Cyclodextrin-containing Supramolecular Structures
From pseudo-polyrotaxanes towards molecular tubes, insulated molecular wires and topological networks

Maarten van den Boogaard

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Cover: examples of cyclodextrin-containing supramolecular structures.

top: cyclodextrin molecular tube. This structure is described in chapters 2, 3 and 4. See scheme 2.1 for their synthesis.

middle: cyclodextrin-containing insulated molecular wire. Insulated molecular wires based on polyaniline and cyclodextrin molecular tubes are described in chapter 5, and insulated molecular wires based on polythiophene and cyclodextrins are described in chapter 6. See figure 5.6 and figure 6.10 for AFM images of these two types of insulated molecular wires.

bottom: topological network. These networks or sliding gels are described in chapter 7.

Rijks*universiteit* Groningen

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From pseudo-polyrotaxanes towards molecular tubes, insulated molecular wires and topological networks

Proefschrift

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Maarten van den Boogaard

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te Oudewater

Promotor:	Prof. Dr. G. Hadziioannou
Beoordelingscommissie:	Prof. Dr. C. Marques Prof. Dr. D.N. Reinhoudt Prof. Dr. B. Feringa

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Maarten

Contents

Chapter 1 Introduction **1**
1.1 Cyclodextrins 2
1.2 Cyclodextrin-containing inclusion compounds 5
1.3 Functionalization 7
1.4 Cyclodextrin-containing supramolecular structures 11
1.5 Aim and outline of this thesis 21
1.6 References 23

Chapter 2 Synthesis of α-cyclodextrin molecular tubes **29**
2.1 Introduction 30
2.2 Design of cyclodextrin molecular tubes 31
2.3 Synthesis of cyclodextrin molecular tubes 35
2.4 Discussion and conclusion 43
2.5 Experimental 43
2.6 Reference 55

Chapter 3 Characterization of α-cyclodextrin molecular tubes **57**
3.1 Introduction 58
3.2 Methodologies 59
3.3 Characterization of α-cyclodextrin molecular tubes 63
3.4 Discussion and conclusion 80
3.5 Experimental 82
3.6 Reference 85

Chapter 4 Modeling **87**
4.1 Introduction 88
4.2 The model 88
4.3 Length of the antiferromagnetic domains in the pseudo-polyrotaxane 92
4.4 Discussion and conclusion 104
4.5 References 106

Chapter 5 Inclusion of polyaniline by α-cyclodextrin molecular tubes **107**
5.1 Introduction 108
5.2 Results 110
5.3 Discussion and conclusion 115
5.4 Experimental 116
5.5 References 117

Chapter 6 Synthesis of polyrotaxanes based on polythiophene and β-cyclodextrin **119**
6.1 Introduction 120
6.2 Synthesis of polythiophene polyrotaxanes 121
6.3 Results 129
6.4 Discussion and conclusion 135
6.5 Experimental 136
6.6 References 138

Chapter 7 Sliding gels **141**
7.1 Introduction 142
7.2 Design and synthesis of the sliding gels 144
7.3 Results 145
7.4 Discussion and conclusion 148
7.5 Experimental 149
7.6 References 152

Summary **153**

Samenvatting **155**

Chapter 1

Introduction

Abstract

This chapter starts with a brief historical overview of the discovery of cyclodextrins. Then the structure and the physical properties of cyclodextrins are reviewed.

Due to their structure and physical properties cyclodextrins are known to form inclusion complexes with a variety of low molecular weight compounds. These complexes are applied in a number of fields.

The properties that play a role in the formation of inclusion compounds by cyclodextrins can be altered by the functionalization of the hydroxyls on the rim of the cyclodextrins. There are two ways in which the cyclodextrins can be functionalized. First of all, it is possible to functionalize only one hydroxyl. Secondly, it is possible to functionalize a complete set of hydroxyls.

Inclusion compound formation by cyclodextrins can be used for obtaining several cyclodextrin-containing supramolecular structures. One of the most referred cyclodextrin-containing supramolecular structure is the α-cyclodextrin molecular tube.

Finally, the aim of this work and the outline of the thesis will be given at the end of this chapter.

1.1 Cyclodextrins

1.1.1 History

The compounds nowadays called cyclodextrins were first isolated in 1891 by Villiers. He discovered the formation of an oligosaccharide, when starch was enzymatically cleaved.[1] Schardinger confirmed his result in 1904. He further identified the cyclic structure of the glucose oligomers and the enzyme responsible for the synthesis of cyclodextrins.[2] Because of his pioneering work the name Schardinger dextrins is often used for cyclodextrins in early literature. In the early literature cyclodextrins are also sometimes called cycloamyloses or cyclomalto-oligosaccharides.
The correct chemical structure of the cyclodextrins was not published until 1938. It was Freudenberg, who characterized them as cyclic structures composed of α-1,4-linked glucose units (§ 1.1.2).[3] After this publication it still took some years before the molecular weights of the three most important cyclodextrins were determined.
The foundations of cyclodextrin chemistry were laid down in the first part of the 20th century. Only in 1953 the first patent on cyclodextrins and their inclusion complexes was registered.[4] Cramer and French were the first, who recognized and studied possible applications by forming complexes with these compounds. Because of their research the way was paved for the use of cyclodextrins as enzyme models.[5,6,7,8,9] However, until 1970 only small amounts of cyclodextrins could be produced and high production costs prevented their wide spread usage. Today the cost of cyclodextrins is reduced dramatically and as a result the group of scientists interested in cyclodextrins is continually growing.

1.1.2 Structure

Cyclodextrins are obtained biotechnologically in large scale by the enzymatic degradation of starch, by making use of a glycosyl transferase from *Bacillus macerans*.[10] In this process cleavage of a turn from the starch helix, is followed by intramolecular cyclization.[11]
Mainly three cyclic oligosaccharides are obtained. They are called α-, β- and γ-cyclodextrin. These cyclodextrins consist of six, seven and eight D-glucose units, respectively, attached by α-1,4-linkages (figure 1.1). Cyclodextrins consisting of more D-glucose units also exist,[5] but they are too expensive for the development of practical applications.

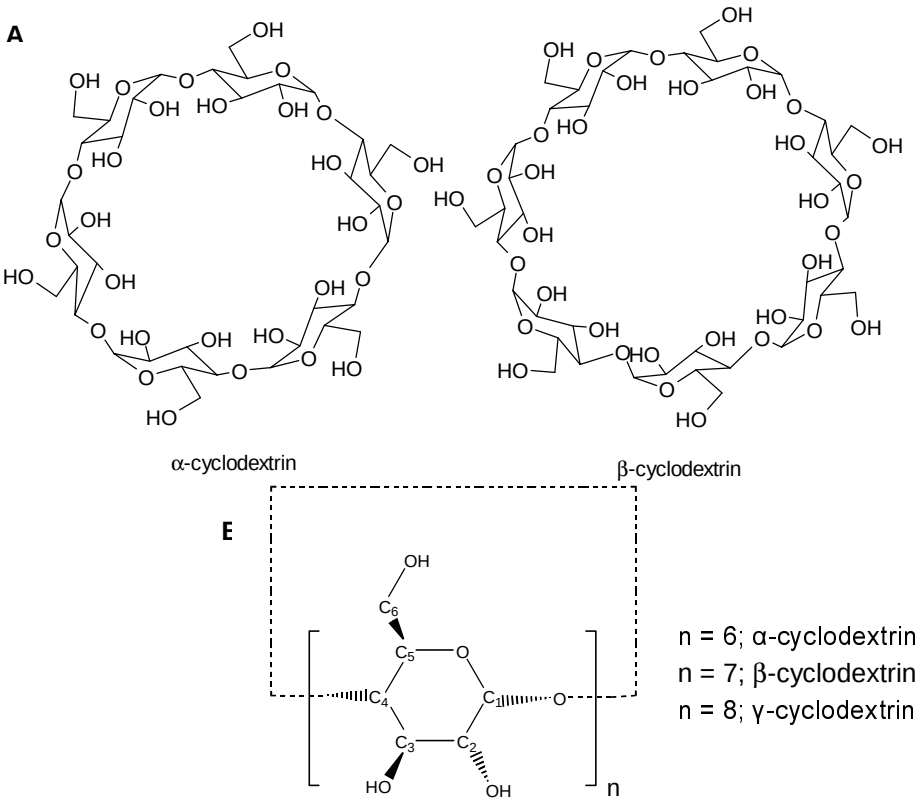


Figure 1.1. *A) Structure of α- and β-cyclodextrin and B) General structure of cyclodextrins.*

Each of the chiral glucose units is in the rigid $^4C_1$-chair conformation, giving the macrocycle the shape of a hollow truncated cone. The cone is formed by the carbon skeletons of the glucose units and the glycosidic oxygen atoms in between those. The primary hydroxyls of the glucose units are located at the narrow face of the cone and the secondary hydroxyls at the wide face. A schematic side view is shown in figure 1.2.
The primary hydroxyls on the narrow side of the cone can rotate, to partially block the cavity. In contrast the secondary hydroxyls are attached by relatively rigid chains and as a consequence they can not rotate.

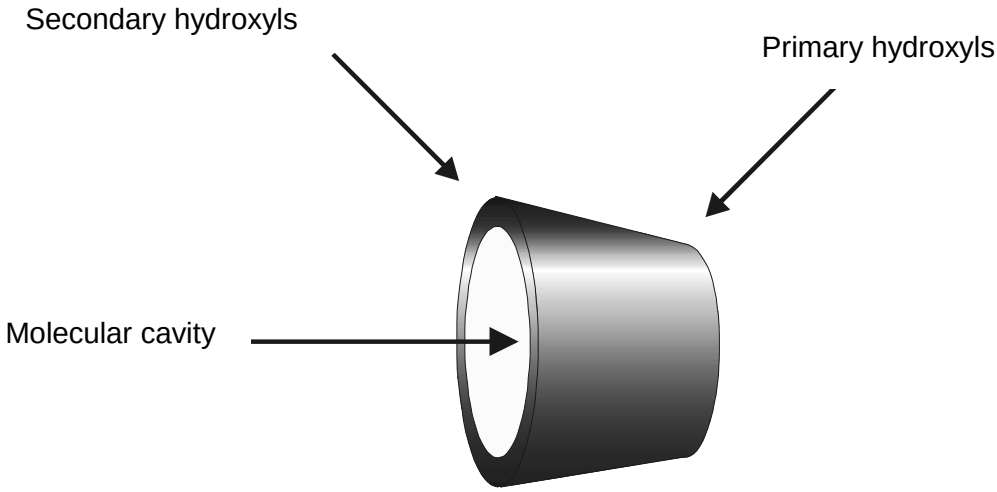


Figure 1.2. *Schematic side view of cyclodextrin.*

1.1.3 Properties

The primary and secondary hydroxyls on the outside of the cyclodextrins make cyclodextrins water-soluble. Cyclodextrins are insoluble in most organic solvents. The cavity of the cyclodextrin rings consists of a ring of C-H groups, a ring of glycosidic oxygen atoms and again a ring of C-H groups. This renders the interior of the cyclodextrin rings less polar. Table 1.1 lists some important properties and the molecular dimensions of the three most common cyclodextrins.[11,12]

Cyclodextrins are stable under alkaline conditions. They can, however, be cleaved by acid hydrolysis. When acid hydrolysis of cyclodextrins takes place glucose is produced.

Cyclodextrins are almost nontoxic. One of the few toxicities of cyclodextrins is hemolysis.[13,14] The hemolysis is a secondary event, resulting from the interactions of cyclodextrins with membrane components. It is reported that cyclodextrins at lower concentration protect the human erythrocytes against osmotic and heat-induced hemolysis. At higher concentrations, 37 °C, pH 7.4, in 10 $mmol.dm^{-3}$ isotonic phosphate buffer, however, they cause the release of cholesterol and phospholipids from the cell membrane resulting in cell disruption.[13,15,16] The activity of the cyclodextrins follows the order β-, γ- and α-cyclodextrin, where β-cyclodextrin is the most toxic.

Cyclodextrin complexation can give beneficial modification of guest molecules such as solubility enhancement, stabilization of labile guests, physical isolation of incompatible compounds and control of volatility and sublimation. Furthermore, the chemical reactivity of the guest is changed by the incorporation into the cavity.

Table 1.1. *Physical properties and molecular dimension of cyclodextrins.*

Property	*α-cyclodextrin*	*β-cyclodextrin*	*γ-cyclodextrin*
Number of glucose units	6	7	8
Molecular weight ($g.mol^{-1}$)	972	1,135	1,297
Water solubility ($g.100\ ml^{-1}$) 25 °C	14.5	1.85	23.2
Specific rotation $[\alpha]_D^{25}$	150.5 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Internal diameter (Å)	4.9	6.2	7.9
External diameter (Å)	14.6	15.4	17.5
Height cone (Å)	7.9	7.9	7.9
Cavity volume ($Å^3$)	176	346	510

1.2 Cyclodextrin-containing inclusion compounds

1.2.1 Formation

Because of the relatively apolar cavity in comparison to the polar exterior, cyclodextrins can form inclusion compounds with hydrophobic guest molecules in aqueous solutions predominantly due to hydrophobic interactions.[17,18] However, the possibility to form hydrophobic interactions represents only one of the requirements. Another requirement is the guest molecule must be able to fit inside the cavity of the cyclodextrin. When a complex is formed the surface of the hydrophobic interior of the cyclodextrin and the hydrophobic exterior of the guest molecule exposed to hydrophilic solvent is decreased. It must be emphasized that the phenomenon of cyclodextrin inclusion compound formation is a complicated process and in reality there are many factors that play a role.[19] This is illustrated by the fact that not only apolar compounds can be included but also acids, amides, small ions and even rare gases.[20,21]

Small molecules normally form 1:1 inclusion compounds. In such an inclusion compound, one cyclodextrin ring includes one guest. It is also possible, that the guest is only partly included by one cyclodextrin. This is the case when molecules larger than the cavity have to be included. When the molecule is even larger also 2:1 and other types of inclusion compounds can be formed.

Inclusion compound formation by cyclodextrins is historically carried out in water. However, also inclusion compound formation in dimethylformamide is described.[22] It is also possible to form inclusion compounds in the crystalline state.[23]

1.2.2 Application of inclusion compounds

As discussed in § 1.1.1 until 1970 cyclodextrins were produced at small scale. Recent biotechnological advancements have resulted in dramatic improvements in cyclodextrin production, which has lowered their production costs. This has led to a wider commercial availability of purified cyclodextrins and cyclodextrin derivatives.

The beneficial modification of guest molecular properties after the formation of an inclusion compound leads to a large number of applications related to pharmaceutical chemistry, food technology, analytical chemistry, chemical synthesis and catalysis.[11,14,24] As already mentioned cyclodextrins are practically nontoxic and as a result they are allowed in pharmaceuticals and foods. Stabilization of labile compounds and long-term protection of color, odor and flavor represent some of the possible applications in these areas.[11,13,14]

1.2.3 Detection of inclusion compounds

Inclusion compounds can be detected by a variety of spectrometric methods. The most direct evidence for the inclusion of a guest into the cyclodextrin cavity in solution can be obtained by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). The chemical shifts for the protons attached to C^3 and C^5 move significantly upfield in the ^{1}H-NMR spectrum in the presence of a guest. The magnitude of the shifts increases slightly on going from α-cyclodextrin to β-cyclodextrin and dramatically on going to γ-cyclodextrin. Additionally the shift for the C^5 protons is larger, than for the C^3 protons due to the rigid conical shape of the cyclodextrins. On the other hand the C^1, C^2 and C^4 protons located at the exterior of the cavity, show only a marginal upfield shift.[5]

Usually, the ^{1}H-NMR signals of the included guest molecules shift downfield compared to the free molecules.[25,26] In the ^{1}H-NMR spectra of inclusion compounds the signals of the guests are significantly broadened.

Except the magnetic properties of the protons, also other physicochemical properties of the guest molecules are varied upon inclusion complexation. Among others the electronic absorption, fluorescence, phosphorescence and optical rotation properties for the guests are more or less varied as a result of incorporation into a cyclodextrin cavity.[27,28,29,30,31,32,33,34]

The structure of the inclusion compound can be detected with X-ray diffraction.[35,36,37,38,39,40] Especially X-ray analysis of cyclodextrin inclusion compounds containing organometallics as guests has been used to investigate the structural and to some extent the dynamic,

host–guest interactions.[35] When the temperature is decreased, the disorder attributed to the absence of strong host–guest interactions, is reduced. This allows a more precise determination of the molecular parameters of the included species, and analysis of the influence of the geometry on the molecular conformation and electron density.
Recently, thermal analysis has also been used in the study of inclusion compounds.[41,42] In some cases no melting peaks of the guests are observed after the formation of complexes. The thermal decomposition of inclusion compounds was studied only scarcely.[43,44] It was observed that the decomposition of the complexed guest occurs above the decomposition temperature of the uncomplexed molecule. Although scarcely studied this thermal decomposition behavior of guests included inside cyclodextrins and the increase of the stability of the guest when included, is used in a variety of applications.

