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Recognition of Monomers and Polymers by Cyclodextrins

Gerhard Wenz

Abstract Cyclodextrins (CDs), cyclic oligomers consisting of 6, 7, 8, or more $\alpha(1 \rightarrow 4)$-linked glucose units, are readily available, water-soluble organic host compounds that are able to complex organic guest molecules if the latter contain a suitable hydrophobic binding site. The main driving forces are nonpolar interactions such as hydrophobic and van der Waals interactions. CDs are able to recognize the thickness, polarity, and chirality of monomeric and polymeric guest molecules. In addition, functional groups can be covalently attached to CDs to modify or improve the molecular recognition capability of CDs. In this review, the binding potentials of the most important CDs and CD derivatives are summarized, and general rules for the recognition of monomeric and polymeric guests are derived. A supramolecular tool box of water-soluble hosts and guests is provided, which allows the assembly of many sophisticated supramolecular structures, as well as rotaxanes and polyrotaxanes.

Keywords Inclusion Compounds, Molecular recognition, Polyamphiphiles, Polyrotaxanes, Supramolecular Chemistry

Contents

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Abbreviations

α-CD	α-Cyclodextrin
β-CD	β-Cyclodextrin
γ-CD	γ-Cyclodextrin
CD	Cyclodextrin
CE	Capillary electrophoresis
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DS	Degree of substitution
FITC	Fluoresceine-4-isothiocyanate
GPC	Gel permeation chromatography
IC	Inclusion compounds
ITC	Isothermal titration calorimetry
LCST	Lower critical solution temperature
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear-Overhauser-effect
OLED	Organic light emitting diode
PCL	Polycaprolactone
PDLA	Poly(D-lactide)

PDMS	Polydimethylsiloxane
PEO	Polyethylene glycol
PIBMA	Poly(isobutene-*alt*-maleic acid)
PPO	Polypropylene glycol
PLLA	Poly(L-lactide)
PTHF	Polytetrahydrofuran, poly(tetramethylene oxide)
r.t.	Room temperature
THF	Tetrahydrofuran
UV–vis	UV–vis spectroscopy
WAXS	Wide angle X-ray scattering

1 Introduction

The recognition of one person from a crowd of people requires the distinction of certain human attributes, such as tallness, voice, hair color, or gestures. Recognition becomes more selective when increasing numbers of these attributes are checked for various persons. Our society would not function without the ability to recognize certain people. Recognition is one of the most important prerequisites of the development of the human culture, since it allows creation, transformation, and collection of information. The information content of a system increases with the selectivity of recognition of one event out of many others. Therefore, selectivity gained by recognition allows for writing of information into and reading from a system, which would be otherwise random, arbitrary and chaotic [1].

The recognition of one molecule out of a crowd of many other molecules requires distinction of certain molecular attributes, such as size, polarity, hydrogen bond pattern, chirality, or other physicochemical properties. If several attributes can be checked simultaneously, recognition becomes more selective. Recognition between an enzyme and a substrate was described first by Emil Fischer as the well-known *lock and key principle* [2]. Molecular recognition between complementary DNA strands [3] or protein ligand interactions [4] is very important for the molecular function of living systems.

Recognition between two sorts of molecules, A and B, is caused by reversible, noncovalent interactions such as Coulomb, van der Waals, and solvophobic interactions, as well as hydrogen bonds. D.J. Cram coined the terms host and guest for two complementary molecules [5]. The complex of both is called a *host–guest complex* or, according to Lehn, *supramolecular structure* or *super molecule* [6]. Supramolecular structures may also be composed of more than two molecules. Selectivity of recognition increases as hosts and guests fit together better. Binding constants increase with increasing preorganization of a host for a certain guest [7].

Intelligent molecular systems can be created based on host–guest recognition, which can self-organize and behave differently than nonorganized matter. Supramolecular structures formed by molecular recognition can be used to create molecular systems with specific functions, such as motors or stimulus-responsive

artificial muscles [8, 9], surfaces with photo-switchable polarities [10], intelligent drug carriers [11], or high density information storage systems [12, 13].

Therefore, supramolecular structures will be of great importance for the development of new technologies in the near future. Despite there being a plethora of secondary literature available about molecular recognition of monomeric guests by organic host molecules, little systematic and comprehensive knowledge is available about molecular recognition of polymers. Therefore, I wish to address this topic in this chapter, focusing on one important class of organic host molecules, namely, the cyclodextrins (CDs). CDs form complexes, so-called "Einschlussverbindungen" [14], or inclusion compounds (ICs), with hydrophobic or amphiphilic guests. Among other hosts [15], such as crown ethers [16], cryptands [17], spherands [7], cucurbiturils [18], cyclic amides [19], and cyclic peptides [20], CDs offer several advantages:

- CDs are produced on an industrial scale in high purity (>5,000 tons per year)
- CDs form supramolecular structures in water
- CDs are highly biocompatible, biodegradable and show low toxicity
- CDs can be selectively modified
- CDs already have some industrial applications [21]

Since the literature about CDs is rapidly expanding (∼45,000 references in the CAS database from September 2008), this review is focused on stating basic principles exemplified by original literature. Older literature about CDs has already been summarized in several review articles dealing with CDs in general [22, 23], CD crystallography [24, 25], CD derivatives [26], stabilities of CD ICs [27], CD rotaxanes [28], and CD polyrotaxanes [29–31].

2 Cyclodextrins and Cyclodextrin Derivatives

2.1 Cyclodextrins

CDs are cyclic oligomers consisting of 6, 7, 8, or more $\alpha(1 \rightarrow 4)$ linked anhydroglucose units called α-, β-, γ-CDs, and so on, respectively (see Fig. 1). They were discovered by Villiers [32], identified by Schardinger [33], and systematically investigated by Freudenberg [34] and Cramer [35]. They are produced by enzymatic degradation of starch by CD glucosyltransferases (CGTases), already on an industrial scale. The ring sizes $n = 6$, 7, and 8 are isolated from the reaction mixture with high purities by specific precipitation agents (*n*-octanol, toluene, and cyclohexadec-8-en-1-one for α-, β-, and γ-CD, respectively) [23]. Since there are no precipitation agents available for the higher oligomers, these oligomers still need to be isolated by chromatographic methods. Nevertheless, even the structure of the 26-membered ring is known [24]. In addition, the five-membered cyclic oligomer, cyclomaltopentaose, has been obtained by chemical synthesis in small quantities [36]. We shall focus in

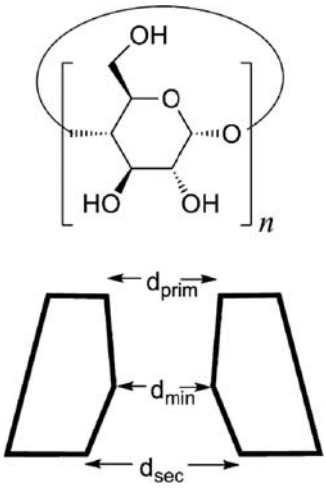


Fig. 1 Schematic drawings of cyclodextrins (CDs), $n = 6, 7, 8$ for α-, β-, γ-CD, respectively

Table 1 Inner widths of cyclodextrins obtained by molecular modeling

Cyclodextrin	n	d_{prim} [Å] CPK[a]	d_{sec}[Å] CPK[a]	d_{min}[Å] AM1[b]
α-CD	6	4.7	5.2	4.4
β-CD	7	6.0	6.4	5.8
γ-CD	8	7.5	8.3	7.4

[a]Measured from CPK models [22]

[b]Calculated by Gaussian03 [42] and MolShape [40]

the review mainly on the hosts α-, β-, and γ-CDs because of their ready availability. These CDs are moderately to highly soluble in water (see Table 2) [37] and highly soluble in strongly polar organic solvents like DMF, DMSO, and pyridine.

As shown by X-ray and neutron beam crystallography, α-CD, β-CD, and γ-CD molecules look like hollow truncated cones (Fig. 1) [24]. The primary C-atoms C-6 are located at the narrow side, called the primary rim, while the secondary C-atoms C-2 and C-3 are located at the wide side, called the secondary rim. Since the glucose moieties cannot rotate within these rings because of steric constraints, no conformational isomers are possible, unlike for calixarenes [38]. Furthermore, the CD macrocycles are rigidified by intramolecular hydrogen bonds between the secondary hydroxyl groups [39]. The diameters of the internal cavities range from about 4.5 to 8 nm, depending on the ring size (see Table 1). These cavities are not cylindrically shaped but conical with a constriction in the middle, as depicted in Fig. 1 [22,40,41]. The heights of α-CD, β-CD, and γ-CD molecules are very similar and around 0.8–0.9 nm [24].

2.2 Cyclodextrin Derivatives

The hydroxyl groups at the primary (C-6) and the two secondary positions (C-2, C-3) are prone to displacement reactions at the O- or C-atoms leading to CD derivatives [26]. There are several motivations for the derivatization of CDs:

- Improvement of solubility in water
- Improvement of solubility in organic solvents
- Improvement of molecular recognition potential
- Reduction of toxicity

Derivatizations can be performed in well-defined regioselective ways, in which 1, 2, $2n$, or $3n$ ($n = 6$, 7, or 8 for α-CD, β-CD, or γ-CD, respectively) substituents were attached at certain positions of the CD scaffold [26]. In addition, CDs have also been derivatized statistically at various positions. Statistical derivatizations require much less effort for synthesis and purification and give rise to higher yields than regioselective ones, but the products are difficult to reproduce and to characterize because of their heterogeneity. All synthetic methods will be briefly summarized subsequently. Those derivatives used most often are listed in Table 2.

The main entry for CD derivatives, mono-substituted at the C-6 position, are the tosylates for α-CD and β-CD and 2,4,6-triisopropylbenzene sulfonate for γ-CD [43–45]. The 6-*O*-sulfonates of CDs can be converted to functional CD derivatives,

Table 2 The supramolecular toolbox: CDs and common CD derivatives and their solubilities in water

Abbreviation	Ring size, *n*	Substituents	Positions	Degree of substitution per CD	Aqueous solubility at 25 °C, %	Aqueous solubility at 60 °C, %
α-CD	6	No		0	13	>33
β-CD	7	No		0	1.8	9
γ-CD	8	No		0	26	>50
RAMEA	6	Methyl	All	10	>50	>50
RAMEB	7	Methyl	All	12–13	>50	>50
DIMEB	7	Methyl	2,6-O	14	>50	1.8
TRIMEB	7	Methyl	All	21	29	2.6
HPα-CD	6	Hydroxypropyl	All	3–5	>50	>50
HPβ-CD	7	Hydroxypropyl	All	4–5	>50	>50
HPγ-CD	7	Hydroxypropyl	All	4–6	>50	>50
Tosyl-β-CD	7	Tosyl	6-O	1	0.06	0.6
NH_2-β-CD	7	Amino	6-C	1	7.5	>30
SBE7-β-CD	7	Sulfonatobutyl	All	7	>50	>50
SET7-β-CD	7	Sulfonatoethylthio	6-C	7	>50	>50
AET7-β-CD	7	Aminoethylthio	6-C	7	>50	>50

such as the 6-azido [46], 6-amino [44], or 6-thioether [47] by nucleophilic displacement reactions. Additionally, different regio-isomers (AB, AC, or AD) of CDs, disubstituted at O-6 [48, 49], and trisubstituted at O-6 [50] can be obtained by a reaction of β-CD with sulfonyl chlorides. Furthermore, sulfonates at the secondary hydroxyl groups can be synthesized and readily transferred to the 2,3-anhydro-CDs, which can further react with nucleophiles to furnish β-CD derivatives functionalized at the secondary rim [51]. On the other hand, hepta-2,3,6-tri-*O*-methyl-β-CD and hepta-2,3,6-tri-*O*-benzyl-β-CD can be regioselectively dealkylated at two well-defined primary positions with DIBAL [52, 53]. The resulting free OH groups can be further modified to other functional groups [54, 55]. Per-6-iodo-6-deoxy-CDs, readily available by reaction of CDs and triphenylphosphine/I_2 [56], are the key intermediates for the synthesis of CD derivatives with *n* substituents at the primary rim by nucleophilic displacement reactions. Substitution by azide and subsequent reduction furnishes the corresponding per-6-amino-6-deoxy-CD derivatives [57]. Reaction of the per-6-iodo-6-deox-CDs with thiol functions leads to various *n* functional thioethers, such as heptaamines, heptacarboxylates, and heptasulfonates [47,58]. Several glycoclusters bearing *n* sugar groups (mannose, glucose, galactose) at the primary rim were synthesized this way, as well [59].

All regioisomers of per-*O*-methyl-CDs (2-*O*-, 3-*O*-, 6-*O*-) and per-di-*O*-methyl-β-CDs (2,6-di-*O*-, 2,3-di-*O*-, 3,6-di-*O*-) have been synthesized by regioselective methods using protecting group chemistry [60–63]. Analogous functional β-CD derivatives bearing 7, 14, or 21 carboxymethyl groups, as well as 7 amino and 7 carboxymethyl groups, were synthesized by Kraus et al. via the corresponding allyl ethers [64–67].

In addition to the regioselectively derivatized CDs, a number of statistically substituted CDs are in use. Highly water-soluble statistic derivatives are obtained by reaction of CDs with methyl halides [68], with epoxides (e.g., ethylene oxide, propylene oxide [69,70], or allyl glycidylether [71]), and with cyclic sulfates (e.g., butane sultone [72]). Statistical allyl ethers were converted to sulfonates by addition of sulfite [71]. Monochlorotriazinyl-β-CD is another available reactive CD. Since these synthetic procedures are rather simple compared to the regioselective ones, many of these statistical compounds are available at the technical scale.

The solubilities of native CDs in water are moderate, with β-CD showing the lowest solubility, as shown in Table 2 [37]. Solubilities generally increase drastically with increasing temperature. Only methylation leads to lower solubilities at elevated temperatures. In other words, methylated CDs show a lower critical solution temperature (LCST). Hydroxypropyl-CDs are highly water-soluble at any temperature [69, 70]. Ethylated CDs are amphiphilic [73], while alkylated CDs with alkyl chain lengths >2 are already insoluble in water, but soluble in organic solvents like chloroform or toluene [74]. Both anionic CD derivatives like SBE-β-CD or SET7-β-CD and cationic CD derivatives like AET-β-CD are also highly water-soluble and therefore well suited for the solubilization of hydrophobic guest molecules [47,58,75].

2.3 Cyclodextrin Dimers and Polymers

Since space is limited within the internal cavities of α-, β-, and γ-CDs, it was desirable to connect two and more CD rings to achieve some cooperativity in binding large guests. Two α-CD rings had been connected by one or two bridges at the primary rims [76]. Two β-CD had been connected, as well, via one or two bonds to a dimer by Breslow et al. [49, 77–81]. Recently, a heterodimer of α-CD and β-CD was also synthesized [82].

CD polymers can be synthesized (1) by radical polymerization of monofunctional CD monomers, (2) by polymer-analogous reaction of polymers with CDs, and (3) by partial crosslinking of CDs, as exemplified below.

α-CD and β-CD, both conjugated with an acryloyl group, were polymerized by radical initiators [83]. Similarly, phenylacetylene [84] and polyphenylene ethynylene [85] backbones with pendant α-CD, β-CD, and γ-CD groups were synthesized by polymerization of the respective CD monomers. Polymer-analogous reaction turned out to be a highly efficient method of CD polymer synthesis. Native CDs were attached via an ester bond to alternating poly(maleic anhydride) copolymers in high yields to produce water-soluble poly CD maleates [86–89]. α-CD and β-CD were also conjugated to polyallylamine [90], poly(ethyleneimine) dendrimers [91], chitosane [92, 93], and alginate [94]. Similarly, 6-amino-β-CD was attached via an amide bond to a succinylated α-CD-PEO polyrotaxane [95].

