion of regular ones, because a hydrophilic end group has to pass through the hydrophobic CD cavity anyway. The penetration of the hydrophilic end group requires a considerable amount of activation energy, due to steric repulsion and desolvation work. Consequently, the guest remains within the cavity for a noticeably long time. Therefore, NMR signals are not averaged, as observed for inclusion compounds of regular amphiphiles, but split into distinct signals of the free and associated CD and guest molecules (Figure 7).[75−77] The amount of complex formation is obtained conveniently from the integrals of these separate ^{1}H NMR signals. The nuclear Overhauser effect (NOE) between protons of CD and guest is rather strong due to the long residence time of the guest within the CD.[78]

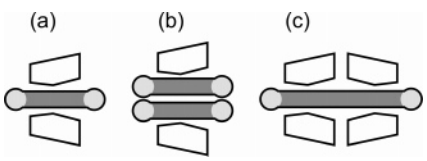

Figure 6. Schematic drawings of CD inclusion compounds of bola-amphiphiles: (a) 1:1; (b) 2:1; and (c) 1:2 stoichiometry.

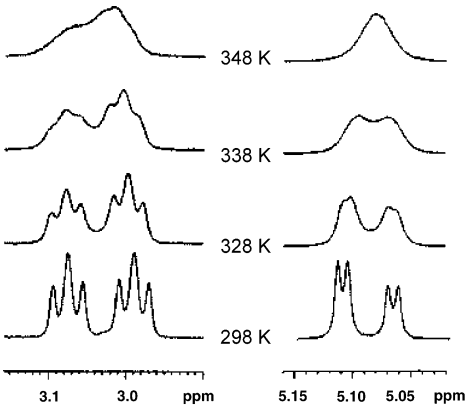

Figure 7. Partial ^{1}H NMR spectra of a D_2O solution of 1 equiv of $NH_3^+-(CH_2)_{12}-NH_3^+$ and 1.7 equiv of α-CD at various temperatures showing free and associated entities: (a, left) section of the α-methylene groups of the guest; (b, right) anomeric protons H-1 of α-CD. Reprinted with permission from ref 77. Copyright 2002 American Chemical Society.

Table 2. Kinetic and Thermodynamic Data for the Dissociation of Axial Inclusion Compounds of Bola-Amphiphiles E−(CH$_2$)$_n$−E in Aqueous α-CD Solution at Room Temperature[a]

end group E	n	$\tau_{1/2}$	$\Delta G^{\ddagger}_{diss}/RT$	$\Delta H^{\ddagger}_{diss}/RT$	$\Delta G^{\circ}_{diss}/RT$	ref
COO^-	12	1 s	29.8	29.5	8.7	76
NH_3^+	10	0.25 s	28.4		7.7	77
NH_3^+	12	1.3 s	30.1		8.9	77
3-CN−pyridinium	10	4.3 min	35.4	37.5	6.8	86
NMe_3^+	10	8 h	40.1	36.5	8.0	87
		1.8 h	38.4		7.4	88

[a] ΔG°_{diss} = free energy of dissociation; $\Delta H^{\ddagger}_{diss}$ and $\Delta G^{\ddagger}_{diss}$ = activation enthalpy and free activation energy (Eyring's free energy) of dissociation; $\tau_{1/2}$ = half-life of the supramolecular structure.

Those bola-amphiphiles which contain a linear alkyl chain were mainly investigated. The thermodynamic stabilities scarcely depend on the nature of the hydrophilic end groups of these bolas (Table 2) but strongly increase with the length of the alkyl chain. Charged end groups prefer to stay outside the CD cavity. They even seem to exert some repulsive force on the CD ring. This explains why short bolas (for example, $NH_3^+-(CH_2)_6-NH_3^+$) are not complexed at all by α-CD,[77] whereas very long bolas, e.g., $NMe_3^+-(CH_2)_{22}-NMe_3^+$, are able to take up two CD rings, as shown in Figure 6c.[79]

The inclusion dynamics strongly depend on the size and the charge number of the end groups (Table 1). Both the activation enthalpy, $\Delta H^{\ddagger}_{diss}$, and the free activation energy, $\Delta G^{\ddagger}_{diss}$, are similar within the experimental error (Table 2), which means that entropic effects are neglectable. Kinetics are mainly controlled by steric hindrance. Amino end groups are small enough to provide a fast exchange between complexed and uncomplexed guests, whereas ammonium groups already lead to a slow exchange at room temperature. The guest $NH_3^+-(CH_2)_{12}-NH_3^+$ already remains for seconds within the cavity, while the exchange becomes more rapid at higher temperatures (Figure 7 and Table 2).[77] The larger trimethylammonium groups cause such a high steric hindrance for α-CD that the half-life $\tau_{1/2}$ of the complex reaches several hours (Table 2). Even longer complexation times were observed for bolas with 4,4′-bipyridinyl end groups.[80] On the other hand, if the larger β-CD ring was threaded on a bis-trimethylammonium bola-amphiphile, rapid exchange was observed on the NMR time scale,[79] showing again that inclusion kinetics are mainly determined by steric effects. Recently, kinetically controlled undirectional threading of α-CD was observed for a bola-amphiphile equipped with two different bulky end groups. α-CD preferentially threads onto the smaller end group with its wider secondary side first.[81,82]

Inclusion compounds of bola-amphiphiles with quarternary ammonium end groups are nearly as stable as rotaxanes. This raises the question: *Are* they rotaxanes? It is still under discussion.[83] We decided on not classifying them as rotaxanes as they are not really stable compounds, but supramolecular structures. A free activation energy of dissociation, $\Delta G^{\ddagger}_{diss}$, of more than 50*RT* should be required for a rotaxane to guarantee a lifetime of more than several years. Isolatable supramolecular structures[84] stabilized by less than 50*RT* are herein called pseudorotaxanes.[20]

Bola-amphiphiles derived from hydrophobic spacers other than linear alkyl chains were also included in CDs. The aromatic azo dye congo red was threaded through γ-CD.[78] 4,4′-Bis(*N*,*N*-dimethylaminomethyl)stilbene is axially included in α-CD (1:1) and γ-CD (2:1).[89] The 2,6-disubstituted naphthalene dye PRODAN forms axial 1:1 inclusion complexes with β-CD and 2:1 complexes (Figure 6b) with γ-CD. Inclusion was well detectable by fluorescence spectroscopy due to the strong solvatochromism of this dye.[90] Together, naphthalene-2,6-dicarboxylate and 2,6-bispyridinomethylnaphthalene form a very stable ternary inclusion compound with γ-CD. This inclusion compound gains additional stabilization from attractive Coulomb forces between the two complementary guests.[69]

3. Synthesis of CD [2]-Rotaxanes and [3]-Rotaxanes

3.1. General Considerations

There are two different approaches currently available for the synthesis of CD rotaxanes, depicted in Figure 8. CD rotaxanes are generally synthesized by method *a* by attaching bulky substituents (so-called stoppers) to both ends of an included axis molecule, the so-called "threading" approach (Figure 8a$_1$).[36] The coupling reaction of the stoppers to the threaded axis is termed the "rotaxanation reaction" (Figure 8a$_2$). CD rotaxanes are also synthesized by method *b* by threading a CD ring over a dumbbell, called "slippage" (Figure 8b), which mostly leads to pseudorotaxanes.[75,77,83,91−93] A third, hypothetical method, called "clipping",[36] would be a ring closure of an acyclic maltooligosaccharide around a dumbbell. The "clipping" approach has not been put in practice yet and, as a matter of fact, does not sound very promising at all for the synthesis of CD rotaxanes. Interaction between the acyclic oligomer and the dumbbell would be

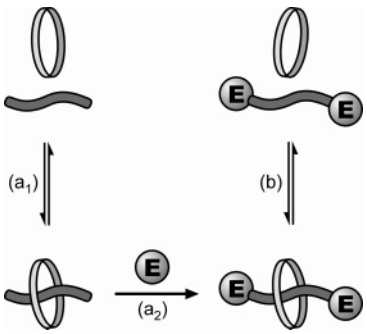

Figure 8. Reaction scheme for the synthesis of CD [*n*]-rotaxanes: (a$_1$) by threading; (a$_2$) by rotaxanation; (b) by slippage. E = end group.

too weak, and cyclizations leading to CDs suffer from low yields.[94] Clipping might rather be the favorite approach for rotaxane synthesis from those cyclic oligosaccharides[94] different from CDs.

Synthesis of CD rotaxanes according to the threading approach is not as simple as it may look at first glance. Several requirements have to be met for a high yield rotaxane synthesis: (a) The axis molecule has to form a stable axial inclusion compound with the CD. (b) The axis has to be long enough to outreach the CD cavity in order to allow the attachment of stoppers. (c) The inclusion compound of the axis has to be soluble. (d) The solvent should not cause dissociation. Since the inclusion is mainly driven by hydrophobic interactions, only water and, to some extent, other highly polar solvents, such as dimethyl sulfoxide and dimethyl formamide, are applicable. (e) The rotaxanation reaction should provide high yields within the solvent necessary for threading. (f) Both stopper and rotaxane should be soluble in this solvent to allow homogeneous reaction conditions. (g) The stopper should be large enough to prevent dethreading. (h) The resulting rotaxane should be isolable from the reaction mixture.

As a consequence of these requirements, coupling reactions with high steric demand and those needing inert anhydrous conditions have to be avoided. Bola-amphiphiles are best suited as axis molecules for stability and solubility reasons. In addition, hydrophobic stoppers can cause solubility problems and high reaction temperatures may lead to dissociation of the axial inclusion compound, both aspects unfavorable for rotaxane formation. The polarities and solubilities of CDs and stoppers should differ enough from each other to allow the separation of the rotaxane from free CD and the free dumbbell by chromatography or precipitation.

3.2. Rotaxanation Reactions

Coupling reactions of terminal amino groups are quite useful for the synthesis of CD rotaxanes. Bola-amphiphiles with amino end groups are well suited if the length of the hydrophobic spacer exceeds 1.0 nm (8 bond lengths). In the year 1981, Ogino reported the first synthesis of a CD rotaxane in 19% yield by coupling bulky bis(ethylenediamine)cobalt(III) complexes to 1,10-diaminodecane threaded through α-CD in DMSO solution. The rotaxane was isolated by size exclusion chromatography over Sephadex.[95] Later, coordination of terminal nitrogen ligands to transition metals, for example, coordination of pyridine, pyrazine, or nitrile ligands to $[Fe(CN)_5OH_2]^{3-}$, was also used for high yield synthesis of rotaxanes in aqueous solution.[86,96,97] A major drawback of the use of iron complexes in rotaxane synthesis is their insufficient long-term stability. Addition of competitive ligands such as DMSO to such rotaxanes already causes their cleavage. Coordination of Ru^{3+} by *N*-heterocycles leads to more stable rotaxanes, as these complexes are kinetically inert.[98] The Co^{3+} complex cobalamin (vitamin B_{12}) reacts with 1,12-dibromododecane in a displacement reaction under formation of stable Co−C bonds. When this coupling reaction was carried out in the presence of α-CD, a stable rotaxane with bulky cobalamine stoppers was formed in 50% yield.[99]

Terminal amino groups of bola-amphiphiles were also coupled to stoppers via C−N bonds. Thus, 1,12-diaminododecane complexed by methylated α-CDs was reacted with 2,4,6-trinitrobenzenesulfonic acid in aqueous solution to provide the corresponding [2]-rotaxanes in 42−48% yields. Methylated CDs, hexakis(2,3,6-tri-*O*-methyl)-α-CD and hexakis(2,6-di-*O*-methyl)-α-CD, were used as ring components because their inclusion compounds are more water-soluble than those of α-CD. Since the resulting rotaxanes are insoluble in water but soluble in organic solvents, they could easily be isolated.[100] The same stopper was used for the synthesis of other α-CD rotaxanes with longer axes[101] and for those with stilbene axes **1**.[102,103] Amino groups were also coupled to stoppers functionalized with chlorotriazine to furnish azobenzene rotaxanes.[104] The azo coupling of terminal diazonium groups and electron rich aromatic stoppers leads to [2]- and [3]-rotaxanes **2** and **3** in moderate (9% and 12%) yields.[105,106]

Besides the described coupling reactions of nitrogen nucleophiles, transition metal catalyzed C−C bond formation is also useful for rotaxanation. While Cu-catalyzed Glaser coupling was tested unsuccessfully for the synthesis of CD rotaxanes,[108] Pd-catalyzed Suzuki coupling of bola-shaped α,*ω*-bisboronic esters of biphenyl, stilbene, and tolane (1,2-diphenylethyne) with water-soluble aromatic iodides gave rise to [2]-rotaxanes in high yields.[107] $Pd(OAc)_2$, having little steric demand, was used as the catalyst. 5-Iodoisophthalic acid was more suitable as a stopper than the larger 1-iodonaphthalene-3,6-disulfonate, possibly because of steric reasons. The α-CD rotaxane **4** (Figure 9) with isophthalic acid stoppers was synthesized in an excellent yield of 73%.[107] The same strategy also furnished the α-CD divinylbenzene rotaxane **5** (Figure 9) in 46% yield.[109] On the other hand, the isophthalic acid stopper was too small to prevent *β*-CD from dethreading. Therefore, the larger naphthalene-3,6-disulfonate stopper was necessary to create *β*-CD rotaxanes by Suzuki coupling.[107] The classical aldol type condensation of an aldehyde with a CH-acidic 4-methylpyridinium derivative also furnished a rotaxane of a cyanin dye in low yield (6%).[110,111]

3.3. Structural Evidence for Rotaxane Formation

The only unambiguous proof for the formation of a rotaxane is a highly resolved X-ray structure. This method requires suitable rotaxane crystals, which are only seldom available. The only X-ray structures available thus far are those of the rotaxanes **1**,[102] **4**,[107] and **5**[109] (Figure 9), which show that the diameter of the stopper only needs to be a little bigger than the diameter of the CD cavity to guarantee stability of the rotaxane.

Mass spectrometry (MS) indeed provides some fast and straightforward evidence for the existence of [2]- or [3]-rotaxanes, but conclusions have to be drawn with care.[108,112] The absence of the molecular ion of the rotaxane does not necessarily imply that no rotaxane was formed, because other constituents, such as salts, might prevent evaporation of the rotaxane. Conversely, the detection of the molecular ion does not sufficiently prove the existence of a rotaxane, as both rotaxane and an aggregate of a ring and a dumbbell cannot be distinguished by MS. Control experiments have to be performed to distinguish aggregates from the rotaxane. The absence of any exchange of constituents of a rotaxane, especially at elevated temperatures, gives proof of its stabilty.[113]

NMR spectroscopy provides some direct evidence for rotaxanation, if the signals of the axis atoms are doubled due to the asymmetry of the surrounding CD ring.[105] The nuclear Overhauser effect (NOE), especially between the

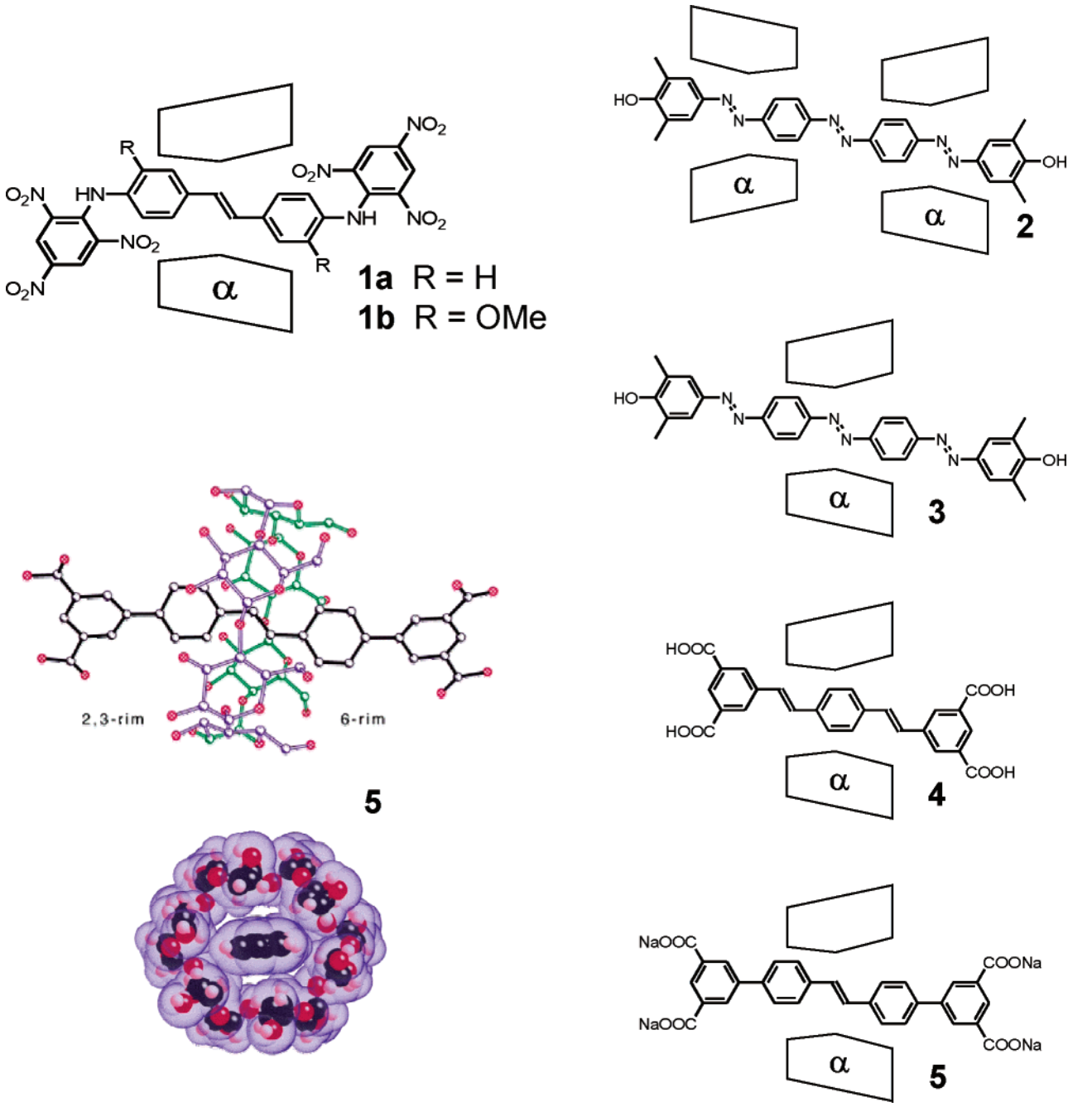

Figure 9. Selected CD rotaxanes. (X-ray structure of **5** reprinted with permission from ref 107. Copyright 2001 The Royal Society of Chemistry.)

internal protons C3−H and C5−H of CD and the protons of the axis, is indicative for rotaxane formation as well (Figure 10).[102,103,114] If the CD ring can move along the rotaxane axis, its favorite place at the axis can be localized by an NOE. No NMR method is able to distinguish rotaxanes from pseudorotaxanes. A temperature program has to be run up to at least 80 °C to demonstrate the stability of a rotaxane.

4. Functions of CD Inclusion Compounds and Rotaxanes

4.1. Shielding of the Guest

A guest molecule within a CD cavity experiences a well-defined unreactive nonpolar environment. This effect is more pronounced in rotaxanes than in inclusion compounds, because the CD environment remains permanently around the guest. The CD environment can reduce thermal deactivation of the excited state of a dye molecule, which leads to improved fluorescence quantum yields.[108,110] In addition, dyes can be chemically stabilized, because the surrounding CD ring shields the excited dye against attack by other molecules. Consequently, photobleaching can be strongly retarded by CD inclusion.[104,110,115,116] These shielding effects can be applied to improve both quantum yields and stabilities of laser dyes in aqueous solution.[117] Shielding by CD rotaxanation also has facilitated electron transfer between Fe and Ru complexes via an interrupted π-electron system.[98]

CD rotaxanation of dyes was used to fix those at surfaces within color image processes.[118] α-CD encapsulation of azo sensitizer dyes was employed to attach the dye to a nanocrystalline TiO_2 film via the adsorption of the CD

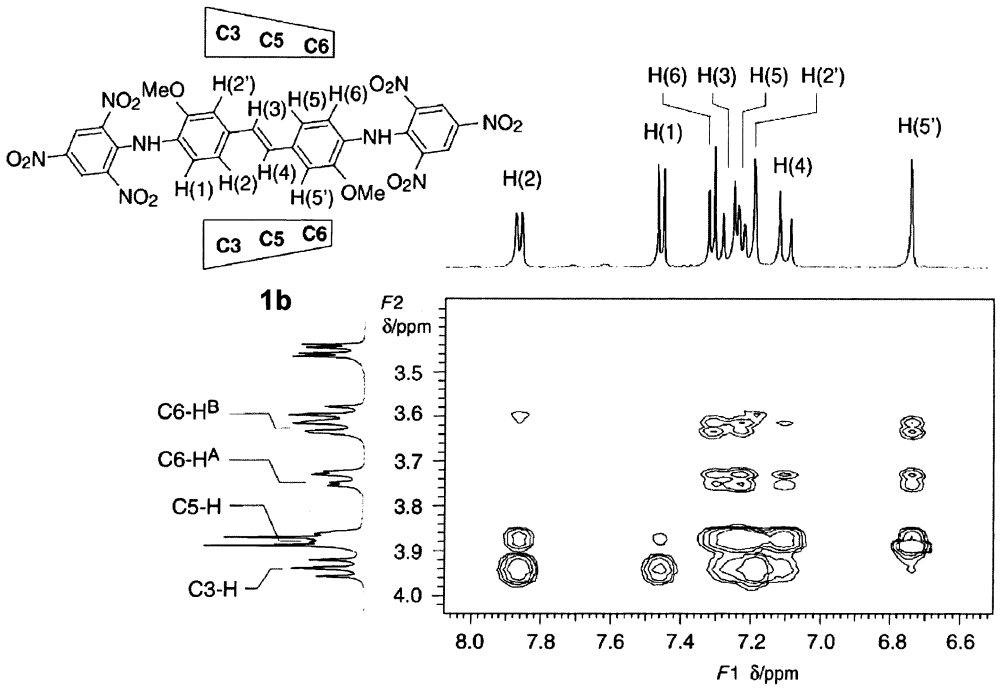

Figure 10. ROESY−NMR spectrum of the α-CD [2]-rotaxane **1b**. Reprinted with permission from ref 102. Copyright 2003 Wiley-VCH.

hydroxyl groups and to stabilize the charge-separated excited state of the dye. The charge recombination half-life was increased by CD rotaxanation from 0.3 to 4.0 μs. The hydrophobic inner cavity of CD seems to be a barrier for charge recombination.[106] Slow charge recombinations and the absence of side reactions are requirements for the creation of highly efficient light harvesting systems. Therefore, CD rotaxanes of dyes are good candidates for solar energy utilization.[119]

Shielding by CDs also applies for reactions other than photoreactions. For example, stilbenes are prone to addition reactions on the double bond. Rotaxanation by CD can protect a stilbene moiety against the attack of reagents such as dimethyl dioxirane that would otherwise immediately react to form stilbene epoxides.[107] In this case, the CD ring acts like a protective group. Shielding by trimethylated α-CD also dramatically enhanced the stability of an azobenzene dye toward chemical bleaching, for example, by dithionite.[104,115]

4.2. Improvement of Switching Processes

Molecules that reversibly change their properties due to external stimuli such as light, magnetic field, or pH changes are called molecular switches.[120] The incorporation of a molecular switch within a rotaxane might be advantageous in two respects. First of all, rotaxanation might reduce undesirable side reactions. This protective effect leads to a much better repeatability of the switching process. Secondly, rotaxanation can amplify changes in physical or chemical properties triggered by a switching process. Some examples for both effects will be given in the following.