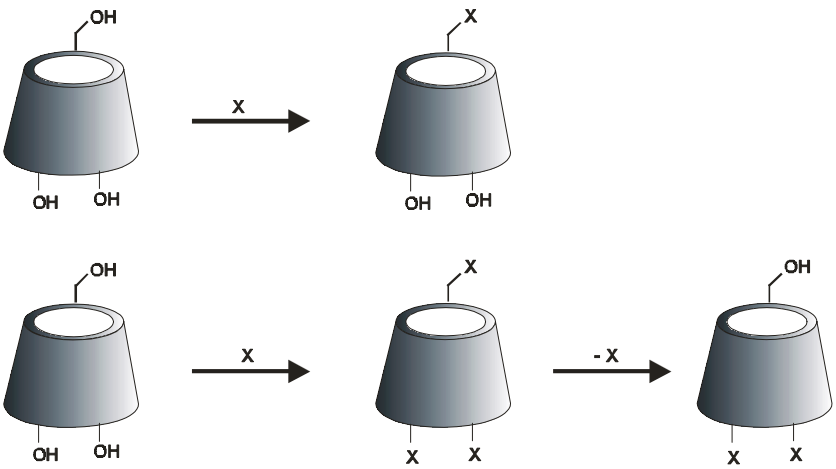
1.3 Functionalization

A hydrophilic exterior, formed by two rims of hydroxyl groups surrounds the hydrophobic molecular cavity. Various functional groups can covalently be attached to the hydroxyl groups.[45,46] When the hydroxyl groups are modified, the complexation behavior of cyclodextrins can be altered and the relatively low water-solubility of β-cyclodextrin can be enhanced. Selective modification of cyclodextrins with catalytic groups can create an enzyme like activity. For these purposes, several functional groups were placed on the periphery of cyclodextrins. Based on their availability and cavity size most of the studies have utilized α- and β-cyclodextrin.
The binding properties of functionalized cyclodextrins are in many cases identical to the binding properties of the parent cyclodextrins.[24,47] Complexation with functionalized cyclodextrins can, however, also take place in organic solvents since many of the functionalized cyclodextrins are soluble in organic solvents.
Functionalization of cyclodextrins can concern complete sets of hydroxyls or partial functionalization (i.e. monofunctionalization). First, functionalization of complete sets will be discussed while monofunctionalization will be discussed later.

1.3.1 Functionalization of complete sets

As can be seen in figure 1.1 (§ 1.1.2) the glucose repeating unit of a cyclodextrin contains three different hydroxyls. The glucose repeating unit contains one primary hydroxyl group at position 6. These primary hydroxyls are located at the narrow side of the cyclodextrin molecule. Each glucose unit also contains two secondary hydroxyl groups connected to C^2 and C^3. The primary and secondary hydroxyl groups have different reactivities. Also the

two secondary hydroxyl groups have slightly different reactivities. This last difference is due to the fact that the hydroxyl groups attached to C^2 are closer to the hemi-acetal then the hydroxyl groups attached to C^3. This makes the hydroxyl groups attached to C^2 slightly more acidic and so they are slightly more reactive than the hydroxyl groups attached to C^3.
There are several reasons for the functionalization of a complete set of hydroxyls. The reason is often the enhancement of the solubility in water or in organic solvents, the protection of hydroxyl groups so other hydroxyl groups can react, or the activation of a set of hydroxyl groups by the introduction of good leaving groups for further fictionalization of that set. Acylation, alkylation, or silylation of complete sets of hydroxyls can enhance the solubility of cyclodextrins in common organic solvents.
The problem of discriminating between a set of primary hydroxyl groups and the double amount of secondary hydroxyl groups raises the question of the strategy to be followed. There are two possible strategies: 1) An indirect or reverse method based on non-selective reaction followed by selective deprotection of one set of hydroxyl groups and 2) A direct approach involving the selective reaction of one set of hydroxyl groups (scheme 1.1).



Scheme 1.1. *Reaction scheme for the direct (top) and indirect (bottom) functionalization of a complete set of hydroxyls (In the schematic representation of the cyclodextrin used here every hydroxyl shown represents one set of hydroxyls).*

The direct approach has two major problems a statistical and a steric problem. First, the selectivity of the primary- compared to the secondary hydroxyls is about 10:1 this makes the selective reaction of the secondary hydroxyls very difficult.
The geometry of the molecule introduces another factor, which further lowers the yield of selective direct reactions. Progressive reaction with bulky reagents of one set of hydroxyl

groups decreases the selectivity for steric reasons when the degree of substitution increases. It was shown that sulfonylation of the primary hydroxyls of β-cyclodextrin with *p*-toluenesulfonyl chloride did not proceed with sufficient selectivity. With the more selective mesitylenesulfonyl chloride, the reaction proceeds rapidly at the primary hydroxyl face, however, never exclusively with that set of hydroxyls.

There is one more reason why selective reaction of the primary hydroxyls is very difficult. Even in water there is a network of hydrogen bonds. These hydrogen bonds link the hydroxyl groups at C^3 with the hydroxyl groups at C^2 on the adjacent glucose unit and this lowers the pK_a of the secondary hydroxyls.[48,49,50,51,52] Some reactions take place as fast or even faster at the secondary hydroxyls attached to C^2 than at the primary hydroxyl groups.[12] Hence, it is obvious that the direct strategy is only possible with a limited number of reagents.[48] Normally these reagents should be bulky to first effect the discrimination between the different hydroxyl groups.

The indirect strategy relies on the amplification of the steric difference between the two sets of hydroxyls. The diameter of the rim of secondary hydroxyl groups at the wider side of the cone is almost the same as that of the rim of primary hydroxyl groups at the narrow face.

Functionalization of all the hydroxyl groups crowds the wider side of the cone even more than the narrow side. This makes the deprotection of the primary hydroxyl groups easier, because these groups are more easily accessible.

The success of the functionalization of a set of hydroxyl groups of a cyclodextrin can be verified by NMR spectroscopy.[53] Especially ^{1}H-NMR in DMSO-d_6 is often employed. As expected, the peak due to one of the hydroxyl groups disappears when this group reacts and a new peak due to the functional group attached to the cyclodextrin will appear.

Among the first cyclodextrin derivatives that appeared in the literature, were acylated cyclodextrins. Since then, many acylated cyclodextrins with different functionalization have been reported. In many case these compounds were prepared for purification purposes and the acyl groups were removed after purification of the compound.

Alkylation of the hydroxyls of cyclodextrins first takes place at the more nucleophilic C^6 and the more acidic C^2 hydroxyl groups.[48] Because the C^3 hydroxyl groups point to the center of the cavity when the C^2 hydroxyl groups are functionalized, they tend to react very slowly in the alkylation reaction.

One of the most common alkylations is methylation. Methylation can be used to enhance the solubility of cyclodextrins in water. Methylation of free cyclodextrins can be performed for example with methyl iodide.[54,55]

Protection of the nucleophilic primary hydroxyls by silylation leads to cyclodextrin derivatives, which are soluble in organic solvents and relatively easy to obtain as pure compounds. Because the formed silyl ethers are stable under most reaction conditions, the silylated cyclodextrins can be used as intermediates for further functionalization. Selective

silylation of the primary hydroxyls is described for α-, β- and γ-cyclodextrin. After this functionalization the secondary hydroxyl groups can be modified. Using more vigorous reaction conditions, also the C^2 hydroxyls can be silylated. There are various methodologies to remove the silyl groups.

The primary hydroxyls of α-, β- and γ-cyclodextrin can also be sulfonylated. Sulfonylation takes place at the primary hydroxyl groups. In this way, the primary hydroxyl groups attached to C^6 are transformed into good leaving groups and this offers the possibility to introduce other functional groups at the primary face that can not be attached directly. Especially the introduction of tosyl groups at the primary face was studied extensively.[48] Analytical data about the products are scarce and if reported, they are not always in agreement with those in other reports. Unfortunately tosylated cyclodextrins have poor solubility. This makes the purification of hexakis(6-O-tosyl)-α-cyclodextrin and heptakis(6-O-tosyl)-β-cyclodextrin very difficult. There are some reports on the selective sulfonylation of the primary face of α-, β- and γ-cyclodextrin.[56,57,58,59,60]

Alternatively, halogenation of sets of hydroxyls is possible. Direct bromination or iodation produces cyclodextrins that are fully halogenated at the primary face.[12]

1.3.2 Monofunctionalization

Besides the functionalization of complete sets of hydroxyl groups it is also possible, to selectively functionalize one hydroxyl group of a cyclodextrin molecule. The selective monofunctionalization of cyclodextrins has been extensively studied for the primary hydroxyl face and less well for the secondary hydroxyl face. The reason is that selective functionalization of the more nucleophilic primary hydroxyls over the more acidic secondary hydroxyls is easier than the reverse.[61] In organic solvents, the primary hydroxyl groups are more reactive than the secondary hydroxyls and sulfonylated hydroxyls at the secondary face can easily be decomposed by epoxide formation under alkaline reaction conditions. However, monofunctionalization at the secondary hydroxyl face of cyclodextrins is more important in view of the application of cyclodextrins as catalytically active compounds.[62] For example, for catalytic purposes the catalytically active function is generally attached to the more open face of the conically shaped cyclodextrin molecule (where the secondary hydroxyls are located) rather than to the almost closed face of the primary hydroxyls.

Several different methodologies are known for the selective introduction of one sulfonyl group at the primary hydroxyl face of α-, β- and γ-cyclodextrin.[63,64,65,66,67] Monotosylation of α- and β-cyclodextrin is important since a good leaving group is introduced, which can be easily transformed into an other functional group.[48,63,64,65,66]

Monosulfonylation at the secondary face of cyclodextrins is more difficult than the monosulfonylation at the primary face. However, as already mentioned it is more important since in this case the good leaving group is attached to the wide side of the conically shaped cyclodextrin molecule which makes the interaction with a guest molecule easier. Some procedures for the selective introduction of one sulfonyl group at the secondary face have been described in the literature for α-, β- and γ-cyclodextrin.[68,69,67]

1.4 Cyclodextrin-containing supramolecular structures

The hydrophobic cavities of cyclodextrins are responsible for the accommodation of various kinds of molecules and in this way inclusion compounds are formed. Using this inclusion compound formation in combination with chemical synthesis new and exciting structures can be designed. Here some of these structures will be introduced.

1.4.1 Supramolecular chemistry

Supramolecular chemistry uses self-assembly processes for the formation of large molecular and polymolecular structures. Catenanes, rotaxanes and knot compounds are some of the prototypes used in this new synthetic methodology which might eventually be used to attain nanometer-scale structures (figure 1.3).[70] There are several interactions that can drive self-assembly, needed for the construction of these supramolecular structures, more efficient. These interactions are hydrophobic interactions, hydrogen bonding, donor-acceptor interactions, and transition metal coordination.[71]
A large number of completely synthetic supramolecular structures have been reported.[71] Concurrently with this activity on completely synthetic systems, cyclodextrins have attracted a lot of attention as building blocks for self-assembling supramolecular structures. The cyclodextrin based structures are formed efficiently due to hydrophobic interactions. These structures are usually formed in aqueous media, but they can also be formed in organic solvents when functionalized cyclodextrins are used.[72,73,74]

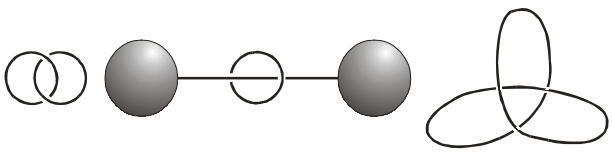


Figure 1.3. *Schematic presentation of a [2]catenane, a [2]rotaxane and a trefoil knot.*

1.4.2 Cyclodextrin dimers

The moderate size of the hydrophobic molecular cavities of α-, β- and γ-cyclodextrin prevents the accommodation of large substrates by one cyclodextrin. However, efficient binding of large substrates can be achieved in 2:1 inclusion compounds. In this way a type of dimer is obtained.[75]

The enthalpic gain due to the hydrophobic binding of a substrate by a cyclodextrin is partly compensated by the loss of entropy because of the molecular association. Binding of a second cyclodextrin to a cyclodextrin/substrate inclusion compound shows a decreased binding constant compared to the binding of the first cyclodextrin to the substrate.[76] The decreased enthalpic gain and the increased entropic loss on binding of the second cyclodextrin may be due to geometrical interferences between the two cyclodextrins.

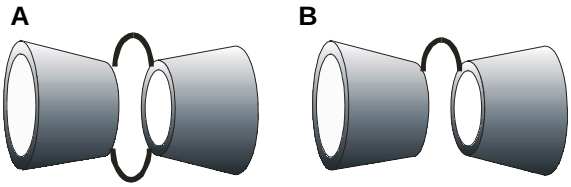


Figure 1.4. *Two types of covalently linked cyclodextrin dimers.*

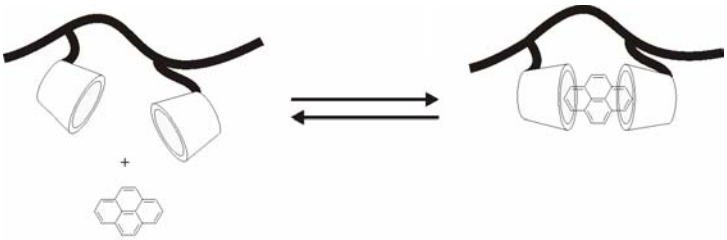


Figure 1.5. *Schematic representation of the 2:1 complex formation between cyclodextrin-containing polymer and pyrene.*

1.4.2.1 Covalently linked cyclodextrin dimers

A part of the entropic loss can be overcome, by using cyclodextrin dimers for the complexation of large substrates. As in biological interactions the chelate effect of multiple point recognition leads to substrate binding with a lower entropic loss. The translational entropy has to be paid only once when the two connected cyclodextrin residues are carrying the same guest molecule. The classical description of the chelate effect is not free from

ambiguity, as shown in a study of the guest inclusion by various cyclodextrin dimers.[76] Figure 1.4 shows two types of covalently linked cyclodextrin dimers.

Instead of short bridges between the cyclodextrins it is also possible to covalently connect cyclodextrins to polymers. Because of the linkage with the polymer, the cyclodextrins molecules interact cooperatively to a certain extent. Both 1:1 and 2:1 complex can be formed by the cyclodextrins that are attached to the polymer chain. Investigations of the polymer influence on the formation of inclusion compounds have been reported.[77,78,79,80] These investigations used large aromatic guests and assumed, the cyclodextrins attached to polymers only favor the formation of 2:1 inclusion compounds according to figure 1.5. The proposed mechanism for the complexation of the guests by the cyclodextrin-containing polymer is both the formation of host-guest inclusion complexes as well as physical adsorption in the polymer network.