Crosslinking of α-CD with epichlorohydrin in aqueous solution under well controlled conditions furnished hyperbranched water-soluble α-CD polymers [96, 97]. On the other hand, template directed crosslinking of α-CD, threaded on PEG, gave rise to linear CD polymers with two to three bridges between every two neighboring rings, or so-called molecular tubes, as shown in Fig. 2 [98–101].

3 Recognition of Monomeric Guests by CDs and CD Derivatives

3.1 General Remarks

The following section exemplifies how different molecular attributes of a guest, such as length and thickness, chirality, functional groups, and end groups are recognized by CDs and CD derivatives. Molecular recognition is always controlled by interactive forces between the guest and the host, as described below.

The internal cavities of CDs are mainly hydrophobic and able to attract guest molecules by hydrophobic, van der Waals, and other dispersive interactions [102]. Since these interactions are strongly distance dependent [103], thickness recognition is especially pronounced. The dominance of solvophobic interactions is evident in the fact that the inclusion of guests in CDs occurs preferentially in aqueous solutions. The addition of small amounts of organic solvents to aqueous solutions is enough to render ICs significantly less stable [104]. These attractive interactions are mainly controlled by space filling: the more the hydrophobic part of the guest fills

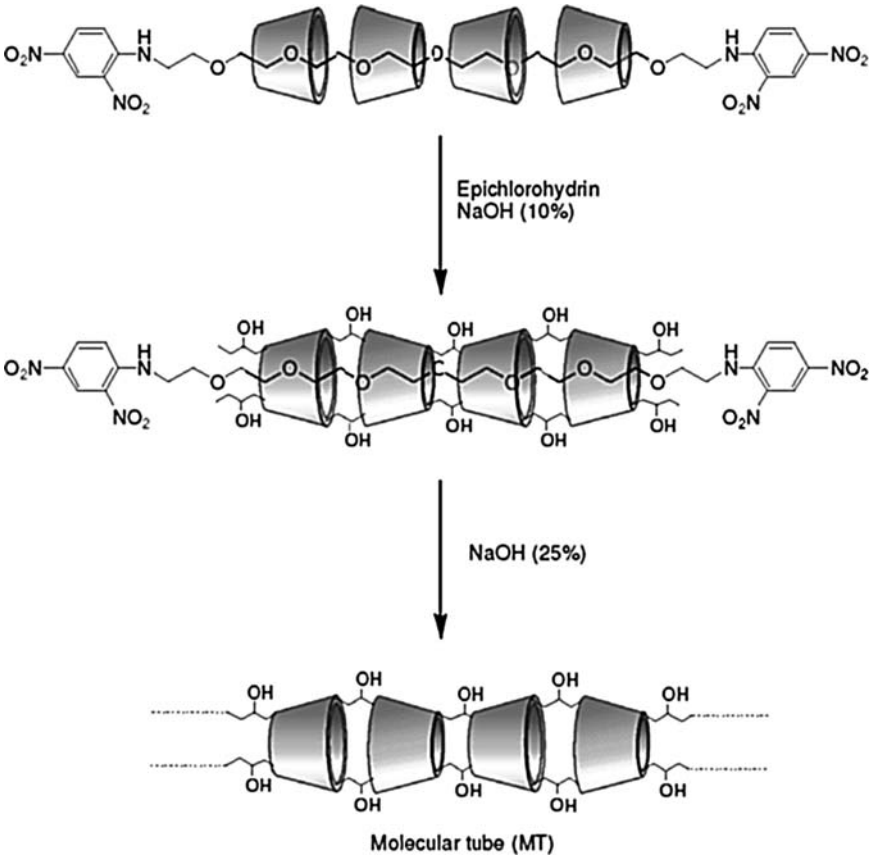


Fig. 2 Template directed synthesis of molecular tubes (MT) Harada et al.

the internal space of the CD host, the stronger the host–guest interaction. Therefore, the hydrophobic area of the guest mainly determines the nonspecific attractive interactions. For example, binding free energy values $-\Delta G^0$ of several homologous series of guests in β-CD linearly increase by $2.8 \pm 0.6\,\mathrm{kJ\ mol^{-1}}$ per methylene group [27, 105].

Molecular recognition of guests by CDs is not only controlled by interactions between CD and guest but also indirectly by interactions between CDs and between guests. Four different types of CD ICs can be classified, as depicted in Fig. 3. ICs of type I consist of a native CD and a hydrophobic guest. These ICs are generally insoluble in water, since channel ICs are formed by hydrogen bonds between the hydroxyl groups of the CDs and hydrophobic interactions between the guests. In general, at least one hydrophilic group at the guest leads to the formation of soluble ICs of type II. Solubility of the guest is increased by IC formation because the hydrophobic part of the guest is masked by the CD. So-called *bola-amphiphiles* [106, 107], amphiphilic molecules with two terminal hydrophilic groups, form ICs

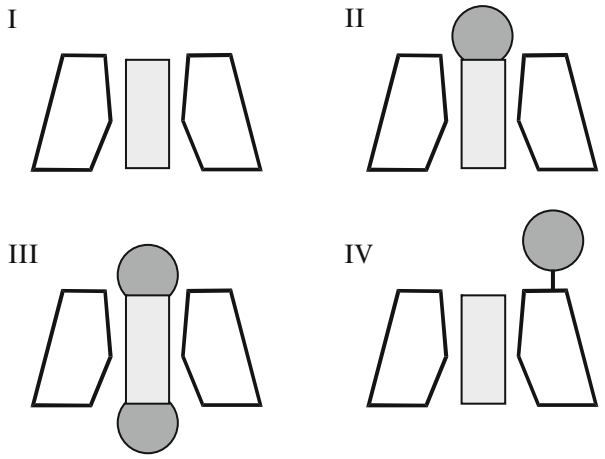


Fig. 3 Classification of CD ICs: type I: hydrophobic guest, insoluble channel IC, type II: amphiphilic guest, solubilization of a guest, type III: bola-amphiphilic guest, homogenous IC formation, type IV: charged CD derivative, solubilization of a hydrophobic guest

of type III under homogenous conditions, since all of CD, guest, and IC are highly water-soluble. Furthermore, charged CD derivatives form water-soluble ICs of type IV even with hydrophobic guests. In ICs of types II–IV, repulsive interactions between the hydrophilic groups and solvation effects prevent the formation of water insoluble channel ICs typical for type I.

For the quantification of molecular recognition, binding constant K and binding free energy ΔG^0 are defined by (1) and (2), respectively. Since determination of K requires at least measurable concentrations of each component, K and ΔG^0 can only be accurately determined for ICs of types II–IV:

$$K = \frac{[CD \cdot G]}{[CD][G]}, \tag{1}$$

$$\Delta G^0 = -RT \ln K. \tag{2}$$

Molecular recognition is not only limited to differentiation of binding free energies ΔG^0, called *thermodynamic recognition*, but can also originate from differentiation of the kinetics of IC formation and dissociation, denoted as *kinetic recognition*. Activation energies of both complex formation and dissociation influence the binding kinetics, which can influence binding selectivities in nonequilibrium states. Kinetic recognition occurs especially for bola-amphiphiles because the bulky end groups can significantly hinder formation and dissociation of the ICs. Inclusion becomes an activated process controlled by an activation energy, which increases with increasing size of the bulky end groups (see Fig. 4). Activation energies $E_A = \Delta H^{\neq}$ are determined according to the Arrhenius equation from the temperature dependence of the respective rate constants. Activation free energies, $\Delta G^{\neq}$, are directly

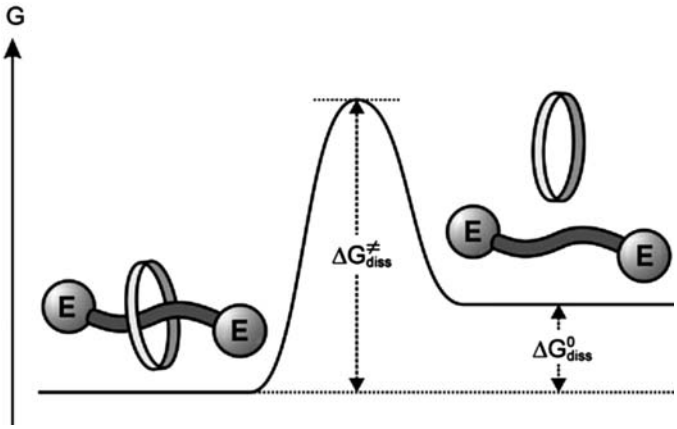


Fig. 4 Energy diagram for the dissociation of the IC of a bola-amphiphile, E: hydrophilic end group, $\Delta G^{\neq}_{\mathrm{diss}}$: activation free energy of dissociation, $\Delta G^{0}_{\mathrm{diss}} = -\Delta G^{0}$: free energy of dissociation (reprinted with permission from [31], copyright of the American Chemical Society)

calculated from the corresponding rate constants k using the Eyring theory [108] (3), with Planck's constant h and Boltzmann's constant k_{B}. Both activation energies are often in the same range. Those ICs in which dissociation is sterically hindered are *pseudorotaxanes*, and those where activation energy exceeds 50 RT (the 50-fold average thermal energy) are *rotaxanes* [31]:

$$\Delta G^{\neq} = -RT \ln \frac{k\mathrm{h}}{k_{\mathrm{B}} T}. \tag{3}$$

3.2 Thermodynamic Recognition of the Size of a Guest

Due to their well-defined internal diameters (see Table 1) and their rigid structure, CDs are able to recognize the thicknesses of various guest molecules. Thermodynamic thickness recognition of some often used guests by α-, β-, and γ-CDs is summarized in Table 3. α-CD is capable of complexing linear aliphatic chains. Benzene, naphthalene, adamantane, or ferrocene moieties fit well within β-CD. γ-CD can accommodate pyrene or two azobenzene moieties. $-\Delta G^{0}$ values of 30 kJ mol^{-1} can be reached if the guest fits well inside a CD cavity. More detailed information about ICs of α-, β-, and γ-CDs is provided subsequently.

3.2.1 ICs of α-CD

The minimal internal diameter of α-CD, $d = 4.4$ Å, limits the formation of ICs mainly to linear alkyl chains. For example, α-CD forms crystalline ICs with

Table 3 Recognition of the thicknesses of guests by CDs according to their binding free energies ΔG^0 in kJ mol^{-1} at pH 7

Guest	$-\Delta G^0$/kJ mol^{-1} α-CD	$-\Delta G^0$/kJ mol^{-1} β-CD	$-\Delta G^0$/kJ mol^{-1} γ-CD	Ref.
1,10-Decandiol	22	19	<10	[109, 110]
1-Adamantane-carboxylate	13	26	21	[111]
4-*tert*-Butybenzoate	13	24	<10	[58, 112]
2-Naphthalene sulfonate	15	31	7	[113]
Pyrene	12	15	17	[114]
methyl orange anion	23	19	41[a]	[115]

[a]2:1 Complex formed

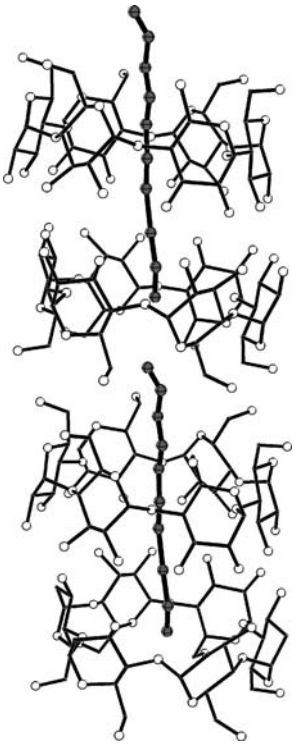


Fig. 5 Crystal structure of the channel IC of *n*-decane in α-CD [116]

n-alkanes insoluble in water. These ICs show a channel structure in which CDs are oriented in a nearly parallel fashion, and the alkane is confined within the channel, as exemplified in Fig. 5. The α-CD rings are connected by hydrogen bonds between the primary rims and the secondary rims each. Since the alkyl chain nearly fills the α-CD cavity, the internal water molecules of native α-CDs are totally ejected by the guest. Most C–C bonds of the guest are in the *trans* conformation.

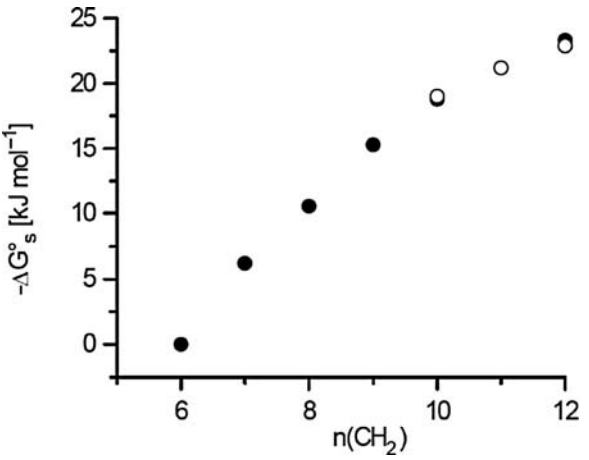


Fig. 6 Binding free energies $-\Delta G^0$ as a function of the lengths of the hydrophobic binding sites, quantified by the number of methylene groups n(CH_2), for (*filled circle*) bola-amphiphiles, α, ω-diaminoalkanes, and (*open circle*) poly-bolaamphiphiles, poly(imino-oligomethylene)s at pH 6.7 and 25 °C, determined by ITC [119]

Some limited mobility of the alkanes was detected by solid state DNMR as a function of temperature [117]. This mobility explains why alkanes such as pentane can be driven out of the ICs by heating, leaving behind empty channel structures that differ from the well known native herringbone type structures of CDs [118].

There is no binding data of *n*-alkanes available, since the α-CD type I ICs are insoluble in water. Hydrophilic groups, such as carboxylate, amino, or hydroxyl groups, at one or both ends of linear alkyl chains render the ICs water-soluble and allow the determination of binding data [27]. The binding free energies ΔG^0 are becoming linearly more negative with increasing number n of methylene groups, as shown for the homologous series of α, ω-diamino alkanes in Fig. 6.

For $n = 6$ or less, no binding was found at all because the highly hydrophilic protonated amino groups avoid staying inside the hydrophobic CD cavity [119]. For comparison, the corresponding α, ω-diols are able to form ICs with shorter spacer lengths, since the hydroxyl groups are less hydrophilic than the protonated amino groups [109]. For short spacer lengths n, repulsive interactions between end-groups of bola-amphiphiles and α-CD are pronounced, but they level off with increasing n. If n is 12 or greater, even two α-CDs can thread onto bola-amphiphiles [120]. At present, no systematic binding data is available for amphiphilic guest molecules with unsaturated and branched alkyl chains, such as isoprenoids.

Benzene or cyclohexane rings can still pass through the α-CD ring, but they are already too thick to be complexed within the center of the α-CD cavity. Therefore, only rather unstable ICs are formed, in which the ring is situated at the wider secondary rim of the α-CD cavity. They are called *shallow ICs*. Benzoic acid derivatives are complexed exceptionally well and deeply, since the COOH group prefers to remain in the cavity [121]. Biphenyl derivatives are not bound at all as well as the dibromo–diphenylethane derivative in Fig. 7.