Photochemically induced *trans* → *cis* isomerization of stilbene [2]-rotaxanes causes shuttling of the CD ring along the axis. This shuttling was unidirectional according to NOE measurements, possibly because the secondary side of CD draws closer to the isophthalic acid stopper (Figure 11). If the axis is too short for a shuttling of the ring, photoisomerization becomes completely inhibited due to the enlacement caused by the rigid CD.[121]

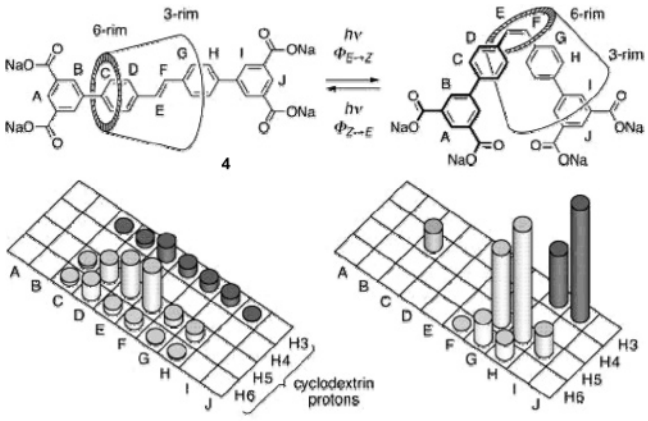

Figure 11. Photoswitchable stilbene rotaxane **4** and localization of the ring by NOE measurements. Strengths of the NOEs are given by the heights of the columns. (Reprinted with permission from ref 121. Copyright 2002 Wiley-VCH.)

A similar stilbene rotaxane, published recently by Wang,[122] showed an even more extensive light-induced shuttling than the previous example. Shuttling was accompanied by a 50% change of fluorescence intensity. The ability to shuttle was switched on and off by pH variation. At pH < 9, shuttling was locked due to strong hydrogen bonds between the isophthalate stopper and the CD hydroxyl groups. Photoisomerization was therefore inhibited. On the other hand, at pH > 9 both shuttling and photoiomerization were allowed, because the isophthalate groups and some secondary CD hydroxyl groups become deprotonated. The charge repulsion of the resulting anions seems to facilitate shuttling of the ring.[122]

Nakashima et al.[123] assembled the first photoswitchable azobenzene pseudorotaxane by slippage of α-CD onto an azobenzene bola-amphiphile with 4,4′-bipyridinium end groups. It showed full reversibility of the switching process accompanied by a significant color change (photochromism). The color change was used to read the information of the

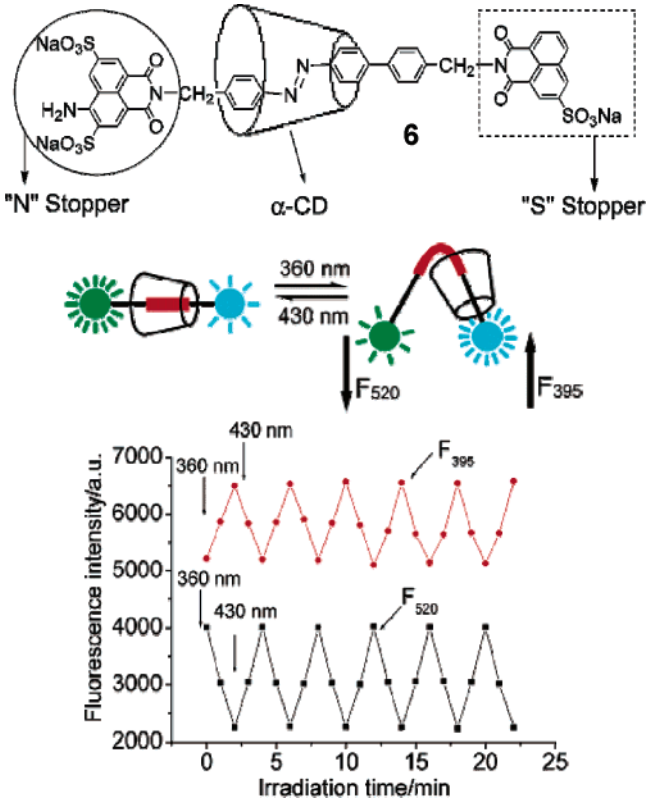

Figure 12. Changes in the fluorescence of an azobenzene rotaxane (F_{395} = emission at 395 nm; F_{520} = emission at 520 nm) along with irradiation time. Light sources of 360 and 430 nm were alternated every 2 min. (Reprinted with permission from ref 124. Copyright 2004 American Chemical Society.)

state of the switch.[123] An even more sophisticated photoswitchable azobenzene rotaxane, **6**, was constructed by Tian et al.[124] Two different fluorescent stoppers, emitting at 520 and 395 nm, respectively, were attached to the azobenzene axis. Unidirectional shuttling of the CD ring was triggered by photoinduced *trans* → *cis* isomerization. Due to this CD shuttling, the 395 nm fluorophore becomes partially included, leading to a 25% increase of its fluorescence. Simultaneously, the fluorescence of the deshielded 520 nm fluorophore drops by 45%. Switching was highly reversible and rapid. The state of the rotaxane was readable from the fluorescence intensities (Figure 12). In contrast to this finding, the free dumbbell did not show any changes of fluorescence intensities upon irradiation.

Consequently, rotaxanation indeed leads to an amplification of the switching effect and an improvement of its repeatability. Such switchable photochromic rotaxanes might find interesting applications as high-density data storage materials, such as for rewritable DVDs. Storage density would only be limited by the diameters of the light beams necessary for the recording and reading processes. With optical near field microscopy, this diameter might be as small as 50 nm. In addition, high storage densities can be achieved by 3D recording.[125,126] The highest resolutions achievable right now are those with blue laser diodes (405 nm).[127]

Rotaxanation in CDs can improve not only photoswitching but also electroswitching. A cyanine dye, incorporated in a CD rotaxane, showed a much better reversibility of electrochemical oxidation and reduction.[111] Electrical switching of rotaxane dyes is applicable for the construction of color displays showing excellent visibility.[128]

5. Daisy Chains: Rotaxanes from Conjugates of CDs and Axes

If an axis is covalently linked to a ring, the resulting conjugate becomes self-complementary and it resembles a hermaphrodite. Such conjugates can form several types of inclusion compounds, which can be transformed to different types of rotaxanes (Figure 13). In the simplest case, the conjugate can be included by itself. Attachment of a stopper furnishes an intramolecular rotaxane, called a [1]-rotaxane (Figure 13a). Two conjugates can stick together to form a cyclic dimer, which can be stabilized by the attachment of two stoppers to form cyclic [2]-rotaxanes. Cyclic [3]-rotaxanes can also be synthesized in an analogous way (Figure 13b and c).[129] Polymeric inclusion compounds are formed by self-organization of many conjugates, and subsequent attachment of stoppers leads to a special type of polyrotaxanes, so-called "*daisy chain polyrotaxanes*" (Figure 13d).[130]

The first CD [1]-rotaxane, **7**, was synthesized starting from a CD [2]-rotaxane by fixing a covalent linkage between the stilbene axis and the α-CD ring (Figure 14).[114] Despite this linkage, the ring is still able to rotate around the axis. A bulky substituent, R, at the axis can stop the rotation of the ring like a pawl. This blockade of the rotation was proven by ROESY/NOESY/TOCSY NMR spectroscopy. Hindered rotation leads to six different glucose units per α-CD. Those glucose units oriented in parallel to a benzene ring show

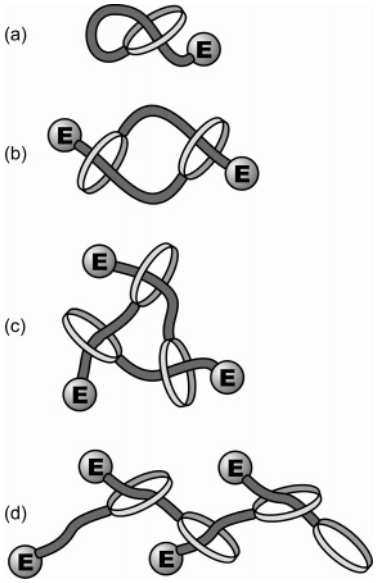

Figure 13. Daisy chain inclusion compounds and rotaxanes (E = end group): (a) cyclic monomer ([1]-rotaxane); (b) cyclic dimer ([2]-rotaxane); (c) cyclic trimer ([3]-rotaxane); (d) polymer (daisy chain polyrotaxane).

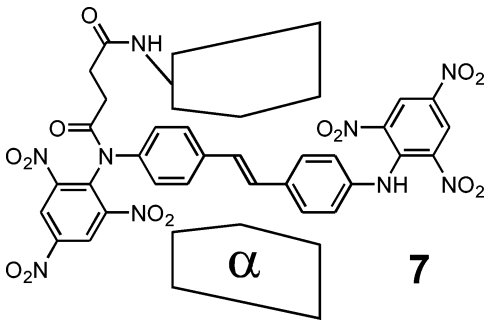

Figure 14. Schematic representation of restricted rotational motion in CD [1]-rotaxane **7**.[114]

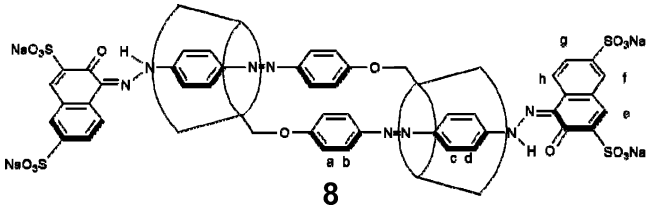

Figure 15. Dimeric [2]-rotaxane **8**. (Reprinted with permission from ref 131. Copyright 2000 The Royal Society of Chemistry).

NMR signals shifted downfield due to the anisotropy effect of the aromatic ring current.[114]

The first dimeric [2]-rotaxane, **8**, from an α-CD conjugate was synthesized by Fujimoto et al. Azo coupling of 2-naphthol-3,6-disulfonate stoppers to the dimeric cyclic inclusion compound of a permethyl-α-CD-azobenzene diazonium salt furnished the [2]-rotaxane in 84% yield (Figure 15).[131] Only the *trans* isomer of the α-CD-azobenzene conjugate formed a cyclic dimer. Photochemical *trans* → *cis* isomerization caused its dissociation. Thus, the formation of the dimer could be switched on and off repeatedly by light.[132] An analogous [2]-rotaxane was synthesized by the attachment of 2,4,6-trinitrobenzene stoppers to a dimeric inclusion compound of 4,4′-aminostilbenyl-α-CD in 64% yield. The structure was proven by ROESY.[133]

The conjugate of α-CD and 4-aminocinnamic acid spontaneously forms mainly trimeric cyclic inclusion compounds which could be blocked with 2,4,6-trinitrobenzene sulfonic acid to form the first cyclic CD [3]-rotaxane, a trimeric daisy cycle, according to Figure 13c, in 38% yield. Structural evidence was provided by ROESY and MALDI TOF mass spectrometry.[134]

Polymeric inclusion compounds, according to Figure 13d, are dominating, as long as conjugated axes are rather stiff. Thus, cinnamoyl-α-CD forms water-soluble oligomeric inclusion compounds. Cinnamoyl-*β*-CD forms insoluble polymeric ones. The degree of association can be reduced by addition of competitive guests such as *p*-iodoaniline or adamantane-1-carboxylic acid.[135] α-CD with a *p-tert*-butoxyaminocinnamoylamino group at the 3-position forms a helical supramolecular polymer consisting of more than 15 repeat units.[136]

If a guest for α-CD (such as a cinnamoyl group) is conjugated to *β*-CD and a guest for *β*-CD (such as an adamantanyl residue) is conjugated to α-CD, little self-complexation to monomeric or dimeric daisy chains ocurrs for each conjugate, because of the miss-fits of hosts and guests. In contrast, a 1:1 mixture of both heteroconjugates spontaneously associates to alternating polymeric inclusion compounds (Figure 16). These inclusion compounds are water-soluble, because their alternating sequence is unsuitable for crystallization. These very interesting supramolecular polymers resemble biological systems, such as microtubules, which are formed by alternating association of α-tubulin and *β*-tubulin.[137]

Another amino−cinnamoyl conjugate of *β*-CD forms dimeric daisy chain inclusion compounds. Cinnamoyl guests were removed from the *β*-CD cavities by the stronger guest 1-adamantanecarboxylic acid. Afterward the expelled cinnamoyl groups were complexed by α-CD rings and stoppered at their amino termini by trinitrobenzene sulfonate. The resulting asymmetric [2]-rotaxane self-organizes to a supramolecular polymer, in which the trinitrophenyl stoppers are complexed by the *β*-CD rings (Figure 17).[138]

6. CD Pseudopolyrotaxanes

6.1. General Considerations

The possibility to covalently link many axes to various polymers gives rise to a great variety of supramolecular structures with CDs. Both linear and branched polymers are known to be complexed by CDs. We shall focus on the inclusion of linear polymers first, since this type of self-organization has been investigated most intensively. Complexation of branched polymers will be discussed at the end of this section.

A linear CD pseudopolyrotaxane is formed in general by threading many CD rings onto a polymer chain (Figure 18a).[139] However, monomeric axial CD inclusion compounds can also be polymerized (Figure 18b). Recently, 4,4′-bipyridine complexed in *β*-CD was claimed to be polycondensated by coordination to Ni^{2+} ions.[140] Inclusion prior to polymerization is hampered by the fact that inclusion and polymerization conditions rarely match. CD inclusion needs aqueous or at least highly polar media, whereas polycondensations often require inert conditions. Only low threading yields were found, when polyamides were synthesized in the presence of *β*-CD by interfacial polycondensation of diamines and diacid chlorides.[141]

One interesting alternative is the polymerization in the solid state. Monomers could be included in CD channel structures and polymerized within the channel. Dissociation of the inclusion compound during the course of the polymerization was excluded this way. Polyamides were formed by polycondensation of α,*ω*-aminocarboxylic acids within α-CD channels, leading to low degrees of polymerization (∼10) because the necessary polycondensation temperature (180 °C) was close to the decomposition temperature of α-CD (∼200 °C).[142,143] Recently, styrene was also claimed to be polymerized within *γ*-CD channels.[144]

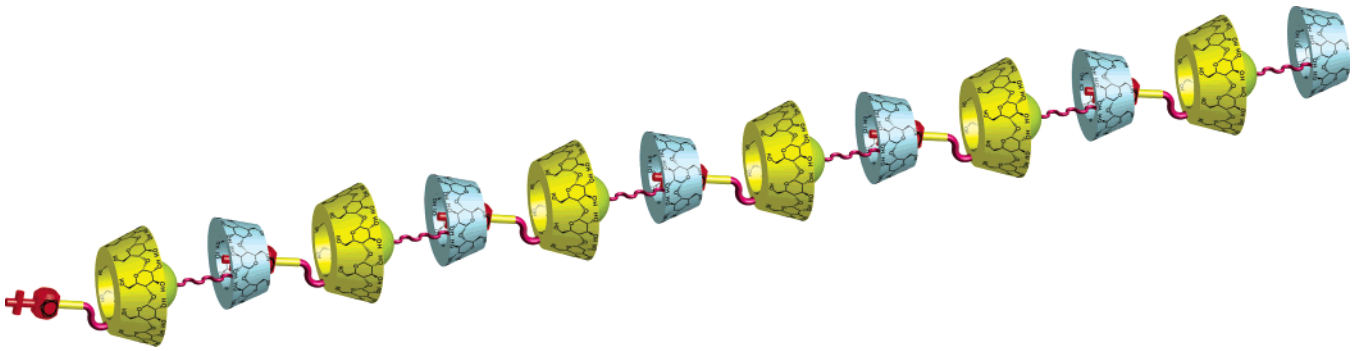

Figure 16. Alternating α- and *β*-CD supramolecular polymer. (Reprinted with permission from ref 137. Copyright 2004 American Chemical Society.)

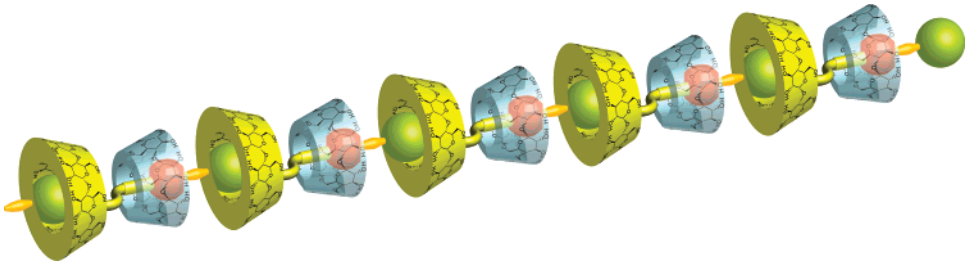

Figure 17. Schematic structure of a supramolecular [2]-rotaxane polymer consisting of cinnamoyl-conjugated β-CD (yellow) and α-CD (blue). Trinitrophenyl stoppers are depicted as green spheres. (Reprinted with permission from ref 138. Copyright 2005 American Chemical Society.)

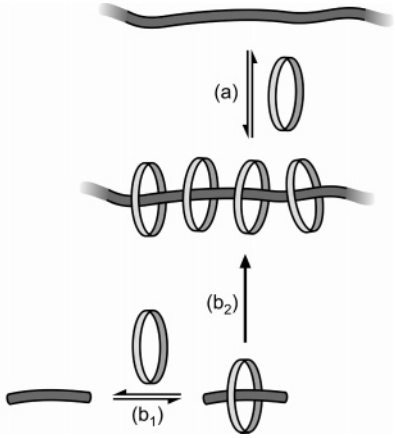

Figure 18. General reaction scheme for the synthesis of CD polyrotaxanes.

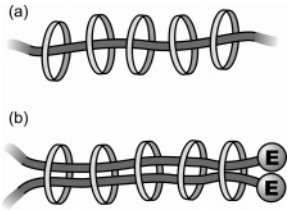

Figure 19. Schematic drawing of pseudopolyrotaxanes: (a) single stranded; (b) double-stranded. E = end group.

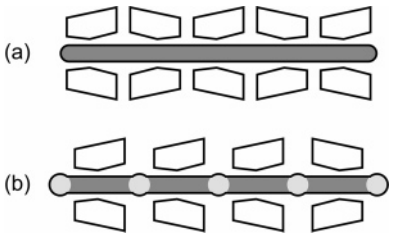

Figure 20. Schematic drawing of pseudopolyrotaxanes: (a) channel type; (b) poly(bola-amphipile) type.

Threading polymers with CD rings has proven to be the more versatile and more successful approach to obtain linear CD polyrotaxanes. A great variety of polymers, most of them commercially available, have successfully been included in the appropriate CDs, as discussed below. The length of the polymer thread determines the length of the pseudopolyrotaxane. Polymers with narrow molecular weight distributions are available for the assembly of well-defined inclusion compounds. In principle, sequential information can be stored by subsequent threading of different CD rings.

Threading of polymers by CDs is often applicable, but how to predict whether a polymer forms an inclusion compound with a certain CD or not remains a difficult task. The task is complex, because inclusion is both thermodynamically and kinetically controlled.

Inclusion of a polymer generally requires a highly negative binding enthalpy. Entropy does not play a big role and generally favors the dissociation of an inclusion compound. Binding sites attracting CD rings are necessary within the polymer chain. There are two major contributions to the binding enthalpy: (a) from hydrophobic and van der Waals interactions between the polymer and the CD, and (b) from hydrogen bonds between adjacent CD rings. The better the polymer fills the CD cavity, the stronger will be the binding forces. The binding forces are low if the CD ring is too wide for the polymer, as van der Waals interactions significantly drop with increasing intermolecular distances. For example, α-CD forms complexes with poly(ethylene oxide) (PEO), whereas the wider β-CD ring generally does not. The wider γ-CD rings provide space for even two polymer chains. They can form double-stranded inclusion compounds, for example, with PEO (Figure 19). On the other hand, if a CD ring is too narrow to accommodate a polymer chain, no complexation will occur. So, polyisobutylene is complexed by γ-CD but not by α- and β-CDs.[139,145]

There is a good correlation between the cross-sectional areas of CD cavities and the cross-sectional areas of the polymers.[145] We tried to quantify the space-filling of the CD cavity by the introduction of the space-filling quotient $\Phi = A_{pol}/A_{CD}$ with the cross-sectional areas of CD, A_{CD} (Table 1), and the polymer, A_{pol} (Table 3).[45] Cross-sectional areas of polymers, A_{pol}, are obtainable from structural data of the polymers in bulk.[146] They can also be empirically estimated from the polymer structure by addition of increments.[147] As the space-filling coefficient, Φ, listed in Table 3, ranges well between 0.9 and 1.2 for the known inclusion compounds of polymers, space-filling appears to be the main criterion for inclusion compound formation. Consequently, it should be possible to select the most suitable CD for the complexation of a given polymer from its cross-sectional area. Even the formation of double-stranded inclusion compounds[148] (Figure 19b) from γ-CD is predicted correctly by this approach.