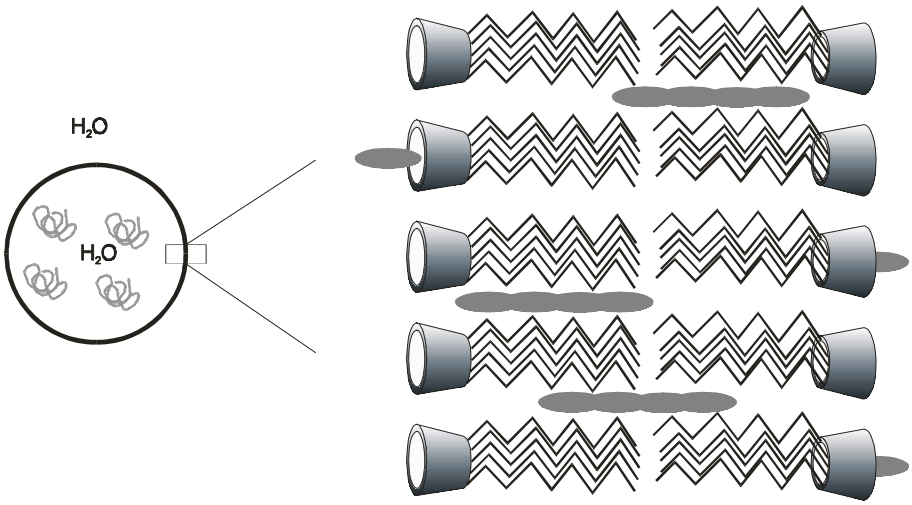


Figure 1.6. *Schematic of molecular inclusion by a cyclodextrin vesicle.*

1.4.3 Cyclodextrin amphiphiles

It was already mentioned that cyclodextrin inclusion compound formation is not limited to 1:1 complexes. It was then mentioned that larger guests can be included by cyclodextrin dimers (both covalent and non-covalent). In addition to these dimers or cyclodextrin-containing polymers, the assembly of amphiphilically modified cyclodextrins into micelles or vesicles provides another way in which the guest molecules can interact with cyclodextrins.[81,82,83,84] A vesicle formed of amphiphilic cyclodextrins can include guests either within the individual cavities or in the interior of the bilayer, which consists of

multiple lipophilic hydrocarbon chains or, for hydrophilic compounds, within the aqueous vesicle core (figure 1.6).
Many amphiphilic cyclodextrins have been described in the literature in which either the primary- or the secondary hydroxyl face or both is modified.[81,83] Often the products used are a mixture of isomers since it is difficult to separate the isomers.[85]
In limited percentages amphiphilic cyclodextrins can be admixed to phospholipid monolayers[86,87,88] and liposomes,[89,90,91] they can also be dispersed as "nanoparticles" of pharmaceutical interest.[92]

1.4.4 Catenanes

The catenanes represent a group of supramolecular structures in which two cyclic molecules are mechanically linked together. No covalent bonds hold the rings together, but rather mechanical bonds are responsible for the connection of the rings. The disruption of a catenane into its separate components requires the breaking of one or more covalent bonds in the mechanically linked molecule. Thus, catenanes behave as well defined molecular compounds with properties significantly different from those of their individual components.[71] When two rings are linked together the structure is called a [2]catenane. The prefix indicates the number of interlocked components, so when 3 rings are mechanically linked with each other the compound is called a [3]catenane.
Already in 1957 an attempt was reported to synthesize a [2]catenane by ring closure of a long guest molecule included in α-cyclodextrin (figure 1.7).[93,94] The experiment failed, however, it is important in the history of catenated compounds, because it was the first reported attempt to synthesize such a supramolecular structure.
Only 35 years later the catenation of cyclodextrins succeeded.[95] [2]- and [3]catenanes were obtained from heptakis(2,6-di-O-methyl)-β-cyclodextrin.

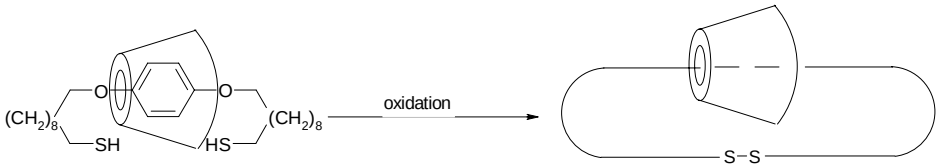


Figure 1.7. *Attempt to synthesize a catenane by linking both ends of a thiol threaded into α-cyclodextrin by air oxidation in the presence of copper(II) ions.*

1.4.5 Rotaxanes

The word rotaxane is derived from the Latin words “rota” meaning wheel and “axis” meaning axle. In chemistry, a rotaxane is a supramolecular structure in which a dumbbell-shaped molecule is encircled by a macrocycle, and dethreading of the macrocycle from the dumbbell-shaped molecule is prevented by bulky blocking groups. No covalent bonds are present between the two individual components, only mechanical bonds are responsible for the linking of the components. When no blocking groups are present and the macrocycles do have a chance of dethreading, the supramolecular structure is called a semi- or pseudo-rotaxane. Just as with catenanes a prefix is used to indicate the number of interlocked components.[71] The simplest rotaxane is a [2]rotaxane in which one dumbbell-shaped molecule and one macrocycle are interlocked.

A rotaxane with a cyclodextrin threaded around the axis can be synthesized via two routes. In the first route a chain molecule is complexed by a cyclodextrin and then the chain molecule is blocked at both ends by bulky blocking groups. When this route is applied, a rotaxane can be obtained in relatively high yield (figure 1.8).

In the second route the cyclodextrin is complexed on a chain molecule, already blocked by a bulky blocking group at one end. The final rotaxane can be obtained by blocking the other end of the chain molecule. A schematic representation of this route is shown in figure 1.9.

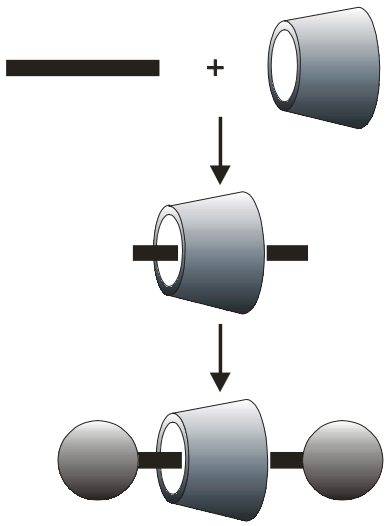


Figure 1.8. *Synthesis of rotaxane by first the formation of a pseudo-rotaxane and the subsequent blocking of both ends of the guest molecule by a bulky blocking group.*

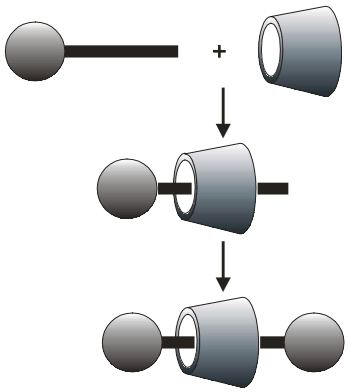


Figure 1.9. *Synthesis of rotaxane by first the formation of an inclusion compound containing a guest already blocked at one end and the subsequent blocking of the other end.*

A lot of different blocking groups can be used. The size of the blocking group used for synthesizing rotaxanes depends on the diameter of the cyclodextrin used.[96] To be an effective blocking group the size of the blocking group should at least be as large as the diameter of the cyclodextrin at the narrow side. Since this diameter increases upon going from α- to β- to γ-cyclodextrin, the blocking groups used should also increase.
Depending on the orientation of the cyclodextrin on an asymmetric main chain, isomers can be obtained (figure 1.10). ^{1}H-NMR in DMSO-d_6 can detect the presence of isomers.

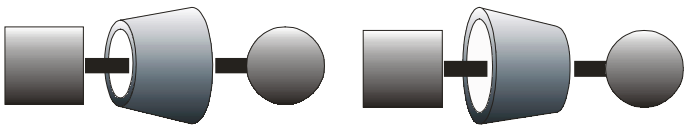


Figure 1.10. *Two isomeric rotaxanes.*

1.4.6 Cyclodextrins threaded on polymers

The inclusion of hydrophobic guest molecules inside the cavity of cyclodextrins is mainly driven by hydrophobic interactions between host and guest. Some polymers are hydrophobic and so it was attempted, to obtain pseudo-polyrotaxanes composed of cyclodextrins and polymer chains (figure 1.11).
There are two methods for obtaining a pseudo-polyrotaxane composed of a polymer chain and cyclodextrins. The first method is the in situ formation of the pseudo-polyrotaxane by

polymerization of a monomer complexed inside a cyclodextrin. The first report about pseudo-polyrotaxanes composed of cyclodextrins and polymers used this in situ formation of cyclodextrins threaded on polymers.[22,97] The pseudo-polyrotaxanes were obtained by radiation polymerization of crystalline monomeric inclusion compounds consisting of vinylidene chloride and β-cyclodextrin. The product contained molecules of β-cyclodextrin and vinylidene chloride polymer. Because of the high stability of the system, non-chemical linkage between polymer and β-cyclodextrin molecules was expected. However, the possibility of chemical bonds was not excluded. Covalent bonds could be formed in grafting or in chain transfer to the β-cyclodextrin molecule. Nowadays it is known, no covalent bonds exist in the product obtained and that the product is a pseudo-polyrotaxane composed of cyclodextrins and polymer. Also other monomer inclusion compounds were polymerized by Maciejewski *et al.*, however, the products obtained were unstable and polymers dissociated when purified with hot water.[97] Other groups studied this kind of polymerizations too.[98] The group of Anderson has studied the polymerization of cyclodextrin inclusion compounds in order to obtain conjugated pseudo-polyrotaxanes.[99,100] The group of Lacaze used cyclodextrin complexation to increase the solubility of a thiophene monomer. These monomer complexes were then polymerized electrochemically. Surprisingly the polymers obtained were not included by cyclodextrins anymore.[101,102,103,104]

The second method for obtaining a pseudo-polyrotaxane composed of cyclodextrin and polymer is threading cyclodextrins on preformed polymer. The formation of pseudo-polyrotaxanes composed of α-cyclodextrin and poly(ethylene glycol) was the first report on threading cyclodextrins on polymers.[105] When aqueous solutions of poly(ethylene glycol) were added to a saturated aqueous solution of α-cyclodextrin, the solution became turbid. The pseudo-polyrotaxanes formed, were obtained as precipitates. This happened almost quantitatively when the average molecular weight of the poly(ethylene glycol) was between 400 and 10,000 $g.mol^{-1}$. No precipitate was obtained below this molecular weight, because the pseudo-polyrotaxanes formed are soluble.[105,106]

The pseudo-polyrotaxanes formed between β-cyclodextrin and poly(ethylene glycol) do not form a precipitate. It, however, does form high molecular weight pseudo-polyrotaxanes with poly(propylene glycol), which has methyl groups substituted to the poly(ethylene glycol) chain. A precipitate is obtained when poly(propylene glycol) is added to a saturated aqueous solution of β-cyclodextrin. β-Cyclodextrin forms insoluble pseudo-polyrotaxanes with poly(propylene glycol) when the average molecular weight of poly(propylene glycol) is higher than 400 $g.mol^{-1}$. Pseudo-polyrotaxanes are obtained most quantitatively, when the molecular weight is about 1,000 $g.mol^{-1}$, the yield decreases when the average molecular weight of the poly(propylene glycol) increases.

γ-Cyclodextrin also forms insoluble pseudo-polyrotaxanes with poly(propylene glycol) in high yields even when the molecular weight of poly(propylene glycol) is low. It also forms

insoluble pseudo-polyrotaxanes with poly(isobutene) and poly(methyl vinyl ether) in high yields. As expected α- and β-cyclodextrin do not form pseudo-polyrotaxanes with these bulky polymers at all.
These pseudo-polyrotaxanes confine the conformation of the polymer chain to rod-like owing to the infinitesimal cavities and close-packing of the molecules.[107]
The inclusion compounds mentioned before are obtained as precipitates in aqueous solution so the pseudo-polyrotaxanes are insoluble in water.[105,108] Water-soluble pseudo-polyrotaxanes can also be formed, for example such a pseudo-polyrotaxane is formed when solutions containing α-cyclodextrin and poly(iminooligomethylene)s containing alkyl segments longer than seven methylene groups are mixed together.[108,109,110] These soluble pseudo-polyrotaxanes allow the investigation of the kinetics of the threading process. The axial inclusion of a main chain is of special interest, as it is a one-dimensional transport process.[109,111] It has been possible to follow the threading process of α-cyclodextrin molecules on water-soluble polymers by ^{1}H-NMR spectroscopy under homogeneous conditions.[106,111] The ^{1}H-NMR signals of the included guest molecules are shifted as usual for inclusion complexes (§ 1.2.3).[25] It was found, that the speed of the ring along the chain highly depends on the size of the rings as well as on the thickness of the polymer.[108,111]
Threading of cyclodextrins on the polymer can take place along the main chain. When the polymer has side chains, however, also these side chains can be included.[111,112]

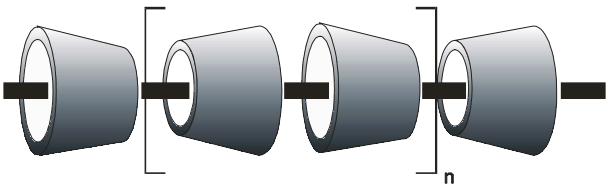


Figure 1.11. *Cyclodextrins threaded on a polymer chain.*

1.4.7 Polyrotaxanes containing cyclodextrins

Rotaxanes and catenanes are relatively small molecules. Rotaxanes and catenane structures can be incorporated into polymers to create polyrotaxanes or polycatenanes, respectively (figure 1.12). In the literature no reports on cyclodextrin-containing polycatenanes can be found. There are, however, reports on polyrotaxanes containing cyclodextrins. Polyrotaxanes not only have remarkable structures, but they may also provide fundamental insight for the development of new materials. They are expected to show different physical, mechanical and rheological properties, compared with classical polymers, due to topological differences.

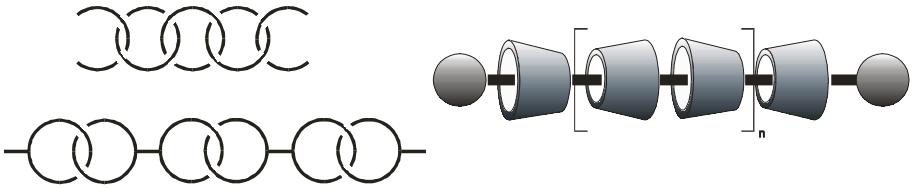


Figure 1.12. *Schematic examples of polycatenanes (left) and a cyclodextrin containing polyrotaxane (right).*

Polyrotaxanes containing cyclodextrins can be synthesized by first threading many cyclodextrins on a polymer chain and then blocking the ends of the polymer chain with bulky groups.[25,113] A different type of polyrotaxane is obtained, when a polymer with reactive groups in the main chain is threaded by cyclodextrins (figure 1.13). This pseudo-polyrotaxane of cyclodextrins and polymer can be reacted with a bulky group in such a way there are bulky substituents along the polymer chain. The attachment of at least two blocking groups at arbitrary positions along the chain prevents unthreading along a part of the chain. In this way the cyclodextrins are mechanically trapped and the product is also a polyrotaxane (figure 1.13).

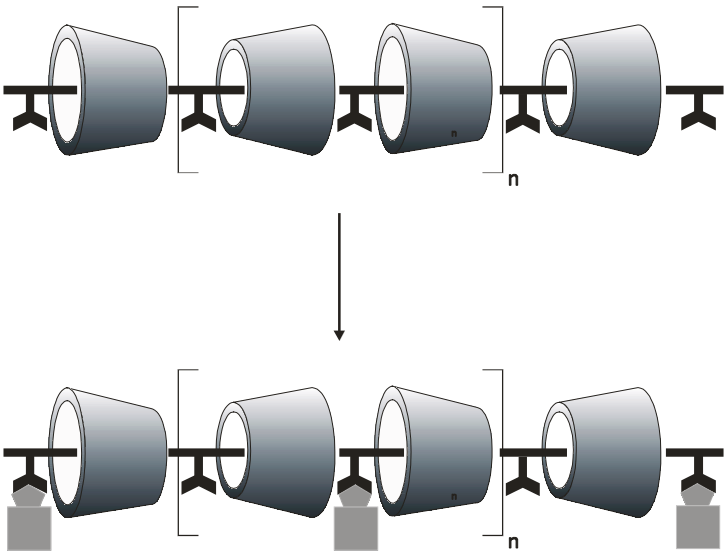


Figure 1.13. *The formation of a polyrotaxane by attachment of blocking groups at arbitrary positions along the chain.*

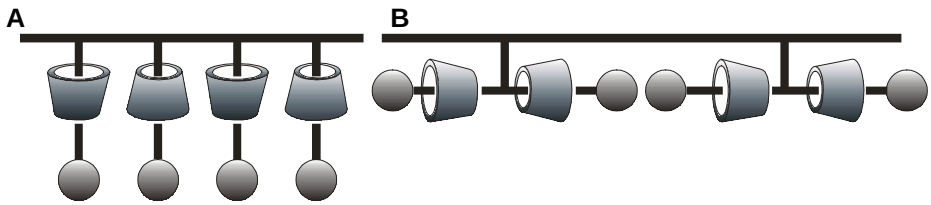


Figure 1.14. *Two types of side-chain polyrotaxanes: A) Side-chain polyrotaxane; B) "Tandem polyrotaxane".*

A third group of polyrotaxanes are the side-chain polyrotaxanes (figure 1.14A).[53,111,112,114] These polyrotaxanes are based on comb polymers and the cyclodextrins are complexed along the side-chains. These polyrotaxanes can be synthesized in two different ways.
First it is possible, to complex a low molecular weight guest molecule in such a way that a pseudo-(poly)rotaxane is obtained. The unblocked reactive end of the guest molecules can then react with an appropriate main chain polymer to produce the desired side-chain polyrotaxanes.[112,114,115] In the second approach for synthesizing side-chain polyrotaxanes cyclodextrins complex the side-chains of a comb polymer and the activated ends of the side-chains are blocked with bulky blocking groups.
Also "tandem polyrotaxanes" are described in the literature.[53,54] In these polyrotaxanes each polymeric side chain is complexed by a cyclodextrin (figure 1.14B).