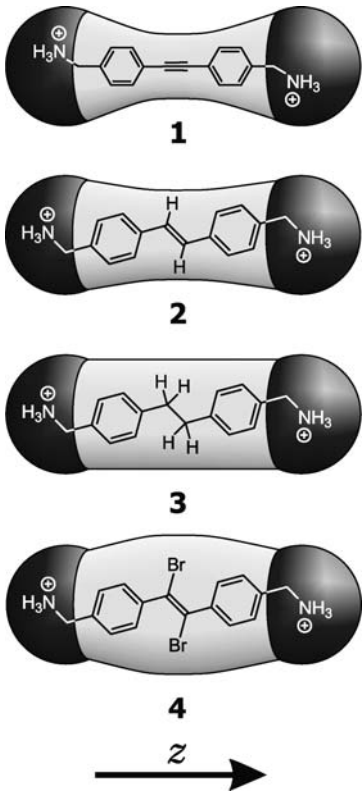


Fig. 7 Recognition of bola-amphiphiles by α-CD (Reprinted with permission of [40], copyright of Wiley)

On the other hand, stilbene and tolane derivatives are tightly complexed by α-CD, since the narrow parts (waists) of these guests fit perfectly within the constriction of the host [40]. Interestingly, the values of ΔG^0 of tolane derivatives are more negative than the ones of corresponding stilbene derivatives, despite the space filling of the α-CD cavity is better with the stilbene moiety. Perfect space filling is accompanied with a high loss of entropy, which counteracts the attractive forces. The slimmer tolane moiety is bound better because it loses less entropy due to a looser fit. Consequently, a loose fit between host and guest supports binding as long as no water molecules can intrude in the empty space between host and guest. The preference of a slightly loose fit was also found earlier [122].

3.2.2 ICs of β-CD

Since the internal diameter of β-CD is 5.8 Å, it is able to accommodate guest molecules that are thicker than the ones complexed by α-CD. Hydrophobic moieties such as benzene [123], naphthalene [113, 124], anthracene [125], adamantane [126, 127], and ferrocene [128] are bound well by the β-CD cavity. Again, hydrophilic groups have to be attached to these hydrophobic binding sites to insure water

Fig. 8 Structure of bile salts

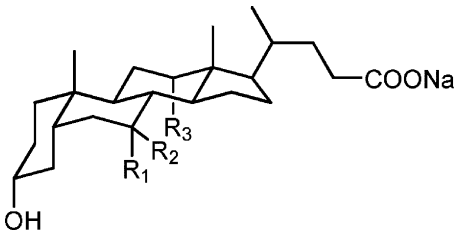


Table 4 Recognition of the pattern of hydroxylation of bile salts by β-CD [129]

Steroid	R^1	R^2	R^3	$-\Delta G^0$/kJ mol^{-1}
Cholate	OH	H	OH	21
Deoxycholate	H	H	OH	20
Chenodeoxycholate	OH	H	H	30
Ursodeoxycholate	H	OH	H	34
Lithocholate	H	H	H	36

solubility of the ICs. Binding constants K of up to $10^5\,M^{-1}$ are reached with unsubstituted β-CD for the guest 1-adamantyl ammonium [27]. The bola-amphiphilic guest 4,4′-bis(imidazolyl-methylen)-biphenyl is already long enough for being complexed by two β-CD molecules, while the corresponding benzene derivative is only complexed by a single one. Furthermore, amphiphilic steroids such as bile salts cholate, deoxycholate, and lithocholate depicted in Fig. 8 form very stable complexes with β-CD. The binding data collected in Table 4 show that hydroxyl groups at the center of the guest diminish binding, while the highest $-\Delta G^0$ of 36 kJ mol^{-1} was found for lithocholate, the guest with no hydroxyls at positions 7 and 12 [129]. This example shows that a large continuous hydrophobic surface is necessary at the guest to achieve a strong affinity to CDs. The hydrophilic hydroxyl groups seem to prevent a deep inclusion of the guest within the host.

If many hydroxypropyl groups, or one or more ionic substituents, are attached to β-CD, fully hydrophobic guests can be solubilized in water by formation of type IV ICs. For example, sulfobutyl-β-CD SBE7-β-CD is even able to solubilize steroids like testosterone in water [75]. Naphthalene was solubilized in water by 3-sulfonatopropyl-oxy-hydroxypropyl-β-CD [71]. Hepta-6-aminoethyl-thio-β-CD, AET7-β-CD, renders the anticancer drug camptothecin soluble in water to a high degree. In every case, the highly hydrophilic ionic group at the β-CD prevents formation of water-insoluble channel ICs.

3.2.3 ICs of γ-CD

γ-CD possesses an internal diameter that is even larger than the previously discussed CDs, $d = 7.4$ Å (see Table 1), allowing inclusion of large guests such as polycyclic aromatics, e.g., pyrene [130, 131], perylene [132], and even C_{60} [133, 134].

Furthermore, γ-CD can complex two guests at the same time. For example, two stilbene [135], naphthalene [136], or anthracene [137] moieties can fit in the γ-CD cavity. Attractive interactions between the end groups of two included guests enhance the stability of the ICs [136]. Because of the close proximity between two included guests, bimolecular reactions like [2 + 2]-cycloadditions [135] and Diels–Alder-reactions [138–140] are strongly accelerated by these ICs.

3.3 Thermodynamic Recognition of Chiral Guests

Since CD hosts are chiral molecules, enantiomers of a chiral guest can indeed be distinguished due to diastereomeric interactions, but differences in binding free energy $\Delta\Delta G_{R,S}$ are generally small $(0.1–2\,\mathrm{kJ\,mol^{-1}})$ because CDs deviate only slightly from a cylindrical shape. The influence of substituents at β-CD on $\Delta\Delta G_{R,S}$ was systematically investigated for amino acids and their *N*-protected derivatives, shown in Table 5.

For native β-CD, chiral recognition is very small; alkyl substituents lead to an increase, while mono phenylseleno derivatives show exceptionally high selectivities, with $\Delta\Delta G_{R,S}$ of up to $8\,\mathrm{kJ\,mol^{-1}}$. One polar substituent appears to have the greatest disturbance of the symmetry of the CD, providing a suitable asymmetric environment for the chiral guest. For example, 6-monoamino-β-CD and 6-*O*-carboxymethyl-β-CD show stronger chiral selectivity for amino acids than native β-CD does [144–147], while disubstituted β-CD derivatives performed even better [148]. This idea was already expressed by the three-point rule by Kano, which states that the guest has to strongly interact at least at three points with the host to gain high enantioselectivity [149].

Despite the values of $\Delta\Delta G^0_{R,S}$ being generally small, they are large enough to be resolved by high performance chromatographic methods such as gas and liquid chromatography. Thousands of successful separations of enantiomers by CD

Table 5 Chiral recognition of enantiomeric guest molecules by β-CD derivatives

Host	Guest	Method	$\Delta\Delta G_{R,S}$	Ref.
Mono-[6-(*o*-tolylseleno)-6-deoxy]-β-CD	Alanine	UV–vis	8.10	[141]
Mono-[6-(phenylseleno)-6-deoxy]-β-CD	Alanine	UV–vis	3.40	[141]
TRIMEB	AQC[a]-alanine	CE	0.16	[142]
β-CD polymer	AQC-alanine	CE	0.11	[142]
HP-β-CD	AQC-alanine	CE	0.10	[142]
DIMEB	AQC-alanine	CE	0.10	[142]
β-CD	AQC-alanine	CE	0.05	[142]
6-*O*-(4-chlorophenyl)-β-CD	Camphor	ITC	3.44	[143]
β-CD	Camphor	ITC	1.25	[143]

[a]AQC = 6-aminoquinolyl-carboxy derivative of amino acid

bonded phases using high performance liquid chromatography [150, 151], gas chromatography [152–154], or capillary electrophoreses [155] have been reported in the literature [156].

3.4 Thermodynamic Recognition of Polar Guests by CD Derivatives

Binding selectivities can be increased by polar interactions, e.g., Coulomb interactions or hydrogen bonds, between functional groups of CD derivatives and functional groups at the guest. Recently, we demonstrated the superior binding properties of hepta-6-*S*-6-deoxy-β-CD derivatives towards the cancer treatment drug camptothecin [47].

The contribution of Coulomb interactions to the binding of charged guests with statistically substituted sulfobutyl ether β-CD derivatives [75] and charged hepta-6-*S*-6-deoxy-β-CD derivatives, e.g., AET7-β-CD and SET7-β-CD, has already been demonstrated [58]. We found binding constants K exceeding $10^6\,M^{-1}$ for complexes of the heptacationic β-CD derivative AET7-β-CD and negatively charged derivatives of *tert*-butyl benzene, listed in Table 6. The orientations of charged guests in the CD cavity are also influenced by Coulomb interactions, exemplified in Fig. 9. Coulomb repulsion forces the guest into a "downward" orientation, while Coulomb attraction forces the guest into an "upward" orientation.

Binding free energy ΔG^0 was strongly dependent on the solvent, and it could be subdivided into two parts: (1) the part ΔG^{00}, due to nonpolar interactions, called *binding affinity*, and (2) the part $\Delta\Delta G^0$, due to polar interactions, called *binding selectivity*, by comparison of the binding data of neutral and charged guest molecules, respectively. On one hand, binding affinity *increased* with increasing salt concentration. This increase of affinity is due to increasing hydrophobic interactions, the so-called salting out effect [124]. On the other hand, binding selectivity *decreased* with increasing salt concentration because of the shielding effects of ion clouds

Table 6 Molecular recognition between charged hosts[a] and guests [58]

Functional group	Number of functional groups	$-\Delta G^0$/kJ mol^{-1} for cationic guest[b]	$-\Delta G^0$/kJ mol^{-1} for anionic guest[c]
$S-CH_2COO^-$	1	23	22
$S-CH_2NH_3^+$	1	22	25
$S-CH_2COO^-$	7	35	22
$S-CH_2NH_3^+$	7	23	37

[a] 6-Deoxy-β-CD derivatives
[b] 4-*tert*-Butyl-1-guanidinium-benzene
[c] 4-*tert*-Butyl-benezenesulfonic acid

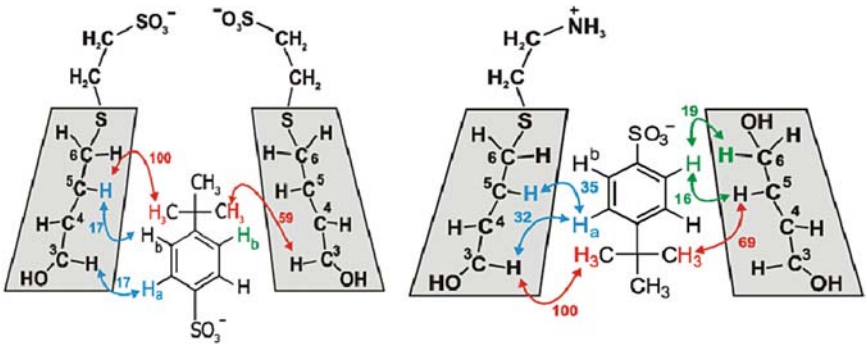


Fig. 9 Influence of charged groups at β-CD (*left*: SET7-β-CD, *right*: AET1-β-CD) on the orientations of the anionic guest *tert*-butylbenzenesulfonate in the CD cavity, as determined by ROESY NMR spectroscopy (Reprinted with permission of [58], copyright of Wiley)

formed around the functional groups, which diminish Coulomb interactions. This shielding effect can be quantitatively described by the Debye–Hückel–Onsager theory [58].

3.5 Thermodynamic Recognition of Guests by CD Dimers and CD Polymers

CD dimers are ditopic hosts, providing two connected cavities that can accommodate a guest with two binding sites for CDs, a ditopic guest. Since the complexation of the two sites is synergetic, high binding free energies $\Delta G^0{}_2$ can be expected, ranging up to twice the value of $\Delta G^0{}_1$ of the corresponding monotopic CD IC. This maximum value of $\Delta G^0{}_2 = 2\Delta G^0{}_1$ is never reached because the CD dimer and the guest lose conformational entropy upon complex formation, as shown in Table 7 [79, 81, 157]. Therefore, the excess binding free energy $\Delta G^0{}_2 - \Delta G^0{}_1$ of CD dimers decreases with increasing flexibility of the linker between the two CDs, as shown by comparison of the excess binding free energies, $\Delta G^0{}_2 - \Delta G^0{}_1$, calculated from $\Delta G^0{}_2$ of entries 1, 5, 7, and 9 diminished by $\Delta G^0{}_1$ of the corresponding monotopic complexes (entries 2, 4, 6, and 8, respectively) in Table 6.

In general, CD polymers perform worse than CD dimers, since the CD rings are connected to each other by rather flexible covalent bonds, as shown by comparison of entries 3 and 1 in Table 7. Nevertheless, CD polymers can be advantageous over CD dimers, especially because of their better availabilities and solubilities in water. For example, the fullerene C_{60} can be solubilized by CD polymers [159]. Ditopic binding between a ditopic guest and a CD polymer might be hampered by a mismatch of the distance of the binding sites in the guest and the distance of the CD cavities at the polymer. Therefore, it appears to be favorable to conjugate CD rings to a polyrotaxane, since these CD rings can migrate along the polymer thread to adopt the proper distance for binding the ditopic guest. Dissociation free energies

Table 7 Comparison of binding potentials of β-CD, β-CD dimers and a β-CD polymer

No.	Spacer	DP CD	Guest	$-\Delta G^0$/kJ mol^{-1}	Ref.
1	−S−	Dimer	Cholesterol	39	[158]
2	No	Monomer	Cholesterol	24	[158]
3	$-OCH_2-CHOH-CH_2-O-$	Polymer	Cholesterol	27	[158]
4	No	Monomer	Cholate	21	[129]
5	$-OCH_2CH_2NHCH_2CH_2O-$	Dimer	Cholate	31	[129]
6	No	Monomer	Lithocholate	36	[129]
7	$-OCH_2CH_2NHCH_2CH_2O-$	Dimer	Lithocholate	40	[129]
8	−S−S−	Dimer	*tert*-Butylphenol	24	[77]
9	−S−S−	Dimer	*tert*-Butylphenyl-*tert*-butylbenzoate	46	[77]

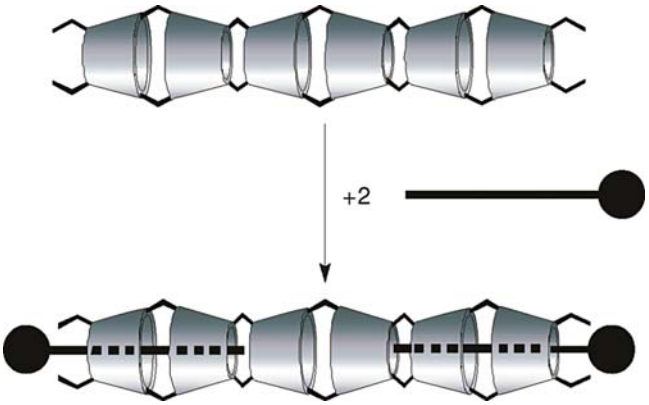


Fig. 10 Inclusion of dodecyl sulfonate by CD molecular tube [160]

$-\Delta G^0$ for the guest pyrene are significantly higher for β-CD conjugated to a polyrotaxane, $-\Delta G^0 = 19\,\text{kJ mol}^{-1}$, compared with β-CD conjugated to a regular polymer, $-\Delta G^0 = 15\,\text{kJ mol}^{-1}$, and native β-CD, $-\Delta G^0 = 14\,\text{kJ mol}^{-1}$ [95].