A dense packing of threaded CD rings along the polymer leads to an additional stabilization of the complex by multifold intermolecular hydrogen bonds.[164] In general, CD rings are threaded in alternating orientations because hydrogen bond interactions are maximized in that case (Figure 20a). These highly ordered polymer complexes crystallize in channel structures almost insoluble in water, similar to those of hydrophobic monomeric guests. They only dissolve in polar solvents such as DMSO under dissociation into their components. The complex stoichiometries are controlled by the ratio q of the length of a CD, L_{CD}, in the direction of its

Table 3. Characterization of CD Channel Inclusion Compounds of Linear Polymers[a]

polymer	A_{pol} (Å^2)[146]	CD	Φ	q_{exp}	q_{theor}	N_{CD}	ref
oligoethylene	18.3	α	1.2	3	3.1	8	149
poly(oxyethylene)	21.5	*β*	1.4	2	2.1	113	150−152
poly(oxyethylene)	2 × 21.5	*γ*	1.0	1	1.0	40	148
poly(oxytrimethylene)		α		1.6	1.6	22	153
poly(oxytetramethylene)	17.6	α		1.5	1.2	19	154
nylon-6	17.9	α	1.2		0.9		155, 156
nylon-11	17.3	α	1.2	0.5	0.5	32	142, 143
poly(2-oxypropylene)	24.5	*β*	0.9	2	2.1	35	157, 158
oligotetrafluoroethylene	27.1	*β*	1.0		3.1		159
$(CF_2-CF_2-O-CF_2)_n$		*β*		1.3	1.6	15	160
poly(perfluoro-2-oxypropylene)		*γ*		2	2.1	13	160
polyisobutene	41.2	*γ*	1.0	3	3.1	15	161, 162
polymethylvinyl ether	41.3	*γ*	1.0	3	3.1	115	163

[a] A_{pol} = cross-sectional area of polymer; Φ = space-filling quotient; q_{exp} = stoichiometry quotient, polymer/CD; N_{CD} = maximum number of threaded CD rings observed.

symmetry axis and the length of the polymer repeat unit, L_{pol}. The latter can be estimated according to $L_{pol} = 1.25n$ Å, where n is the number of single bonds per repeating unit. 1.25 Å is the projection of a C−C or C−O bond length onto the chain direction assuming tetrahedral bond angles. Taking an average height of CD, $L_{CD} = 7.8$ Å, from crystallographic data of channel inclusion compounds,[165−167] the stoichiometry quotient q_{theor} can be estimated by eq 1. It agrees well with the experimental value, q_{exp}, as long as perfect channel structures are formed (Table 3).

$$q_{exp} = \frac{[\text{polymer repeat unit}]}{[\text{CD}]} \geq q_{theor} = \frac{L_{CD}}{L_{pol}} \approx \frac{7.8}{1.25n} = \frac{6.24}{n} \quad (1)$$

Substituents at the CD rings disfavor the formation of densely packed channel inclusion compounds, because the increased distance between the rings makes intermolecular hydrogen bonds impossible. Therefore, inclusion compounds of CD derivatives are generally less stable than those of the unsubstituted ones. On the other hand, inclusion compounds of CD derivatives, especially those of methylated CDs, are much more soluble in water and other solvents.[168−170]

Hydrophilic substituents at the polymer backbone also thermodynamically disfavor CD inclusion, as the polymer needs to be desolvated prior to inclusion. The desolvation energy for hydrophilic groups, especially ionic ones, is much higher than that for hydrophobic groups. On the other hand, the better the polymer dissolves in water, the faster the threading kinetics. Hydrophilic groups within the polymer chain therefore accelerate the inclusion process as long as they are slim enough to allow threading. Consequently, hydophilic groups at a polymer show opposing effects on threading: they increase formation rates but diminish thermodynamic stabilities. Neither highly hydrophilic polymers such as polyethyleneimine,[171] poly(vinyl alcohol), polyacrylamide, and poly(*N*-vinylpyrrolidone)[151] nor totally hydrophobic ones such as polyethylene or poly(tetrafluoroethylene) are complexed by CDs. A quantification of the driving force of a threading process is the maximum number of threaded CD rings, N_{CD}, observed. N_{CD} was derived according to $N_{CD} = DP_{max}/q_{exp}$ from the maximum degree of polymerization of included polymer, DP_{max}, and the stoichiometry quotient observed, q_{exp}. These data (Table 3) demonstrate that weakly hydrophilic polymers, such as poly(oxyethylene) and polymethylvinyl ether, are included best of all. Another measure of the driving force of threading is provided by competitive inclusion experiments. For example, if α-CD is added to a *γ*-CD inclusion compound of poly(caprolactone), the polymer changes over to the more stable α-CD inclusion compound. Likewise, poly(caprolactone) is able to swamp out poly(L-lactid acid) from its α-CD inclusion compound as poly(caprolactone) forms a more stable one.[172]

Charged groups within a polymer chain cannot be complexed by CDs. They prevent a dense packing of threaded CD rings. Inclusion of charged polymer chains is only observed if the distance between two adjacent charges exceeds 1 nm, which is little more than the length of a CD ring, L_{CD}. The chain segments between two charges have to exert strong binding forces to CDs, because there is no additional stabilization of the inclusion compound by interactions between adjacent CDs. By analogy with the monomeric bola-amphiphiles, these polymers are herein called *poly(bola-amphiphile)s* (Figure 20b). Up to now, polyamines,[87,173] polycarboxylates,[112] and polysulfonates[174] are known to fit into this category.

6.2. Experimental Evidence for the Formation of CD Pseudopolyrotaxanes

Threading of CD rings onto polymer chains can be demonstrated by several methods. Most of them were developed by Harada's group. Formation of channel inclusion compounds generally leads to precipitation of the product from aqueous solution of the CD. If the polymer is sparingly soluble in water, this heterogeneous process has to be accelerated by heating or sonication. Excessive CD is washed off by water from the precipitate. The yield of inclusion compound depends on the molar fraction of CD, x_{CD}, in the mixture. The molar fraction for the maximum in a so-called continuous variation plot (Figure 21) is related to the stoichiometry quotient q_{exp} according to eq 2. In addition,

$$q_{exp} = \frac{1 - x_{CD}}{x_{CD}} \quad (2)$$

the value of q_{exp} can be determined from the composition of the inclusion compound, for example, by NMR spectroscopy. If this q_{exp} remains constant and if it resembles the theoretical value according to eq 1, there is some good evidence for the existence of a channel inclusion compound.[151]

Additional evidence is obtainable by the attachment of stoppers at both ends of the polymer thread. If these stoppers

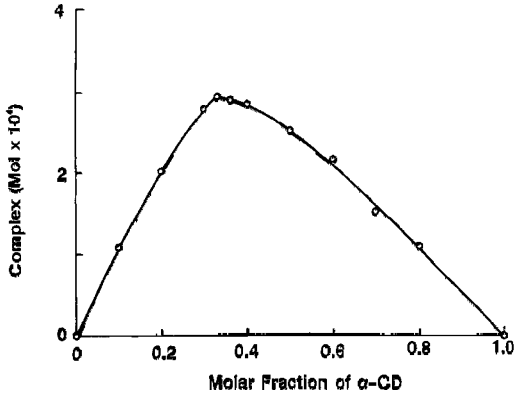

Figure 21. Continuous variation plot for the complex formation of α-CD and poly(oxyethylene) (M_w = 1000) for a fixed total concentration of both components of 1.13 mM. (Reprinted with permission from ref 151. Copyright 1993 American Chemical Society.)

prevent the precipitation of the inclusion compound, an inclusion must have happened in the absence of these stoppers.

X-ray structure analysis, which would give the clearest evidence, was seldom used because of the difficulty to grow sufficiently large single crystals. Channel inclusion compounds are often obtained as powders, because their low solubility causes a rapid nucleation of crystals. Therefore, only X-ray structures of more soluble weak complexes[165] and of oligomers[175,176] are known. On the other hand, X-ray powder diffractograms are generally applicable. They provide enough information to distinguish between the herringbone packing of free CDs and the channel packing of inclusion compounds. The herringbone packing has a lower symmetry and leads to a great number of reflections. The α-CD channel inclusion compounds show hexagonal symmetry and have fewer reflections, with a characteristically strong reflection at $2\theta = 20°$ (Figure 22), very similar to the diffractograms of monomeric channel inclusion compounds.[151] The X-ray structure of the α-CD channel inclusion compound of hexa(ethylene glycol) revealed both head-to-head and tail-to-tail orientations of the CD rings along the chain.[176] More detailed investigations lead to two structural modifications for the inclusion compound of poly(ethylene oxide) in α-CD: modification I with a head-to-head and tail-to-tail arrangement of the CD rings and a hexagonal unit cell $a = b =$ 13.65 Å and $c = 16.4$ Å, and modification II with a head-to-tail arrangement and a hexagonal unit cell $a = b = 13.65$ Å and $c = 7.43$ Å, where c is in the direction of the channel axis. The strong peak at $2\theta = 20°$ was assigned for both modifications as the (210) reflection (Figure 22). Modification I is formed first and slowly interconverts to modification II, which also contains empty α-CD rings.[167]

Because of the lower symmetry of β-CD, the differences in X-ray powder diffractograms between herringbone and channel packings are less pronounced.[158]

Solution NMR spectroscopy indeed does not prove the existence of channel inclusion compounds, as these com-

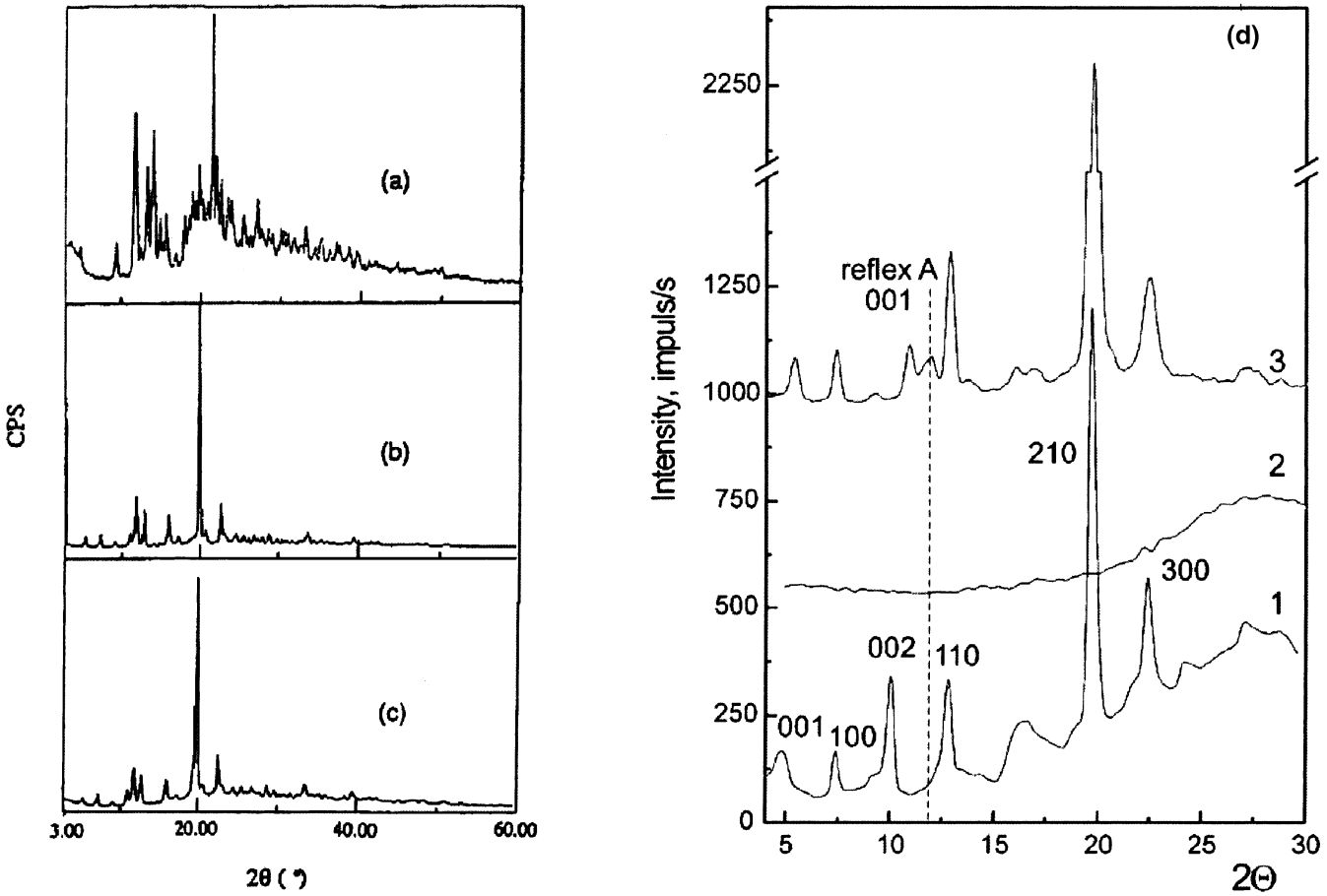

Figure 22. X-ray powder diffractograms of α-CD compounds: (a) free α-CD; (b) inclusion compound of valeric acid in α-CD; (c) inclusion compound of poly(oxyethylene) in α-CD. (Reprinted with permission from ref 151. Copyright 1993 American Chemical Society.) (d) X-ray powder diffractograms of oriented samples: 1, wet; 2, solution; 3, dried. (Reprinted with permission from ref 167. Copyright 2004 American Chemical Society.)

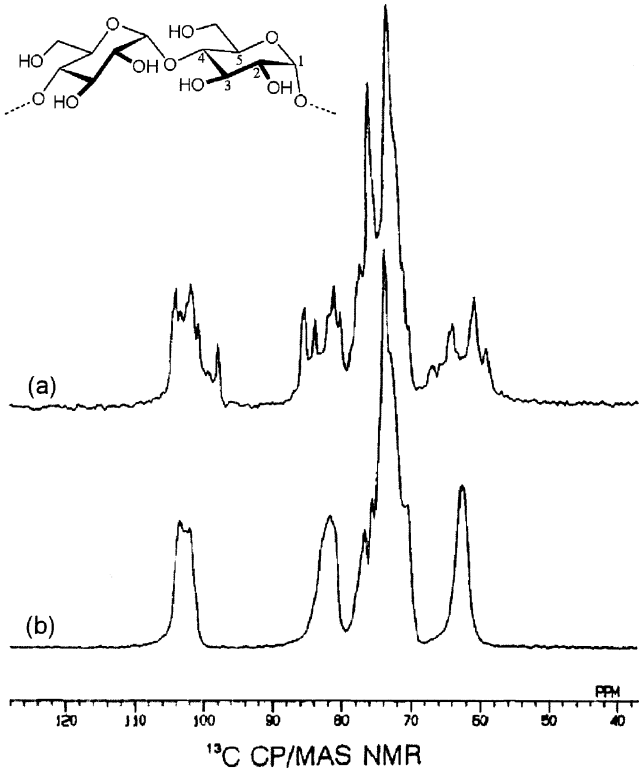

Figure 23. ^{13}C CP/MAS solid-state NMR spectra of (a) α-CD and (b) α-CD poly(oxyethylene) inclusion compound. (Reprinted from ref 177 with kind permission of Springer Science and Business Media. Copyright 1997.)

pounds immediately dissociate in polar solvents such as DMSO, but compositions can be determined. ^{13}C CP/MAS solid-state NMR spectroscopy gives some valuable structural information about crystalline CD inclusion compounds. The C_n symmetry of free CDs is lost if they crystallize in the herringbone packing. As a consequence, broad multiplets are observed instead of a singlet for each carbon of the glucose unit. In channel inclusion compounds, the respective multiplets of C-1, C-4, and C-6 at 102, 81, and 63 ppm coalesce to three singlets because the C_n symmetry is recovered by the inclusion of the polymer and the columnar arrangement of the CD rings. Consequently, sharp signals for carbons C-1, C-4, and C-6 are a clear hint for the existence of highly ordered channel inclusion compounds (Figure 23).[177]

Single pseudopolyrotaxane chains of the channel type can also be directly visualized by microscopic methods such as transmission electron microscopy (TEM),[140] atomic force microscopy (AFM),[178] and scanning tunneling microscopy (STM),[179−181] because they are rather stiff and often even rodlike due to the hydrogen bonds between threaded CDs (Figure 24).

Other methods of structural proof have to be applied for pseudopolyrotaxanes derived from poly(bola-amphiphile)s. As the threading process happens under homogeneous conditions in water, it can be followed by solution NMR. There are changes in the ^{1}H NMR spectra of both the CD and the polymer which allow one to distinguish between free and occupied CD and free and covered polymer segments as well. The yield of occupied CDs can be determined best from the integrals of the signals of the anomeric protons at 5.10 ppm (occupied) and 5.05 ppm (free). By this means, the complete threading kinetics are measurable from a single NMR tube (Figure 25).[87] Residual free CD rings were

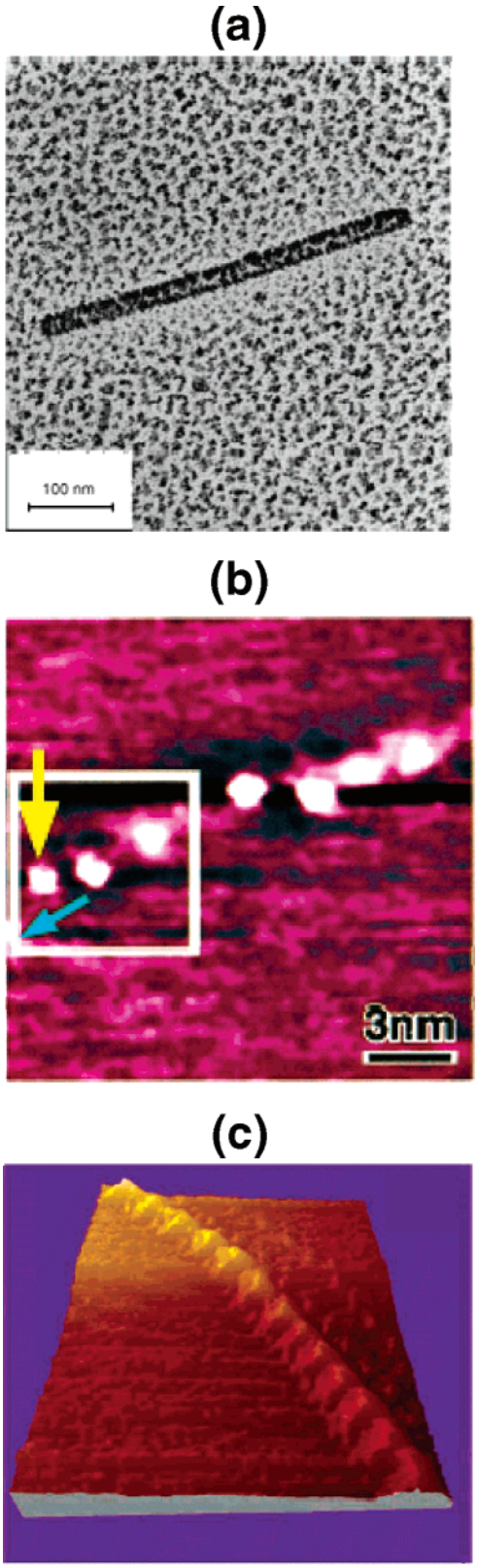

Figure 24. (a) TEM of a single β-CD pseudopolyrotaxane created by coordination of 4,4′-bipyridine by Ni^{2+}. (Reprinted with permission from ref 140. Copyright 2003 Wiley-VCH.) (b) STM picture of a single α-CD−PEO polyrotaxane; single α-CD rings are visible. (Reprinted with permission from ref 179. Copyright 2000 American Chemical Society.) (c) STM picture of single polyazomethine pseudopolyrotaxane **9**. (Reprinted with permission from ref 180. Copyright 2004 American Chemical Society.)

separated from the pseudopolyrotaxane by ultrafiltration. Pseudopolyrotaxanes of poly(bola-amphiphile)s are stable for

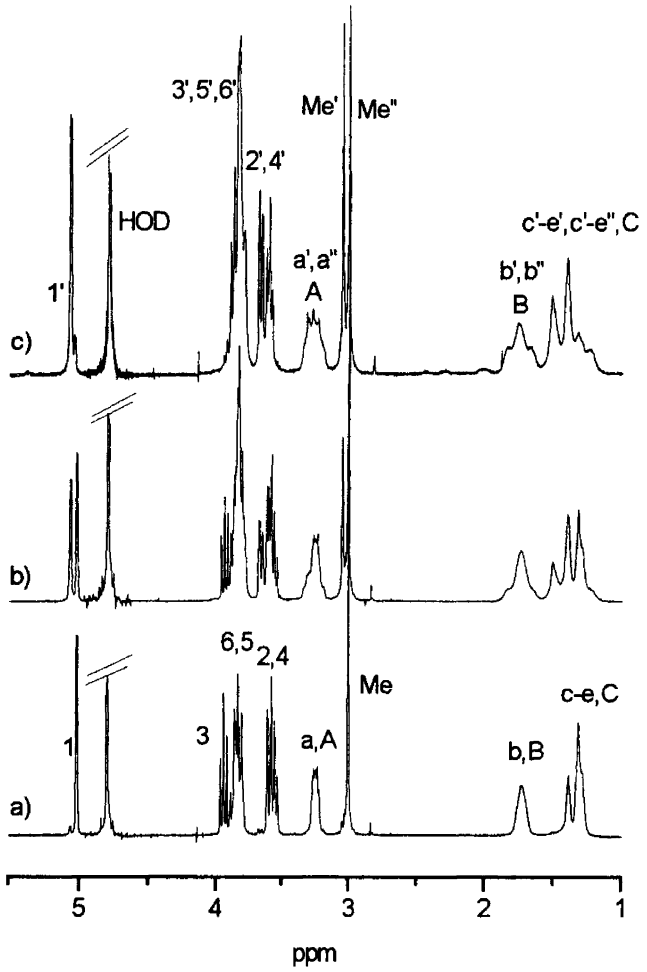

Figure 25. ^{1}H NMR spectra of a mixture of ionene-6,10 and α-CD in D_2O: (a) after 3 h; (b) after 2 years at 25 °C, conversion 55%. (c) ^{1}H NMR spectra of the isolated pseudopolyrotaxane, conversion 95%. (Reprinted with permission from ref 87. Copyright 1997 American Chemical Society.)

days in aqueous solution because of the high activation energies of dissociation.