1.4.8 Cyclodextrin molecular tubes

Some rod like structures involving cyclodextrins such as rotaxanes, cyclodextrins threaded onto polymer and polyrotaxanes are mentioned before.[53,116,117,118,119,120,121] There is one other very interesting rod like structure, which is not yet mentioned. This structure is the nanotubular structure.[117,119,122]
Several different cyclodextrin-containing compounds are called "nanotubes" in the literature. One type of cyclodextrin "nanotube" described in the literature, are "nanotubes" obtained from γ-cyclodextrin.[117] The γ-cyclodextrins are threaded onto α,ω-diphenylpolyenes. However, the term tube is not completely correct, since the γ-cyclodextrins are not linked together. It is a supramolecular structure belonging to the group of cyclodextrins threaded on polymers described in § 1.4.6. The γ-cyclodextrins are lined up along the axis of the polyene so close-packed hydrogen-bonding interactions between the rim hydroxyl groups of neighboring γ-cyclodextrins are favored. Because the

polyenes penetrate the cavities of neighboring γ-cyclodextrins, the superstructure is stabilized by Van der Waals interactions.
The crucial contribution of both γ-cyclodextrin − γ-cyclodextrin and polyene − γ-cyclodextrin interactions to the formation of these "nanotubes" was demonstrated. First, these tubes did not form in the absence of polyene. Second, when the rim hydroxyls of γ-cyclodextrin were replaced by the non-hydrogen-bonding methoxy groups, or when the pH of the solvent is high enough to render hydrogen-bonding ineffective, "nanotubes" did not form.[117,123] The same kind of molecular "nanotube" aggregates were obtained from β- and γ-cyclodextrin linked by diphenylhexatrienes.[122]
Another "nanotube" structure was described by Ohira *et al.* In this structure, β-cyclodextrins adsorbed on gold surfaces, aligned in channels.[124]
The simplest way to synthesize a real tube in which the cyclodextrins are linked together is by first synthesizing a polyrotaxane in which the cyclodextrins are close-packed on the polymer chain.[119] Then the adjacent cyclodextrins in the polyrotaxane can be cross-linked to create the nanotube.[119] Finally, the bulky ends of the "template polymer" can be removed, and an empty tube is obtained. These tubes are expected to be able to complex host molecules in an identical manner as single cyclodextrins can form inclusion compounds with small molecules.
Using this general strategy α-cyclodextrin tubes have been synthesized by first threading many α-cyclodextrins on poly(ethylene glycol). The α-cyclodextrins are close-packed from end to end on the polymer chain. Then the polyrotaxane is synthesized by reaction of the ends of the "template polymer" chain with bulky blocking groups to prevent the unthreading of the cyclodextrin from the polymer chain. Subsequently the cyclodextrin molecular tube is synthesized, by removing the bulky blocking groups and release of the "template polymer".

1.5 Aim and outline of this thesis

The aim of this thesis is to synthesize, characterize and study cyclodextrin-containing supramolecular structures. Eventually cyclodextrin-containing supramolecular structures are obtained that might be used as insulated molecular wires.
In **chapter 2**, the design and synthesis of a cyclodextrin molecular tube is described in detail. The cyclodextrin molecular tube is obtained by formation of pseudo-polyrotaxane composed of cyclodextrins and poly(ethylene glycol) "template polymer". It is possible to obtain a pseudo-polyrotaxane in which the cyclodextrins are close-packed from end to end on the polymer chain. This pseudo-polyrotaxane can be converted to a polyrotaxane by the reaction of the ends of the template polymer with bulky blocking groups. The cyclodextrins

can be connected intramolecularly and in this way a cyclodextrin molecular tube is obtained, however, the “template polymer” is still inside the tube. When the blocking groups are removed, the polymer chain is released from the molecular tube and a cyclodextrin molecular tube is obtained.

The characterization of this cyclodextrin molecular tube is described in **chapter 3**. Among others especially Atomic Force Microscopy and Small-angle Neutron Scattering are used to obtain information about the dimensions and rigidity of the obtained cyclodextrin molecular tube.

In order to find possible explanations for the shorter than expected length of the empty α-cyclodextrin molecular tubes, in **chapter 4** models are discussed describing the cyclodextrin pseudo-polyrotaxanes.

Chapter 5 is concerned with a possible application of this cyclodextrin molecular tube. Complexes can be formed between the α-cyclodextrin molecular tubes and polyaniline. Polyaniline is a conjugated polymer and when doped electrically conducting. The complexes composed of the α-cyclodextrin molecular tubes and the polyaniline chains might be regarded as an insulated molecular wire. Surprisingly, two types of inclusion compounds were obtained. One structure consisted of one polyaniline chain complexed by multiple α-cyclodextrin molecular tubes. The other structure consisted of multiple polyaniline chains and multiple α-cyclodextrin molecular tubes.

The synthesis of a different type of potential insulated molecular wire is described in **chapter 6**. This potential insulated molecular wire is obtained by first performing the complexation of a monomer inside the cavity of a cyclodextrin. The polymer obtained after polymerization of this included monomer is a conjugated polymer. The polymer obtained is still threaded by cyclodextrins, so this is a pseudo-polyrotaxane. This pseudo-polyrotaxane can be converted to a stable polyrotaxane by reaction of the ends of the polymer obtained with bulky blocking groups.

In **chapter 7**, an extension of the inclusion of poly(ethylene glycol) by α-cyclodextrin is described. In this case a higher molecular weight of the “template polymer” is used in order to obtain a completely different material. Due to this higher molecular weight “template polymer” the cyclodextrins are not close-packed along the polymer chain anymore. In the polyrotaxane obtained, the cyclodextrins have the ability to slide along the polymer chain. When the cyclodextrin rings are connected with each other intermolecularly, a new type of network is obtained. Due to the ability of the cyclodextrins to slide along the polymer chains this network is proposed as material, able to attain large amounts of water.

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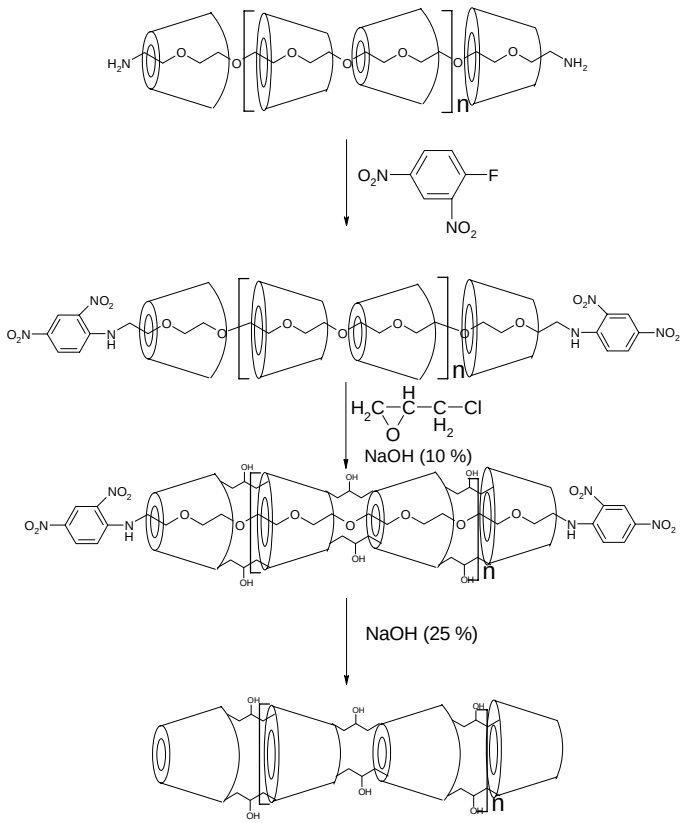
Chapter 2

Synthesis of α-cyclodextrin molecular tubes

Abstract

α-Cyclodextrin molecular tubes were successfully synthesized according to the following scheme:



Using this scheme several different filled- and empty tubes were obtained by using different procedures for the threading and the crosslinking of the α-cyclodextrins.

2.1 Introduction

Nanotubes have captured the imagination of physicists, chemists and materials scientists, not only because of their peculiar structure, but for their potential applications as well. One of the first nanotubes described were the carbon nanotubes. The discovery of the bucky ball pointed in the direction of carbon nanotubes having a much more perfect structure. These carbon nanotubes in which the carbon atoms in the wall have a hexagonal arrangement were first described in 1991. The diameter of these single-walled carbon nanotubes is approximately 1.4 nm. However, after heating under controlled conditions, the tubes can have diameters two or three times the diameter of the original single-walled carbon nanotubes. Multi-walled carbon nanotubes having such a hexagonal arrangement of the carbon atoms range in outer diameter from about 2.5 nm to 30 nm, and in length from a few tens of nanometers to several micrometers.[1]

An idea that attracted early interest was to use these carbon nanotubes as “molecular containers”. The carbon nanotubes can also be used as “nano-wires”.[2,3] Another application is their use as tip for scanning probe microscopy.[1]

Because of their potential applications chemists have developed methods in order to be able to synthesize molecular-scale tubules. Peptide nanotubes are constructed by highly convergent non-covalent processes by which cyclic peptides rapidly self-assemble and organize into ultra large well-ordered three-dimensional structures, when there is an appropriate chemical or medium-induced triggering. These tubes can be hundreds of nanometers long and have internal diameters of less than 1 nm.[4,5] It is suggested these peptide nanotubes can mimic biomembrane channels and pore structures.[6]

It is also possible to synthesize tubes with an even larger size. These larger tubes can be obtained from lipids. Tubes of about 500 nm in diameter and up to 1 mm long have been obtained.[7]

The group of Harada synthesized tubes from α-cyclodextrin. The inside diameter of these tubes is approximately 1 nm.[8,9,10] Their synthesis is based on a self-assembly process of cyclodextrins threading on a “template polymer”. After the connection of the α-cyclodextrins and the release of the “template polymer”, α-cyclodextrin molecular tubes could be isolated (scheme 2.1).[8,9,10]

Although the binding properties of the cyclodextrins in the cyclodextrin molecular tubes might be different compared to single cyclodextrins, it is expected, that the cyclodextrin molecular tubes are able to form inclusion complexes with various kinds of guests, based on the excellent complexation properties of their building blocks. Modification of the binding properties of cyclodextrins by the introduction of functional groups has been studied by many groups.[11,12]

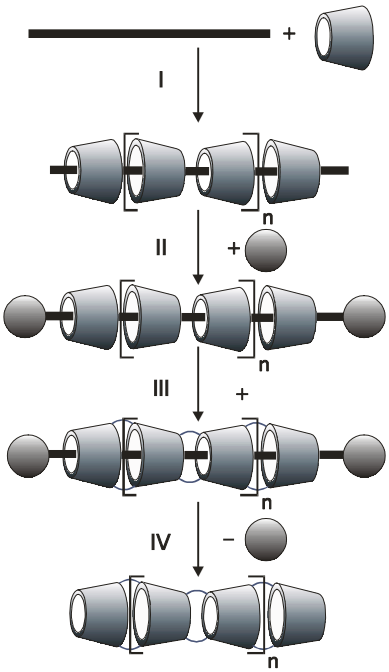
Cyclodextrin molecular tube inclusion complex formation has been theoretically predicted.[13] These complexes can then be used to render guest molecules insoluble in water soluble, just like the parent cyclodextrins can render a guest molecule insoluble in water, water-soluble. Inclusion of sodium dodecanesulfonate inside α-cyclodextrin molecular tubes is reported.[14] The complexation of polyaniline in α-cyclodextrin molecular tubes is described in chapter 5.[15]
Since these α-cyclodextrin molecular tubes have only been studied sparsely, a drawback for the practical application of these α-cyclodextrin molecular tubes is their inadequate characterization.[10,16] In this chapter the design of cyclodextrin molecular tubes and the synthesis of α-cyclodextrin molecular tubes are described. The α-cyclodextrin molecular tubes obtained are synthesized using the same synthetic route as described by Harada, main difference is the modification of the temperature at which the blocking groups are attached (§ 2.3.2.1). Their characterization is described for the first time in Chapter 3.

2.2 Design of cyclodextrin molecular tubes

In this section, the requirements for obtaining cyclodextrin molecular tubes are discussed. Scheme 2.1 shows the schematic synthetic route used eventually.

2.2.1 Threading of cyclodextrins on the polymer chain

The pseudo-polyrotaxane should fulfill the following requirements: 1) It should be possible to be isolated; 2) The cyclodextrins should be close-packed on the “template polymer” chain; 3) The ends of the “template polymer” chain should be able to react with bulky blocking groups.
The first requirement might seem to be straightforward. However, as mentioned in § 1.4.5, some polymer/cyclodextrin pseudo-polyrotaxanes are water soluble and this complicates their isolation. The pseudo-polyrotaxanes composed of α-cyclodextrin and poly(ethylene glycol), β-cyclodextrin and poly(propylene glycol), and γ-cyclodextrin and polymers such as poly(propylene glycol), poly(isobutene) and poly(methyl vinyl ether) mentioned in § 1.4.5, are all good candidates.
These complexes precipitate in high yields from solution upon the formation of the pseudo-polyrotaxane. Another advantage of these polymers is the close-packing of the cyclodextrins on the polymer chains. This is essential, because in a later stage the cyclodextrins have to be crosslinked (scheme 2.1). Close-packing of the cyclodextrins favors intra- over intermolecular crosslinking, since due to this close-packing neighboring cyclodextrin hydroxyls are the most abundantly present.



Scheme 2.1. *Schematic synthetic route for the synthesis of cyclodextrin molecular tubes.*

It would energetically be most favorable for the cyclodextrins to have head-to-head and tail-to-tail orientation.[17,18] The reason is that with such an arrangement in the case of α-cyclodextrins at the wide side then 12 hydrogen bonds can be formed, and at the narrow side 6 hydrogen bonds. When there is head-to-tail packing of the cyclodextrins on the "template polymer" chain, the distance between the hydroxyl groups can become larger and the formation of hydrogen bonds becomes more difficult. If it is still possible to form hydrogen bonds between the head-to-tail packed cyclodextrins a maximum of 6 hydrogen bonds can be formed with each head-to-tail added cyclodextrin, compared to 6 and 12 hydrogen bonds alternately in the case of head-to-head and tail-to-tail packing.

The other procedure for obtaining complexes of cyclodextrins and polymers described, is the polymerization of complexed monomers (§ 1.4.5). This produces polymers threaded with cyclodextrins. However, the cyclodextrins are normally not close-packed on the polymer chains obtained.

The last requirement is that the ends of the "template polymer should be able to react with bulky blocking groups. This requirement is fulfilled when the polymer chains have two functionalized end groups capable to react with the blocking groups. Examples of functional groups are hydroxyl groups, amine groups and halogen groups.

2.2.2 Blocking group for the prevention of the unthreading of the cyclodextrins

The blocking group should fulfill the following requirements: 1) It should be bulky enough to prevent the unthreading of cyclodextrins from the polymer chain; 2) The blocking groups should be able to react with the end groups of the "template polymer" chain; 3) The blocking groups should be stable under the crosslinking conditions; 4) It should be possible to remove the blocking groups at a later stage in order to release the cyclodextrin molecular tubes.

The blocking group should be bulky enough to prevent the unthreading of the cyclodextrins from the polymer chain. Many different blocking groups are used in the literature.[19]

The next requirement for the blocking group is the ability to react with the "template polymer" in the pseudo-polyrotaxane in order to obtain a polyrotaxane. It has been found that the pseudo-polyrotaxanes can only be dissolved in a limited number of solvents similar to their building blocks the cyclodextrins.[20] Therefore the choice of solvent for the pseudo-polyrotaxanes is limited. Pseudo-polyrotaxanes are always in equilibrium with their components. This equilibrium depends on the solvent used for dissolving the complex. Complex formation is most favored in water, while *N*,*N*-dimethylformamide (DMF) does not drive the equilibrium completely towards the loose components like most other solvents do. In order to minimize unthreading of the cyclodextrins from the "template polymer" chains, the pseudo-polyrotaxanes should be dissolved in concentrated solution during the addition of the blocking groups, even when water or DMF are used as solvent. Furthermore, for the addition reaction of the blocking groups to the functionalized end groups of the "template polymer" a fast reaction should be chosen.