Moreover, CD molecular tubes should be very promising ditopic and multitopic hosts because of their high rigidity due to multifold linkages between the CD rings. Indeed, very stable complexes were found for the α-CD molecular tube and the guest dodecyl sulfonate with $-\Delta G^0 = 29\,\text{kJ mol}^{-1}$. Only two guests were complexed by one α-CD molecular tube because the anionic end groups of the guests prefer to remain outside the tube, as shown in Fig. 10 [160].

3.6 Steric Effects on Thermodynamic Recognition

Steric effects between hosts and guests generally lead to very high selectivities, since repulsive energies steeply increase with decreasing intermolecular distance *r*

according to the Lennard–Jones potential $V \sim r^{-12}$. As a consequence, guests not fitting in a CD cavity show depressed values of $-\Delta G^0$. For example β-CD binds 3-nitroaniline much weaker ($-\Delta G^0 = 9\,\mathrm{kJ\ mol^{-1}}$) than the well fitting 4-nitroaniline ($-\Delta G^0 = 14\,\mathrm{kJ\ mol^{-1}}$) [161]. Similarly, *m*-substituted benzoic acids form less stable ICs than *p*-substituted ones [123]. The interaction of α-CD with stilbene derivatives is even photo switchable: the *cis* isomer is more weakly bound, with $-\Delta G^0 = 14\,\mathrm{kJ\ mol^{-1}}$, than the *trans* isomer, with $-\Delta G^0 = 18\,\mathrm{kJ\ mol^{-1}}$ [135]. At this point, little is known about the flexibility of CDs and CD derivatives to adapt to a certain size of a guest.

3.7 Kinetic Recognition by Steric Effects

Steric hindrance exerts a very strong influence on the kinetics of the inclusion of bola-amphiphiles. Before the CD ring reaches the hydrophobic binding site, it must overcome an activation barrier in passing the bulky hydrophilic end group. Due to this steric hindrance, both the formation and the dissociation of ICs of bola-amphiphiles are exceptionally slow (see Table 8).

Since the half-lives of ICs of these bola-amphiphiles range from minutes to hours, they are termed pseudorotaxanes. We denominate the bulky end groups that control the kinetic stabilities as "*pseudostoppers*," in analogy to the term "stoppers" applicable to rotaxane formation. From the first order rate constants of dissociation, k_{diss}, Eyring's free activation energies, $\Delta G^{\neq}_{\mathrm{diss}}$, were calculated according to (3) and listed in Table 8. Additionally, the Arrhenius activation energies can be derived from the temperature dependence of k_{diss}. These had been uptill now in reasonable agreement with $\Delta G^{\neq}_{\mathrm{diss}}$. The activation energies increase with increasing size of the pseudostoppers. Therefore, the strong influence of steric effects is obvious. The activation energy of dissociation $\Delta G^{\neq}_{\mathrm{diss}}$ increases with the length of the hydrophobic binding site, since the binding free energy $-\Delta G^0$ also increases. On the other hand,

Table 8 Kinetic recognition of the size of end groups of bola-amphiphiles by α-CD; k_{diss}, first order dissociation rate constant; $\Delta G^{\neq}_{\mathrm{diss}}$, Eyring's free activation energy of dissociation

Binding site	$-\Delta G^0$/kJ mol^{-1}	End group[a]	k_{diss}/s^{-1}	$\Delta G^{\neq}_{\mathrm{diss}}$/kJ mol^{-1}	Ref.
$-(CH_2)_9-$	13	NMe_3	3.90×10^{-4}	92	[162]
$-(CH_2)_{10}-$	15	NMe_3	8.65×10^{-5}	96	[163]
$-(CH_2)_{11}-$	20	NMe_3	1.60×10^{-5}	100	[162]
$-(CH_2)_{12}-$	22	NMe_3	9.00×10^{-6}	102	[162]
$-(CH_2)_{10}-$	17	NMe_2Et	2.70×10^{-6}	105	[163]
$-(CH_2)_{12}-$	10	C(OH)MeEt	1.45×10^{-3}	89	[164]
$-(CH_2)_{12}-$	15	C(OH)MeBu	3.45×10^{-4}	93	[164]
$-(CH_2)_{10}-$	17	2-MePyr	9.50×10^{-8}	113	[165]
$-(CH_2)_{10}-$	16	2,5-Me_2Pyr	8.50×10^{-8}	113	[165]

[a]Smaller, rate determining end group, if there are two different end groups

the activation energy of IC formation $\Delta G^{\neq}_{\text{form}} = \Delta G^{\neq}_{\text{diss}} + \Delta G^{0}$ remains nearly constant, which is reasonable, considering that the thermodynamic stability of the IC should not influence its formation rate. The largest currently known pseudostopper is the 2,5-dimethylpyridinium group, which causes a remarkable half-life of the IC of 48 days [165]. Pseudostoppers might prove to be very useful in the future, since they allow the design of supramolecular structures with a programmed lifetime. Since their formation rate is highly temperature dependent, they can be easily formed at elevated temperatures. Currently, pseudostoppers are only known for the smallest ring size, α-CD.

3.8 Directional Control by Steric Effects

Since the CD molecule has a conical shape in which the primary rim is narrow and the secondary side is wide, steric hindrance should depend on the direction of threading. If the bulky end group approaches the CD cavity from the primary rim, inclusion should be more hindered than for the approach from the secondary rim. Consequently, big pseudostoppers should force CD rings to thread with a preferential orientation. Preferential orientation can indeed be detected for unsymmetrical bola-amphiphiles composed from a pseudostopper and a real stopper, as shown in Fig. 11 and Table 9.

Orientational selectivity depends on the size of the pseudostopper: the smaller trimethyl ammonium group gives rise to a preference of 2:1 for the end group approaching the wide side α-CD [163]. The preference ratio reaches 7:1 for the bigger

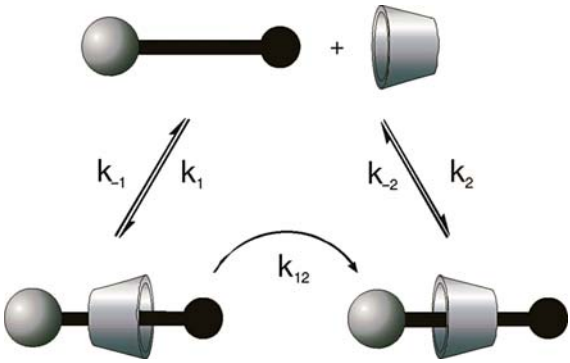


Fig. 11 Control of the orientation of CD during threading onto unsymmetrical bola-amphiphiles [166]

Table 9 Control of the orientations of α-CD rings threaded onto asymmetric bola-amphiphiles

Stopper	Pseudostopper	Orientational selectivity	$-\Delta\Delta G_{\text{orient}}$ kJ mol^{-1}	Ref.
3,5-Dimethyl-pyridinium	2-Me-pyridinium	7:1	6	[165, 167]
Quinuclidinium	4-*tert*-Butylpyridinium	3:1	3	[166]
3,5-Dimethyl-pyridinium	NMe_3	2:1	2	[163]

2-methylpyridinium group, equivalent to $\Delta\Delta G_{\text{orient}}$ of 6 kJ mol^{-1} [165]. These selectivities were based on the formation kinetics, which solely depend on the size of the pseudostopper. The thermodynamic selectivities controlling the final distribution of products might be different, since they also depend on interactions of the CD with the binding site and the stopper. Examples are known where the CD rings changed their mind: they began by threading in one direction (kinetically controlled) but, in the end, they threaded in the other direction (thermodynamically controlled) [166, 168].

3.9 Formation of Rotaxanes

[*n*]-Rotaxanes are molecular entities consisting of one or more rings and one or more axes, where the axes are confined inside the rings by bulky substituents (so-called *stoppers*) at both ends of the axes. The number of interlocked components is represented by *n* [169, 170]. This number is implicitly 2 if it is not specified. In contrast to the aforementioned pseudostoppers, stoppers completely prevent dissociation of a rotaxane. Since rotaxanes are not in dynamic equilibrium with their components, they cannot be classified as supramolecular structures. Nevertheless, they are briefly described with focus on molecular recognition they are readily synthesized from ICs by attachment of stoppers. This coupling reaction, called 'rotaxanation,' has to proceed in high yield, preferably in aqueous solution, since the use of inert organic solvents immediately causes dissociation of most ICs. Details of rotaxane synthesis have been summarized elsewhere [31, 171].

A stopper for α-CD has to significantly exceed the internal diameter of α-CD, $d = 4.4$ Å. The smallest known stopper groups for α-CD are 3,5-dimethylphenyl [172], 3,5-dimethylpyridinium, and 3,5-phenyldicarboxylate [173] groups. It is striking that the 2,5-dimethylpyridinium group can still pass through α-CD, being a pseudostopper, whilst the 3,5 isomer cannot, already being a stopper. This difference demonstrates the high sensitivity of steric interactions. Beside the above-mentioned blocking groups, larger ones such as TEMPO [174], picryl [175], naphthalene disulfonate [176], Fe- [177] Co- [178], and Pt- [179] complexes have also been employed as stoppers for rotaxanation of α-CD.

Since the internal diameter of β-CD, $d = 5.8$ Å, is larger than the one of α-CD, larger stoppers, such as *m*-terphenyl [125] or β-CD [180, 181], must also be used. Alternatively, an axis molecule containing azobenzene was functionalized at both ends with 4,4′-bipyridinium groups. After complexation of the azo benzene moiety with α-CD, the 4,4′-bipyridinium groups were complexed with the cyclic host cucurbituril- [7], acting as a supramolecular stopper because of its very high binding constant (shown in Fig. 12) [182]. This work shows a very striking example of *orthogonal molecular recognition*: the azobenzene moiety is selectively recognized by α-CD, while the 4,4′-bipyridine group is selectively recognized by cucurbituril- [7]. Orthogonal recognition, known from natural systems such as base pairing of RNA and DNA, remains one of the challenges in supramolecular chemistry.

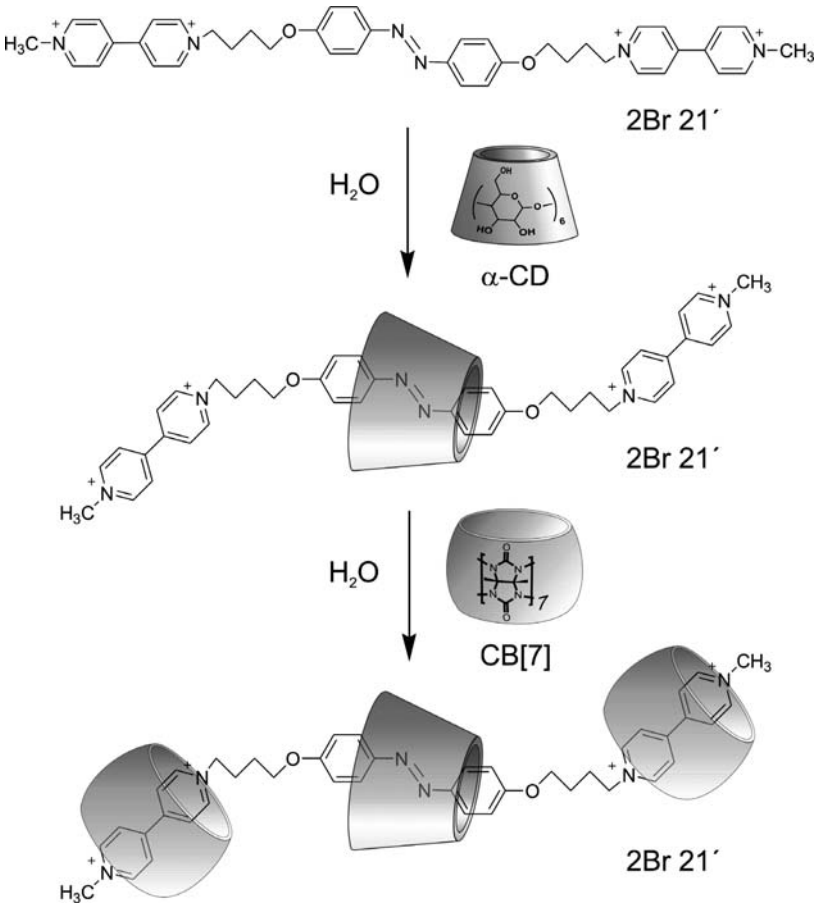


Fig. 12 Supra molecular stoppering of a β-CD inclusion compound by cucurbituril [182]

Finally, γ-CD, with an internal diameter of 7.4 Å, requires very large stoppers for rotaxane synthesis. Therefore, only a few γ-CD rotaxanes are presently known. The Anderson group showed that *m*-terphenyl-4,4′dicarboxylic acid is sufficiently large. They were able to synthesize a [2]-rotaxane from the IC of γ-CD and a stilbene derivative using this stopper. The [2]-rotaxane obtained had sufficient space remaining to accommodate another axis molecule that could be stoppered, as well to furnish the first [3]-rotaxane with two axes through one CD ring. Both homo- and hetero- [3]-rotaxanes with two equal and two different axes, respectively, could be synthesized this way, as shown in Fig. 13 [183].

In principle, CD rotaxanes can be used for molecular information processing if they are reversibly switchable between two states, such as CD [2]-rotaxanes comprising two different binding sites within their axes, as shown in Fig. 14. In the "off" state, the threaded CD recognizes the better binding site and settles there. Once the

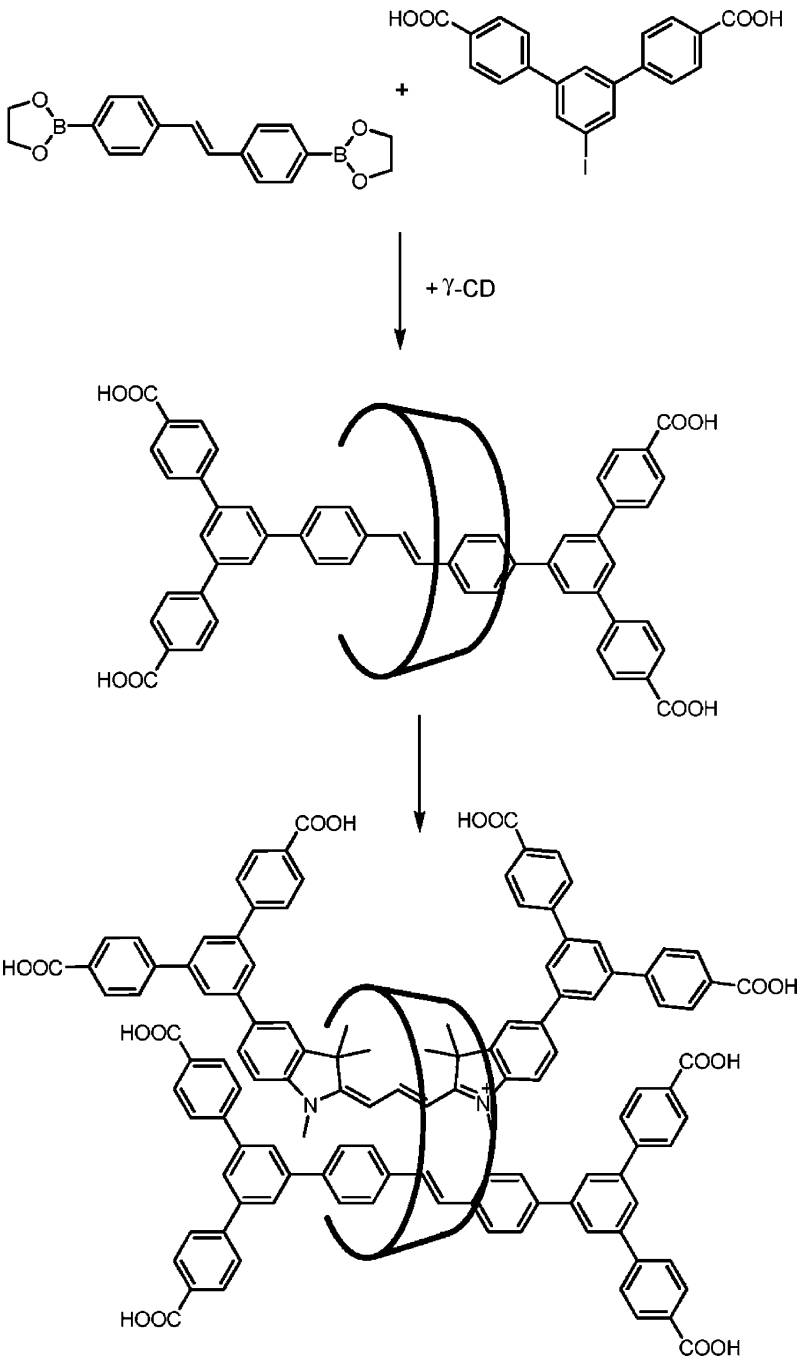


Fig. 13 Stepwise synthesis of a [3]-rotaxane from γ-CD [183]