6.3. Examples of Inclusion Compounds of Polymers

Poly(ethylene oxide). Poly(ethylene oxide) (PEO, poly(oxyethylene)) was discovered by Harada's group as the first polymer being included in α-CD.[150,151] Preparation of the inclusion compound is very straightforward, because PEO and α-CD are both water-soluble, while the inclusion compound is not. The inclusion compound is even formed from a slurry of crystalline α-CD and neat PEO.[182,183] A minimal degree of polymerization DP > 5 is required, possibly because the hydrophilic OH end groups disturb inclusion. The CD rings are densely packed along the polymer chain. The PEO chains confined into α-CD channels mainly consist of *trans*-conformations, but also a small amount of *cis*-conformations migrating along the polymer chain were observed by ^{2}H NMR spectroscopy.[184] For high molecular weights, the stoichiometry quotient q_{exp} exceeds the theoretical value of 2, which means that parts of the chain, especially the chain ends, are not covered by CD rings.[152,185] PEOs of very high DP (>1000) are difficult to include due to kinetic reasons.[150] Hydrogen bonding of the PEO terminal OH groups with the primary or secondary OH groups of CD somehow inhibits the threading process. Therefore, the monomethyl ether of PEO is included more completely.[186] While inclusion compounds of PEO are fine crystalline powders, those of monodisperse oligomers yield single crystals suitable for X-ray structure analysis.[175,187]

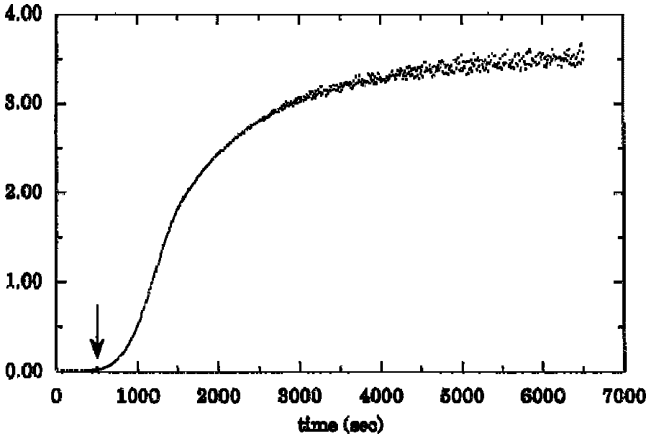

Figure 26. Threading kinetics of PEO (DP = 76) and α-CD observed by turbidity measurements. The end of the induction period is marked by the arrow. (Reprinted with permission from ref 188. Copyright 1997 American Chemical Society.)

Threading kinetics were followed by turbidity measurements (Figure 26). An induction period was observed which was attributed to the time required for threading a chain. After this induction time, the pseudopolyrotaxane chains start to aggregate, leading to a sudden increase of turbidity. This hypothesis explains why the induction period becomes shorter with increasing concentrations of CD and polymer. The induction period also increases with rising temperature. Consequently, threading is entropically disfavored, because the entropies of solvent, CD, and polymer increase with temperature.[188]

It has always been emphasized that PEO inclusion is very selective with respect to the size of the CD.[177,189] Only α-CD immediately forms precipitates. This size selectivity was already explained by the space-filling quotients Φ listed in Table 3. Nevertheless, single crystals of the inclusion compound were formed if a mixture of PEO and β-CD plus very small amounts of water was heated for several months at 60 °C. The X-ray structure shows a head-to-head and tail-to-tail arrangement of the CD rings with hydrogen bonds between the secondary hydroxyls.[166]

Likewise, γ-CD does not include PEO spontaneously either. But, if certain end groups are attached to PEO, the formation of double-stranded inclusion compounds (Figure 19b) was observed. [148] These end groups have the function to bring together two chain ends and hence allow both chains to thread simultaneously through the first γ-CD ring. The double-stranded structure was proven by the inclusion compound stoichiometry and detection of an energy transfer between the end groups, showing a close proximity.[148] The cross-sectional area of γ-CD is twice that of α-CD (Table 3). Therefore, it is perfectly suited to accommodate two PEO chains.

Poly(oxytrimethylene) and Poly(oxytetramethylene). α-CD is also suited to include homologous polymers of PEO, namely poly(oxytrimethylene)[153] and poly(oxytetramethylene).[154] Because of the lower water solubility of these polymers, threading is slower and needs to be accelerated by sonication. The stoichiometry quotients q_{exp} = 1.6 and 1.5 are a little higher than the theoretical values q_{theor} = 1.5

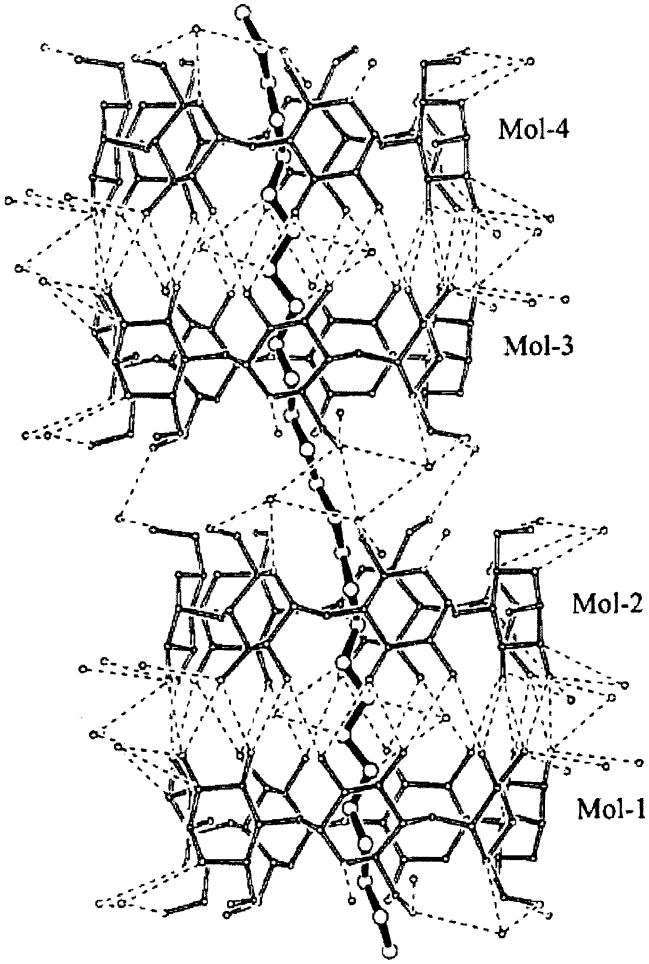

Figure 27. X-ray structure of the inclusion compound of poly(oxytrimethylene) in β-CD. (Reprinted with permission from ref 165. Copyright 2000 American Chemical Society.)

and 1.2, respectively (Table 3). Poly(oxytrimethylene) also forms inclusion compounds with β-CD. Even single crystals, suitable for X-ray structure analysis, could be obtained.[165] The structure of the inclusion compound (Figure 27) clearly demonstrates a head-to-head and tail-to-tail arrangement of the CD rings with intermolecular hydrogen bonding between the CD hydroxyl groups providing the major contribution to the complex stability.[165] Partially or totally methylated α-CD and β-CD thread onto poly(oxytetramethylene) as well. The polymer is solubilized by methylated CDs at low concentration, while crystalline precipitates are formed at high CD concentrations. The methyl substituents reduce the interactions between the rings and favor a less dense complexation of the polymer chain. Consequently, solubilities of the inclusion compounds are higher.[168]

Poly(propylene oxide). Poly(propylene oxide) (PPO, poly(oxy-2-propylene)) forms insoluble inclusion compounds in high yields only with β-CD. Again, space-filling is quite perfect (Table 3).[157,158] The interaction of PPO with methylated CDs was also investigated. While permethyl-α-CD and -β-CD did not show any interaction, heptakis(2,6-di-*O*-methyl)-β-CD (DiMeb) was able to complex PPO. The permethylated CDs failed because they lack any possibility to form hydrogen bonds. The effect of DiMeb on the water solubility of PPO was rather strange: after addition of DiMeb, a clear solution of the polymer was observed at first, but after some days, the inclusion compound precipitated. There may be a loose coverage of the polymer chain by this host, which causes the solubilization. The coverage of the polymer chain slowly increases in the course of time, accompanied by a stiffening of the chain. Precipitation occurs as soon as densely packed channel inclusion compounds are formed. This explanation was supported by a control experiment: bulky trityl substituents were attached to both ends of the polymer. With this stoppered polymer, no solubilization and no subsequent precipitation with DiMeb was found. Therefore, a threading process should be responsible for the observed behavior.[169]

Poly(perfluoroalkyl ether)s. Perfluoroalkyl compounds have a larger cross-sectional area than the corresponding alkyl compounds. For example, the cross-sectional area of poly(tetrafluoroethylene) is 50% larger than that of polyethylene (Table 3). The same is true for poly(perfluoroalkyl ether)s. Therefore, oligo(tetrafluoroethylene oxide-*co*-difluoromethylene oxide) forms inclusion compounds with β-CD and γ-CD but not with α-CD, while oligo(hexafluoropropylene oxide) only forms inclusion compounds with γ-CD.[160]

Poly(methylvinyl ether). Poly(methylvinyl ether) has quite a high cross-sectional area due to the bulkiness of the methoxy side groups (Table 3). Therefore, only γ-CD is able to accommodate this polymer. The density of threaded rings is quite high, and high molecular weight polymers can still be complexed. Consequently, the driving force appears to be very high. The channel inclusion compound is completely insoluble in water.[163]

Polyesters. Aliphatic poly(adipates) $[-(CH_2)_xOOC(CH_2)_4COO-]$, with $x = 2$, 3, or 4, form crystalline channel inclusion compounds with α- and γ-CD in high yields, even at high molecular weights. When the melts of the polyesters were sonicated with a concentrated aqueous solution of CDs at elevated temperatures, the insoluble inclusion compounds precipitated.[190] Conformations of poly(butylene succinate) chains included in α-CD or γ-CD were investigated by the analysis of the IR spectra.[191] The structures of the inclusion compounds were investigated by X-ray powder diffractometry, CP MAS ^{13}C NMR, and differential scanning calorimetry.[192−195] The crystalline channel inclusion compound of poly(caprolactone) and α-CD was prepared similarly. The dynamics of the poly(caprolactone) chains isolated within CD channels was investigated by relaxation time measurements of the solid-state ^{13}C NMR signals.[196] Poly(3-hydroxyproprionate) and poly(4-hydroxybutyrate) are also complexed by α-CD.[197,198]

Polyamides. Polyamides are difficult to include because of their low solubility and their strong intermolecular hydrogen bonds. The first inclusion compound of a polyamide, namely nylon-11, was not prepared from the polymer but by solid-state polycondensation of the monomer, 11-aminoundecanoic acid, included in α-CD at high temperatures. This monomer formed axial inclusion compounds with 2:1 CD/monomer stoichiometry. During the polycondensation, this packing remained. Interestingly, the resulting pseudopolyrotaxane was soluble in water until it dissociated into the insoluble polymer and the soluble α-CD.[142]

The formation of polyamide inclusion compounds was also obtained by threading. For this purpose, nylon-6 was dissolved in formic acid, whereas α-CD was dissolved in water or DMSO. The inclusion compound precipitated on mixing both solutions.[155,156,199] Another insoluble inclusion compound precipitated when the acetone solution of the side chain polyamide poly(*N*-propionylethylenimine) was mixed

with γ-CD. A channel crystal modification of γ-CD, unlike the usual herringbone modification, has been used for this complexation. This empty channel structure seems to incorporate the polymer chains directly from solution. The consumption of the polymer by the inclusion process was monitored by solution NMR spectroscopy.[200]

Polyurethanes. Polyurethane CD inclusion compounds were prepared by polyaddition of linear aliphatic diols and methylenediphenyl-4,4′-diisocyanate (MDI) in the presence of permethylated α- or β-CD in DMF solution. α-CD resides mainly on linear aliphatic segments of the polymer chain. Benzene rings are too large to be complexed by α-CD but can pass through its cavity. Some activation energy has to be overcome for this penetration.[201]

Polyolefines. Since polyethylene is one of the most hydrophobic and most insoluble polymers known, only ethylene oligomers form α-CD inclusion compounds. The stoichiometry quotient of $q_{exp} = 3$ reveals that the CD rings are densely packed in channel structures.[149,162] The solid-state structures of both polyethylene and *trans*-polyacetylene included in α-CD were calculated by molecular mechanics using the TRIPOS force fields.[202]

Inclusion of substituted polyethylenes is easier to perform because of their higher solubility and their weaker intermolecular interactions. Since the cross-sectional areas of these derivatives are larger, the wider CDs have to be used for complexation. Thus, squalene (hexa(isopentane)) is included by β-CD, while polyisobutylene is included by γ-CD.[161,162] Poly-1,4-butadiene also forms inclusion compounds with β- and γ-CD in low yields. The experimental stoichiometry quotient $q_{exp} > 2.2$ is higher than the theoretical one $q_{theor} = 1.5$, which is an indication for just a partial coverage of the polymer chain.[203]

Polypropylene of DP 38 was solubilized in water by heptakis(2,6-di-*O*-methyl)-β-CD. The solution NMR spectra showed broad signals.[170] The same polypropylene was dissolved in 1,2,4-trichlorobenzene and mixed with a DMSO solution of γ-CD at high temperature (120 °C). An inclusion compound precipitated which showed characteristics of a CD channel structure. Unfortunately, the stoichiometry of the inclusion compound was not quantified. Poly-1-butene showed a similar behavior.[204]

Polysilanes and Polysiloxanes. Liquid poly(dimethylsiloxane) (PDMS) is included by γ-CD. The complex precipitates from the aqueous solution of γ-CD upon sonication. Its stoichiometry ratio $q_{exp} = 1.5$ and the solid-state NMR spectra are indicative of a tight channel structure. The α-CD cavity is too small to incorporate PDMS, while β-CD only complexes PDMS oligomers up to DP 4.[205,206]

Polydimethylsilane [$-SiMe_2-$] forms partially water-soluble channel inclusion compounds with CDs, too. Again, β-CD only complexes oligomers up to DP 5, whereas γ-CD complexes them up to DP 16. The high value of $q_{exp} = 3$ is due to the short repeat unit ($L_{pol} = 0.19$ nm) of this polymer and is in fair agreement with a dense packing of the CD rings which should show a value of $q_{calc} = 4.1$.[207,208] Axial inclusion was additionally proven by the circular dichroism induced by the CD rings.[209]

Conductive Polymers. The inclusion of polymers with extended conjugated π-electron systems, so-called conductive polymers, represents a real challenge because of their very low solubility and their sensitivity toward oxygen and water. Still, a few examples of pseudopolyrotaxanes prepared by the threading approach are known: polyaniline was complexed by β-CD in *N*-methylpyrrolidone/water mixtures, leading to a blue precipitate at temperatures below 2 °C. Doping of polyaniline by iodine was inhibited due to the molecular encapsulation by the CD rings.[181] Polythiophene and poly(3-methylthiophene) are also complexed by β-CD in water. In the beginning, the solubility was increased by inclusion, but after some days, a precipitate was formed.[210] Single-walled carbon nanotubes (SWCNTs) were sonicated in an aqueous solution of η-CD, a CD composed of 12 glucose units, yielding a clear solution of the formed inclusion compound. The solubility might be due to a partial coverage of the SWCNT surface by the CD rings. The outer diameter of the SWCNT is about 1.2 nm. SWCNT should loosely fit into the cavity of η-CD with an inner diameter of approximately 1.8 nm (Figure 28).[211]

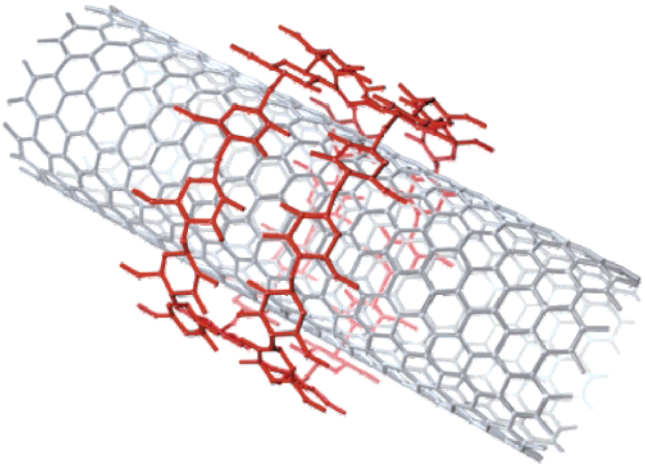

Figure 28. Schematic drawing of an inclusion compound of a single-walled carbon nanotube (SWCNT) in η-CD. (Reprinted with permission from ref 211. Copyright 2003 The Royal Society of Chemistry.)

On the other hand, CD inclusion compounds of conjugated polymers were obtained by polycondensation reactions in the presence of CDs. Polyazomethine **9** was synthesized by polycondensation of terephthalaldehyde with a benzidine derivative. Both were complexed by β-CD in DMF solution (Figure 29), and the amino end groups were capped with Sanger's reagent. The coverage of both the phenylene and the biphenylene moieties was close to 100%, but the DP of 3 was low.[180] Higher values of DP were reached by a similar polycondensation of terephthalaldehyde and phenylene diamine, but the coverage with β-CD was lower (30%).[212] Several attempts were made to synthesize CD inclusion compounds of polythiophene, polypyrrole, and polyaminobiphenyl by oxidative polymerization of the monomers (thiophene, thiophene derivatives, pyrrole, 4-aminobiphenyl) in the presence of β-CD or dimethyl-β-cyclodextrin. Up to now, full structural evidence for the formation of pseudopolyrotaxanes is still missing.[213−216]

Polyamines. Polyamines are difficult to include in CDs, because they are too hydrophilic to attract the CD cavity, especially in the protonated state. Therefore, the yield of complex formation depends strongly on the pH value. In the case of poly(ethylene imine) (PEI), no inclusion occurred with α- or γ-CD at pH < 8 due to the protonation of the polymer. Inclusion started at pH > 9 and nearly reached completeness at pH = 11. The yield of inclusion compounds droped again at higher pH, because CD rings became partially deprotonated, leading to repulsion of the negative charges (Figure 30). Both α- and γ-CD are appropriate hosts

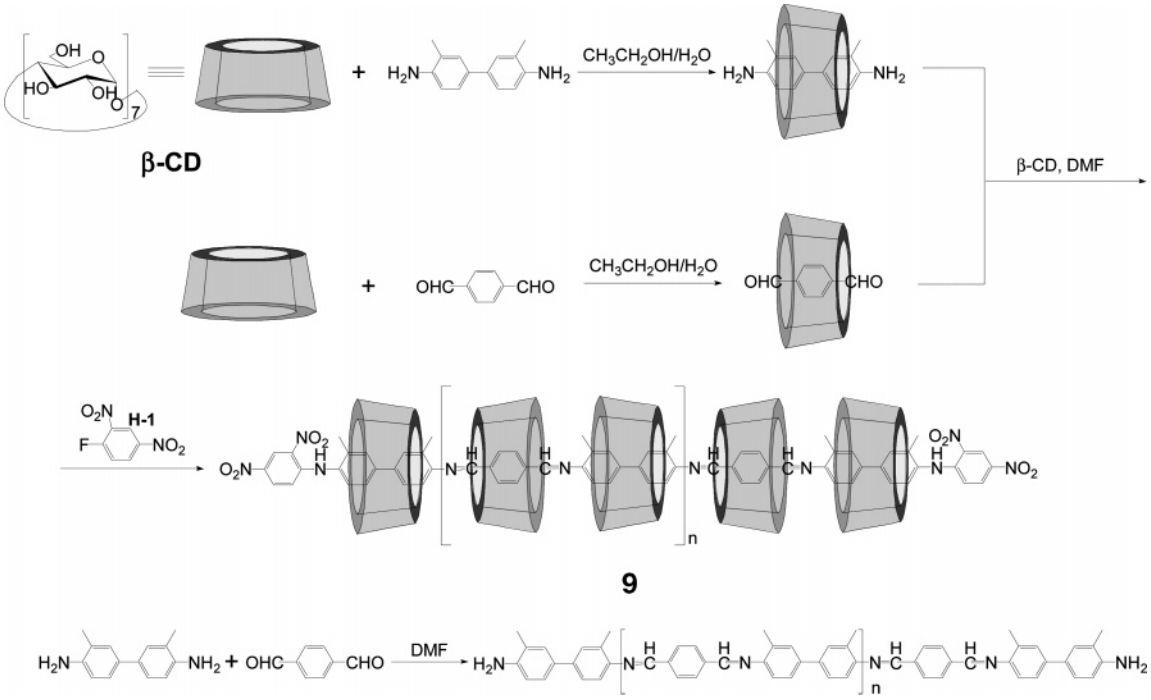

Figure 29. Synthesis of pseudopolyrotaxane **9** by polycondensation of the CD inclusion compounds of a benzidine derivative and terephthalaldehyde. (Reprinted with permission from ref 180. Copyright 2004 American Chemical Society.)