The blocking groups should not react with the large number of cyclodextrin hydroxyls in the pseudo-polyrotaxanes. This means that the "template polymer" should have end groups more reactive than these hydroxyl groups.

The last two requirements are that the blocking groups must be stable under the crosslinking conditions and that it should be possible to remove them from the filled tubes in order to obtain the empty tubes.

2.2.3 Crosslinking the cyclodextrins in the polyrotaxane

The compound used for crosslinking the cyclodextrins should fulfill the following requirements: 1) It should be bifunctional; 2) It should fit between two close-packed cyclodextrins; 3) The crosslinks that are formed should be stable, when the blocking groups are removed. The last requirement is that the reaction conditions used for the crosslinking of the cyclodextrins should be compatible with the rest of the polyrotaxane.

Since the cyclodextrins only have hydroxyls groups the compound used for cross-linking should have two functional groups able to react with these hydroxyl groups. The reactivity of both functions of the crosslinking agent should be comparable. Otherwise two hydroxyl groups close to each other but on neighboring α-cyclodextrins can both react with the most reactive side of a crosslinking compound and then both hydroxyl groups contain dangling cross-linking groups. These two hydroxyls can not be connected with each other anymore and the tube, if obtained, will have less real crosslinks and instead have many dangling crosslink groups.

The compound used for the crosslinking of the cyclodextrins in the polyrotaxane should have an appropriate size in order to fit between the hydroxyls of the close-packed cyclodextrins. When the length of the crosslinking compound does not correspond to the distance between two hydroxyl groups it will be difficult to obtain connections between adjacent cyclodextrins and probably intermolecular crosslinks might be formed.

The last requirement was that the reaction conditions used for the crosslinking of the cyclodextrins should be compatible with the rest of the polyrotaxane. First, the reaction conditions should be compatible with the structure of the cyclodextrins. As mentioned in § 1.1.3 cyclodextrins are relatively stable compounds, however, they can be cleaved under acidic conditions.[21,22] Secondly, the bond between the blocking groups and the “template polymer” should be stable under the reaction conditions used for crosslinking the cyclodextrins.

Finally, the bond formed between the cyclodextrins and the crosslinking compound must be stable under the reaction conditions used for the removal of the blocking groups from the “template polymer” chain (step IV in scheme 2.1).

2.2.4 Release of cyclodextrin molecular tubes

The requirement for the reaction conditions used to release the cyclodextrin molecular tubes is that the cyclodextrin molecular tube should be stable under these reaction conditions. A further requirement in order to obtain empty tubes is that the “template polymer” is removed out of the cyclodextrin molecular tube.

Once the cyclodextrins are crosslinked, the blocking groups prevent the unthreading of the cyclodextrin molecular tube from the “template polymer” chain. For the applications of the cyclodextrin molecular tubes it is necessary that the “template polymer” chain is removed from the cyclodextrin molecular tubes, and this means that first the blocking groups should be removed.

Since the reaction conditions for the removal of the blocking groups from the “template polymer” chain may not harm the cyclodextrin molecular tubes and taking into account the instability of cyclodextrins under acidic conditions this means that no acidic reaction can be

used.[21,22] Also, the crosslinks between the cyclodextrins should be stable under these reaction conditions.
In the last step the "template polymer" has to be removed out of the cyclodextrin molecular tube. Since complex formation is always an equilibrium process, the "template polymer" can be removed by dissolving the complex of the cyclodextrin molecular tube and "template polymer" in a large excess of solvent. Especially dimethyl sulfoxide (DMSO) is a good solvent for this purpose since the equilibrium is shifted towards the individual components.[23]

2.3 Synthesis of cyclodextrin molecular tubes

The general synthetic route for the synthesis of cyclodextrin molecular tubes is depicted in scheme 2.1. It was attempted to synthesize α- and β-cyclodextrin molecular tubes.

2.3.1 Cyclodextrin pseudo-polyrotaxane

For the α-cyclodextrin molecular tube α,ω-bis-amine-terminated poly(ethylene glycol) (2,000 $g.mol^{-1}$) was used as "template polymer". The polydispersity of the "template polymer" used was 1.05 as determined by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF). The molecular weight corresponds to approximately 45 repeating units. In the literature it is reported that α-cyclodextrins close-pack on poly(ethylene glycol) of this molecular weight (§ 1.4.5). The packing is approximately 2.3 ethylene glycol repeating units per cyclodextrin.[24,25,26] The length of 2 ethylene glycol units corresponds closely to the depth of the cavity of α-cyclodextrin (figure 2.1).[27] So the pseudo-polyrotaxane is expected to consist of approximately 20 α-cyclodextrins.[24,25,26]
Several different complexation procedures were used for obtaining the complex of α-cyclodextrin and poly(ethylene glycol). In the standard complexation procedure (**2**) all the cyclodextrin is added to the dissolved polymer at 60 °C, after the addition the mixture is stirred for 30 min. (see § 2.5 for the details and for a description of the other complexation procedures). The yield of the pseudo-polyrotaxanes is almost 100 % for all procedures.
The ^{1}H-NMR spectra of the synthesized compounds are discussed in more detail in § 3.3.1. Here it is already mentioned that from the ^{1}H-NMR spectra of the pseudo-polyrotaxanes obtained after mixing the poly(ethylene glycol) (2,000 $g.mol^{-1}$) with the α-cyclodextrins it can be calculated that there are approximately 20 α-cyclodextrins per polymer chain (compound **2** § 2.5).
For the β-cyclodextrin molecular tube α,ω-bis-amine-terminated poly(propylene glycol) (2,000 $g.mol^{-1}$) was used as "template polymer". The polydispersity of the "template

polymer" used was 1.07. The molecular weight corresponds to approximately 34 propylene glycol repeating units. In the literature it is reported, that β-cyclodextrins close-pack on this molecular weight of poly(propylene glycol) (§ 1.4.5). The packing is again 2 propylene glycol units per cyclodextrin.[27,28,29] The length of 2 propylene glycol units corresponds to the depth of the cavity of β-cyclodextrin (figure 2.2). So the complex is expected to consist of approximately 17 β-cyclodextrins.

From the ^{1}H-NMR spectrum of the complex obtained after mixing the poly(propylene glycol) (2,000 g.mol^{-1}) with the β-cyclodextrin it could be calculated that there are approximately 17 cyclodextrins per polymer chain (compound **8** § 2.5). This leads to a value of 2.0 monomer units per cyclodextrin.

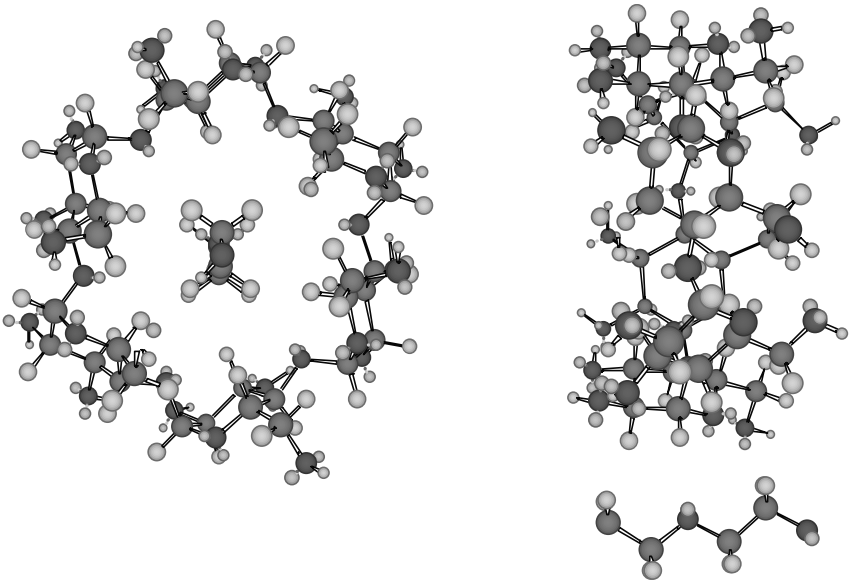


Figure 2.1. *Molecular model of a-cyclodextrin containing two ethylene glycol repeating unit (left), a side view of a cyclodextrin (top right) and of two ethylene glycol repeating units (bottom right).*

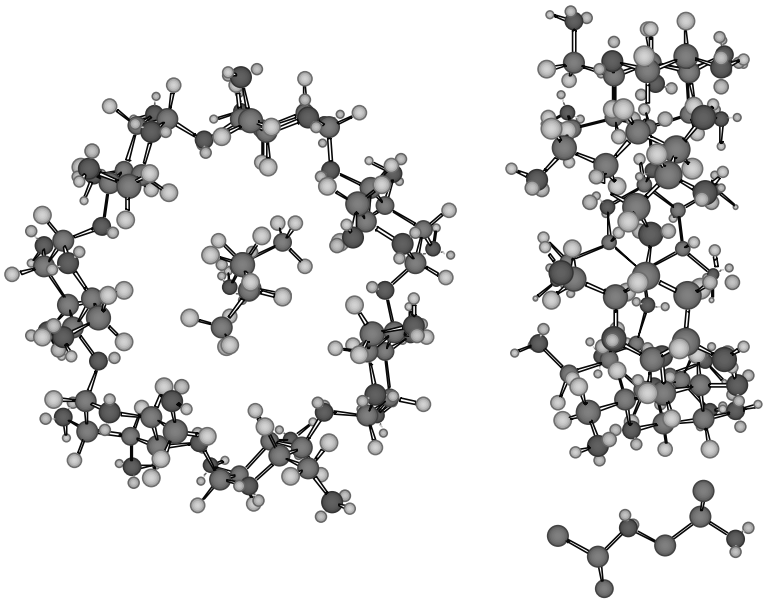


Figure 2.2. *Molecular model of β-cyclodextrin containing two propylene glycol repeating units (left), a side view of a cyclodextrin (top right) and of two propylene glycol repeating unit (bottom right).*

2.3.2 Polyrotaxane

To synthesize a polyrotaxane from the complex it is necessary to attach a blocking group at either end of the "template polymer" in the complex. For the poly(ethylene glycol)/α-cyclodextrin pseudo-polyrotaxane two different blocking groups were used. First 2,4-dinitrofluorobenzene was applied by using a slightly modified previously reported procedure.[30] This yielded 2,4-dinitrophenyl groups by the reaction of the fluorine of 2,4-dinitrofluorobenzene with the amine end groups of the poly(ethylene glycol) "template polymer". The 2,4-dinitrophenyl groups are bulky enough to prevent the unthreading of α-cyclodextrins from the "template polymer". The reaction can be performed in DMF and the reaction is fast.

Because HF is formed in the reaction, a base has to be added to ensure the reaction mixture does not become acidic. *N,N*-Diisopropylethylamine is used as a base. *N,N*-Diisopropylethylamine is a bulky compound and can not be included in α-cyclodextrin, so there is no competition between the "template polymer" and the base. In addition it is not nucleophilic due to steric hindrance and therefore there is no risk of its reaction with the 2,4-dinitrofluorobenzene.

The presence of 2,4-dinitrophenyl groups in the product can be identified with UV−Vis. The UV−Vis spectrum of the polyrotaxane in DMF shows a peak at 342 nm due to the 2,4-dinitrophenyl groups.
Under the reaction conditions used for the crosslinking of the cyclodextrins (to be discussed in § 2.3.3), the secondary amine formed in the previous reaction is stable. In contrast the 2,4-dinitrophenyl groups can be removed under strong basic conditions.
Again the ^{1}H-NMR spectra of the compounds obtained are discussed in more detail in § 3.3.1. However, it was found that there was no evidence of unthreading of the cyclodextrins from the polymer chain during the reaction of the blocking groups with the polymer chain.
Besides 2,4-dinitrophenyl also triphenylmethyl was used as blocking group, for obtaining a poly(ethylene glycol)/α-cyclodextrin polyrotaxane. Triphenylmethyl is bulkier than 2,4-dinitrophenyl and can be used for the synthesis of β-cyclodextrin tubes as well. It can be attached to the amine end groups of the "template polymer" by reaction with triphenylmethyl chloride in DMF. The reaction between the chloride and the amine end groups is fast as well.
The bond formed between the triphenylmethyl group and the poly(ethylene glycol) is stable under the conditions used for crosslinking the cyclodextrins. The removal of the triphenylmethyl group after the formation of the filled cyclodextrin molecular tubes is, however, more difficult. The triphenylmethyl group can be removed by the addition of trifluoroacetic acid and triphenylsilane (see § 2.3.2.1).
The ^{1}H-NMR of the polyrotaxane obtained shows substantial peak broadening. The number of cyclodextrins was determined by removing the blocking groups in order to obtain the individual components and a ^{1}H-NMR spectrum of the resulting reaction mixture was taken. This yielded a value of 15 cyclodextrins/polymer chain. This corresponds to a value of 3.0 monomer units/cyclodextrin. This might be a significant difference and thus be evidence of unthreadeding of cyclodextrins from the "template polymer" chain during the synthesis of the polyrotaxane. A possible explanation for the difference might be a slower reaction of the chlorine of triphenylmethyl chloride compared to the fluorine of 2,4-dinitrofluorobenzene.
The removal of the triphenylmethyl groups can be facilitated, if methoxy groups are attached to the phenyls of the triphenylmethyl groups, e.g., by using *p*-anisyldiphenylmethyl groups or 4,4'-dimethoxytriphenylmethyl groups. The 4,4'-dimethoxyltriphenylmethyl group can be removed by the addition of trifluoroacetic acid and triisopropylsilane (see § 2.3.2.1). Disadvantage is that those blocking groups are also more labile under the conditions used for crosslinking the cyclodextrins.
It was attempted to synthesize a polyrotaxane from the β-cyclodextrin/poly(propylene glycol) pseudo-polyrotaxane, but this failed. The reason probably is, that the β-cyclodextrin/poly(propylene glycol) pseudo-polyrotaxane is too soluble in the reaction

medium and the cyclodextrins dissociate before a blocking reaction takes place. As already explained inclusion compound formation is an equilibrium process and the equilibrium is shifted towards the inclusion compound in the case that both components are dissolved in water. In all other solvents the equilibrium shifts more or less in the direction of the individual components. Water and DMF are the solvents in which the equilibrium is mainly directed towards the complex. Since it is hard to find a blocking group that can be attached to the polymer chain in water DMF has to be used as solvent in step II in scheme 2.1. Other attempts performed were: Working in more concentrated DMF solutions or the addition of non solvents in order to obtain a suspension instead of a solution. Although in all cases the "template polymer" reacted with the blocking group, all cyclodextrins were unthreaded from the "template polymer" chain.

In another attempt 2,4-dinitrofluorobenzene was employed as blocking groups instead of triphenylmethyl chloride similar to the α-cyclodextrin polyrotaxanes. Of course in this case there is a risk, the 2,4-dinitrophenyl groups are not bulky enough to prevent the unthreading of the β-cyclodextrins and this is the reason, that it was not used initially. In this case again no polyrotaxane was obtained. Instead 2,4-dinitrophenyl terminated poly(ethylene glycol) and β-cyclodextrin was obtained, probably because all cyclodextrins unthreaded before the termination reaction took place.

2.3.2.1 Model reactions

Since the identification and quantitative measurement of the blocking groups attached to the polymer in the polyrotaxane is difficult by ^{1}H-NMR, due to the small number of hydrogen atoms in the blocking groups compared to the number of hydrogen atoms in the "template polymer" and the cyclodextrins, model reactions were performed using the polymers depicted in figure 2.3. The aim of synthesizing these polymers was to confirm that the blocking groups react fast with the "template polymer". Thus, 2,4-dinitrofluorobenzene and triphenylmethyl chloride were reacted with the poly(ethylene glycol) "template polymer" alone (figure 2.3). In all cases a polymer with two bulky groups was obtained fast. The triphenylmethyl-terminated polymers **10** and **11** are less stable than the 2,4-dinitrophenyl-terminated polymers **9**. When column chromatography using silica gel is performed to purify the triphenylmethyl-terminated polymer a base is needed to neutralize the slightly acidic silica gel otherwise the triphenylmethyl groups are cleaved from the polymer chains. This instability towards acids increases when the number of methoxy groups in the end group is increased. In the case of 4,4'-dimethoxytriphenylmethyl neutralization of the silica gel is not sufficient anymore. It is possible to obtain the pure compound by selective precipitation.