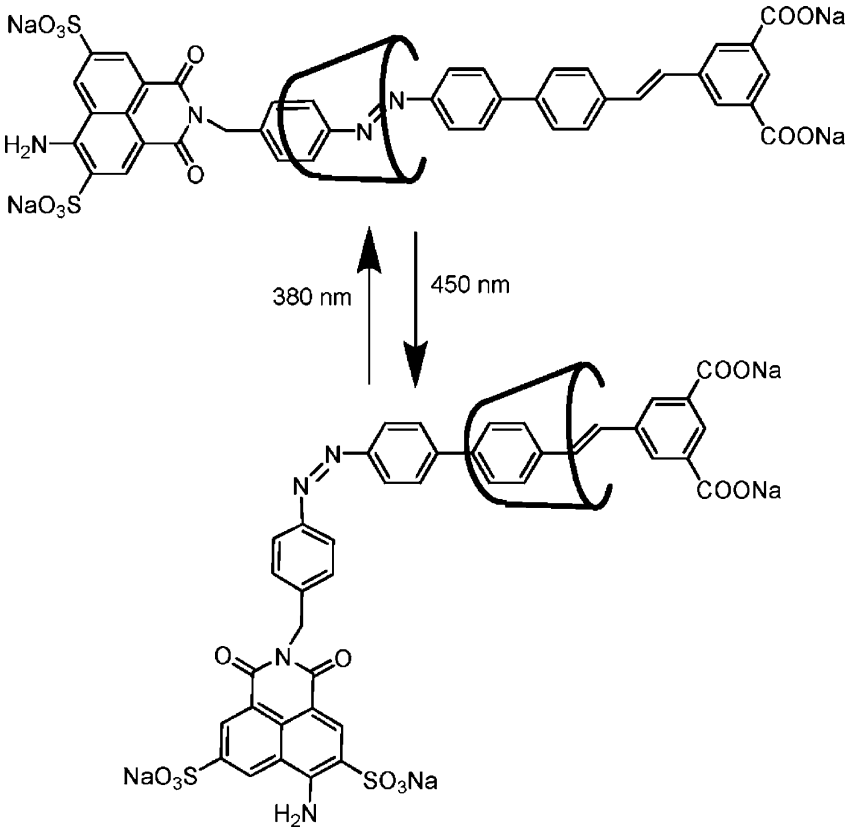


Fig. 14 [2]-Rotaxane, switchable by light [184]

Table 10 Stimulus-responsive, switchable α-CD [2]-rotaxanes

Binding site 1	Binding site 2	"On" stimulus	"Off" stimulus	Ref.
Tetrathiafulvalene	1,2,3-Triazole	$-e^-, +0.32\,V$	$+e^-, +0.22\,V$	[185]
Azobenzene	Biphenyl	$h\nu$, 365 nm	Δ, 60 °C	[186]
Azobenzene	Stilbene	$h\nu$, 380 nm	$h\nu$, 450 nm	[184]
Stilbene	Azobenzene	$h\nu$, 313 nm	$h\nu$, 280 nm	[184]
Azobenzene	$-CH_2-CH_2-$	$h\nu$, 360 nm	$h\nu$, 430 nm	[187]

structure of this binding site is changed by an external stimulus, such as light or an electron, the CD ring moves to the other binding site. This places the system in the "on" state until it is switched off by another external stimulus. Then the ring will move back to its original position. Several switchable CD rotaxanes are already known and summarized in Table 10. Switching was highly reversible in most cases.

4 Recognition of Polymers with Pending Binding Sites

4.1 Recognition of Guest Polymers by Monomeric CDs

Guest moieties attached as side chains to a polymer backbone are complexed by CD hosts in the same fashion as corresponding monomeric guests, as depicted in Fig. 15. Again, the size of the hydrophobic binding site of a polymer is recognized by the CD cavity. In general, the observed binding free energies for the guest polymers are somewhat lower than the ones for the monomeric guests (see Table 11). This might be due to repulsion between CD rings complexing adjacent binding sites because of steric constants.

The first example of the inclusion of a guest polymer was reported by Harada's group. *n*-Alkyl and *tert*-butyl groups were attached to a polyacrylamide chain. Polymeric ICs were formed with α-CD and β-CD, respectively. Similarly, *tert*-butyl-phenyl and adamantanyl groups were attached to poly(maleicacid-*alt*-methylvinylether) and poly(maleic acid-*alt*-isobutylene), respectively [189, 190]. Dissociation free energies of these polymers with β-CD were in the range of $-\Delta G^0 = 22$–$25\,\mathrm{kJ\,mol^{-1}}$, compared to $-\Delta G^0 = 24$–$26\,\mathrm{kJ\,mol^{-1}}$ for the corresponding monomeric guests. It is also evident from the data in Table 11 that $-\Delta G^0$ decreases with increasing degree of substitution of the pending binding sites at the

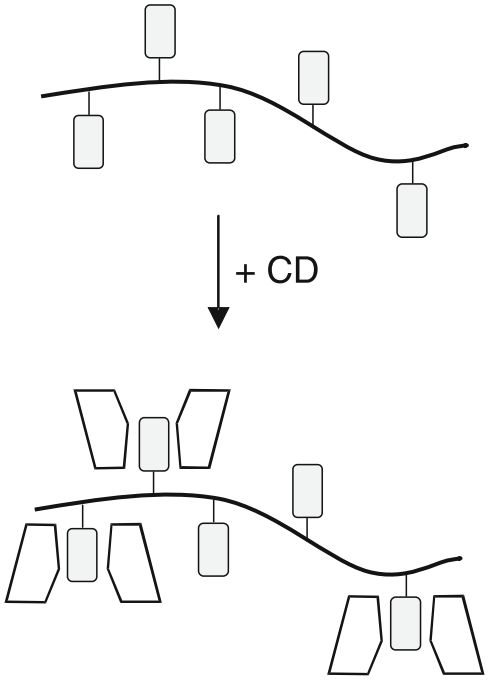


Fig. 15 Schematic drawing of inclusion of side chain guest polymers by CDs

Table 11 Recognition of binding sites conjugated as side chains to polymers

Polymer backbone	Binding site	DS	CD	$-\Delta G^0$/kJ mol^{-1}	Ref.
Hydroxypropyl-methylcellulose	Azobenzene	0.0035	α-CD	20	[188]
Hydroxypropyl-methylcellulose	Azobenzene	0.031	α-CD	17	[188]
Poly(maleic acid-*alt*-isobutene)	*tert*-Butylanilide	0.08	β-CD	25	[189]
Poly(maleic acid-*alt*-isobutene)	1-Adamantane-amide	0.1	β-CD	22	[190]
Poly(maleic acid-*alt*-isobutene)	1-Adamantane-amide	0.2	β-CD	21	[190]
Polyacrylamide	*n*-Dodecyl	0.17	α-CD	17	[191]
Polyacrylamide	*tert*-Butyl	0.17	β-CD	14	[191]

polymer backbone. This decrease of complex stability may also be due to steric hindrance of complexation between adjacent binding sites.

Amphiphilic polymers tend to aggregate and to form gels or micelles. The inclusion of hydrophobic groups at such polymers generally leads to an increase of solubility and a reduction of viscosity in water. One commercial application was patented by Rohm and Haas, in which viscosity of an associative thickener was controlled by addition of CDs [192, 193]. Hydrophobically modified polyurethanes form highly viscous aqueous solutions, which are very difficult to handle. Addition of CDs, especially RAMEB, dramatically reduces the viscosity and allows for preparation of highly concentrated stock solutions. Complexation of the hydrophobic groups eliminates the polymer–polymer interactions. The high viscosity can be restored on demand by addition of sodium dodecyl sulfate (SDS). Since SDS is a competitive guest forming more stable ICs than the polymer, bound CDs are removed from the polymer chain. As a consequence, the liberated hydrophobic sites of the polymer aggregate, causing a large increase in viscosity (see Fig. 16).

Both RAMEB and SDS are called *rheology modifiers*, since they greatly increase and decrease viscosity. Since their discovery, CD-based rheology modifiers have been found for a great variety of associative polymers, such as α-CD for dodecylamido–polyacrylic acid [194], HP-β-CD for hexadecyl modified hydroxyethyl-cellulose [195], and RAMEB for adamantane modified polyacrylamide [196].

The IC of RAMEB and an adamantane modified polyacrylamide is thermosensitive: heating of the aqueous solution of the IC of this guest polymer leads to a very steep increase of both viscosity and turbidity at a certain temperature, which is due to temperature induced decomplexation, followed by an aggregation of the polymer [196].

In addition, photosensitive associative hydrogel systems have been constructed based on dodecyl modified polyacrylic acid, α-CD, and a photoresponsive competitive guest 4,4′-azodibenzoic acid. This guest can be switched from the *trans* to the *cis* state by light back and forth. Since only the *trans* state is complexed by α-CD, gel formation can be switched on and off by light [197]. Thus, molecular recognition and photo switching together induce changes of macroscopic material properties.

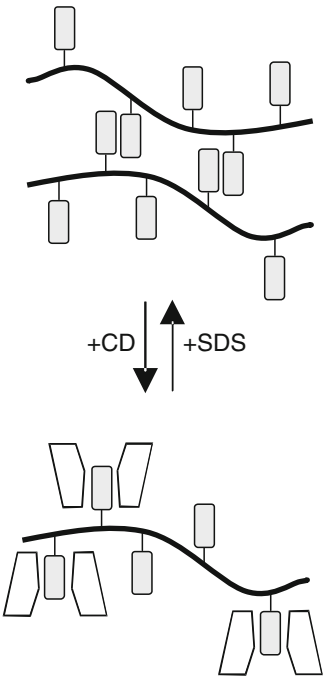


Fig. 16 CDs as rheology modifiers: addition of CD reduces viscosity because it breaks intermolecular hydrophobic interactions; addition of SDS (sodium dodecyl sulfate) regenerates the original hydrogel [192, 193]

4.2 Recognition of Guest Polymers by Dimeric and Polymeric CDs

The interaction of CD dimers or CD polymers with side chain guest polymers leads to the reversible formation of three-dimensional supramolecular networks, as shown in Fig. 17.

The first supramolecular networks of CD polymers and guest dimers or guest polymers were described in 1996 [87, 198]. Sebille's group used β-CD epichlorohydrin polymers and adamantane terminated PEO [198–200], while we combined β-CD conjugated to poly(isobutene-*alt*-maleic acid) PIBMA and *tert*-butyl aniline conjugated to PIBMA [87, 88, 201, 202]. With both systems, viscosity increased by four to five orders of magnitude after mixing solutions of the two components because of formation of crosslinked host–guest complexes. Molecular recognition between polymer bound CD and guest moieties was clearly demonstrated by a continuous variation plot of the viscosity shown in Fig. 18, which revealed a maximum of viscosity at a 1:1 stoichiometry of β-CD and guest moieties [190]. Viscosity decreased with increasing shear rate, possibly because of mechanical ruptures of the host–guest interactions.

Gel formation could be switched off either by dilution with water or by addition of monomeric β-CD or guest [190]. Several other polymeric systems, with complementary binding sites conjugated to polyacrylic acid [194, 203], polyacryl amide [204], and chitosan [205–207] backbones, have been described subsequently, all with similar properties. Compared to regular covalent networks, these noncovalent, supramolecular networks offer several advantages:

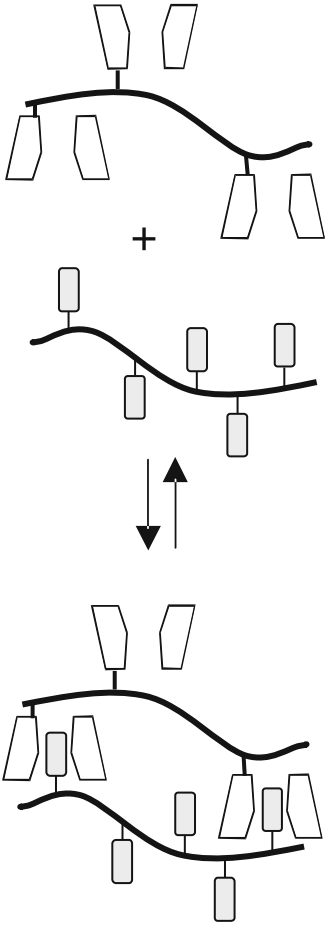


Fig. 17 Formation of supramolecular networks from CD polymers and guest polymers

- CD supramolecular networks are uniform and transparent
- Supramolecular network formation is reversible
- Supramolecular networks can adapt to a certain form, e.g., in a mold
- Supramolecular network formation can be switched on and off by an external stimmulus
- Supramolecular networks can be dissolved by high dilution
- Supramolecular networks are water-based and biocompatible

Therefore, these gelling systems based on two components might find interesting applications in the future. These and other CD based gels have been described by Li et al. [208].

A remarkably different system comprised of a β-CD polymer and a guest polymer was recently described by Gref et al. [209]. They mixed aqueous solutions of neutral β-CD epichlorohydrin polymer and a neutral lauryl ester of dextran, both of high molecular weights, and received no macroscopic gels but well-defined and

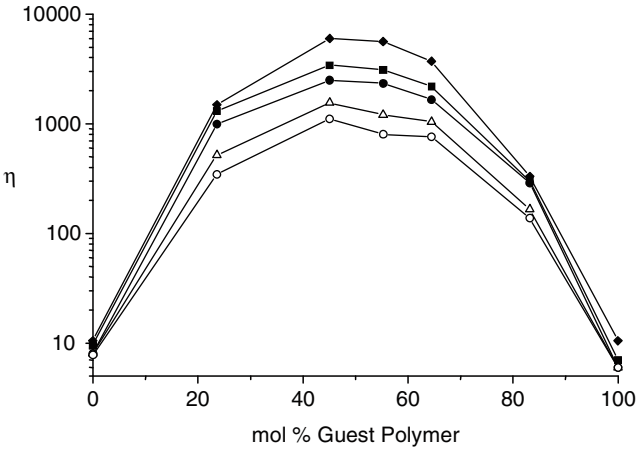


Fig. 18 Viscosities of mixtures of a β-CD polymer (β-cyclodextrinyl-PIBMA) and a guest polymer (*tert*-butyl anilide of PIBMA) as functions of the molar fraction of guest groups in water for different shear rates D (s^{-1}) of 66 (*filled diamonds*), 131 (*filled squares*), 196 (*filled circles*), 393 (*open triangles*), and 590 (*open circles*) at constant total polymer concentration of 2 wt% [202]

stable nanoparticles with diameters of about 200 nm. These nanoparticles may be very interesting as carriers for targeted drug delivery.