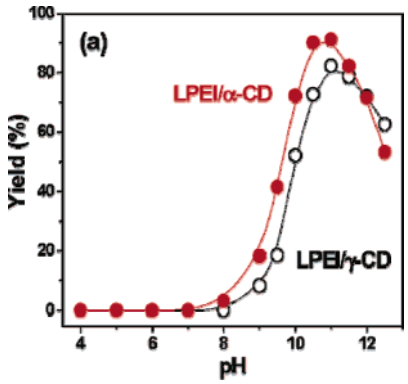

Figure 30. Dependence of pseudopolyrotaxane formation of polyethylenimine and CDs on the pH. (Reprinted with permission from ref 171. Copyright 2004 American Chemical Society.)

for PEI, as they are for PEO. By analogy with the case of PEO, the stoichiometry quotients of 2 for α-CD and 4 for γ-CD are indicative of channel packings.[171]

Poly(ϵ-lysine) [−$(CH_2)_4$CHNH_2−CONH−] is a polyamide with amino side groups. Because of the longer hydrophobic segments, it is more suitable for inclusion by CDs than poly(ethylene imine). The inclusion compound precipitates as soon as aqueous solutions of the polymer and α-CD are mixed. Its stoichiometry quotient is around 1, characteristic for a dense channel inclusion compound. Similar to the case for poly(ethylene imine), a pH optimum at pH 10.5 was found for complex formation, which indicates that the uncharged polymer is complexed.[217,218]

Polyamines with longer alkyl segments −$(CH)_n$− ($n \geq 10$) are complexed by CDs even at acidic conditions. The hydrophobic segments are long enough to accommodate a CD ring in a way that the charged groups can stay outside the cavity. These protonated polyamines are poly(bola-amphiphiles). Both polymeric secondary and quarternary amines were complexed by α-CD under homogeneous conditions in aqueous solution.[87,173,219] Threading kinetics were investigated by solution NMR (Figure 25). In the case of polymeric secondary amines, threading rates strongly increased with increasing pH values.[219] In the case of polymeric quaternary ammonium salts, they strongly depend on temperature. For the poly(bola-amphiphile) ionene-6,10, it took 2 days at 80 °C to reach 50% coverage of the hydrophobic segments. At 25 °C, even a period of 2 years was necessary to reach the same coverage (Figure 31).

Threading rates strongly decrease with the DP of the polymer. Threading proceeds fast in the beginning but slows down significantly (Figure 31), because some kind of "molecular traffic jam" happens on the chain. The threading kinetics were described by a Monte Carlo simulation program, called ABAKUS, assuming a hopping process from one polymer segment to the next hindered by the ionic groups between the polymer segments (Figure 32).[87]

The rate constant k_{diss} for hopping of a CD ring from one segment to the next or off the chain could be determined by fitting the experimental kinetic data with ABAKUS. The half-life $\tau_{1/2} = \ln(2)/k_{diss}$ of a CD ring resting on a chain segment was calculated from k_{diss}. This so-called segment resting time, $\tau_{1/2}$, increases with the size and the length of the hydrophilic groups within the polymer chain (Table 4). From the temperature dependence of k_{diss}, the corresponding activation enthalpy, $\Delta H^{\ddagger}_{diss}$, was determined by an Arrhenius plot (Table 4). The corresponding free activation energy, $\Delta G^{\ddagger}_{diss}$, was calculated using the Eyring equation.[220] Both values $\Delta H^{\ddagger}_{diss}$ and $\Delta G^{\ddagger}_{diss}$ were similar within the experimental error (Table 4), which means that the activation entropy was negligible in first approximation, and these values are similar to those of monomeric bola-amphiphiles (Table 2). Activation enthalpies strongly increased with the size and the length of the hydrophilic groups, X. This shows that the simple hopping model is suitable for describing threading kinetics. The binding constant, K_s, and the dissociation free energy, ΔG°_{diss}, were calculated from the limiting conversion y of the threading process. ΔG°_{diss} increased with the length of

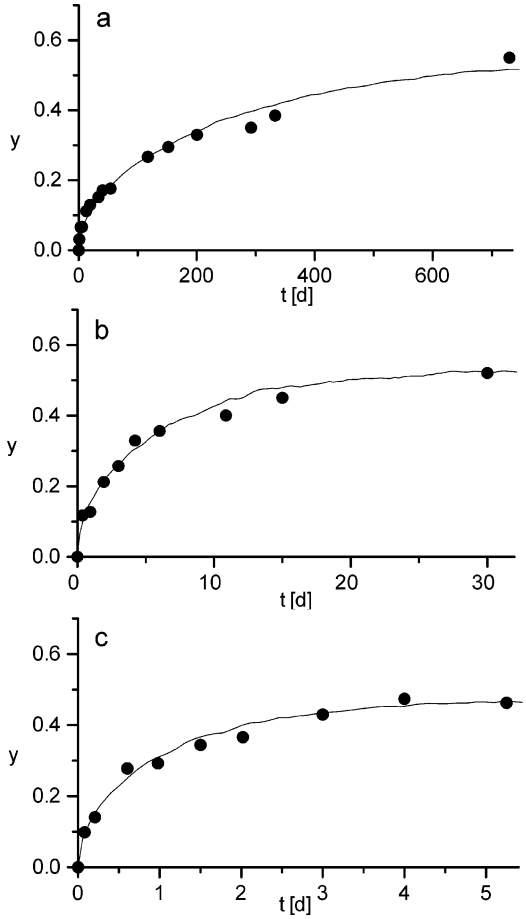

Figure 31. Model for the inclusion kinetics of poly(bola-amphiphile)s and experimental data for the inclusion of [$-NMe_2^+-(CH_2)_6-NMe_2^+-(CH_2)_{10}-$] (ionene-6,10) in α-CD at (a) 25 °C, (b) 60 °C, and (c) 80 °C; y = conversion of inclusion. (Reprinted with permission from ref 87. Copyright 1997 American Chemical Society.)

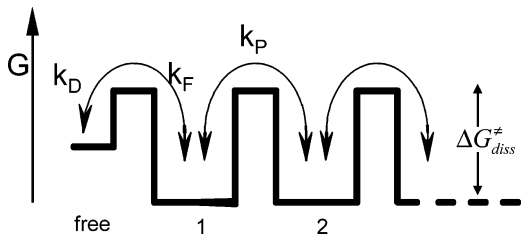

Figure 32. Schematic representation of the free energy, G, of a CD ring as a function of its location: 1 and 2, segments 1 and 2 of the polymer; free, free CD; k_D, k_F, and k_P = rate constants of dissociation, formation, and propargation; $\Delta G^{\ddagger}_{diss}$ = free activation energy for dissociation and propargation. (Reprinted with permission from ref 87. Copyright 1997 American Chemical Society.)

the hydrophobic binding segment (Table 4), in analogy to the cases of the monomeric bola-amphiphiles (Table 2). Since these activation enthalpies are high, threading can be perfomed only at elevated temperatures (80 °C) within reasonable time. The resulting pseudopolyrotaxane was quite stable at room temperature, being an interesting example of a thermally induced slippage.[87]

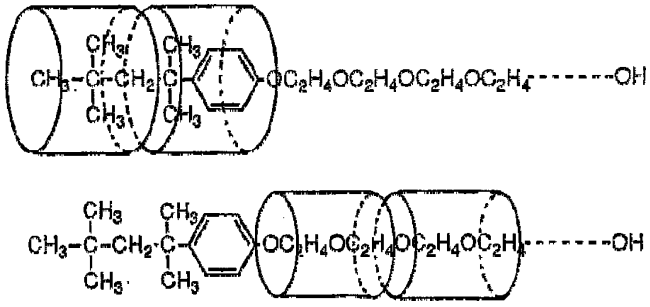

Figure 33. Schematic drawing of site-selective complexation of Triton X-405 with (a, top) α-CD and (b, bottom) β-CD. (Reprinted with permission from ref 221. Copyright 2000 Chemical Society of Japan.)

6.4. Site-Selective Complexation of Block Copolymers

If there are several different binding sites for CDs within a polymer chain, a selective partial complexation (so-called "site-selective complexation") with CDs of one or more ring sizes becomes possible. Partial complexation might be advantageous to gain higher solubilities, especially for channel inclusion compounds, because the uncomplexed part of the chain can still contribute to solubility. Regioselective complexation of block copolymers is also a good method to compare the different binding affinities of the blocks. The block with the highest affinity for a certain ring size will be preferentially covered.

Complexation of block copolymers might also lead to a programmed complexation by different CDs. But there are some steric restrictions because of the one-dimensionality of the system. If a CD of wrong ring size has been threaded by mistake, rings threading afterward will hinder this unsuitable ring from dissociation. The only method of error correction would be all rings leaving the chain to allow the dissociation of the unsuitable ring. Therefore, a long time is required until different rings have found their appropriate binding sites at a copolymer chain.

Site-selective complexation was found for Triton X-405. α-CD forms an insoluble complex in which only the PEO block is covered. Insolubility is due to the formation of a channel structure. On the other hand, β-CD forms a soluble complex in which only the iso-octyl group and the benzene ring are covered. The uncovered PEO segment provides solubility (Figure 33).[221]

Since the polyester of octanedicarboxylic acid and poly(ethylene oxide) (DP 20) and its CD inclusion compound are water-soluble, the threading process could be investigated under homogeneous conditions by ^{1}H NMR spectroscopy

Table 4. Kinetic and Thermodynamic Data for the Dissociation of Axial Inclusion Compounds of Poly(bola-amphiphiles) ($-(CH_2)_n-X-$) and α-CD in Aqueous Solution at Room Temperature[a]

hydrophilic group X	n	DP	$\tau_{1/2}$ (s)	$\Delta G^{\ddagger}_{diss}/RT$	$\Delta H^{\ddagger}_{diss}/RT$	$\Delta G^{\circ}_{diss}/RT$	N_{max}	ref
NH_2^{+b}	11	50	3.3	31.0		8.5	48	85
$NH_2^+-(CH_2)_6-NH_2^{+b}$	10	27	1620	37.2		7.7	24	85
$NMe_2^+-(CH_2)_6-NMe_2^+$	10	68	4951	38.3	36.5	6.2	65	87

[a] ΔH°_{diss} and ΔG°_{diss} = enthalpy and free energy of dissociation; $\Delta H^{\ddagger}_{diss}$ and $\Delta G^{\ddagger}_{diss}$ = activation enthalpy and free activation energy (Gibbs energy of activation) of dissociation; $\tau_{1/2}$ = half-life of a ring at a chain segment. Values are for low polymer concentrations, 1 mM. [b] pH = 4.7.

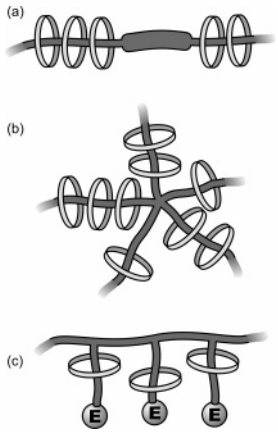

Figure 34. Schematic drawing of inclusion compounds of (a) block copolymers, (b) star-shaped polymers, and (c) side groups of polymers.

and titration microcalorimetry. Both α-CD and *β*-CD form complexes. The rings are located exclusively at the octamethylene segments, because these are much better binding sites than the PEO segments.[222]

Site-selective complexation also takes place with block copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO), so-called pluronics. α-CD selectively binds to PEO segments, while *β*-CD selectively binds to PPO segments.[223,224] Heptakis(2,6-di-*O*-methyl)-*β*-CD regioselectively complexes the PPO segments of the triblock copolymers PEO−PPO−PEO and PPO−PEO−PPO (Figure 34a), leading to water-soluble inclusion compounds because the hydrophilic PEO segments remain uncovered. Therefore, solutions of these inclusion compounds were accessible to static and dynamic light scattering experiments. The PPO−PEO−PPO triblock copolymers were also complexed by α-CD regioselectively at the PEO segments. The inclusion compounds were insoluble in water, because the hydrophobic PPO segments remained uncovered. Interestingly, PPO segments can thread through α-CD, despite the fact that they are not complexed by it. Some activation energy has to be overcome for this process.[225,226] A random copolymer of 80% PEO and 20% PPO was also included in α-CD. Its coverage was lower (80%) than that of pure PEO, indicating that only PEO segments were complexed.[227]

Triblock copolymers PPO−PCL−PPO of poly(caprolactone) (PCL) and poly(propylene oxide) (PPO) were regioselectively complexed at the PCL blocks by α-CD. In contrast, both PCL and PPG blocks were included by *γ*-CD.[228] In the cases of triblock copolymers of PCL and PEO, PCL−PEO−PCL, both blocks were complexed by α-CD because there is no preference for one block.[229] The same was found for triblock copolymers of PEO and poly((*R*)-3-hydroxybutyric acid) (PHB), PEO−PHB−PEO, and for copolymers of poly(L-lactid acid) (PLLA), PLLA−PEO−PLLA.[230−232]

6.5. Threading Star-Shaped Polymers

Threading of star-shaped polymers by CDs provides a new tool for the design of more complex supramolecular structures. Star-shaped polymers offer some advantages to linear polymers: (a) higher molecular weights can be reached without a prolongation of the threading length, (b) solubilities of polymers are higher and viscosities are lower compared to those of linear polymers of the same molecular weight, (c) inclusion compounds are more soluble or swellable, and (d) cooperative effects between adjacent polymer chains can be exploited (Figure 34).

Star-shaped PEOs with three, four, and six arms have been investigated first. The DPs of the arms were 8, 42, and 27, respectively. Inclusion compounds were formed with α-CD with a stoichiometry quotient $q_{exp} = 2.2$ very similar to that of the linear PEO. Interestingly, the star-shaped PEO formed a double-stranded channel inclusion compound with *γ*-CD much easier than the linear PEO, because double-stranded threading is facilitated by the proximity of adjacent PEO arms.[233] Even with larger star-shaped PEOs (13 or 15 arms, DP of one arm 227 or 455), complexation by α- or *γ*-CD was observed, but in contrast to inclusion of linear PEO, gels instead of precipitates were formed.[234] PEO was also grafted from hyperbranched polyether alcohols[235] or from polymethacrylates.[236,237] Gels and lamellar phases were found after complexation of the PEO branches with α-CD.[235−237] Recently, also star-shaped polycaprolactone (PCL), synthesized by grafting PCL from silicon nanoparticles, was complexed by α- and *γ*-CDs.[238]

6.6. Inclusion of Side Groups of Polymers

Until now, inclusion of a polymer was considered as a one-dimensional process: many CD rings thread onto a polymer chain. The dimensionality is determined by the linkage of the hydrophobic binding sites at the main chain. Binding sites for CDs can also be arranged as side groups at a polymer chain, and binding events become independent from each other in this case (Figure 34c). Therefore, inclusion of side groups proceeds much faster than inclusion of a main chain. Inclusion compounds are also more labile because they dissociate much faster for the same reason. Selectivities of α-, *β*-, or *γ*-CDs for various side groups are mainly controlled by the size of the side groups, as already observed for monomeric guests.

Various alkyl groups were attached as side groups to a copolymer of acrylamide and methacrylic acid via ester linkages. Formation of inclusion compounds could be followed by solution NMR spectroscopy under homogeneous conditions. α-CD complexes linear alkyl side groups. The binding constant, K_s, increases with the length of the side chain (*n*-butyl < *n*-hexyl < lauryl). Dodecyl-modified poly(acrylic acid) forms hydrogels in aqueous solution due to intermolecular hydrophobic interactions. Gelation could be switched off by complexation of these side groups with α-CD.[239,240] Likewise, *γ*-CD forms inclusion compounds with these polymers. In contrast, *β*-CD only complexes *tert*-butyl side groups.[241] Poly(maleic acid-*alt*-isobutene) with pending *tert*-butylanilide groups was also compexed by *β*-CD. The binding constant of this guest polymer, $K_s = 25900\ M^{-1}$, was nearly identical to that of the corresponding monomer, *tert*-butylaniline.[242,243]

An alternative route to polymeric side-group inclusion compounds would be the polymerization of inclusion compounds of vinyl monomers. In this way, 11-acryloylaminoundecanoic acid complexed in heptakis(2,6-di-*O*-methyl)-*β*-CD was polymerized in aqueous solution by means of a free radical redox initiator. The polymerization was indeed significantly accelerated by the solubilization effect of the CD host, but no polymeric inclusion compound was formed. Instead, the free polyacrylate crashed out from solution. CD rings dissociated during the polymerization (Figure 35), to allow self-association of the hydrophobic side groups along the polymer chain.[244] CD-promoted aqueous polymerization

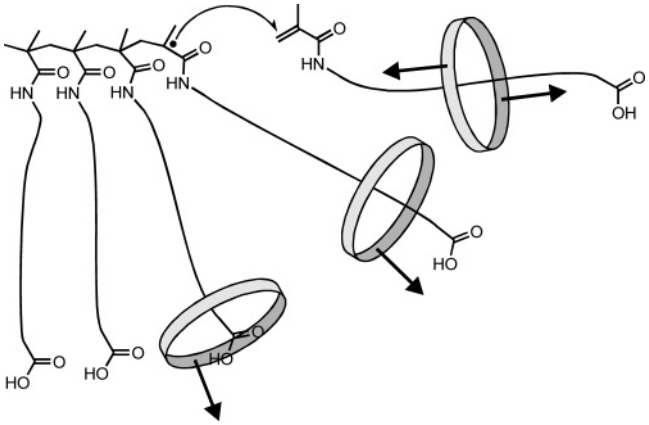

Figure 35. Schematic drawing of radical polymerization of a complexed monomer. CD rings dissociate from the polymer during polymerization.[244]

was applied for a great variety of hydrophobic monomers including fluorinated styrenes.[245]

7. Synthesis of CD Polyrotaxanes

In the preceding section, the preparation of CD pseudopolyrotaxanes has been discussed. Pseudopolyrotaxanes are not kinetically stable, because the CD beads can thread off the polymer chain. In polyrotaxanes, bulky substituents at the polymer, so-called stoppers, hinder the CD beads from leaving the thread. Polyrotaxanes are synthesized by the attachment of stoppers to pseudopolyrotaxanes (a) at the chain end, (b) within the chain, or (c) along the chain. They should be large enough to block a CD ring and hydrophilic enough to avoid aggregation or precipitation of the polyrotaxane. The coupling reaction of the stopper should be compatible with the aqueous solvent usually applied for the formation of CD pseudopolyrotaxanes. The yield of the terminal blocking reaction is critical, because completeness is a requirement for the stability of the polyrotaxane. On the other hand, if stoppers are attached along the polymer chain, yields are less important because of the great number of attached stoppers available. Since there are several possibilities both to assemble pseudopolyrotaxanes and to attach stoppers, the variety of possible polyrotaxane syntheses is great (Figure 36). As the research on preparation of polyrotaxanes has already been summarized some years ago,[36,246,247] the following is focused on the synthetic methodology of efficient stoppering reactions.

7.1. Terminal Stoppering of Pseudopolyrotaxanes

Terminal stoppering of pseudopolyrotaxanes is by far the methodology used most. It is the method of choice for

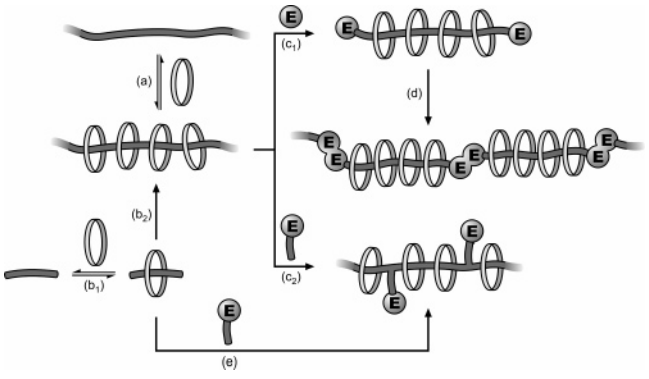

Figure 36. Possible pathways for the synthesis of polyrotaxanes.

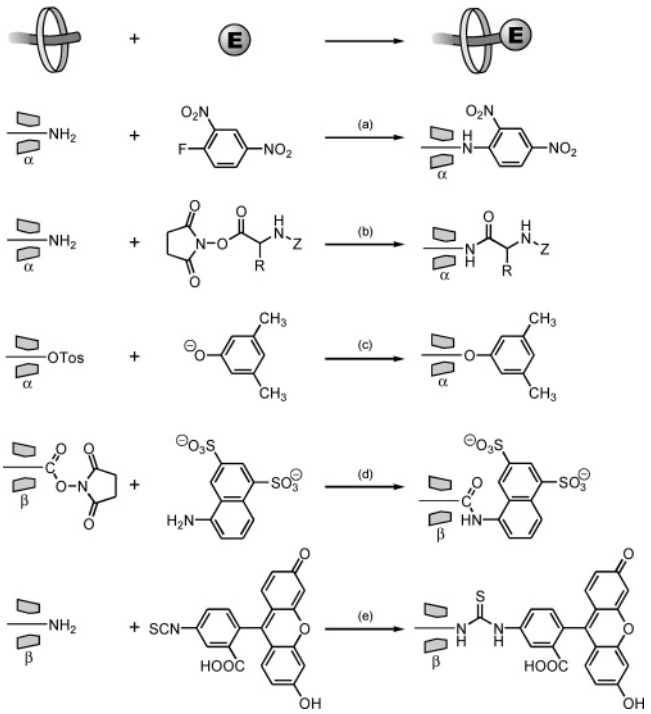

Figure 37. Schematic drawing of terminal stoppering reactions for the synthesis of polyrotaxanes from pseudopolyrotaxanes according to (a) Harada,[248] (b) Ooya,[249] (c) Zhao,[250] (d) Fujita,[251] and (e) Fujita.[252]

blocking channel inclusion compounds of polymers, because the chain ends are much more accessible than the polymer chains densely covered by CDs. The polymer has to be functionalized at both chain ends in advance to facilitate high yield stoppering reactions (Figure 37). Disubstituted benzene rings are large enough to block α-CD rings. Polycyclic entities, such as substituted naphthalenes or fluoresceine, are necessary for blocking β-CD.