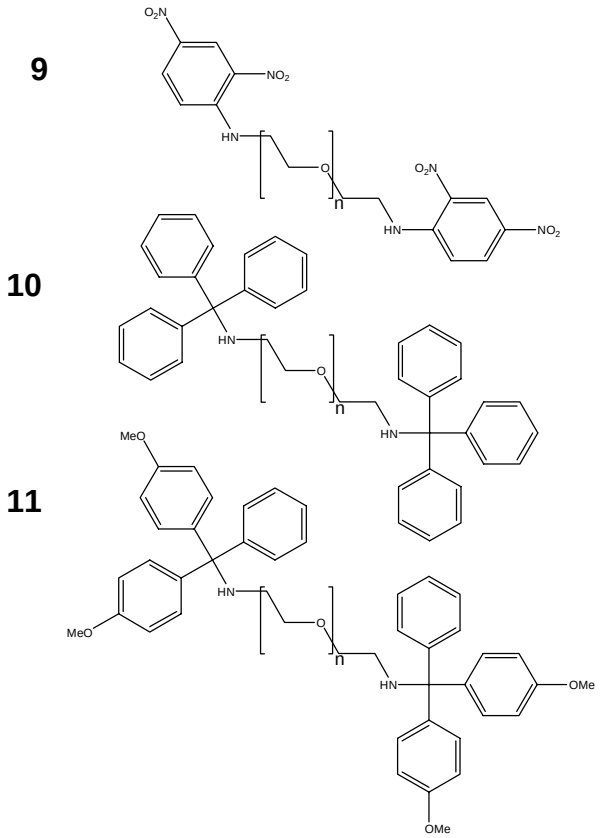


Figure 2.3. *Model polymers used for the study of the stability of the bulky group: 2,4-dinitrophenyl-terminated poly(ethylene glycol)* ***9****, triphenylmethyl-terminated poly(ethylene glycol)* ***10*** *and 4,4'-dimethoxytriphenylmethyl-terminated poly(ethylene glycol)* ***11****.*

Since it should be possible to remove the blocking groups in a later step in order to release the cyclodextrin molecular tubes it was investigated, which reaction conditions could be applied to remove them from the model polymers (figure 2.3). It was found that 2,4-dinitrophenyl groups could quantitatively be removed from the polymer chain by dissolving polymer **9** in 6.25 M (aq) NaOH. On the other hand the triphenylmethyl groups could be removed from polymer **10** using 5 (v/v) % trifluoroacetic acid and 1 equivalent of triphenylsilane. The 4,4'-dimethoxytriphenylmethyl groups could be removed from polymer **11** by adding 1 equivalent of trifluoroacetic acid and 4 equivalents of triisopropylsilane (see § 2.5).

It was mentioned, that cyclodextrins were unstable under acidic conditions. However, for the removal of the triphenylmethyl groups trifluoroacetic acid is required. Model reactions

showed no break down of cyclodextrins. Still, the 4,4'-dimethoxytriphenylmethyl blocking groups are preferred since for this group only 1 equivalent of TFA is necessary and a much shorter reaction time (§ 2.5).

As mentioned in § 2.2.2, the compounds used as blocking group should not react with the hydroxyls of the cyclodextrins. In order to determine if there is a reaction between the hydroxyls of cyclodextrin and the group used for blocking the "template polymer" chains, 2,4-dinitrofluorobenzene and triphenylmethyl chloride were mixed with cyclodextrins under the reaction conditions used for obtaining polyrotaxanes. It was found that under the reaction conditions described in the literature to synthesize polyrotaxane **17**, blocking groups could also be attached to cyclodextrins, as observed by an absorption peak at 342 nm in UV−Vis spectra of the cyclodextrins obtained.[24] When the same model reaction was performed at room temperature instead of at 80 °C no peak due to 2,4-dinitrophenyl absorption was observed in the UV−Vis spectrum of the cyclodextrins after the reaction.

The same result was obtained for triphenylmethyl chloride. It was found, that triphenylmethyl groups could be attached to the hydroxyls of cyclodextrin at elevated temperature. Again, synthesis of the polyrotaxanes at room temperature does not introduce triphenylmethyl groups into cyclodextrins (see reactions **16** and **18** § 2.5).

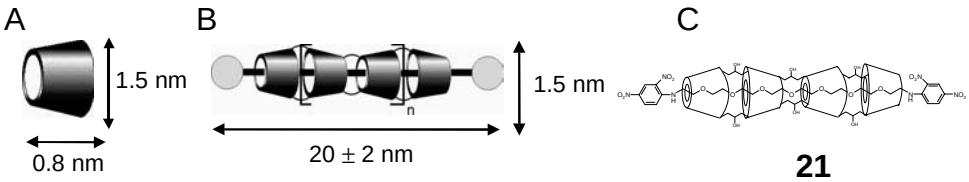


Figure 2.4. *A) Dimensions of α-cyclodextrin; B) Expected dimensions of the cyclodextrin molecular tube still containing the "template polymer; C) A molecular drawing of the filled tube **21**.*

2.3.3 Filled tube

As described in § 2.3.2, the only blocking group found that fulfilled all the requirements, was 2,4-dinitrophenyl. So it was only possible to synthesize α-cyclodextrin/poly(ethylene glycol) polyrotaxanes, and only in these polyrotaxanes the α-cyclodextrins were crosslinked (figure 2.4) (the head-to-head and tail-to-tail orientation of the cyclodextrins shown in figure 2.4 is explained in more detail in chapter 4).

Epichlorohydrin was used for crosslinking the cyclodextrins in the polyrotaxane (figure 2.5). The crosslinking reaction was performed in 2.50 M (aq) NaOH. In this environment

all the hydrogen bonds between the cyclodextrins are broken and some of the hydroxyls are converted to the alkoxydes. The crosslinking reaction was performed in dilute solution and at the beginning of the reaction there are no single cyclodextrins to assure intramolecular crosslinking (see § 3.3.5). During the reaction extra NaOH was added to maintain a basic pH (reaction **21** § 2.5).
Without the extra addition of NaOH the reaction mixture will be acidic at the end of the reaction, due to HCl produced, in the reaction of epichlorohydrin with hydroxyl groups. An acidic reaction mixture might cleave the cyclodextrins.[21,22]

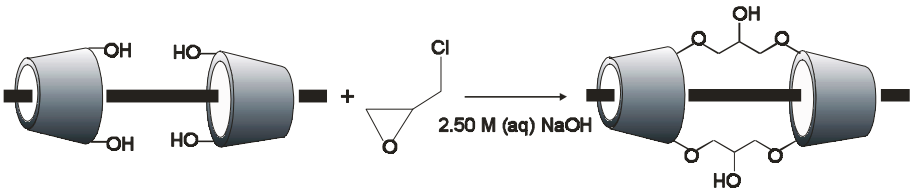


Figure 2.5. *Crosslinking of cyclodextrins in poly(ethylene glycol) polyrotaxane by epichlorohydrin.*

By ^{1}H-NMR it was attempted to determine the number of the cyclodextrins per polymer chain in the filled tube. Normally, since there is no possibility for the cyclodextrins to unthread once the bulky blocking groups are attached to the polymer chain, the number of cyclodextrins in the filled tube should be the same as in the polyrotaxane (see § 2.3.2) (scheme 2.1). This was indeed what was found (see § 3.3.1)
Modifications of the original procedure for the synthesis of the filled tube were used in order to synthesize filled tubes having more crosslinks. A measure of the crosslink density is according to the literature the ratio of the peak due to $C^{1}H$ and $C^{1}H'$ (explained in more detail in § 3.3.1) (table 2.1). A higher crosslink density could be an indication of more rigid α-cyclodextrin molecular tubes.
The starting materials for these filled tubes were polyrotaxanes in which the cyclodextrins were threaded on the polymer chain using the standard threading procedure (60 °C / 30 min (procedure **2** § 2.5))

Table 2.1. *Different procedures used for synthesizing the filed tubes.*

	Procedure	$C^{1}H'$: $C^{1}H$	Yield
21	2000 eq / 48 h	0.80 : 1	80 %
22	2000 eq / 144 h	0.80 : 1	40 %
23	1500 eq / 48 h	0.70 : 1	54 %

Instead of epichlorohydrin also tolylene-2,4-diisocyanate was tried as crosslinking agent. The aim was to obtain more rigid cyclodextrin molecular tubes. When the crosslinking is performed with tolylene-2,4-diisocyanate, an insoluble product is obtained. A possible explanation for the difference in solubility might be the absence of a pendent hydroxyl group in the crosslink in the case of crosslinking with tolylene-2,4-diisocyanate compared to the crosslink obtained from epichlorohydrin.
The introduction of a hydroxyl attached to a urethane crosslink is not easy.

2.3.4 Cyclodextrin molecular tube

The empty cyclodextrin molecular tubes were obtained by removing the 2,4-dinitrophenyl groups from the poly(ethylene glycol) "template polymer" chain in 6.25 M (aq) NaOH. Cyclodextrins and their crosslinks are stable under these reaction conditions. It was found that during this step the threaded polymer is also removed. Since DMSO is known to drive inclusion compounds towards their individual components, the "template polymer" is probably unthreaded from the inclusion compound in the work up, when the reaction mixture is dissolved in DMSO.

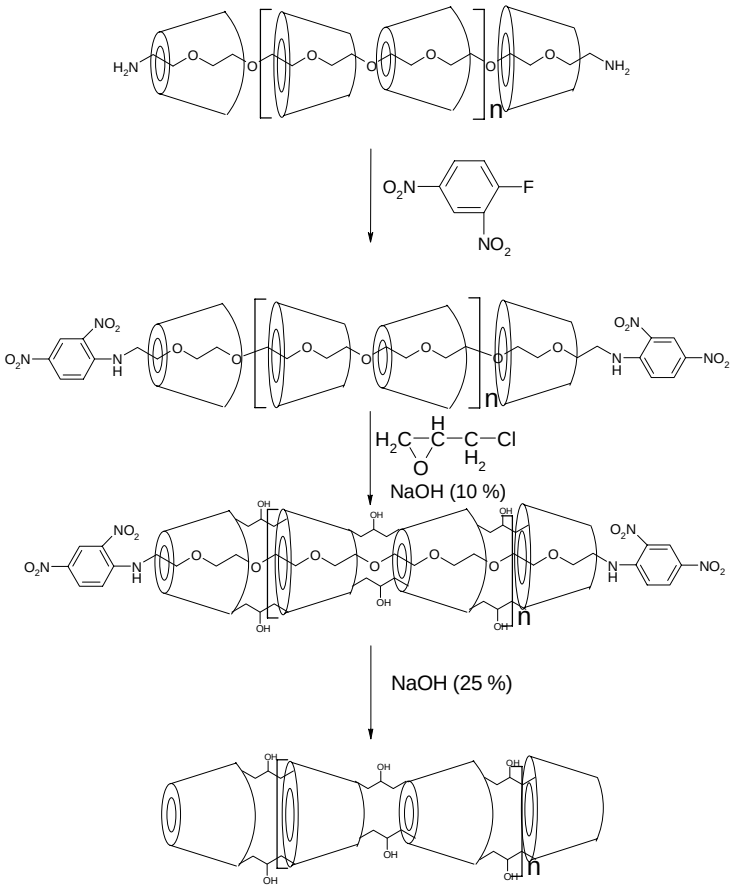
2.4 Discussion and conclusion

α-Cyclodextrin molecular tubes were successfully synthesized. Their synthesis is depicted in scheme 2.2.
Different filled and empty tubes were obtained by using different procedures for the threading and the crosslinking of the α-cyclodextrin (table 2.2, § 2.5).
Despite our effort it was not possible to synthesize β-cyclodextrin molecular tubes.

2.5 Experimental

Measurements
^{1}H-NMR spectra were recorded on a 300 MHz Varian (VXR 300) spectrometer. The deuterated solvent was used as internal standard. All chemical shifts are denoted in δ-units (ppm) and converted to TMS scale. Splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Size Exclusion Chromatography (SEC) was performed using a Waters Associates chromatography pump (model 590), a Waters Associates differential refractometer R 401 as detector, Sephadex G25[31] as the column material (dimensions of the column: length: 30 cm and diameter: 2.2 cm), degassed reversed-osmosis water as the eluent (elution rate 1.4 ml.min^{-1}). MALDI-TOF spectra were taken on

a Micromass TofSpec E mass spectrometer using 2,4-dihydroxybenzoic acid (DHB) as matrix; pulse voltage: 1400 V. UV−Vis spectra were recorded on a SLM Aminco 3000 Array. Thin Layer Chromatography (TLC) was performed using aluminum sheets, coated with silica gel 60 F_{254} (Merck).



Scheme 2.2. *Synthesis of α-cyclodextrin molecular tubes.*

Materials and methods

Poly(ethylene glycol) (PEG, $\overline{M_n}$ = 2,000 g.mol^{-1}), triphenylphosphine and 2,4-dinitrofluorobenzene (DNFB) were purchased from Merck. PEG was dried by an azeotropic distillation from toluene before use. α,ω-Bis-amine-terminated poly(propylene glycol) (PPG-BA, $\overline{M_n}$ = 2,000 g.mol^{-1}) was purchased from Scientific Polymer Products.

Epichlorohydrin, α- and β-cyclodextrin (α- and β-CD), *N*,*N*-diisopropylethylamine (DIPEA), triphenylmethyl chloride, *p*-anisylchlorodiphenylmethane, 4,4'-dimethoxytriphenylmethyl chloride and tetrahydrofuran (THF) were purchased from ACROS. α- And β-CD were dried at 80 °C under vacuum before use. THF was dried by distillation over sodium and benzophenone before use. Phthalimide, diethyl azodicarboxylate, tolylene-2,4-diisocyanate (TDI), *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were purchased from Aldrich. Phthalimide was recrystallized from ethanol before use. DMF was dried by distillation over P_2O_5 before use and DMSO was dried over 3 Å molecular sieves before use. Hydrazine hydrate was purchased from Fluka. The water used for the threading experiments was 18 MΩ ultra pure water obtained from an Elga Maxima water purification system. Column chromatography was carried out with silica gel (230-240 mesh ASTM, Merck).

α,ω-bis-amine-terminated poly(ethylene glycol) (1)

α,ω-Bis-amine-terminated poly(ethylene glycol) (PEG-BA) was synthesized from PEG ($\overline{M_n}$ = 2,000 g.mol^{-1}) according to a procedure described by Pillai *et al.*[32] PEG (5.00 g; 2.50 mmol) was dissolved in 50 ml THF. Triphenylphosphine (1.97 g; 7.51 mmol) and phthalimide (1.10 g; 7.48 mmol) were added and the mixture stirred for 15 min. Diethyl azodicarboxylate (1.31 g; 7.52 mmol) was dissolved in 15 ml THF. This solution was added drop-wise in 30 min to the reaction mixture, which was then stirred at room temperature for 2.5 h. The reaction mixture was evaporated. 73 ml H_2O was added to the residue. The solid insoluble in H_2O was removed by centrifugation (7,500 rpm) and the solid washed with 2 × 25 ml H_2O. The product was precipitated from the supernatant by adding 44 g NaCl. The precipitate was collected by centrifugation (7,500 rpm) and the precipitate was washed with brine and acetone. The acetone supernatant was evaporated (= product fraction 1 = 2.06 g). 42 g KBr was added to the NaCl supernatant. The precipitate was collected by centrifugation (7,500 rpm) and the solid was washed with acetone. The acetone supernatant was concentrated and extracted with CH_2Cl_2/H_2O. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated (= product fraction 2 = 1.61 g). The NaCl/KBr supernatant was evaporated and the residue was washed with CH_2Cl_2. The CH_2Cl_2 was evaporated (= product fraction 3 = 0.33 g). The three product fractions were combined (total amount of product = 4.00 g). The product is obtained as a white solid. This is used without further purification in the second step. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (d, 2H × 2, aromatic CH next to C=O of phthalimide), 7.69 (d, 2H × 2, aromatic CH opposite to C=O of phthalimide), 3.84 (t, 2H × 2, CH_2 next to phthalimide in 1st and last PEG repeating unit), 3.68 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 3.58 (s, 4H × 45, CH_2's of PEG). TLC [CH_2Cl_2:MeOH (7:1)]: Rf = 0.64.