4.3 Recognition of Guest Polymers by CDs Attached to Surfaces

CDs arranged in a two-dimensional order at a surface are also able to interact with side chain guest polymers. Amphiphilic β-CD derivatives were organized as double layers in spherical vesicles. These ordered CDs complexed hydrophobic *tert*-butyl-anilid conjugated to PIBMA, leading to vesicles wrapped by the polymer. These vesicles are stabilized by supramolecular interactions and resemble cells protected by a cyto-skeleton, as shown in Fig. 19. The binding free energy for the guest polymer with this two-dimensional β-CD array, $-\Delta G^0 = 36\,\mathrm{kJ\ mol^{-1}}$, is much higher than for the same polymer with monomeric β-CD, $-\Delta G^0 = 23\,\mathrm{kJ\ mol^{-1}}$, demonstrating the high cooperativity of binding [210].

Furthermore, β-CD heptathioethers were immobilized at planar gold surfaces in regular hexagonal arrays, so-called molecular print boards [211]. Dimers, polymers, and dendrimers with two and more attached adamantane or ferrocene binding sites are nearly irreversibly complexed by these β-CD arrays because of the cooperativity of the binding events and negligible entropic loss due to the high rigidity of the CD array. The polymer coil may first bind with a small number of binding sites before being compressed to a flat conformation, which allows more host–guest interactions, as depicted in Fig. 20 [212–215]. These molecular CD print boards may find very interesting applications for the assembly of molecular devices by ink jet printing or dip pen nanolithography.

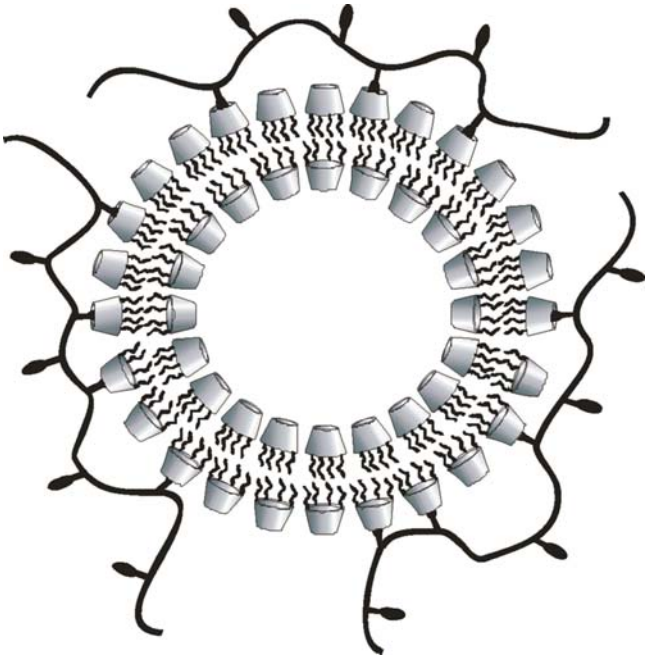


Fig. 19 Cyclodextrin vesicles stabilized by complexation of the guest polymer, *tert*-butylanilid-PIBMA [210]

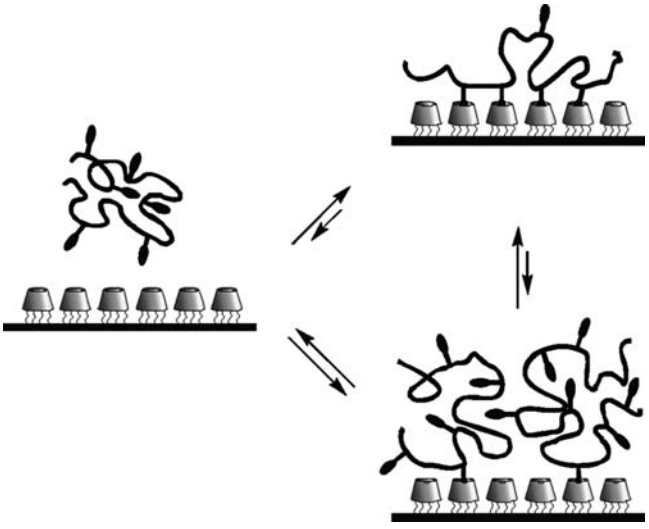


Fig. 20 Schematic representation of different binding modes for guest polymers with planar CD arrays [213]

5 Recognition of Linear Polymers with Binding Sites in the Main Chain

5.1 General Considerations

Complexation of a polymer main chain by CDs differs significantly from complexations of polymer side chains. Complexations of side chains occur in parallel, while complexation of a main chain is a serial process in which consecutive steps are dependent on each other. Since complexation of a main chain polymer, so-called threading, requires a one-dimensional transport of CD rings along the chain, it requires much more time than complexation of a side chain polymer. While the first segments of a polymer chain are rapidly complexed, migration along the polymer is slow and a molecular version of a "traffic jam" can occur.

The linear alignment of threaded CD rings allows attractive interactions between the rings. Native CD rings can each form intermolecular hydrogen bonds between the primary hydroxyls and the secondary hydroxyls. Therefore, alternating head-to-head and tail-to-tail orientations of threaded rings are usually found as soon as the complete polymer chain is covered by CDs, as shown in Fig. 21a. These attractive interactions between threaded CD rings deliver a major contribution to the binding free energy [216]. The rodlike polymer complexes further organize into water-insoluble crystals, so-called channel structures, similar to type I ICs of hydrophobic monomeric guests described in Sect. 3.1.

On the other hand, bulky hydrophilic groups within the polymer chain prevent a dense coverage of the polymer (see Fig. 21b) and therefore lead to water-soluble ICs.

5.2 Recognition of the Thickness of a Polymer Chain

The formation of insoluble channel ICs is a very common feature for the interaction of various polymers with α-, β-, and γ-CDs. The recognition of the thickness of a polymer by the internal diameter of the CD is demonstrated by the data of Table 12. Selectivities of IC formation for polymers are even higher than for similar

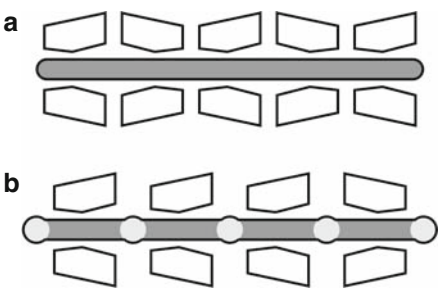
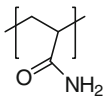
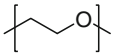
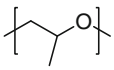


Fig. 21 a,b Schematic representation of different structures of polymer main chain ICs. **a** Channel ICs. **b** ICs of poly(bola-amphiphiles) (reprinted with permission from [31], copyright of the American Chemical Society)

Table 12 Yields of IC formation for various polymers as a function of the CD ring size [217]

Polymer	Structure	MW g^{-1} mol^{-1}	α-CD (%)	β-CD (%)	γ-CD (%)
PVA		22,000	0	0	0
PAAm		10,000	0	0	0
PEG		1,000	92	0	Trace
PPG		1,000	0	96	80
PMeVE		2,000	0	0	82
PE		563	63	0	0
PP		800	0	40	7
PIB		800	0	8	90

monomers, possibly because of the high cooperativity of the inclusion process. The formation rate of channel type ICs decreases with increasing molecular weight and decreasing solubility of the polymer. Therefore, an upper molecular weight limit often exists for IC formation between 3,000 and 20,000 g mol^{-1}. Some more detailed information about IC formation of polymers is given below.

5.2.1 IC Formation of α-CD

The formation of an IC of a polymer main chain was clearly evidenced for the first time by the Harada group in 1990 [218]. They observed precipitation of the polymeric IC a few minutes after mixing saturated aqueous solutions of α-CD and poly(ethylene oxide) (PEO) in high yield. Later, they found that threading occurs even after mixing α-CD and PEO without any solvent present [219]. The stoichiometry of this IC is about one α-CD ring per two PEO units. Since the length of two oxyethylene units is similar to the height of an α-CD torus (8 Å), the authors anticipated complete coverage of the PEO chain with α-CD rings. This hypothesis was confirmed by X-ray diffraction data and solid state NMR-spectroscopy, proving a channel structure [220, 221]. Interestingly, the PEO dimer does not form any IC

with α-CD, probably because of the terminal OH groups, which are too hydrophilic to intrude into the cavity [222]. Formation of the channel structure starts with the trimer, from which an X-ray structure is known [223]. Strong intermolecular hydrogen bonds within the channel structure appear to be necessary to gain sufficient complex stability. This also explains why any substituent at the α-CD ring prevents precipitation of the PEO complex, since this substituent prevents dense packing of CD rings along the PEO thread.

It was found meanwhile that nearly every slim unbranched polymer chain, such as poly(trimethylene oxide) [224], poly(1,3-dioxolane) [225], poly(tetramethylene oxide) [226], poly(ethylene imine) [227], poly(3-hydroxy propionate), poly (4-hydroxybutyrate) and poly(6-hydroxyhexanoate) [228,229], poly(butylene succinate) [229], polyadipates [230], nylon-6 [231], and even oligomers of polyethylene [232], form α-CD ICs with channel structures. In all of these cases, inclusion is a heterogeneous process, since the guest polymer and its CD complex are almost insoluble in water. Therefore, extensive sonication had to be applied to accelerate the diffusion process. The polymer was also dissolved in an organic solvent, e.g., nylon-6 in formic acid, and this solution was added to the solution of α-CD [231]. Alternatively, a monomer, such as 11-aminoundecanoic acid, was included in α-CD and polymerized to nylon-11 by solid state polycondensation within the channels of the IC. Thus, the IC of nylon-11 was formed under conservation of the crystal packing [233–235].

In contrast to monomeric α-CD derivatives, molecular tube (α-CD-MT) shows a high binding affinity to poly(tetramethylene oxide) moieties, which might be due to the high cooperativity of binding exerted by the α-CD rings, rigidly preorganized within the MT. Since these ICs are water-soluble, binding free energies could be determined by ITC. Values of $-\Delta G^0 = 33\,\mathrm{kJ\,mol^{-1}}$ were reached [236].

5.2.2 IC Formation of β-CD

The more spacious β-CD, with its internal diameter of 5.8 Å, is able to complex polymers thicker than PEO. It forms insoluble ICs with channel structures with polypropylene glycol (PPO) [237], and even poly(tetrafluorethylenoxide-*co*-difluormethylenoxide) [238]. This does not mean that slim polymers, such as poly(trimethylene oxide), are complexed less by β-CD, but less stable ICs are formed, in which the polymer does not completely fill the cavity. The structure of the IC is shown in Fig. 22 [239]. Poly(dimethylsiloxane) [217, 240] and poly(dimethylsilane) [241, 242] are also complexed by β-CD when their molecular weights are less than $400\,\mathrm{g\,mol^{-1}}$.

Polyconjugated polymers, such as polyaniline [243, 244] and polythiophene [245, 246], seem to be complexed in β-CD, as well. Because of the low solubilities of these polymers, polymerization and inclusion have to be performed simultaneously. These so-called *molecular wires* are promising electrical and photonic materials [247].

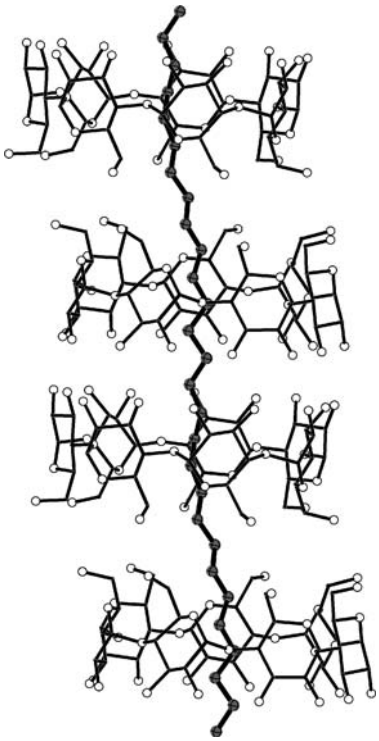


Fig. 22 Structure of poly(trimethylene oxide) complexed in β-CD; the *dotted lines* are intermolecular hydrogen bonds; the *circles* are water molecules

5.2.3 IC Formation of γ-CD

The largest commercially available CD, with a minimum internal diameter of 7.4 Å, γ-CD is wide enough to complex rather thick polymers, such as polyisobutylene [248], polymethylvinylether [249], polystyrene [250,251], polyvinyl chloride [252], polysiloxanes and polysilanes of molecular weights 1,000–3,000 g mol^{-1} [217, 253], poly(perfluorpropylene oxide) [238], and *N*-acetylethylenimine [254], leading to water-insoluble ICs with channel structures. PEO chains are slim enough to form a double stranded IC in γ-CD [255, 256]. However, preparation of these complexes is very difficult because the loss of entropy for the two PEO chains is very high. Naphthalene groups terminating the PEO chains facilitate simultaneous threading of two PEO chains through one γ-CD ring, since they preorganize properly by forming dimeric aggregates in aqueous solution [255]. Similar double stranded ICs of poly(caprolactone-*b*-THF-*b*-caprolacton) triblock-copolymers in γ-CD have been found subsequently [257].

5.3 Site-Selective Complexation of Block Copolymers

As already shown in Table 12, α-CD prefers complexation of nonbranched aliphatic chains, such as *n*-alkyl or oxy-alkyl chains, while β-CD prefers thicker polymers,

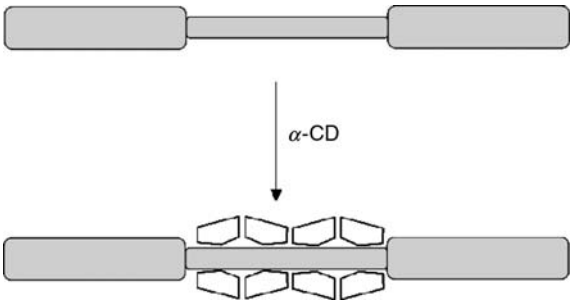


Fig. 23 Schematic drawing of site-selective complexation of PPO-PEO-PPO triblock-copolymer by α-CD

such as PPO. On the other hand, PPO can still thread through α-CD, and β-CD can form a loose complex with PEO, but both of these ICs are unfavorable. Selectivity of IC formation is unveiled by competition experiments using block-copolymers. For example, triblock-copolymers of PEO and PPO were complexed by α-CD. The location of the threaded α-CD-rings can be checked by NOE spectroscopy or by indirect methods such as X-ray diffraction or DSC. As a result, the α-CDs are concentrated at the PEO segments even for PPO–PEO–PPO triblock-copolymers, for which α-CD rings have to pass the bulky PPO blocks, as shown in Fig. 23. Threading times strongly increase here with the lengths of the PPO blocks [258]. On the other hand, β-CD selectively complexes the PPO segments of these block-copolymers [259]. Consequently, the CD-rings can recognize the appropriate segments; such complexation is called *site-selective*. There are many examples of site-selective complexations, e.g., α-CD selectively binds the PEO segments of PEO-poly(3-hydroxybutyrate)-PEO [260] and PEO-poly(*N,N*-dimethylaminoethyl-methacrylate) [261] and the PCL blocks of PCL–PTHF–PCL [257] and PCL–PPO–PCL [262]. Site-selective complexation can be quite useful, since it allows selective masking of the hydrophobicity of a segment in a block-copolymer for some time. In addition, the partially complexed block-copolymers remain more soluble than the fully complexed homopolymers. For example, PEO-poly(*N,N*-dimethylaminoethyl-methacrylate) selectively complexed at the PEO blocks by α-CD forms nanoparticles [261].