Amino end groups do not disturb threading, and they are reactive enough to undergo coupling reactions in aqueous media. Sanger's reagent 2,4-dinitrofluorobenzene has often been employed as the stoppering reagent for α-CD. Amino-terminated poly(ethylene oxide) complexed by α-CD was transformed with 2,4-dinitrofluorobenzene to one of the first CD polyrotaxanes in 60% yield (Figure 37a). The product was insoluble in water but soluble in 0.1 M NaOH or DMSO without dissociation. As the stopper 2,4-dinitrophenyl efficiently blocked α-CD rings from sliding off, the polyrotaxane could be characterized by solution ^{1}H and ^{13}C NMR spectroscopy.[248] The rotaxane structure was unambiguously proven by 2D NOESY NMR spectroscopy.[253] This synthesis was optimized later using PEOs of different of chain lengths. The stoichiometry quotient, q_{exp}, and the number of permanently threaded rings were determined by ^{1}H NMR spectroscopy. The value of q_{exp} increased from 2.2, which is close to q_{theor} for a dense packing of CD rings, to 6.5 with increasing DP of PEO (Table 5).[152] This increase might be due to some loss of threaded rings during the stoppering reaction. The rotaxane formation is favored by low temperatures and the use of solvents allowing strong hydrogen bonding.[188] The CD beads in the polyrotaxane could be visualized by STM.[177] Furthermore, single selected α-CD rings in the polyrotaxane could be reversibly shuttled using a STM tip, like a "molecular abacus".[179] Besides the dominant head-to-head and tail-to-tail orientations, about 20% head-to-tail orientation of CD rings was identified by

Table 5. Synthesis of Polyrotaxanes from α-CD Inclusion Compounds of PEO Bisamines[152]

molecular weight of polyrotaxane	molecular weight of polymer (PEO−BA)	no. of PEO units (included + nonincluded)	no. of threaded α-CD rings	molar ratio of ethylene oxide units to α-CD
16 500	1 450	33 (33 + 0)	15	2.2
20 000	2 000	45 (36 + 9)	18	2.5
19 000	2 001	45 (34 + 11)	17	2.6
23 500	3 350	77 (40 + 37)	20	3.9
44 000	8 500	193 (72 + 121)	36	5.4
89 000	20 000	454 (140 + 314)	70	6.5

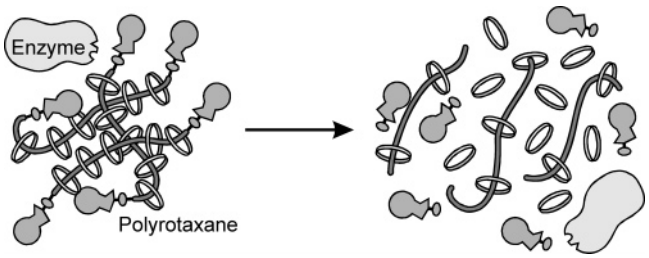

Figure 38. Schematic drawing of liberation of rotaxanated CD rings by enzymatic cleavage of the stoppers.[256]

quantitative analysis of STM images.[254]

The pseudopolyrotaxane of α-CDs and bisaminoethyl-PEO (PEO−BA) was also stoppered with hydroxysuccinimide esters of protected amino acids, such as benzyloxycarbonyl-L-phenylalanine (Z-L-Phe), benzyloxycarbonyl-L-tyrosine (Z-L-Tyr), or *tert*-butoxycarbonyl (Boc)-L-PheGlyGly. The corresponding polyrotaxanes were obtained in 20−40% yields (Figure 37b). They were further hydroxypropylated by reaction of the threaded CD rings with propylene oxide, reaching a degree of substitution of 8−9 per CD. After deprotection of the terminal amino acids, the resulting polyrotaxanes became water-soluble due to the statistic substitution of the CD rings and could be thoroughly characterized by static and dynamic light scattering.[249,255−258] This has been the first example of polyrotaxanes which would not exist as pseudorotaxanes, because the substituents significantly inhibit inclusion compound formation. In fact, the hydroxypropylated CDs escape the polymer chain as soon as a stopper is opened, like a "genie in a bottle". These polyrotaxanes might be useful for programmed drug delivery, because stoppers can be cleaved off by natural enzymes (Figure 38).[256]

PEO was also functionalized by tosylation and complexed by α-CD. Then the tosyl end groups were replaced by bulky 3,5-dimethylphenolate groups, giving rise to polyrotaxanes, where up to 70% of the main chain was covered with CDs (Figure 37c). These polyrotaxanes still behaved as random coils in good solvents.[250] The terminal hydroxyl groups of the block copolymer PEO−PPO−PEO were also carboxyl-functionalized by esterification with succinic anhydride. The carboxyl end groups were transferred in the *N*-hydroxysuccinimide esters by means of dicyclohexylcarbodiimide. The functionalized block copolymer was complexed by β-CD and capped through reaction with 2-naphthylamine-6,8-disulfonate (Figure 37d).[251] Recently, terminal hydroxyls of PEO were also oxidized by TEMPO to COOH groups, which were coupled to 1-aminoadamantane by standard protocols to form an α-CD polyrotaxane.[259] A PEO−PPO−PEO triblock copolymer was amino-functionalized by subsequent reaction of the terminal hydroxyl groups with *N*,*N*′-carbonyldiimidazole and ethylenediamine. It forms pseudopolyrotaxanes with β-CDs, which were capped with fluorescein-4-isothiocyanate (FITC), furnishing a triblock polyrotaxane in 8% yield. The majority of β-CD rings was located on PPG segments, especially at higher temperatures (Figure 37e).[252,260] Recently, pseudopolyrotaxanes of β-CDs threaded onto PPO were terminated by β-CD stoppers, which formed water-soluble inclusion compounds with C_{60}.[261]

7.2. Polyrotaxanes by Coupling of Pseudopolyrotaxanes

Polyrotaxanes can also be synthesized by coupling of end groups of pseudopolyrotaxanes. The group which results from the reaction of the two end groups has to end up large enough to act as a stopper. One example for such an end group is the 2-anthryl group: it is indeed small enough to allow threading of β-CD rings, but its photodimer is large enough to block β-CD rings from unthreading. A pseudopolyrotaxane was formed by threading β-CD onto PPO stoppered by a triphenylmethyl group at one end and by a 2-anthryl group at the other. The 2-anthryl groups were photodimerized by exposure to visible light ($\lambda \geq 340$ nm) for the synthesis of a polyrotaxane (Figure 39).[262]

The same principle was applied for the 9-anthryl group in connection with γ-CD. Poly(propylene oxide) (PPO) with 9-anthryl groups at both ends forms a pseudopolyrotaxane with γ-CD. 9-Anthryl groups are small enough for γ-CD to thread. When the aqueous solution of the pseudopolyrotaxane was irradiated with light, the photodimer of the 9-anthracene groups is large enough to prevent γ-CD from unthreading. The resulting polyrotaxane was insoluble in water and partially soluble in DMSO.[263] Oligomeric rotaxanes from PEO and α-CD stoppered by 9-anthracene groups were coupled in a similar approach by photodimerization to furnish a mixture of linear and cyclic polyrotaxanes. The precursor rotaxanes could be recovered again by thermal cleavage of the anthracenyl dimers at 120 °C.[264]

7.3. Polyrotaxanes by Polycondensation of Axial Inclusion Compounds and Stoppers

Formation of pseudopolyrotaxanes by condensation of axial CD inclusion compounds and the subsequent stoppering can be accomplished in a single batch. This polycondensation approach offers the advantage that the isolation of the labile pseudopolyrotaxane intermediate is not necessary. It was very successfuly employed for the synthesis of polyrotaxanes with polyconjugated axes, so-called insulated molecular wires. Anderson's group have investigated Glaser,[108] Heck, and Suzuki couplings as polycondensation reactions and found that Suzuki couplings provided the highest coupling yields and consequently the highest degrees of polymerization (DPs) of the polyrotaxanes.[109,112,174]

Pd-catalyzed Suzuki couplings of aryl or vinyl boronic acids and aryl bromides or iodides are very well suited as polycondensation reactions to build up polyconjugated polymers. Single-batch Suzuki couplings of 4,4′-biphenyl-bisboronic ester and 4,4′-diiodo-biphenyl-2,2′-dicarboxylic

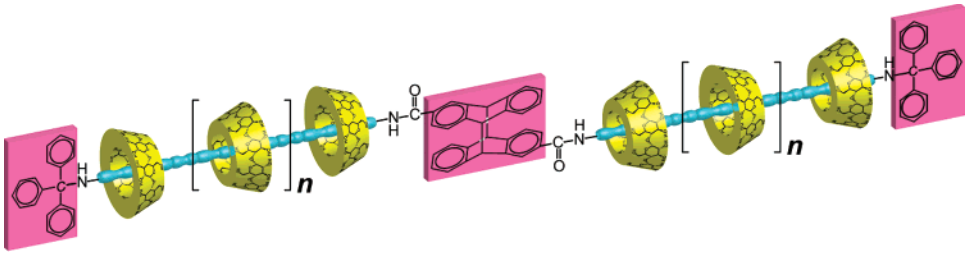

Figure 39. Schematic drawing of preparation of a β-CD polyrotaxane via photodimerization. (Reprinted with permission from ref 262. Copyright 2004 American Chemical Society.)

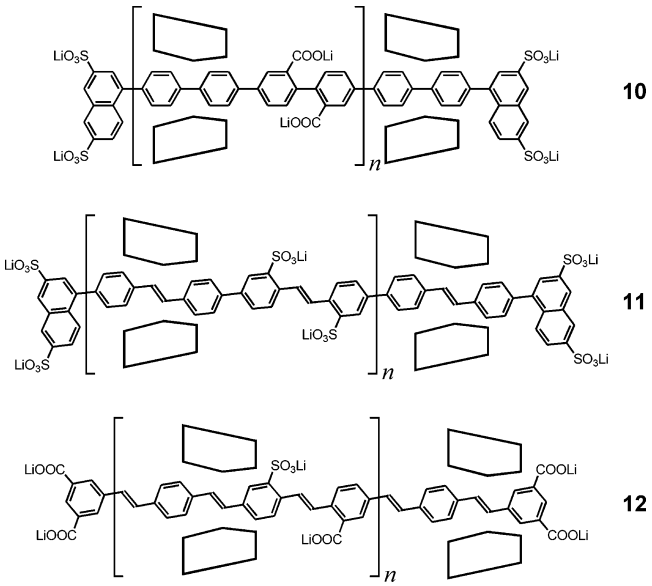

Figure 40. Water-soluble polyconjugated polyrotaxanes **10**−**12** synthesized by Suzuki coupling.[109,112,174]

acid and small amounts of the stopper 1-iodonaphthaline-3,6-disulfonate in the presence of β-CD furnished the water-soluble polyphenylene rotaxane **10** (Figure 40) with DP 8 and about eight threaded CD rings in an excellent 45% yield.[112] In an analogous polycondensation of 4,4′-stilbene-diboronate and 4,4′-diiodo-stilbene-2,2′-disulfonate in the presence of α-CD or β-CD, the corresponding poly(diphenylene vinylene) polyrotaxanes **11** with DP 9−11 and about 11 threaded rings (Figure 40) were synthesized.[174] Again, this polyrotaxane was highly water-soluble, because of its poly(bola-amphiphile) structure. Isolation of the product **11** was achieved by ultrafiltration. Ultrafiltration has been shown to be a very efficient method to distinguish between a polyrotaxane and a pseudopolyrotaxane. Prolonged ultrafiltration forces CD rings to dissociate from the polymer chain, as long as they are not blocked by a stopper. In the case of a pseudopolyrotaxane, the ratio of threaded rings per repeat unit continuously decays to zero; in the case of a polyrotaxane, this ratio remains stable.[174] Recently, also the poly(phenylenevinylene) polyrotaxane **12** with DP 7−12 was obtained from 1,4-divinylbenzene-bisboronate, 4,4′-diiodo-stilbene-2,2′-disulfonate, and α-CD or β-CD, and small amounts of the same stopper again (Figure 40).[109]

5,5′-Dibromobithiophene was complexed inside β-CD and polycondensated using the Ni-catalyzed Yamamoto coupling of arylhalogenides. After stoppering the chain ends with 9-bromoanthracene, a polythiophene polyrotaxane **13** with DP 12 and about seven threaded β-CD rings was isolated in 20% yield (Figure 41). The polyrotaxane **13** was soluble in

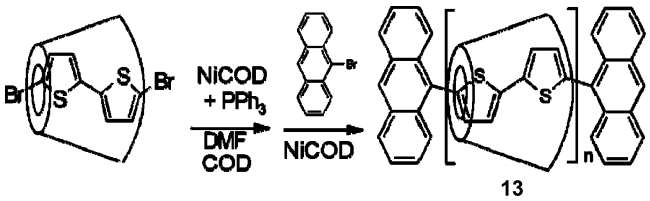

Figure 41. Synthesis of polythiophene rotaxane **13**. (Reprinted with permission from ref 178. Copyright 2004 American Chemical Society.)

water and DMSO and was characterized by small angle neutron scattering (SANS) and STM.[178]

The monomer complexes of *p*-phenylenediamine and terephthalaldehyde with β-CD polycondensate to form poly(azomethine) pseudopolyrotaxanes. The pseudopolyrotaxane was converted into the polyrotaxane by reaction of the terminal amino groups with Buckminster fullerene C_{60} (Figure 42). The resulting C_{60} polyrotaxane **14** was soluble in DMF.[212]

Another polyazomethine polyrotaxane was synthesized by polycondensation of the β-CD complex of 1,4-phenylenediamine with 3,6-diformyl-9-butylcarbazole. In contrast to the uncomplexed polymer, the polyazomethine polyrotaxane is readily soluble in methanol. No stoppers were necessary because of the bulkiness of the carbazoyl moieties.[265]

7.4. Statistical Stoppering of Pseudopolyrotaxanes along the Polymer Chain

Stoppering at both chain ends of pseudopolyrotaxanes was indeed successful for the transformation of channel inclusion compounds to polyrotaxanes, but it has the disadvantage that it must be quantitative to keep the rings from sliding off. An alternative is the random attachment of stoppers along the polymer chain. In this case, it is not necessary to attach stoppers at each repeat unit. Much lower conversions are sufficient to keep the rings on the chain. Only those rings will slide off the chain, which are located close to the ends, where no further stopper can hinder them. The polymer-analogous reaction requires many reactive sites in the chain and a loose coverage of the polymer with CD rings to be assailable by the stoppering reagent. Pseudopolyrotaxanes of poly(bola-amphiphile)s are well suited for such polymer-analogous stoppering reactions, as the hydrophilic groups are not covered by CD rings. If these hydrophilic groups are amino groups, they can easily be modified in aqueous solution.

Polyamines with long aliphatic segments, such as poly(imino-undecamethylene), were complexed by α-CD. Subsequently, a small part (2.5%) of the secondary amino groups were reacted with nicotinoyl chloride in aqueous solution, yielding polyrotaxanes, where the CD rings were confined

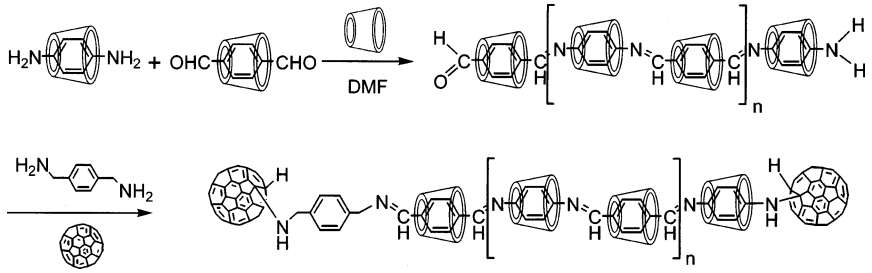

Figure 42. Synthesis of the poly(azomethine) rotaxane with C_{60} stoppers. (Reprinted with permission from ref 212. Copyright 2003 American Chemical Society.)

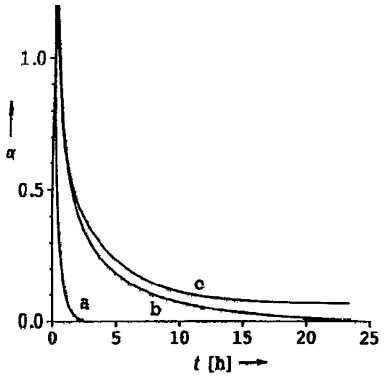

Figure 43. Decay of the optical rotation α of α-CD as a function of the time of dialysis: (a) free CD; (b) pseudopolyrotaxane; (c) polyrotaxane. (Reprinted with permission from ref 173. Copyright 1992 Wiley-VCH.)

by the nicotinoyl substituents. The stability of the rotaxane was tested by prolonged dialysis to continuously remove all free CD molecules. The CD concentration was monitored during dialysis by optical rotation (Figure 43). A certain amount of the CD concentration not removable by dialysis was attributed to rotaxanated CD rings. The amount of rotaxanated CDs increased while more stoppers were attached.[173] Likewise, β-CD rings could also be threaded on this polymer. Nicotinoyl groups were too small to block β-CD rings, but the larger 2,4-dinitro-5-aminophenyl substituents were sufficient.[85]

The polymer-analogous modification of a pseudopolyrotaxane can be catalyzed by supramolecular chemistry. A poly(bola-amphiphile) with stilbene and decamethylene segments was complexed for this purpose by a mixture of β-CD and γ-CD. Threaded γ-CD rings were still large enough to accommodate a second monomeric guest. Therefore, a monomeric stilbene could be co-included within the γ-CD rings of the pseudopolyrotaxane (Figure 44). This co-inclusion not only stabilized the pseudopolyrotaxane but also made further chemical modification possible. Photodimerization between two co-included stilbene entities produced tetraphenylcyclobutadiene entities, which functioned as stoppers for the threaded CD rings (Figure 44). In this way, a polyrotaxane was formed by the action of light.[266] Recently, a polymer-analogous Diels−Alder reaction of cyclopentadiene with the CD inclusion compound of a poly(maleate) was described as well.[267]

7.5. Synthesis of Comblike Side Chain Polyrotaxanes

There are two strategies for the synthesis of side chain polyrotaxanes. Both start from a rotaxane with only one stopper—a so-called semirotaxane: (a) reaction of functional

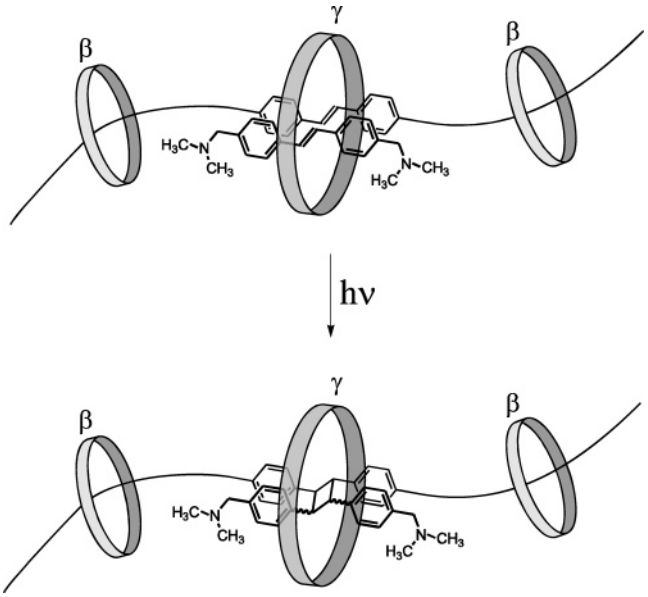

Figure 44. Stoppering of a pseudopolyrotaxane by photochemical [2+2] cycloaddition between the polymer and a co-included monomer.[266]

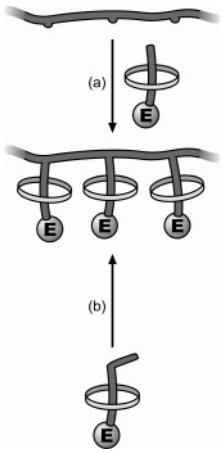

Figure 45. Strategies for the synthesis of side chain polyrotaxanes: (a) reaction of functional polymers with semirotaxanes; (b) polymerization of semirotaxanes.

polymers with semirotaxanes and (b) polymerization of semirotaxanes (Figure 45).

An alkyl chain was blocked at one side by a bulky trityl group and complexed by heptakis-(2,6-di-*O*-methyl)-β-CD to furnish the semirotaxane, which was identified by mass spectrometry. The amino-terminated semirotaxane was attached to a series of polymers with active ester side groups: polyacrylamides,[268] polyether sulfones,[269,270] and polyether ketones (Figure 46).[271] The corresponding side chain poly-

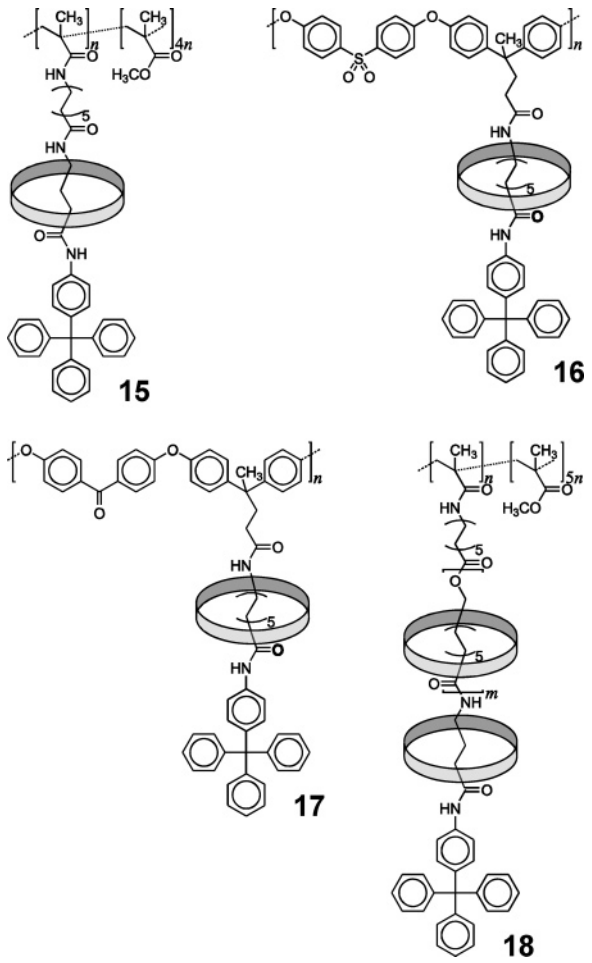

Figure 46. Side chain polyrotaxanes synthesized by attachment of semirotaxanes to functional polymers: polyacrylamides **15** and **16**,[268,272] polyether sulfone **17**,[270] and polyether ketone **18**.[271]

rotaxanes were obtained in high yields. Generally, one CD ring was threaded per side chain. If the side chain is long enough, even two CD rings became rotaxanated (Figure 46).[272] Also a so-called tandem polyrotaxane was synthesized via the same approach starting from a polymer with two active ester groups at each side chain, which were coupled with two semirotaxane moieties.[273] Alternatively, a semirotaxane was equipped at one end with a polymerizable group such as acrylamide group. At the other end was a cholic acid stopper. The polymerization of this semirotaxane yielded a side chain polyrotaxane with a polyacrylamide main chain, with limited water solubility.[244]

In a similar approach, thio functional semirotaxanes of $HS-C_{10}H_{20}-CO-Fc$ (Fc = ferrocene) and α-CD were self-assembled at the surface of gold nanoparticles, to give a novel type of polyrotaxanes, which are capped by the nanoparticle at one end and ferrocene at the other (Figure 47).[274]

8. Rotaxanes from Covalently Linked CDs

Covalent connections between binding sites for CD have already produced a great variety of supramolecular structures and rotaxanes, as described in the previous section. In principle, the same should happen if CDs would be covalently connected. All of these expectations are indeed realistic, but synthesis of well-defined CD−CD conjugates is quite tedious because of the polyfunctionality of CDs. CD dimers were synthesized by bridging two CD rings once or

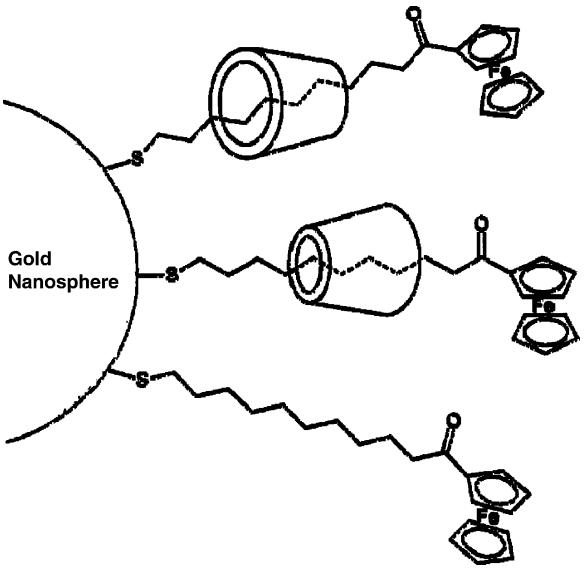

Figure 47. Schematic drawing of α-CD rotaxanes immobilized at gold nanoparticles.[274] (Reprinted with permission from ref 274. Copyright 1998 American Chemical Society.)