α,ω-Bis-phthalimide-terminated PEG (4.00 g), hydrazine hydrate (0.50 ml) and 55 ml absolute ethanol were refluxed for 26 h. Upon cooling to room temperature a precipitate was formed. The precipitate was removed by centrifugation (7,500 rpm). The supernatant was evaporated and the residue was dissolved in 25 ml $CHCl_3$. The product was precipitated by drop-wise addition of 258 ml ether. The precipitate was collected by centrifugation (7,500 rpm) and the solid was dried under vacuum to yield pure PEG-BA (2.04 g; 1.02 mmol) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.60 (s, 4H × 43, CH_2's of PEG), 3.50 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.84 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit). ^{1}H-NMR indicated, the conversion to amine end-groups was 100 %. TLC [CH_2Cl_2:MeOH:NH_3 (20:4:1)]: Rf = 0.64. Overall yield of the synthesis of α,ω-bis-amine-terminated PEG is 41 %.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (2) (standard)

α-CD (5.71 g; 5.87 mmol) was dissolved in 39 ml H_2O at 60 °C. PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate was formed. Extra α-CD (0.72 g; 0.74 mmol) was added and the dispersion was stirred at 60 °C for 30 min. The dispersion was ultrasonically agitated at room temperature for 10 min and the dispersion was left undisturbed at room temperature for 1 h. A white pellet was obtained after centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 100 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 20, O^{2}H of α-CD), 5.45 (s, 6H × 20, O^{3}H of α-CD), 4.80 (d, 6H × 20, C^{1}H of α-CD), 4.50 (t, 6H × 20, O^{6}H of α-CD), 3.79 (t, 6H × 20, C^{3}H of α-CD), 3.55−3.71 (m, 12H × 20, C^{6}H, C^{5}H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 20, C^{2}H, C^{4}H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^{1}H and the CH_2's of PEG revealed a number of approximately 20 CD's/polymer chain.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (3) (longer time)

α-CD (5.71 g; 5.87 mmol) was dissolved in 39 ml H_2O at 60 °C. PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate was formed. Extra α-CD (0.72 g; 0.74 mmol) was added and the dispersion was stirred at 60 °C for 1 h. The dispersion was ultrasonically agitated at room temperature for 30 min and the dispersion was left undisturbed at room temperature overnight. A white pellet was obtained after centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 95 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 18,

O^2H of α-CD), 5.45 (s, 6H × 18, O^3H of α-CD), 4.80 (d, 6H × 18, C^1H of α-CD), 4.50 (t, 6H × 18, O^6H of α-CD), 3.79 (t, 6H × 18, C^3H of α-CD), 3.55−3.71 (m, 12H × 18, C^6H, C^5H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 18, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 18 CD's/polymer chain.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (4) (shorter time)

α-CD (5.71 g; 5.87 mmol) was dissolved in 39 ml H_2O at 60 °C. PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate was formed. Extra α-CD (0.72 g; 0.74 mmol) was added and the dispersion was cooled to room temperature in an ice bath. A white pellet was obtained after centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 90 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 20, O^2H of α-CD), 5.45 (s, 6H × 20, O^3H of α-CD), 4.80 (d, 6H × 20, C^1H of α-CD), 4.50 (t, 6H × 20, O^6H of α-CD), 3.79 (t, 6H × 20, C^3H of α-CD), 3.55−3.71 (m, 12H × 20, C^6H, C^5H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 20, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 20 CD's/polymer chain.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (5) (room temperature)

α-CD (5.71 g; 5.87 mmol) was dissolved in 39 ml H_2O at room temperature. PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O at room temperature. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate was formed. Extra α-CD (0.72 g; 0.74 mmol) was added and the mixture stirred at room temperature for 30 min. The mixture was ultrasonically agitated at room temperature for 10 min and the reaction mixture was left undisturbed at room temperature for 1 h. The white precipitate was collected by centrifugation (7,500 rpm) and dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 98 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 20, O^2H of α-CD), 5.45 (s, 6H × 20, O^3H of α-CD), 4.80 (d, 6H × 20, C^1H of α-CD), 4.50 (t, 6H × 20, O^6H of α-CD), 3.79 (t, 6H × 20, C^3H of α-CD), 3.55−3.71 (m, 12H × 20, C^6H, C^5H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 20, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 20 CD's/polymer chain.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (6) (80 °C)

α-CD (5.71 g; 5.87 mmol) was dissolved in 39 ml H_2O at 80 °C. PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate was formed. Extra α-CD (0.72 g; 0.74 mmol) was added and the mixture was stirred at 80 °C for 30 min. The mixture was ultrasonically agitated at 80 °C for 10 min and the reaction mixture was left undisturbed at 80 °C for 1 h. A white pellet was obtained after centrifugation (7,500 rpm) and dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 100 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 20, O^2H of α-CD), 5.45 (s, 6H × 20, O^3H of α-CD), 4.80 (d, 6H × 20, C^1H of α-CD), 4.50 (t, 6H × 20, O^6H of α-CD), 3.79 (t, 6H × 20, C^3H of α-CD), 3.55−3.71 (m, 12H × 20, C^6H, C^5H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 20, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 20 CD's/polymer chain.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (7) (gradually added cyclodextrin)

PEG-BA **1** (0.50 g; 0.25 mmol) was dissolved in 5.0 ml H_2O. α-CD (5.70 g; 5.86 mmol) dissolved in 38 ml H_2O was added in 19 equal portions over a period of 5 h. Extra α-CD (0.72 g; 0.74 mmol) was added and the mixture was stirred at 60 °C for 30 min. The mixture was ultrasonically agitated at room temperature for 10 min and the reaction mixture was left undisturbed at room temperature for 1 h. A white pellet was obtained after centrifugation (7,500 rpm) and dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 85 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 22, O^2H of α-CD), 5.45 (s, 6H × 22, O^3H of α-CD), 4.80 (d, 6H × 22, C^1H of α-CD), 4.50 (t, 6H × 22, O^6H of α-CD), 3.80 (t, 6H × 22, C^3H of α-CD), 3.52−3.71 (m, 12H × 22, C^6H, C^5H of α-CD), 3.50 (s, 4H × 45, CH_2's of PEG), 3.24−3.43 (m, 12H × 22, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 22 CD's/polymer chain.

β-CD/α,ω-bis-amine-terminated poly(propylene glycol) pseudo-polyrotaxane (8)

β-CD (918 mg; 0.809 mmol) was dissolved in 50 ml H_2O at 60 °C. PPG-BA (60 mg; $3.0.10^{-2}$ mmol) was dissolved in 0.3 ml MeOH and 0.3 ml H_2O. The PPG-BA solution was slowly added to the β-CD solution. Immediately a white precipitate was formed. Extra β-CD (50 mg; $4.4.10^{-2}$ mmol) was added and the dispersion was stirred at 60 °C for 1 h. The dispersion was ultrasonically agitated at room temperature for 20 min and the dispersion

was left undisturbed at room temperature overnight. A white pellet was obtained after centrifugation (7,500 rpm) and dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 100 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.57 (d, 7H × 17, O^2H of β-CD), 5.50 (s, 7H × 17, O^3H of β-CD), 4.85 (d, 7H × 17, C^1H of β-CD), 4.48 (t, 7H × 17, O^6H of β-CD), 3.54−3.75 (m, 21H × 17, C^3H, C^6H, C^5H of β-CD), 3.23−3.50 (m, 3H × 34 + 14H × 17, CH_2's and CH's of PPG, C^2H, C^4H of β-CD), 1.03 (t, 3H × 34, CH_3's of PPG). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H of β-CD and the CH_3's of PPG revealed a number of approximately 17 CD's/polymer chain.

α,ω-Bis-2,4-dinitrophenyl-terminated poly(ethylene glycol) (9)

PEG-BA (100 mg; $5.00.10^{-2}$ mmol) was dissolved in 0.5 ml DMF. DIPEA (26 µl; 19 mg; 0.15 mmol) and DNFB (1.042 g; 5.599 mmol) were added. The mixture was stirred at room temperature for 3h. The reaction mixture was evaporated. The residue was dissolved in $CHCl_3$ and the product was precipitated with ether. The solid was washed with ether and the solid was dried under vacuum yielding the product as yellow oil with a yield of 80 %. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.08 (s, 1H × 2, aromatic CH's at position 3), 8.20 (d, 1H × 2, aromatic CH's at position 4), 6.92 (d, 1H × 2, aromatic CH's at position 5), 3.78 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 3.61 (s, 4H × 43, CH_2's of PEG), 3.08 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit). TLC [CH_2Cl_2:MeCN (3:7)]: Rf = 0.71. UV−Vis: 342 nm.

α,ω-Bis-triphenylmethyl-terminated poly(ethylene glycol) (10)

PEG-BA (100 mg; $5.00.10^{-2}$ mmol) was dissolved in 0.5 ml DMF. DIPEA (26 µl; 19 mg; 0.15 mmol) and triphenylmethyl chloride (42 mg; 0.15 mmol) were added. The mixture was stirred at room temperature for 3h. The reaction mixture was extracted with CH_2Cl_2/H_2O to which some $NaHCO_3$ was added. The CH_2Cl_2 phase was dried over $MgSO_4$ and concentrated. Column chromatography [SiO_2, $CHCl_3$:EtOH:DIPEA (150:10:1)] yielded the product as a light yellow oil with a yield of 90 %. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, 6H × 2, phenyl CH's closest to methyl), 7.22−7.35 (m, 9H × 2, other aromatic CH's), 3.60 (s, 4H × 43, CH_2's of PEG), 3.36 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.74 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit). TLC [CH_2Cl_2:MeCN (3:7)]: Rf = 0.71.

α,ω-Bis-4,4'-dimethoxytriphenylmethyl-terminated poly(ethylene glycol) (11)

4,4'-dimethoxytriphenylmethyl chloride (25 mg; $7.3.10^{-2}$ mmol) was dissolved in 1.2 ml DMF. DIPEA (25 µl; 19 mg; 0.14 mmol) and PEG-BA (50 mg; $2.5.10^{-2}$ mmol) were added. The mixture was stirred at room temperature for 3h. The product was precipitated by

ether and collected by centrifugation (10,000 rpm). The solid was washed with ether. This yielded the product as a light yellow solid (100 %). ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.20−7.26 (m, 3H × 2, aromatic C_3H, C_4H and C_5H in phenyl ring without methoxy group), 7.11 (d, 6H × 2, aromatic CH's closest to methyl), 6.77 (d, 4H × 2, CH's next to methoxy group), 3.74 (s, 6H × 2, methoxy groups), 3.60 (s, 4H × 43, CH_2's of PEG), 3.36 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.74 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit). TLC [$CHCl_3$:MeOH (15:1)]: Rf = 0.88.

Removal of 2,4-dinitrophenyl groups from poly(ethylene glycol) (12)

α,ω-Bis-2,4-dinitrophenyl-terminated PEG **9** (100 mg; $4.30.10^{-2}$ mmol) in 1 ml 6.25 M (aq) NaOH was stirred at 45 °C for 24 h. The reaction mixture was neutralized with 1.00 M (aq) HCl. The solvent was evaporated. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.95 (s, 1 H × 2, aromatic CH's position 3), 8.41 (d, 1H × 2, aromatic CH's position 4), 7.25 (d, 1H × 2, aromatic CH's position 5), 3.60 (s, 4H × 43, CH_2's of PEG), 3.50 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.84 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit).

Removal of triphenylmethyl groups from poly(ethylene glycol) (13)

Triphenylmethyl-terminated PEG **10** (20 mg; $8.9.10^{-3}$ mmol) was dissolved in 1 ml $CDCl_3$. TFA (50 µl; 74 mg; 0.65 mmol) and triphenylsilane (2 mg; 8.10^{-3} mmol) were added. The mixture was stirred at room temperature overnight. A ^{1}H-NMR of the reaction mixture was taken. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.05−7.68 (m, 15H × 2 + 15H, aromatic CH's triphenylmethyl and triphenylsilyl), 3.60 (s, 4H × 43, CH_2's of PEG), 3.50 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.84 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit). TLC [$CHCl_3$:hexane (1:2)]: Rf = 0.84 (triphenylmethane), 0.77 (triphenylsilane), 0.00 (α,ω-bis-amine-terminated poly(ethylene glycol)).

Removal of 4,4'-dimethoxytriphenylmethyl groups from poly(ethylene glycol) (14)

4,4'-Dimethoxytriphenylmethyl-terminated PEG **11** (40 mg; $1.5.10^{-2}$ mmol) was dissolved in 2 ml DMSO-d_6. TFA (1 µl; 2 mg; 8.10^{-3} mmol) and triisopropylsilane (12 µl; 9.3 mg; $5.9.10^{-2}$ mmol) were added and the mixture stirred at room temperature for 15 min. Of this reaction mixture a ^{1}H-NMR spectrum was taken. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 7.41−7.54 (m, 3H × 2, aromatic C_3H, C_4H and C_5H of phenyl group without methoxy group in triphenylmethane), 7.24 (d, 6H × 2, aromatic CH's closest to methyl in triphenylmethane), 7.02 (d, 4H × 2, CH's next to methoxy group in triphenylmethane), 3.72 (s, 6H × 2, methoxy groups), 3.60 (s, 4H × 43, CH_2's of PEG), 3.50 (t, 2H × 2, CH_2 next to O in 1st and last PEG repeating unit), 2.84 (t, 2H × 2, CH_2 next to amine in 1st and last PEG repeating unit).

2,4-dinitrofluorobenzene and α-CD (15)

α-CD (100 mg; 0.103 mmol), DNFB (345 mg; 1.85 mmol) and DIPEA (323 µl; 240 mg; 1.85 mmol) in 0.2 ml DMF were stirred at room temperature overnight. Ether was added to the reaction mixture and the solid formed washed with ether yielding a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.53 (d, 6H, O^2H of α-CD), 5.45 (s, 6H, O^3H of α-CD), 4.80 (s, 6H, C^1H of α-CD), 4.50 (t, 6H, O^6H of α-CD), 3.78 (t, 6H, C^3H of α-CD), 3.54−3.72 (m, 12H, C^6H, C^5H of α-CD), 3.23−3.44 (m, 12H, C^2H, C^4H of α-CD). TLC [H_2O:MeOH (1:1)]: Rf = 0.85. Compare with pure α-CD: ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H, O^2H of α-CD), 5.44 (s, 6H, O^3H of α-CD), 4.80 (s, 6H, C^1H of α-CD), 4.48 (t, 6H, O^6H of α-CD), 3.77 (t, 6H, C^3H of α-CD), 3.52−3.72 (m, 12H, C^6H, C^5H of α-CD), 3.22−3.42 (m, 12H, C^2H, C^4H of α-CD). TLC [H_2O:MeOH (1:1)]: Rf = 0.85. When this reaction is performed at 80 °C, the product obtained shows peaks in the aromatic area of the ^{1}H-NMR spectrum, a UV visible spot on TLC at higher Rf value and a peak in the UV−Vis spectrum.

α-CD and triphenylmethyl chloride (16)

α-CD (100 mg; 0.103 mmol) was dissolved in 0.2 ml DMF. DIPEA (323 µl; 240 mg; 1.85 mmol) and triphenylmethyl chloride (517 mg; 1.85 mmol) were added. The mixture was stirred at room temperature overnight. Ether was added to the reaction mixture and the solid formed washed with ether yielding a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.54 (d, 6H, O^2H of α-CD), 5.40 (s, 6H, O^3H of α-CD), 4.84 (s, 6H, C^1H of α-CD), 4.48 (t, 6H, O^6H of α-CD), 3.74 (t, 6H, C^3H of α-CD), 3.52−3.71 (m, 12H, C^6H, C^5H of α-CD), 3.27−3.42 (m, 12H, C^2H, C^4H of α-CD). TLC [H_2O:MeOH (1:1)]: Rf = 0.85. Compare with pure α-CD: ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H, O^2H of α-CD), 5.44 (s, 6H, O^3H of α-CD), 4.80 (s, 6H, C^1H of α-CD), 4.48 (t, 6H, O^6H of α-CD), 3.77 (t, 6H, C^3H of α-CD), 3.52−3.72 (m, 12H, C^6H, C^5H of α-CD), 3.22−3.42 (m, 12H, C^2H, C^4H of α-CD). TLC [H_2O:MeOH (1:1)]: Rf = 0.85. When this reaction is performed at 80 °C, the product obtained shows peaks in the aromatic area of the ^{1}H-NMR spectrum and a UV visible spot on TLC at higher Rf value.