5.4 Enantioselective Recognition of Chiral Polymers

Since the CD molecule is chiral, it could recognize the winding of a chiral polymer, functioning like a nut threading onto a bolt. Since the spatial differences of two corresponding enantiomers are small, the fit between the CD nut and the polymer bolt should be as tight as possible to allow chiral recognition. The first example of a stereoselective inclusion of a polymer was given by the Tonelli group [263]. They found that isotactic poly(3-hydroxybutyrate) is included in α-CD, while atactic poly(3-hydroxybutyrate) is not. The first enantioselective inclusion

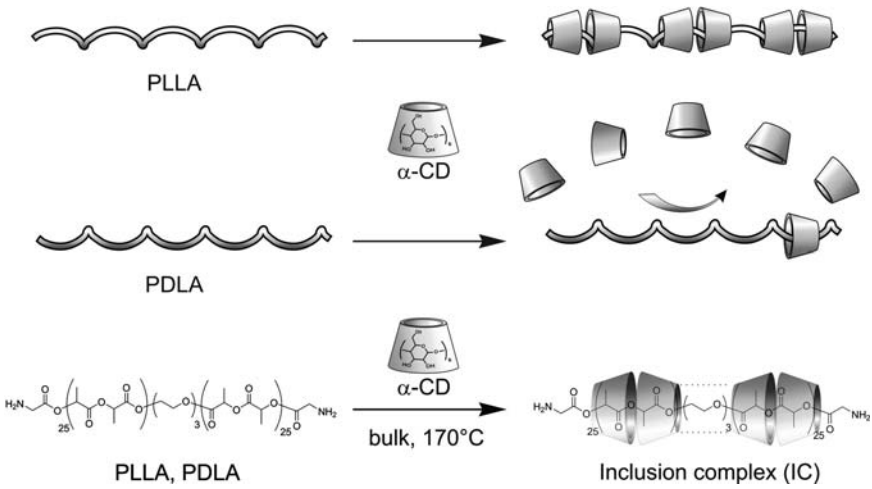


Fig. 24 Schematic drawing of enantioselective complexation of polylactides by α-CD [264]

of a polymer was observed by Yui et al. for isotactic polylactides, which indeed resemble molecular screws by forming 3_{10}-helices. Poly(L-lactide) (PLLA) with α-CD forms an IC of high coverage (42%) at 170°C, which is stable enough even to survive dissolution in DMSO (depicted in Fig. 24). Conversely, the other enantiomer poly(D-lactide) (PDLA) is only complexed by a few α-CD rings, leading to a very low coverage of 7%. Because of its wrong screw sense, this polymer does not fit in the α-CD ring [264]. From the coverages of both enantiomeric polymers, the estimated chiral recognition, $\Delta\Delta G_{R,S} \geq 7\,\mathrm{kJ\ mol^{-1}}$, is higher than the ones observed for enantiomeric monomers, as listed in Table 5. This very high enantioselectivity is indeed remarkable. It might be due to the cooperativity of binding caused by the hydrogen bonds between adjacent α-CD rings within the IC. In the future, molecular machines [265, 266] might be constructed which make use of the unidirectional rotation of an α-CD nut moving along the PLLA screw.

5.5 Recognition of the Polarity of the Polymer

Since the major driving force of inclusion is hydrophobic interaction, stabilities of ICs depend strongly on the polarity of the polymer. The more hydrophobic the polymer is, the higher is the affinity of CDs towards it. On the other hand, solubility in water decreases with increasing hydrophobicity of the polymer. Since affinity and solubility have to be compromised, an optimum of polarity of the polymer should exist for complexation by CDs. It is difficult to quantify the binding free energies of CD channel inclusion compounds, since they are insoluble in water. Stabilities of these polymeric ICs can be qualitatively compared by competition experiments. For example, PLLA and PCL were competitively included in α-CD. The IC of PCL was

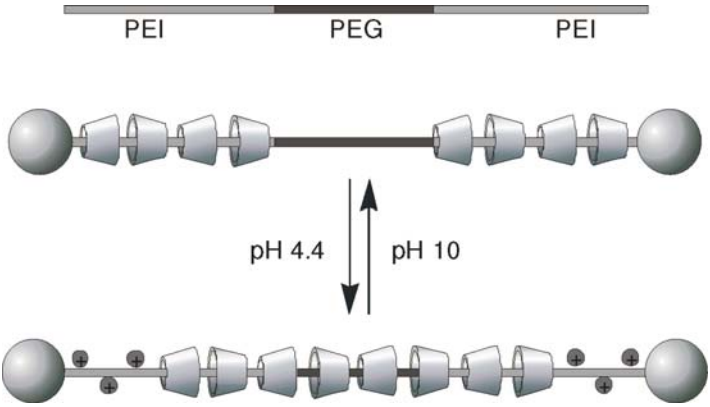


Fig. 25 pH dependent coverage of PEI–PEO–PEI

nearly exclusively formed, which means that the caproate groups are better binding sites for α-CD than lactate groups because caproate is less polar than lactate [267].

Polyethylenimine (PEI) only forms ICs with α-CD and γ-CD at rather basic conditions, pH > 8, since only the nonprotonated PEI is sufficiently hydrophobic to be included in these CDs. These ICs are insoluble in water and behave similarly to the ICs of PEG. Protonated PEI is not included at all by CDs, since it is too polar [227]. Interestingly a triblock-copolymer PEI–PEO–PEI becomes homogenously covered by α-CD at a pH of 10. As soon as the pH is lowered to pH 4.4, α-CD rings escape from the PEI segments to the PEO segments, as shown in Fig. 25 [268].

If anthracene stoppers are attached, this pH driven locomotion of the CD rings becomes completely reversible and can be monitored in situ using fluorescence resonance energy transfer (FRET) of suitable fluorescent probes attached to the CD rings and to both ends of the polymer [269].

5.6 Recognition of the Hydrophobic Segment Lengths of Poly(bola-amphiphile)s

Since longer alkylene segments in polyamines should lead to more stable ICs, we investigated the interaction of α-CD with a homologous series of poly(imino-oligomethylene)s, PI-6, PI-8, PI-10, PI-11, and PI-12 (formulas shown in Fig. 26) in aqueous solution at pH 4.8 [270, 271]. With the exception of PI-6, these formed water-soluble ICs under homogenous conditions. Because of their similarity to bola-amphiphiles, these polymers were classified as *poly(bola-amphiphile)s*. The high solubility of the ICs is caused by the bulky hydrophilic groups within the polymers, which prevent a dense packing of threaded CD-rings that would otherwise lead to an insoluble channel structure. Threading kinetics of α-CD rings onto these polymers could be followed in situ by solution ^{1}H-NMR spectroscopy. Binding free

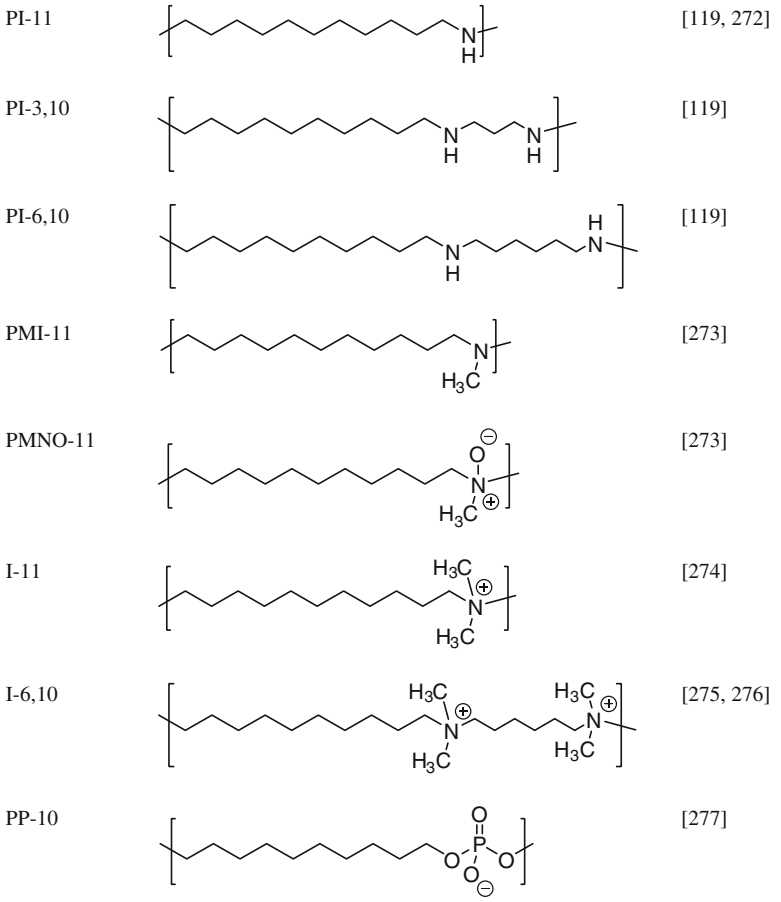


Fig. 26 Poly(bola-amphiphile)s that form water-soluble ICs with α-CD

energies $-\Delta G^0$ could be calculated from the limiting conversions of the threading processes or by ITC. The $-\Delta G^0$ values of the poly(bola-amphiphile)s increase with the lengths of the hydrophobic segments and are nearly identical to those of the monomeric bola-amphiphiles, as depicted in Fig. 6. Polymer PI-6 was not complexed at all by α-CD at pH 4.6, while the most stable IC was obtained for PI-12. From a thermodynamic point of view, these poly(bola-amphiphile)s behave very similarly to their monomeric counterparts.

Thus, molecular recognition of poly(bola-amphiphile)s mainly depends on the structure of one limited binding site and not on the structure of the polymer as a whole. Consequently, the knowledge about molecular recognition of monomeric bola-amphiphiles can be brought forward to understand molecular recognition of polymeric bola-amphiphiles.

Besides poly(imino-oligomethylene)s PI-*n* [272], many other poly(bola-amphiphile)s, such as poly(*N*-methyl-imino-oligomethylene)s PMI-*n* [273], poly

(*N,N*-dimethyl-iminium-oligomethylene)s (also called ionenes) I-*n* [278], poly(*N*, *N*-4,4′-bipyridinium-oligomethylene)s [279], PV-*n* poly(*N*-methyl-imino-oligo methylene-*N*-oxide)s PMINO-*n* [273], and poly(oligomethylene-phosphate)s PP-*n* [277] summarized in Fig. 26, also form water-soluble ICs with α-CD if the length of the hydrophobic segments is sufficient ($n \geq 10$). Binding free energies range from $-\Delta G^0 = 14$ to 20 kJ mol^{-1}, increasing with *n*. This minimum segment length is necessary to allow the ionic groups to stay completely out of the α-CD cavity so that they do not disturb inclusion. Inclusion of poly(bola-amphiphile)s is mainly driven by hydrophobic interactions. The separation of the threaded CD rings by the ionic groups does not allow any additional stabilization of the IC by hydrogen bonds between the rings, as described for the channel inclusion compounds. Beside α-CD, β-CD and γ-CD, as well as CD derivatives, are able to thread onto these poly(bola-amphiphile)s under homogenous conditions [275, 280, 281]. In addition, there is no upper limit of the molecular weight for the formation of ICs, since threading is a homogenous process. Functional CDs and poly(bola-amphiphile)s can form a supramolecular toolbox for the design of functional pseudopolyrotaxanes.

5.7 Kinetic Recognition of Bulky Groups within Poly(bola-amphiphile)s

In Sect. 3.6 we have described how the bulky ionic end groups of monomeric bola-amphiphiles can strongly influence formation and dissociation rates of CD ICs. The same is true for polymeric bola-amphiphiles. The kinetics of IC formation could be measured in real time by ^{1}H NMR spectroscopy, since complexation is a homogenous process. Inclusion times are extremely dependent on the sizes of the hydrophilic groups within the polymer. Threading α-CD onto a secondary polyamine, poly(imino-undecamethylene), was completed after only about 1 h at r.t. [270]. Threading onto a quaternary polyamine, poly(*N,N*-dimethylammonio-hexamethylene-*N′,N′*-dimethylammonio-decamethylene), took more than 2 years at r.t. [278]. Inclusion kinetics could be quantitatively described by an empirical function, a so-called stretched exponential $y = y_\infty(1 - e^{-\sqrt{kt}})$ with the yield of complexation *y* and the limiting yield y_∞. The time t_{90} for reaching 90% of the limiting yield was calculated from the rate constant *k* according to $t_{90} = (\ln 10)^2/k$. Results are listed in Table 13 [273].

The polymers with large hydrophilic groups had to be measured at elevated temperatures (60 °C), since otherwise kinetics are too slow. Kinetics become much faster at higher temperatures, indicating that threading is an activated process. The time t_{90} strongly depends on the size of the bulky groups within the polymer chain. It ranges from a few minutes for the imino group to several weeks for the more bulky dimethylammonium group. If there are two bulky dimethylammonium groups in close proximity to each other, the steric barrier becomes even higher, and the threading time t_{90} is about 2 months at 60 °C.

Table 13 Threading times t_{90} for reaching 90% of final yield for various poly(bola-amphiphiles $-(CH_2)_n-X-$ [273]

X	n	t_{90}/h at 25 °C	t_{90}/h at 60 °C	d/Å	Ref.
$-NH_2^+-$[a]	11	0.47		4.28	[273]
$-N^+HMe-$[a]	11	10.8	0.16	5.06	[273]
$-N^+MeO^--$	11		58	5.49	[273]
$-N^+Me_2-$	11		413	5.73	[273]
$-N^+Me_2(CH_2)_6\ N^+Me_2-$	10		1,370	5.73	[278]

[a]At pH 4.6

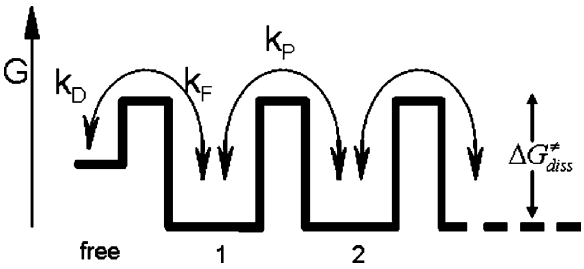


Fig. 27 Model for the threading poly(bola-amphiphile)s; rate constants are: k_D for dissociation, k_F for formation, and k_P for propagation (reprinted with permission from [278], copyright of the American Chemical Society)

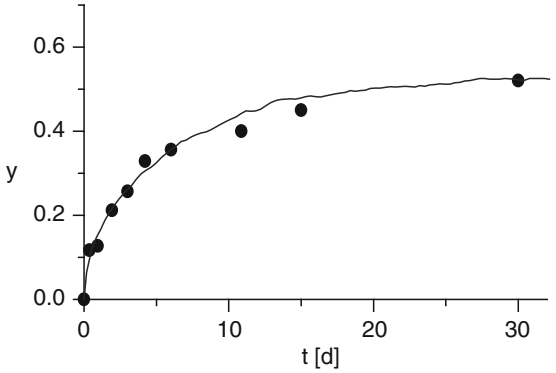


Fig. 28 Kinetics of the inclusion of ionene-6,10 (points) by α-CD, line calculated by the simulation program Abakus (reprinted with permission from [278], copyright of the American Chemical Society)

The slow rate of the threading process can be rationalized on a molecular level as a hopping process of the CD rings over the periodic potential caused by the repulsive interactions exerted by the bulky hydrophilic groups, illustrated in Fig. 27.