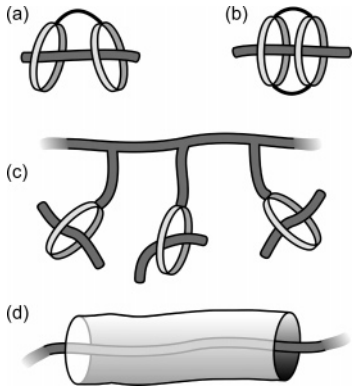

Figure 48. Inclusion compounds of CD−CD conjugates: (a) dimer tethered once; (b) dimer tethered twice; (c) CD polymer; (d) CD molecular tube.

twice.[275] Furthermore, many CD rings were attached as side groups to a polymer chain to form CD polymers. A multifold connection between many CDs such as a bow net is called a molecular tube. The inclusion compounds and rotaxanes from CD dimers, polymers, and molecular tubes (according to Figure 48) will be described in the following.

8.1. Cyclodextrin Dimers

There are a great number of CD dimers already known in the literature. They were reviewed some years ago.[275] Most CD dimers were synthesized to create sophisticated enzyme mimics. In fact, two CD rings were tethered once at the primary[276] and secondary sides,[277,278] respectively. CDs were also tethered twice at the primary sides each to gain a higher rigidity of the molecule, which leads to better preorganization for the inclusion of suitable guests.[279−281] Very high binding constants, $K_s = 10^5-10^6\ M^{-1}$, were achieved between those ditopic hosts and guests, which are due to the cooperativity of binding sites.[279,282] Furthermore, heterodimers consisting of one α-CD and one β-CD, tethered once[281] or twice,[283] were also synthesized.

A urea-bridged α-CD−β-CD heterodimer included a stilbene derivative with a *tert*-butyl group and a phenolate group at the ends. While the *tert*-butyl group was included

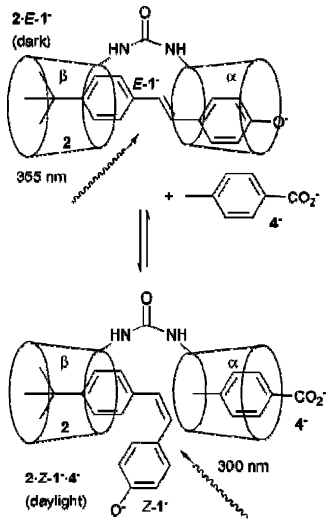

Figure 49. Schematic drawing of the photoisomerization of a guest included in a α-CD/β-CD heterodimer. (Reprinted with permission from ref 276. Copyright 2004 The Royal Society of Chemistry.)

in the β-CD cavity, phenolate was complexed in the α-CD cavity. Irradiation at 355 nm leads to *trans* → *cis* isomerization of the stilbene moiety, which induces the exclusion of the phenolate end from the α-CD cavity. This allows a competitive guest molecule (4-methylbenzoate) to occupy the α-CD cavity, forming a ternary complex. The whole process could be reversed by irradiation at 300 nm (Figure 49).[276] It demonstrates that much higher recognition selectivities can be reached with those CD dimers in comparison to monomeric CD derivatives. On the other hand, CD dimers and dimeric guests organize to supramolecular polymers, if CD and guest moieties are both linked by long spacers.[284,285]

The tether between two β-CD rings was rigidified by coordination of metal cations such as Pt^{2+} (for organoselenium-bridged dimers), Cu^{2+}, and Ni^{2+}. Poly(propylene oxide) was threaded through these dimers to construct a new, ladder-like double-stranded pseudopolyrotaxane **19** (Figure 50). Capping of the amino end groups with Sanger's reagent caused the precipitation of the pseudopolyrotaxane **19**. The 2,4-dinitro group is too small to block β-CD rings totally. The hypothetical structure of **19** was supported by ^{1}H NMR, TEM, and AFM (Figure 50).[286−288]

8.2. Cyclodextrin Polymers

CD polymers were synthesized by (a) polymerization of CD monomers, especially acrylates, (b) cross-linking of CDs, and (c) coupling of CD moieties to reactive polymers.

One acrylate group was attached per CD and polymerized afterward with radical initiators.[289] The resulting CD polymers were water-soluble and showed a somewhat improved binding ability for certain guest molecules, e.g., fluorescence dyes, due to cooperative effects.[290,291]

The statistic cross-linking of CDs is by far the most straightforward method to synthesize CD polymers. Its main disadvantage is the formation of highly branched or even insoluble polymers due to the polyfunctionality of CDs. Careful control of the reaction conditions allows the synthesis of water-soluble polymers from CDs and epichlorohy-

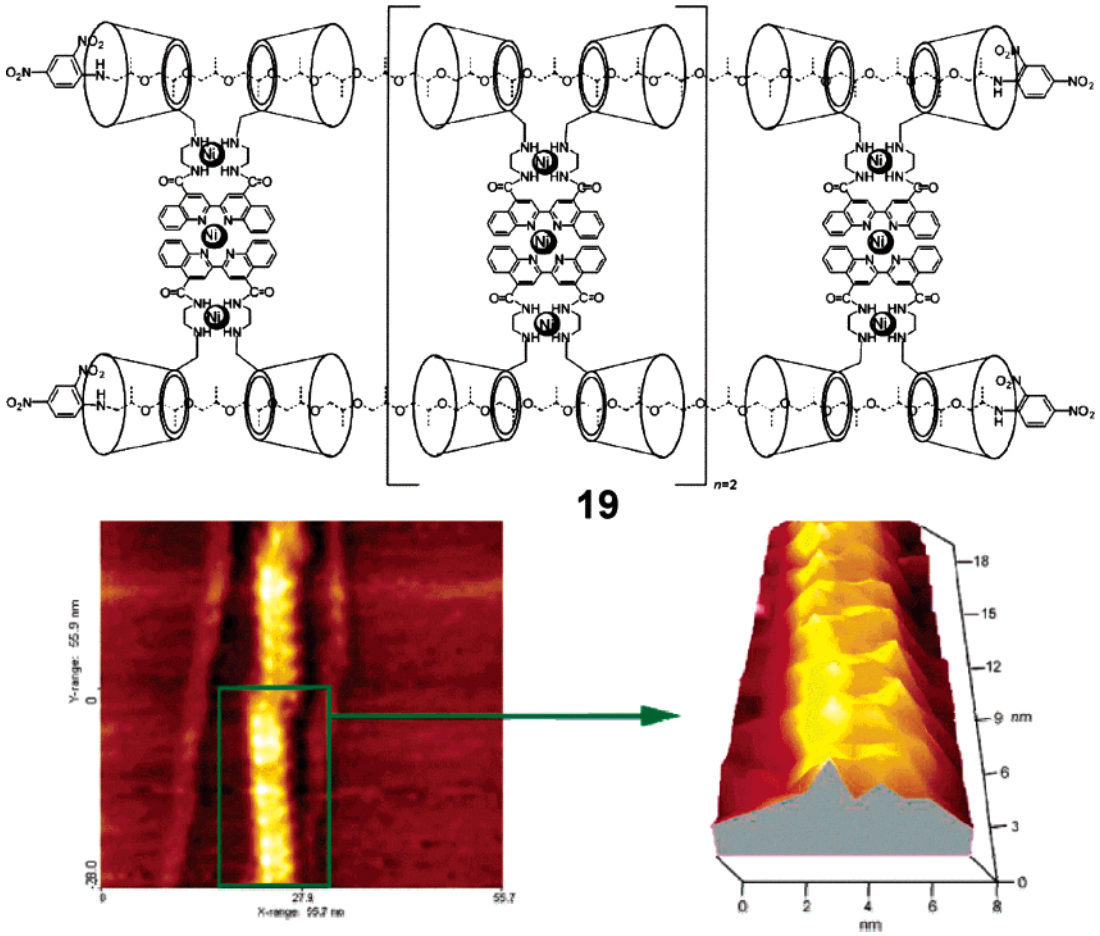

Figure 50. β-CD ladder pseudopolyrotaxane **19**: structural formula and AFM pictures. (Reprinted with permission from ref 286. Copyright 2004 American Chemical Society.)

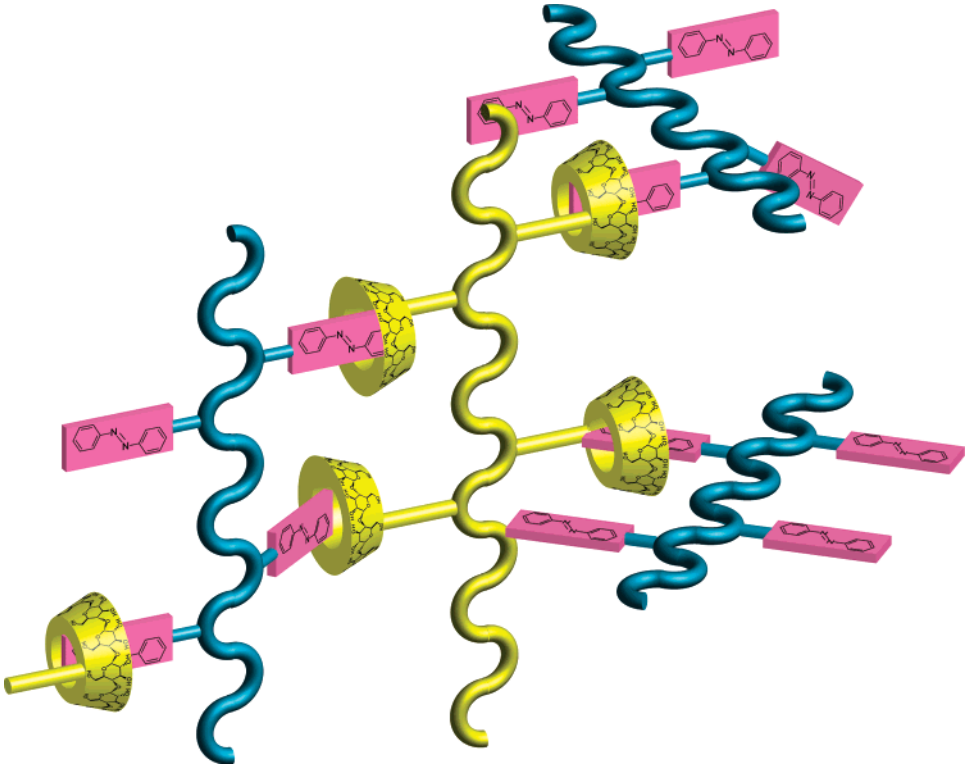

Figure 51. Schematic illustration of supramolecular gels formed from polymers with azobenzene and β-CD side groups. (Reprinted with permission from ref 298. Copyright 2004 Chemical Society of Japan.)

drin.[292,293] This kind of β-CD polymers associates to supramolecular networks with bis-adamantyl-PEO. Complexation of adamantyl groups by the polymer-bound β-CDs leads to physical cross-linking and to the reversible formation of hydrogels.[294−296]

CDs (α-CD, β-CD), deprotonated once, have been coupled via ester linkages to the reactive polymer poly(maleic anhydride-*alt*-isobutene). The resulting linear CD polymers were water-soluble and showed binding abilities toward monomeric guests similar to those of monomeric CDs.[297] The interaction of these CD polymers with side chain guest polymers led to formation of hydrogels due to supramolecular cross-linking. The amount of gelation could be controlled by addition of competitive monomeric CD or guest molecules.[242,243] Similar supramolecular gels were formed later between polyacrylamides with pendant *trans*-azobenzene groups and β-CD entities, respectively (Figure 51),[298] or poly(acrylic acid)s with α-CDs and octadecyl side groups.[299]

α-CD or β-CD was oxidized by Dess−Martin periodinane to the corresponding mono-aldehyde at the primary side. These CD aldehydes were coupled via reductive amination to the pendant amino groups of poly(ϵ-lysine). The resulting cationic CD polymers were indeed soluble in water, but phase separation occurred upon the complexation of 3-(trimethylsilyl)propionic acid.[300−302] The inclusion ability was investigated with the fluorescence dye 6-(*p*-toluidino)-2-naphthalenesulfonate (TNS). Complexation was much stronger than that of the corresponding CDs due to the cooperativity of binding.[303] To the best of our knowledge, no polyrotaxane has been synthesized from CD polymers so far.

8.3. Tubular CD Polymers

CD-based molecular tubes or tubular CD polymers are multifold covalently linked CD rings, forming linear channels of several 10 nanometers length. CD tubes were synthesized

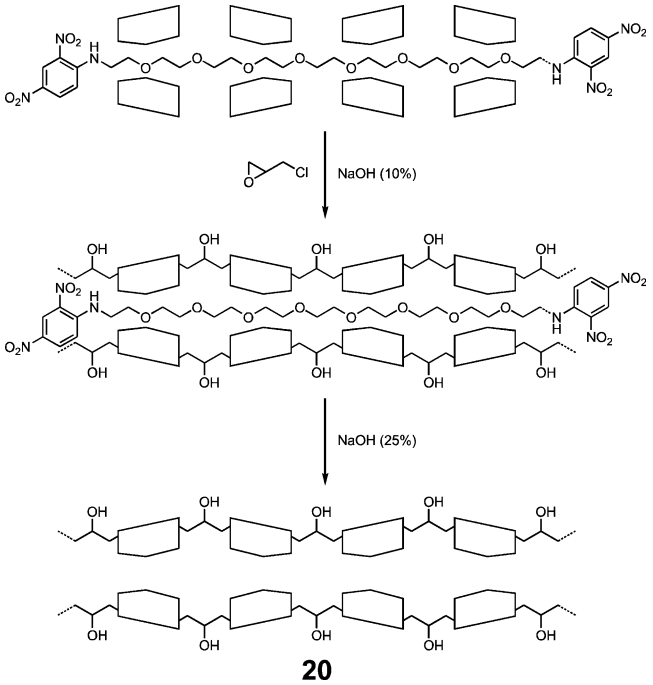

Figure 52. Preparation of a molecular tube **20** from a CD polyrotaxane.[304]

by a template approach. The polyrotaxane from α-CD and poly(ethylene oxide)-bisamine (PEO-BA) stoppered with 2,4-dinitrophenyl groups was used as the starting material. Adjacent CD rings within the necklace were coupled by reaction with epichlorohydrin (Figure 52). After cleavage of the stoppers, the free molecular tube **20** was separated from the PEO thread by size exclusion chromatography (Figure 52).[304] At first glance, it is astonishing why the PEO chain is released so easily, despite the cooperativity of

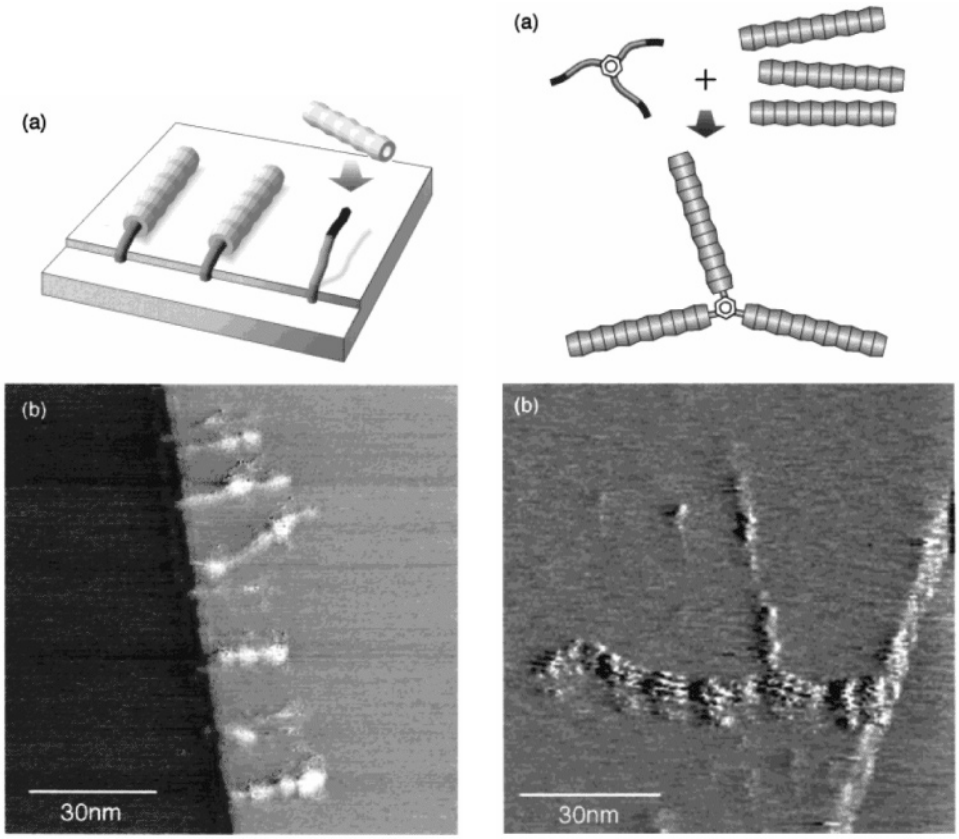

Figure 53. STM pictures of single α-CD molecular tubes threaded on linear polymer (left) and star-shaped polymer (right). (Reprinted with permission from ref 309. Copyright 2000 American Chemical Society.)

binding by the tube **20**. But it has to be taken into account that the polymer gains a lot of entropy as soon as it leaves the tube. The length of the α-CD molecular tube increases with the DP of the PEO employed. The CD rings are held together by about three bridges between two adjacent CD rings. The empty molecular tube **20** was detected by its complexation of iodine or I_3^-, which was similar to that of amylose.

Later on, α-CD molecular tubes **20** with estimated lengths of 16−23 nm were synthesized. The dynamic properties were investigated by carbon spin−lattice relaxation time measurements. The results confirmed the rigidity of the molecular tube **20**.[305] The inclusion behavior of the molecular tube **20** was investigated through monitoring the optical absorption spectra of iodine, which was taken as a probe because it turns red due to complexation. Competitive complexation of linear PEO chains by the nanotube caused a back to yellow color change, because the iodine molecules were expelled off the hydrophobic channel. PEO chains with lengths close to the length of the molecular tube expelled the iodine at lower concentration than those with shorter lengths. In other words, the lengths of the guest polymers were recognized by the molecular tube. The experimental results were consistent with the Flory−Huggins lattice model. An interaction energy of $\Delta\epsilon/kT = 2.7$ per polymer repeat unit was derived from the experimental data.[306,307] The temperature dependence of the inclusion equilibrium between molecular tubes and PEO was investigated by circular dichroism in solution. It was therefore necessary to attach azobenzene chromophores to the chain ends of the polymer. The circular dichroism of the chromophore induced by the inclusion in the chiral molecular tubes was measured as a probe for inclusion. It was found that the inclusion complex indeed was formed at room temperature but that it dissociates at elevated temperature.[308] Threading of the α-CD molecular tube also occurs with PEO monocetyl ether covalently fixed at one end on a pyrolytic graphite substrate. The pseudopolyrotaxane of the molecular tube could be visualized for the first time by STM on this substrate (Figure 53). Furthermore, star-shaped PEO was threaded by molecular tubes. The resulting star-shaped polyrotaxane was nicely visualized by STM (Figure 53).[309] Conducting polyaniline could also be complexed by the α-CD molecular tube as well leading to an insulated molecular wire. The polyaniline chain was fully covered by the nanotubes.[310]

The thermodynamics of the inclusion of the triblock copolymer PEO−poly(tetramethylene oxide)−PEO in the α-CD molecular tube were investigated by isothermal titration calorimetry in aqueous solution.[311] The DP of the PEO blocks was 45 each, and that of the poly(tetramethylene oxide) block was 9. The long hydrophilic PEO blocks provided sufficient solubility in water. The lengths of the molecular tube varied between 39 and 88 Å (Table 6). The observed exothermic calorimetric signals were solely attributed to the inclusion of the poly(tetramethylene oxide) segments. When the tube was titrated with pure PEO, no signals showed up. The dissociation enthalpy strongly increases with the length of the tube, especially from 39 to 52 Å. Contrarily, the free energy of dissociation scarcely depends on the tube length. With increasing length of the tube, the inclusion of the polymer chain becomes more and more entropically disfavored, and the increase of binding enthalpy is compensated by the loss of entropy. The tube acts like a molecular prison and prevents the polymer chain from coiling. This negative entropic effect increases with the length of the rodlike tube.

Table 6. Thermodynamic Parameters for the Inclusion of a PEO−PTHF−PEO Triblock Copolymer by an α-CD Molecular Tube[311] [a]

M_n of tube (g/mol)	length of tube (Å)	$\Delta H^\circ_{diss}/RT$	$\Delta G^\circ_{diss}/RT$	n
4400	39	11.2	10.9	2.1
5900	52	21.1	11.3	1.07
8200	72	30.1	11.4	0.7
10000	88	33.5	13.5	0.6

[a] Measurements at 298 K; enthalpy values refer to 1 mol of molecular tube; n = stoichiometry ratio, tube/polymer.

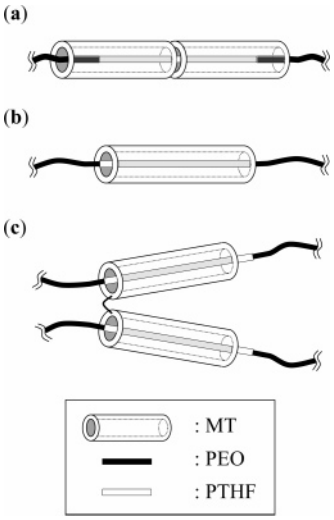

Figure 54. Possible structures of inclusion complexes between molecular tubes (MTs) and the triblock copolymer PEO−PTHF−PEO: (a) 2:1: (b) 1:1; (c) 1:2 inclusion complexes (MT/copolymer). The MT in part c has a kink point to include the two independent strands of the triblock copolymer. (Reprinted with permission from ref 311. Copyright 2003 American Chemical Society.)

Interestingly, recognition between the length of the tube and the length of the hydrophobic block (54 Å) was observed (Table 6).[311] If the tube was shorter than this block, two tubes threaded onto the polymer (2:1 complex). If both lengths were equal, a 1:1 complex was formed, and if the tube was longer than the hydrophobic block, a 1:2 stoichiometry was found. The 1:2 stoichiometry was attributed to a complex constellation, in which two chains thread into one tube. This would lead to a structural defect somewhere in middle of the tube (Figure 54). Another explanation would take into account the polydispersities of both the tube and the hydrophobic blocks: only about half of the polymer chains which could find an appropriate partner might have been complexed. More detailed investigations are necessary to distinguish between both hypotheses. The recognition of the length of a polymer is really a challenging topic. Until now it was only observed within double helices.[312]

9. Functions of and Applications for CD (Pseudo)Polyrotaxanes

CD polyrotaxanes and tubes are fascinating molecular entities. Terms of our daily life, such as threading, stoppering, an abacus, a tube, and an insulated wire, are becoming real in the nanoscopic world of CD molecules. Breathtaking pictures, made by AFM or STM, show that even courageous concepts such as ladder polyrotaxanes are possible to realize. CDs became predictable building blocks for the construction of well-defined nanostructures. Polyrotaxane structures are indeed beautiful. But what are the possible uses?

A polymer molecule experiences four major changes upon rotaxanation, which might be useful: the polymer chain becomes (a) more hydrophilic, (b) better shielded, (c) more rigid, and (d) polyfunctional. Therefore, threading of polymers by CDs can lead to an improved solubility or compatibility of the polymers. New polymer morphologies are obtainable after unthreading of polymers from their CD inclusion compounds. Shielding of a polymer can lead to a higher stability of sensitive polymers against bleaching or autoxidation. Shielding and rigidification lead to improved fluorescence quantum yields of complexed dyes. The polyfunctionality of polyrotaxanes due to the many hydroxyl groups can be exploited, for instance, for the attachment of functional groups or for cross-linking to hydrogels. Linear polyrotaxanes can be used as porogens because of their rigidity. Some examples of functional polyrotaxanes and their possible uses will be given in the following.

9.1. Solubilization of Polymers

Solubilization of monomeric guests in water was already the topic of section 4. Polymers can be solubilized in water by complexation in CDs, too. For example, amphiphilic block copolymers of PEO and PPO (pluronics) were solubilized in water, because the hydrophobic blocks were shielded by hydrophilic CDs.[158,221,313] Complex formation also inhibits both cluster formation and micellization of these polymers.[314,315] In particular, methylated CDs are well suited for the solubilization of hydrophobic polymers such as PPO,[170] because they do not form dense channel inclusion compounds. A polyrotaxane from β-CD and PEO−PPO−PEO triblock copolymers was insoluble in water below room temperature but soluble at elevated temperature. A sharp and reversible phase transition was found. A dense channel packing of threaded β-CD rings at the hydrophobic PPO block was made responsible for the lack of solubility. A less dense distribution of threaded CD rings along the whole polymer caused the observed solubility at higher temperatures.[251] Even single-walled carbon nanotubes (SWCNTs) with an outer diameter of ca. 1.2 nm became water-soluble by complexation in η-CD (12 glucosidic units).[211]

9.2. Processing of Polymers

When CD channel inclusion compounds of polymers were heated with water, polymer chains are extruded out of the channels and often recrystallize in a different way rather than how they would from organic solution. The crystallization from an inclusion compound was coined coalescence by Tonelli's group. Some polymers, such as poly(L-lactid acid) (PLLA)[316] and nylon-6,[156] received a higher crystallinity by coalescence, but others, such as poly(caprolactone) (PCL), received a lower one.[316] The rates of nucleation and crystallization of poly(hydroxybutyric acid) were greatly enhanced by coalescence from its α-CD inclusion compound. This acceleration was attributed to a small fraction of CD rings remaining on the polymer chain improving the mobility of the polymer chains during the crystallization process.[317,318]

Common coalescence of two polymers from a mixture of inclusion compounds often leads to a more intimate blend of the two polymers. Blends of PLLA and PCL were obtained in which the domains for each polymer were much smaller than those obtained by casting from a common

solution.[316] Blends of PCL and poly(*R*,*S*-3-hydroxybutyrate) obtained by coalescence even seem to be homogeneous, because the blend showed only one average glass transition temperature between those of the pure components.[319] Polycarbonate and poly(methylmetacrylate) were also blended this way.[320] Likewise, the coalescence of block copolymers from their CD inclusion compounds leads to materials with lower crystallinities and smaller domain sizes.[321] These materials show a much faster biodegradation, e.g., by lipases, which makes them attractive as sewing threads for surgery applications.[322]

These developments in polymer processing by coalescence from CD inclusion compounds are indeed very promising, but a major disadvantage of this method cannot be ruled out: high amounts of CDs are necessary for processing by coalescence because of the high molecular weights of CDs. For example, the coalescence of 50 g of polymer requires around 1 kg of CD. Therefore, it will only make sense for high value added products, e.g., for medical applications.

9.3. Molecular Insulation of Polyconjugated Polymers

Polyconjugated polymers are indeed very promising materials, because of their electrical conductivity, photoconductivity, electroluminescence, and nonlinear optical properties,[323] but there are also several drawbacks known: they are insoluble and not meltable, and, therefore, are difficult to process; they are sensitive to moisture, light, and oxygen; and they tend to cross-link. Each of these drawbacks limits their applicability. Therefore, it was a good idea to create so-called insulated molecular wires, in which CDs or CD tubes shield polyconjugated polymers from the environment and prevent intermolecular cross-linking reactions.

Anderson's group has developed an approach to produce polyrotaxanes from poly(*p*-phenylene), poly(*p*-diphenylenevinylene), poly(fluorene), and poly(phenylenevinylene), as already described in section 7.3. In contrast to the free polyconjugated polymers, these polyrotaxanes are well soluble in water, processable, and stable to ambient conditions. The polymers show an increased fluorescence, which was attributed to an increased stiffness of the polymer due to the complexation and to less quenching because of the shielding effect of CDs.[108,112,174] Thin films have been produced from these polyrotaxanes by spin-coating, and the optical, morphological, and electroluminescent properties have been investigated.[324]

Polyaniline was complexed by β-CD,[325] or even better by the α-CD molecular tube.[310] The complex of the α-CD tube precipitated from aqueous solution but was soluble in *N*-methyl-2-pyrrolidone. It formed very long (300−400 nm), stiff, wormlike chains, with a constant thickness of the nanotube. Therefore, it was concluded that the polyaniline chain was densely covered by CD tubes. Four point conductivity measurements at single pseudopolyrotaxane molecules showed that the insulated conducting molecular wire is becoming reality.[326]

9.4. Programmed Drug Delivery

Since CD polyrotaxanes are highly polyfunctional molecules, they are well suited for the delivery of drugs. The drug can be covalently attached to the CD rings of a polyrotaxane. The resulting functional polyrotaxane has to be water-soluble. The poor water solubility of dense channel polyrotaxanes was improved by partial hydroxypropylation of the threaded CD rings. Many drug molecules were indeed attached to CD polyrotaxanes. But is there any advantage of polyrotaxanes over any other polysaccharide, e.g., hydroxypropylated starch, for drug delivery? The main advantage of a drug bound to a polyrotaxane is that the drug can be released all at once as soon as the stoppers have been cut off at the desired destination. The liberated CD−drug conjugates are small enough to further degrade rapidly or to diffuse through cell membranes. In Yui's group, α-CD−PEO polyrotaxanes were synthesized stoppered by oligopeptides. First, L-phenylalanine was used as a stopper, which can be cleaved off by proteases such as papain.[249,256,327] The release rate was still sluggish, taking several days. The interaction of polyrotaxanes with the stratum corneum of hairless rat skin was examined by DSC, showing that the designed polyrotaxane could be feasible as a transdermal penetration enhancer.[328] The drug theophylline was attached to the hydroxypropylated CD rings. The enzymatic hydrolysis of the peptide linkages by α-chymotrypsin or papain gave rise to a complete release of the theophylline-conjugated CDs.[255] Likewise, L-phenylalanylglycylglycine (H-L-Phe-Gly-Gly) groups were used as terminal stoppers of a polyrotaxane that could be cleaved off by a membrane-bound metalloexopeptidase (aminopeptidase M).[257]

9.5. Multifold Recognition and Targeting

Attachment of ligands for biological receptors to threaded CDs opens the possibility to direct a polyrotaxane to a certain destination in an organism. The idea behind this is the so-called multivalency concept introduced by G. Whitesides: one ligand−receptor interaction might be weak ($K_s = 10^3-10^4\ M^{-1}$), but the combination of several of those interactions accumulates to give very strong and selective binding.[329] The attachment of ligands to polyrotaxanes allows a straightforward modular implementation of this multivalency concept.

The ligand biotin was attached to the α-CD rings of a PEO polyrotaxane. The binding and dissociation kinetics of this biotin−polyrotaxane to streptavidin immobilized on a gold surface were detected using the surface plasmon resonance (SPR) technique. The affinity of the biotin−polyrotaxane was found to be five times higher to the streptavidine surface than those of the monomeric biotin−CD conjugate.[330]

The ligand maltose was linked onto the α-CD rings of a PEO polyrotaxane. The multivalent interaction with a receptor protein (concanavalin A) was measured by an agglutination assay. Again, the polyrotaxane had a higher affinity to the receptor than the monomeric CD maltose conjugate.[331,332] The mobility of the ligand along the mechanically locked structure of the polyrotaxane significantly enhanced the multivalent interaction.[331,332]

The ligand lactose was appended to α-CD and to partially methylated β-CD. The conjugates were threaded onto hydrophobic polymers, such as PTHP and PPG, in aqueous solution to form pseudopolyrotaxanes.[333] The same α-CD−lactose conjugate was threaded onto the poly(bola-amphiphile), poly(decamethylene-viologen), in aqueous solution. The affinity of the resulting water-soluble lactose−pseudopolyrotaxanes toward the receptor galectin-1 was measured *in vivo* with a T-leukemia cell agglutination assay. The affinity of one lactose−polyrotaxane toward the receptor was 10-fold higher than that of monomeric lactose. This high affinity is possible because of the high but restricted mobility of the

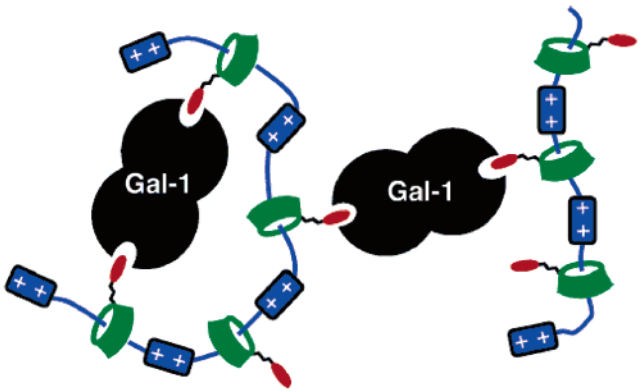

Figure 55. Schematic drawing of multifold interaction of a lactose ligand appended at a pseudopolyrotaxane toward the receptor galectin-1. (Reprinted with permission from ref 334. Copyright 2004 American Chemical Society.)

ligands tethered at the polymer chain, which leads to cooperativity of binding (Figure 55).[334]

9.6. Hydrogel and Network Formation

The (pseudo)polyrotaxanes of CDs and linear or branched polymers can form higher supramolecular assemblies, i.e., hydrogels and networks, through physical or chemical cross-linking.[335] The inclusion compounds of high molecular weight PEO in α-CD form gels in water in a wide range of concentrations. Polymer chains of PEO were only partially included, and the threaded α-CD rings aggregate due to intermolecular hydrogen bonds. These aggregates act as physical cross-links and cause gelation.[336] The pluronic copolymers (triblock copolymer PEO−PPO−PEO) with more than 25 wt % PEO segments also form supramolecular hydrogels induced by association of threaded α-CD rings.[337]

PEO was also grafted to dextrans and a hyperbranched polymer, poly(3-ethyl-3-oxetanemethanol). Threading of α-CD onto the PEO branches of these polymers caused gelation by physical cross-linking.[235,338] PEO was also grafted onto PEO−α-CD polyrotaxanes stoppered with hydrolyzable groups. Threading α-CD onto the PEO arms gave rise to gelation again. The gels could be dissolved again by hydrolytic cleavage of the stoppers. These novel supramolecular hydrogels can find potential application in tissue engineering, where long-term stable but actually hydrolyzable hydrogels are needed.[339] So-called slide-ring gels were obtained by chemical cross-linking of α-CD−PEO polyrotaxanes and investigated by SANS.[340,343] Poly(ϵ-lysine), grafted to dextrane, was also complexed by α-CD, leading to pH and temperature sensitive hydrogels.[341] Supramolecular networks were also formed by interactions between α-CD molecular tubes and cetyl-PEO grafted onto dextran. The polymer chains were physically cross-linked because the molecular tube is able to complex two polymer branches from opposite sides (Figure 56).[342]

9.7. Templating for the Synthesis of Nanoporous Materials

The pseudopolyrotaxanes and polyrotaxanes of linear polymers and CD, and also their aggregates, exhibit stable wormlike shapes in solution, which could be copied into hard material via nanocasting. The *in situ* formed pseudopolyrotaxanes from PEO or PPO polymers or their block copolymers were used as templates in the sol−gel process. Porous silica materials were thus obtained, in which the tubelike pores kept the shape and size of the pseudopolyrotaxanes even after removal of the templates. At low pH (pH = 2.0), the diameters of the pores resembled those of single pseudopolyrotaxane chains. At higher pH, the aggregation of the pseudopolyrotaxanes to bundles led to larger pores.[313] Similar porous silica materials with somewhat wider pores (Figure 57) were formed after templating with α-CD pseudopolyrotaxanes from the poly(bola-amphiphile) poly-(imino-hexamethylene-iminodecamethylene).[344]

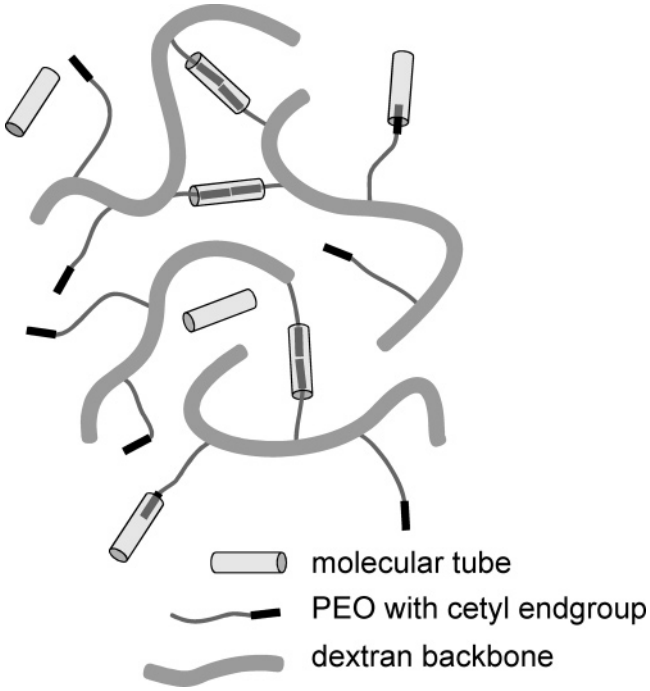

Figure 56. Schematic drawing of physical cross-linking by molecular tubes leading to hydrogels.[342]

10. Concluding Remarks and Future Perspectives

Since the last review[36] eight years ago, there has been overwhelming progress in both quality and quantity of CD polyrotaxane synthesis, characterization, and application. Meanwhile, rotaxanations of monomers and polymers with CDs have become standard procedures.

Furthermore, CD molecular tubes made their way and are already used for many promising applications. Unfortunately, their length is limited and they are only available up to now for α-CD in small quantities. It would be worth the effort to develop this exciting field further and find synthetic procedures for the production of larger quantities and higher internal diameters. Poly-carcerands could be synthesized by stoppering molecular tubes, in which guest molecules had been included before. Monomers could be polymerized within molecular tubes to control the chain length of the polymer.

In the future, the specific functions of polyrotaxanes in terms of solubilization, shielding, or polyfunctionality will be more and more exploited and combined for the creation of highly specialized modular systems.

Because of their relatively high prices,[345] CD polyrotaxanes will never become commodity polymers. The main applications will be small scale, high value added products, such as medical applications. CDs are hydrophilic, nontoxic, and

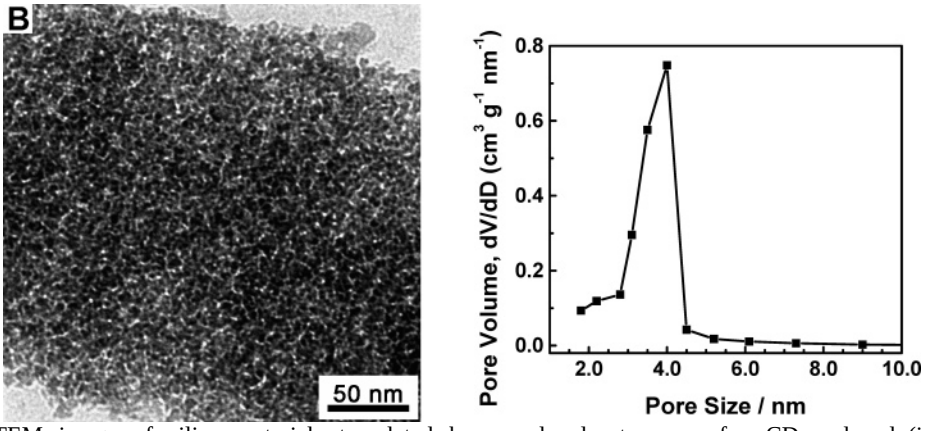

Figure 57. (left) TEM image of silica materials templated by pseudopolyrotaxanes of α-CD and poly(imino-hexamethylene-iminodecamethylene). (right) Corresponding pore size distribution, derived from nitrogen adsorption−desorption isotherms. (Reprinted with permission from ref 344. Copyright 2003 Elsevier Ltd.)

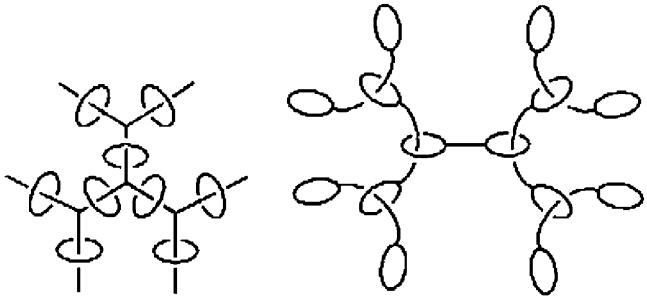

Figure 58. Schematic drawing of polyrotaxane dendrimers. (Reprinted from ref 351 with kind permission of Springer Science and Business Media. Copyright 2003.)

slowly biodegradable. Therefore, CD polyrotaxanes are very interesting candidates for drug delivery systems, sensor devices, implants, contrasting agents,[346] fluorescent probes,[347] or other diagnostic systems. CD polyrotaxanes might be combined with biomolecules, such as genes, antibodies, or enzymes, and used to control their biological functions.

Besides these positive expectations in the biomedical field, CD polyrotaxanes will also have some increasing impact in the development of new materials. Thus, threaded rings are potentially useful for supramolecular catalysis of chemical transformations at polymer chains. Photodimerization[266] and epoxidation[348] of polymer segments have already been catalyzed by threaded rings. Sophisticated catalysts might move along a polymer chain for selective modifications. Also, in the growing field of advanced nanotechnologies, CD polyrotaxanes will play an important role: as insulated molecular wires which can be manipulated by AFM tips or as a molecular abacus[179] for nanocomputers[349] or nanomachines.[10,11,37,114] Certain end groups at one side of a polymer chain may control, like Maxwell's daemon,[350] the directions of threading CD rings,[81] leading to pseudopolyrotaxanes where all CDs are oriented the same way.

Even more sophisticated interlocked structures are conceivable, such as polyrotaxane dendrimers (Figure 58).[351] It seems there is no limit to our fantasy.

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