Threading kinetics was quantitatively described by the Monte Carlo simulation program Abakus [278]. As shown in Fig. 28, the agreement of experimental data and the Abakus fit is reasonably good, demonstrating the validity of the kinetic model.

The binding constant K and the propagation rate constant k_p are obtained as fitting parameters. The time a CD ring rests on a segment, $\tau_{1/2} = \ln 2/k_p$, was derived from the rate constant k_p. From the temperature dependence of this rate constant, the activation energies E_a were estimated by Arrhenius plots. The obtained activation energies of propagation over dimethyl ammonium groups ($E_a = 90\,\mathrm{kJ\ mol^{-1}}$) were on the same order of magnitude as the activation free energy for the corresponding monomeric bola-amphiphile, 1,10-bis-trimethylammonium-decane, already listed in Table 8.

The diameters d of the hydrophilic groups of poly(bola-amphiphile)s were calculated by semiempirical quantum mechanical calculations and are listed in Table 13 [273]. They correlate well with the threading times t_{90}. That means that the diameter d of the hydrophilic groups in poly(bola-amphiphile)s is sensitively recognized by α-CD-rings.

Most α-CD complexes of above-mentioned poly(bola-amphiphile)s are stable enough to be isolated; therefore, they are classified as pseudopolyrotaxanes. Dissociation kinetics of CD pseudorotaxanes can easily be detected by following the CD concentration during dialysis or ultrafiltration, by which free α-CD rings are continuously removed, as depicted in Fig. 29.

The polymers that are rapidly complexed by α-CD also dissociate rapidly. Those polymer ICs, like those of ionenes, which require high temperatures and long threading times to be formed, are almost kinetically stable at r.t.

Threading and dissociation rates of polymeric secondary amines PI-11 and PI-3,10 are highly dependent on the pH: at high pH, threading of PI-3,10 is im-

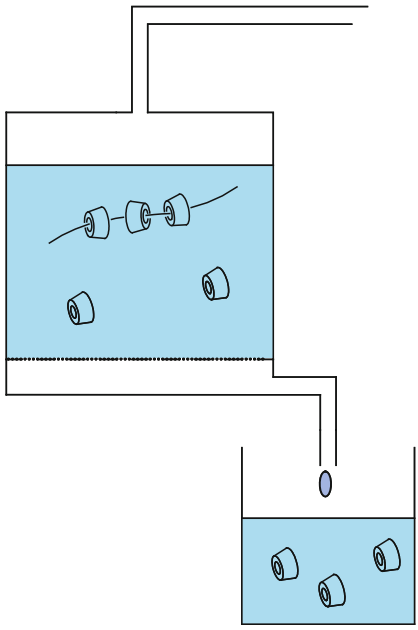


Fig. 29 Schematic drawing of the ultrafiltration system for the measurement of the dissociation kinetics of polymer ICs. Concentrations of CD both in the filtrate and the retentate were determined from the optical rotations of the solutions

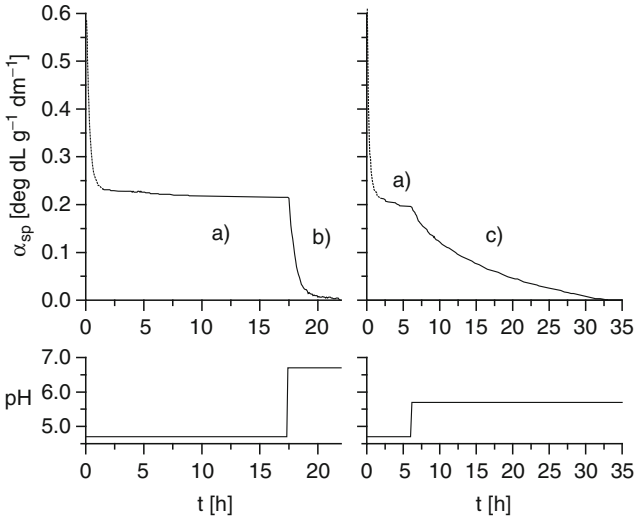


Fig. 30 pH dependence of dissociation of the IC of PI-3,10 and α-CD as measured by the decay of specific optical rotation α_{sp} of α-CD in the retentate during dialysis [271]

measurably fast; at pH 3, it takes several days. Therefore, the rate of threading can be controlled by the pH [282]. A change of pH seems to influence strongly steric hindrance of threading: protonated imino groups significantly hinder threading, while neutral ones do not. Since the steric hindrance of a single proton cannot cause this strong effect, the change of the charge also has to be taken into account. Cationic protonated imino groups attract water molecules, forming a solvation shell, which might exert the observed pronounced steric hindrance. Additionally, the rate of dissociation of the IC can be switched by small variations of the pH, as shown in Fig. 30. At pH 4.6, the IC of PI-3,10 is almost stable, demonstrated by a nearly horizontal line.

The decay at the beginning was due to excess free α-CD still present from the preparation of the IC. Raising the pH from 4.6 to 6.6 causes the immediate release of all threaded CD rings, while raising the pH to 5.6 leads to a much slower release, requiring about 1 day for liberation of the threaded rings [271]. These switchable pseudopolyrotaxanes might be useful for delivery and pH programmed release within organisms of drugs bound to threaded CD rings.

Complexation and dissociation of poly(bola-amphiphile)s by the larger ring, β-CD, is too fast to allow isolation of the ICs. In addition, this complexation is not detectable by ^{1}HNMR, since there is no complexation induced shift of the signals due to the loose fit of the polymers in β-CD. α-CD rings can be used as stoppers to stabilize the β-CD IC. Much higher coverages of the polymer by CD rings are found after subsequent threading of β-CD and α-CD than for α-CD alone, shown in Fig. 31. Apparently, a stable triblock copolyrotaxane with the sequence $(\alpha\text{-CD})_n$ $(\beta\text{-CD})_m$ $(\alpha\text{-CD})_n$ of threaded rings has been formed [276].

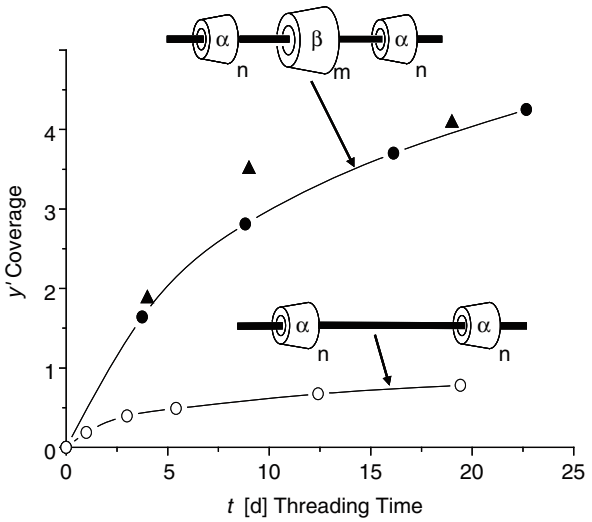


Fig. 31 Formation of $(\alpha\text{-CD})_n$ $(\beta\text{-CD})_m$ $(\alpha\text{-CD})_n$ triblock pseudopolyrotaxane by sequential threading of (1) β-CD and (2) α-CD onto I-10,6. (*filled circles, filled triangles*) Coverage y' (total number of anhydroglucose units of α-CD and β-CD per repeat of I-10,6) as a function of threading time for α-CD, (*open circles*) control, coverage of threading α-CD solely [276]

Since threaded α-CD rings could not be distinguished from threaded β-CD rings by NMR, β-CD rings had to be labeled to prove unambiguously the structure of the triblock copolyrotaxanes. Therefore, 6-amino-6-deoxy-β-CD was covalently labeled with fluorescein isothiocyanate. The fluorescent β-CD derivative FITC-β-CD was threaded onto the polymer I-10,6. α-CD was threaded afterwards to stabilize the supramolecular structure. The resulting pseudopolyrotaxane was purified from free α-CD and FITC-β-CD rings by ultrafiltration. The fluorescence of the isolated product clearly proved that the sequential threading protocol of FITC-β-CD and α-CD onto I-10,6 had worked out as proposed [280]. The α-CD rings acted as supramolecular stoppers for the β-CD rings.

5.8 Synthesis of Polyrotaxanes from Main Chain Pseudopolyrotaxanes

The pseudopolyrotaxanes described above can be converted to polyrotaxanes by the attachment of bulky groups, which completely prevent dissociation of threaded rings. Bulky groups can be attached either (1) along the chain or (2) at both chain ends.

First, CD polyrotaxanes were synthesized by us by polymer analogous reaction of the amino groups of the PI-11/α-CD pseudopolyrotaxane with nicotinoyl chloride. A 25% conversion of the imino groups led to a permanent 67% coverage of

the polymer. The stability of the so-formed polyrotaxane was tested by extensive ultrafiltration, during which the α-CD rings remained on the polymer chain for longer than 1 week [272]. Polyrotaxanes of β-CD and PI-11 were synthesized in an analogous way. Since the nicotinoyl stoppers were too small to block β-CD, a larger reagent, 2,4-dinitrofluor-5-aniline, had to be used for the synthesis of the β-CD polyrotaxane [119].

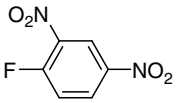
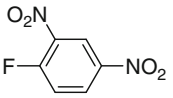
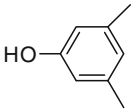
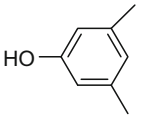
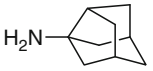
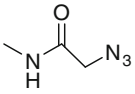
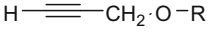
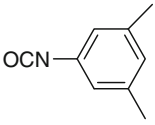
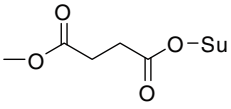
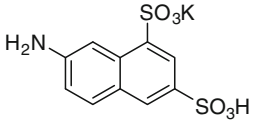
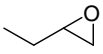
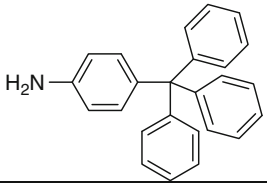
The ICs of PEO by α-CD were also converted to polyrotaxanes by the attachment of various blocking groups at the chain ends. Since the reactivity of the terminal hydroxyl groups is low, chain ends were functionalized prior to complexation by α-CD. Terminal amino groups were used by Harada's group in the first synthesis of a PEO-α-CD polyrotaxane. These were coupled with 2,4-dinitrofluorobenzene to furnish the polyrotaxane in 60% yield, since this end group was large enough to completely prevent dissociation of threaded rings even in organic solvents like DMSO [283]. For low molecular weight PEG $(1{,}450\,\mathrm{g\,mol^{-1}})$, coverage of 91% per diethylene glycol repeat unit was reached, equivalent to 15 threaded rings per chain. For polymer threats of higher molecular weight, coverage was lower, e.g., 31% for molecular weight of $20{,}000\,\mathrm{g\,mol^{-1}}$, equivalent to 70 threaded rings [284].

Subsequently, further rotaxanation reactions, shown in Table 14, were developed, offering several advantages. A high reactivity of the functional chain end with the stopper reagent is very important because dissociation of threaded rings occurs during the reaction, especially when the reaction is performed in an organic solvent like DMF or DMSO, in which the ICs are not stable.

Similarly, the readily accessible PEO tosylates were stoppered by etherification with 3,5-dimethylphenol [286]. As already observed for the synthesis of monomeric α-CD rotaxanes, a 1,3-disubstituted phenyl group or an adamantane group is already large enough to completely block dissociation of threaded α-CD rings. Modern click chemistry, using the Huisgen $[2+3]$ cycloaddition of azides and propargyl derivatives, also appears to be very effective for polyrotaxane synthesis [288]. Oligopeptide stoppers offer the advantage of being enzymatically cleavable on demand by proteases. This might be useful for the controlled release of drugs attached to the threaded α-CD rings [293]. The achievable coverage of the polymer chain with CD rings usually decreases with increasing molecular weight of the polymer thread for all stoppering reactions investigated to date.

Bigger stoppers, such as naphthalene-6,8-disulfonic acid [290] or tetraphenylmethane [292], are necessary for blocking the larger β-CD rings. For the synthesis of a β-CD polyrotaxane, a PEO–PPO–PEO triblock polymer functionalized with terminal amino groups was regioselectively complexed at the PPO block with β-CD and stoppered with fluorescein-4-isothiocyanate. The hydrophilic PEO blocks offer the advantage of increasing solubility in water, since they are scarcely covered by β-CD rings. Five β-CD rings were threaded within the polyrotaxane. The fluorescein blocking group was large enough to prevent their dissociation. At room temperature, these five β-CD rings were distributed over the full length of the polyrotaxane axis, while they were concentrated at the PPO segment at elevated temperatures [291, 294].

Table 14 Synthesis of polyrotaxanes by terminal coupling of stopper groups at polymer ICs with X coverage, number of CD rings per two polymer repeat units

Polymer	MW g mol^{-1}	End group	CD	Reagent	X%	Ref.
PEG	1,450	$-NH_2$	α		91	[285]
PEG	20,000	$-NH_2$	α		31	[285]
PEG	1,500	–O – Tos	α		70	[286]
PEG	20,000	–O – Tos	α		19	[286]
PEG	35,000	–COOH	α		22	[287]
PEG	1,500		α		75	[288]
PTHF	1,100	$-NH_2$	α		96[a]	[289]
PEG–PPG – PEG	4,200		β		49	[290]
PEG–PPG – PEG	4,200	$-NH_2$	β	FITC	12	[291]
PDMS	1,250		β		28	[292]

[a]Per single repeat unit

Su: *N*-succinimide; FITC: fluorescein-4-isothiocyanate

Finding stoppers for γ-CD is difficult, because of its large diameter. Therefore β-CD and γ-CD were cothreaded on a polymer and rotaxanated by stoppers which block β-CD rings. Since the threaded γ-CD rings cannot overtake β-CD rings, they were blocked as well [275].

6 Conclusions and Outlook

It was shown that CDs and CD derivatives are very versatile hosts for the recognition of various monomeric and polymeric guests. Experience collected from binding studies with monomeric guests can often be applied and generalized for polymeric guests as well. Side chain and main chain guest polymers behave quite differently. While the recognition events happen in parallel for side chain guest polymers, they occur sequentially for main chain guest polymers. Slow inclusion of bola-amphiphiles and poly(bola-amphiphile)s offers certain advantages in comparison to other guests, since the ICs with them are kinetically stable for a defined time. Complex molecular architectures can be created without the necessity of covalent chemistry in water by using a supramolecular tool box.

Recognition potential of CDs can be greatly enhanced by regioselective derivatization of CDs. Recognition of polymers by CD derivatives is still an open field. Recognition might also be combined with catalytic activity of CDs or functional CD derivatives. Catalytic CDs might selectively bind to certain regions of destination of a block-copolymer to perform a specific reaction. Additionally, molecular machines might be created that exploit switchable site-selective binding.

Since molecular recognition of CDs and guests functions in water, it can also be combined with bio-molecular recognition. Ligands for certain cell specific receptors, such as lactose, were already linked to CD polyrotaxanes. These functional polyrotaxanes selectively bound to the human receptor protein galectin-1, inhibiting agglutination with T-cells already at low concentrations [295–297]. Therefore, CD polyrotaxanes might be very useful as vehicles for targeted drug delivery.

Since CDs are highly biocompatible, readily available, and easy to functionalize, and since they self-organize in a rather predictable way in aqueous solutions, they will become one of the most important supramolecular building blocks of the future.

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