α-CD/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxane (17)

α-CD/PEG pseudo-polyrotaxane (4.10 g; 0.191 mmol), DNFB (6.77 g; 36.4 mmol) and DIPEA (0.13 ml; 0.10 g; 0.75 mmol) were mixed in 49 ml DMF and stirred at room temperature for 2 h. The product was precipitated by adding ether. The solid was washed with ether, dried under vacuum and dissolved in 37 ml DMSO. Adding 160 ml H_2O precipitated the product. The precipitate was washed with H_2O, MeOH and acetone. The solid was dried under vacuum and the solid was dissolved in 48 ml DMSO. Adding 94 ml MeOH precipitated the product. The precipitate was washed with ether. The solid was dried

under vacuum and dissolved in 57 ml DMSO. The product was precipitated by the addition of 200 ml H_2O. The precipitate was washed with acetone and dried under vacuum. The solid was dissolved in DMSO. Adding acetone yielded the pure polyrotaxane (30 %) as a yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.55 (s, 6H × 20, O^2H of α-CD), 5.43 (s, 6H × 20, O^3H of α-CD), 4.80 (d, 6H × 20, C^1H of α-CD), 4.49 (s, 6H × 20, O^6H of α-CD), 3.52−3.87 (m, 18H × 20, C^3H, C^6H, C^5H of α-CD), 3.52 (s, 4H × 45, CH_2's of PEG), 3.11−3.50 (m, 12H × 20, C^2H, C^4H of α-CD).

α-CD/poly(ethylene glycol)/triphenylmethyl polyrotaxane (18)

α-CD/PEG pseudo-polyrotaxane (400 mg; $1.87.10^{-2}$ mmol), triphenylmethyl chloride (354 mg; 1.27 mmol) and DIPEA (221 µl; 164 mg; 1.27 mmol) in 10 ml DMF were stirred at room temperature for 2 h. Adding ether precipitated the product. The solid was washed with ether, dried under vacuum and dissolved in 2.5 ml DMSO. Adding 20 ml H_2O precipitated the product. The precipitate was washed with H_2O, MeOH and acetone. The solid was dried under vacuum and dissolved in 2.5 ml DMSO. Adding 13 ml MeOH precipitated the product. The precipitate was washed with ether yielding the pure polyrotaxane (39 %) as a beige solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.56 (s, 6H × 15, O^2H of α-CD), 5.44 (s, 6H × 15, O^3H of α-CD), 4.82 (s, 6H × 15, C^1H of α-CD), 4.50 (s, 6H × 15, O^6H of α-CD), 3.57−3.90 (m, 18H × 15, C^3H, C^6H, C^5H of α-CD), 3.54 (s, 4H × 45, CH_2's of PEG), 3.06−3.24 (m, 12H × 15, C^2H, C^4H of α-CD).

α-CD/poly(ethylene glycol)/*p*-anisyldiphenylmethyl polyrotaxane (19)

α-CD/PEG pseudo-polyrotaxane (400 mg; $1.87.10^{-2}$ mmol), *p*-anisylchlorodiphenylmethane (392 mg; 1.27 mmol) and DIPEA (221 µl; 164 mg; 1.27 mmol) in 10 ml DMF were stirred at room temperature for 2 h. Adding ether precipitated the product. The solid was washed with ether, dried under vacuum and dissolved in 2.5 ml DMSO. Adding 20 ml H_2O precipitated the product. The precipitate was washed with H_2O, MeOH and acetone. The solid was dried under vacuum and dissolved in 2.5 ml DMSO. Adding 13 ml MeOH precipitated the product. The precipitate was washed with ether. The pure polyrotaxane was obtained as a beige solid with a yield of 40 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.56 (s, 6H × 15, O^2H of α-CD), 5.44 (s, 6H × 15, O^3H of α-CD), 4.82 (s, 6H × 15, C^1H of α-CD), 4.50 (s, 6H × 15, O^6H of α-CD), 3.57−3.90 (m, 18H × 15, C^3H, C^6H, C^5H of α-CD), 3.54 (s, 4H × 45, CH_2's of PEG), 3.06−3.24 (m, 12H × 15, C^2H, C^4H of α-CD).

α-CD/poly(ethylene glycol)/4,4'-dimethoxytriphenylmethyl polyrotaxane (20)

α-CD/PEG complex (400 mg; $1.87.10^{-2}$ mmol), 4,4'-dimethoxytriphenylmethyl chloride (430 mg; 1.27 mmol) and DIPEA (221 µl; 164 mg; 1.27 mmol) in 10 ml DMF were stirred

at room temperature for 2 h. Adding ether precipitated the product. The solid was washed with ether and dried under vacuum. The solid was dissolved in 2.5 ml DMSO. Adding 20 ml H_2O precipitated the product. The precipitate was washed with H_2O, MeOH and acetone. The solid was dried under vacuum and dissolved in 2.5 ml DMSO. Adding 13 ml MeOH precipitated the product. The precipitate was washed with ether yielding the pure polyrotaxane (39 %) as a beige solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 15, O^2H of α-CD), 5.44 (d, 6H × 15, O^3H of α-CD), 4.80 (d, 6H × 15, C^1H of α-CD), 4.51 (t, 6H × 15, O^6H of α-CD), 3.63−3.84 (m, 18H × 15, C^3H, C^6H, C^5H of α-CD), 3.58 (s, 4H × 45, CH_2's of PEG), 3.37−3.56 (m, 12H × 15, C^2H, C^4H of α-CD).

Filled α-CD molecular tube (TF 21)
(standard)

α-CD molecular tubes were synthesized according to a procedure reported by the group of Harada.[10] Some steps were slightly modified. Polyrotaxane **17** (1.00 g; $4.59.10^{-2}$ mmol) was dissolved in 35 ml 2.50 M (aq) NaOH. Epichlorohydrin (7.00 ml; 89.5 mmol) was added in 7 equal portions over a period of 2h. 0.800 ml 2.5 M (aq) NaOH was added. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was neutralized with 1.00 M (aq) HCl. The mixture was centrifuged (7,500 rpm) and the supernatant evaporated. The residue was dissolved in 22 ml H_2O and adding 200 ml acetone precipitated the product. The product was isolated by centrifugation (7,500 rpm) and dried over P_2O_5 under vacuum. 50 ml DMSO was added to the solid and the dispersion was centrifuged (7,500 rpm). Adding 300 ml ether and a small amount of MeOH to the supernatant precipitated the product. The solid was collected by centrifugation (7,500 rpm) and washed with ether. Finally the solid was dried under vacuum and further by SEC. The high molecular weight fraction was collected and evaporated. The product was obtained as yellow solid with a yield of 80 %. ^{1}H-NMR (300 MHz, D_2O, 25 °C): δ = 5.22 (s, C^1H' of α-CD), 5.08 (s, C^1H of α-CD), 3.79−4.17 (broad, C^3H, C^6H, C^5H of α-CD), 3.73 (s, 4H × 45, CH_2's of PEG), 3.46−3.70 (broad, C^2H, C^4H of α-CD, CH and CH_2's of crosslink).

Filled α-CD molecular tube (TF 22)
(longer reaction time)

Polyrotaxane **17** (1.00 g; $4.59.10^{-2}$ mmol) was dissolved in 35 ml 2.50 M (aq) NaOH. Epichlorohydrin (7.00 ml; 89.5 mmol) was added in 7 equal portions over a period of 2h. 0.800 ml 2.5 M (aq) NaOH was added. The reaction mixture was stirred at room temperature for 140 h. The reaction mixture was neutralized with 1.00 M (aq) HCl. The mixture was centrifuged (7,500 rpm) and the supernatant evaporated. The residue was dissolved in 30 ml H_2O and adding 257 ml acetone precipitated the product. The product was isolated by centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under

vacuum. 100 ml DMSO was added to the solid and the dispersion centrifuged (7,500 rpm). Adding 250 ml ether and a small amount of MeOH to the supernatant precipitated the product. The solid was collected by centrifugation (7,500 rpm) and washed with ether. Finally the solid was dried under vacuum and further purified by SEC. The high molecular weight fraction was collected and evaporated. The product was obtained as yellow solid with a yield of 40 %. ^{1}H-NMR (300 MHz, D_2O, 25 °C): δ = 5.24 (s, C^1H' of α-CD), 5.08 (s, C^1H of α-CD), 3.80−4.18 (broad, C^3H, C^6H, C^5H of α-CD), 3.76 (s, 4H × 45, CH_2's of PEG), 3.52−3.73 (broad, C^2H, C^4H of α-CD, CH and CH_2's of crosslink).

Filled α-CD molecular tube (TF 23)
(less epichlorohydrin, no additional NaOH)

Polyrotaxane **17** (1.00 g; $4.59.10^{-2}$ mmol) was dissolved in 35 ml 2.50 M (aq) NaOH. Epichlorohydrin (6.00 ml; 76.7 mmol) was added in 7 equal portions over a period of 2h and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was neutralized with 1.00 M (aq) HCl. The mixture was centrifuged (7,500 rpm) and the supernatant was evaporated. The residue was dissolved in 20 ml H_2O and the product was precipitated by the addition of 150 ml acetone. The product was collected by centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under vacuum. 25 ml DMSO was added to the solid and the dispersion was centrifuged (7,500 rpm). 100 ml ether and a small amount of MeOH were added to the supernatant to precipitate the product. The solid was collected by centrifugation (7,500 rpm) and was washed with ether. Finally, the solid was dried under vacuum and was further purified by SEC. The high molecular weight fraction was collected and evaporated. The product was obtained as yellow solid with a yield of 54 %. ^{1}H-NMR (300 MHz, D_2O, 25 °C): δ = 5.25 (s, C^1H' of α-CD), 5.06 (s, C^1H of α-CD), 3.82−4.15 (broad, C^3H, C^6H, C^5H of α-CD), 3.74 (s, 4H × 45, CH_2's of PEG), 3.55−3.71 (broad, C^2H, C^4H of α-CD, CH and CH_2's of crosslink).

Filled α-CD molecular tube (24)
(TDI connections)

Polyrotaxane **17** (100 mg; $4.59.10^{-3}$ mmol) was dissolved in 4 ml DMSO. TDI (120 µl; 0.841 mmol) was added in 7 equal portions over a period of 2h. The reaction mixture was stirred at room temperature for 24 h in which period a precipitate was formed. This precipitate appeared to be insoluble.

α-CD molecular tube (TE 25)

The filled α-CD molecular tubes TF (0.500 g; $1.69.10^{-2}$ mmol) were dissolved in 5.0 ml 6.25 M (aq) NaOH and stirred at 45 °C for 24 h to remove the 2,4-dinitrophenyl groups. The reaction mixture was neutralized with 1.00 M (aq) HCl. The solvent was evaporated

and 40 ml DMSO was added to the residue. The dispersion was centrifuged (7,500 rpm) and the product was precipitated from the supernatant by adding 200 ml ether. The solid was washed with ether and dried under vacuum. SEC finally yielded pure α-CD molecular tubes. The high molecular weight fraction was collected and evaporated. The product was obtained as beige solid with a yield of 60 %. ^{1}H-NMR (300 MHz, D_2O, 25 °C): δ = 5.24 (s, C^1H' of α-CD), 5.08 (s, C^1H of α-CD), 3.81−4.22 (broad, C^3H, C^6H, C^5H of α-CD), 3.48−3.74 (broad, C^2H, C^4H of α-CD, CH and CH_2's of crosslink).

Table 2.2. *Different types of filled- and empty tubes obtained depending on the procedures used for the threading or the crosslink reaction.*

Threading procedure		Crosslink procedure		Filled tube	Empty tube
Number	Description	Number	Description		
2	60 °C / 30 min	**21**	2000 eq / 48 h	**21**	**25**
3	60 °C / 60 min	**21**	2000 eq / 48 h	**26**	**27**
4	60 °C / 1 min	**21**	2000 eq / 48 h	**28**	**29**
5	25 °C / 30 min	**21**	2000 eq / 48 h	**30**	**31**
6	80 °C / 30 min	**21**	2000 eq / 48 h	**32**	**33**
7	addition over a period of 5h	**21**	2000 eq / 48 h	**34**	**35**
2	60 °C / 30 min	**22**	2000 eq / 144 h	**22**	**36**
2	60 °C / 30 min	**23**	1500 eq / 48 h	**23**	**37**

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Chapter 3

Characterization of α-cyclodextrin molecular tubes

Abstract

For the application of the empty tubes a characterization was necessary. The polyrotaxanes and the filled α-cyclodextrin molecular tubes were characterized as well.
^{1}H-NMR showed that the pseudo-polyrotaxane and polyrotaxane both contained 20 α-cyclodextrins. This number of cyclodextrins should also be present in the filled tubes. However, it was not possible to determine the number of cyclodextrins in the filled- and empty tube.
Dissolution of the polyrotaxanes in DMSO did give optically clear solutions. However, it was concluded that the compound was aggregated in solution. The filled- and empty tubes were soluble in both H_2O and DMSO, however, in pure solvent these compounds were aggregated as well.
According to AFM, the filled tubes had dimensions close to the expected dimensions. However, the empty tubes were smaller than the filled tubes.
SANS measurements showed that the filled tubes have an elongated shape. If a solid cylinder was fitted to the data of the filled tube, the dimensions of this solid cylinder corresponded to the expected dimensions. Also the molecular weight of this filled tube corresponded to the expectations. The results for the empty α-cyclodextrin molecular tubes were very different compared to the filled tubes. The SANS curves for the empty tubes leveled off to small angles, those for the filled tubes did not. When a hollow cylinder had to be fitted, this cylinder should be shorter then the filled tubes. Also the molecular weight of the empty tubes was lower than expected.
The shorter than expected length of the empty tubes can probably be explained by defects in the orientation of the cyclodextrins threaded on the polymer chain. Different complexation- or crosslink conditions did not supply larger empty tubes.

3.1 Introduction

It is expected that the cyclodextrin molecular tubes, of which the design and synthesis is described in chapter 2, are able to form inclusion compounds just as their building blocks the cyclodextrins, although the complexation properties might be changed. Formation of inclusion compounds by α-cyclodextrin molecular tubes was predicted in the literature based on theoretical considerations.[1]

Since α-cyclodextrin molecular tubes have only been studied sparsely, a drawback for their practical application is their inadequate characterization.[2,3] The complexation of sodium dodecyl sulfate by α-cyclodextrin molecular tubes was recently reported.[4] In chapter 4 of this thesis the complexation of polyaniline in α-cyclodextrin molecular tubes will be described.

In this chapter the characterization of the α-cyclodextrin molecular tubes synthesized, according to the experimental procedures described in chapter 2 and schematically depicted in scheme 2.2, is discussed.[2,5,6] ^{1}H-NMR, UV−Vis, Atomic Force Microscopy (AFM), mass spectrometry (MALDI-TOF) and Small-angle Neutron Scattering (SANS) were used to characterize the α-cyclodextrin molecular tubes obtained. First, AFM and SANS will be explained.

The numbers used for the different filled- and empty tubes synthesized in chapter 2 are explained in table 2.2/table 3.1. The numbers of the procedures refer to the procedures described in § 2.5.

Table 3.1. *Different types of filled- and empty tubes obtained depending on the procedures used for the threading or the crosslink reaction.*

Threading procedure		Crosslink procedure		Filled	Empty
Number	Description	Number	Description	tube	tube
2	60 °C / 30 min	**21**	2000 eq / 48 h	**21**	**25**
3	60 °C / 60 min	**21**	2000 eq / 48 h	**26**	**27**
4	60 °C / 1 min	**21**	2000 eq / 48 h	**28**	**29**
5	25 °C / 30 min	**21**	2000 eq / 48 h	**30**	**31**
6	80 °C / 30 min	**21**	2000 eq / 48 h	**32**	**33**
7	addition over a period of 5h	**21**	2000 eq / 48 h	**34**	**35**
2	60 °C / 30 min	**22**	2000 eq / 144 h	**22**	**36**
2	60 °C / 30 min	**23**	1500 eq / 48 h	**23**	**37**

3.2 Methodologies

For the complexation of guest molecules inside cyclodextrin molecular tubes, the shape and size of the molecular tube is important. Several techniques are used for determining the shape and size of the cyclodextrin molecular tubes. Two of these techniques, Atomic Force Microscopy (AFM) and Small Angle Neutron Scattering (SANS) are explained here. A description of the other characterization techniques used can be found in the literature: proton Nuclear Magnetic Resonance spectroscopy (^{1}H-NMR),[7] Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF),[8,9,10] Ultra-Violet − Visible light spectroscopy (UV−Vis)[7].

3.2.1 Atomic Force Microscopy[11]

In an AFM a sharp tip is attached to the end of a cantilever, which moves relative to the sample in a raster-like manner. Due to the height differences on the sample surface, the cantilever will be deflected up and down. This defection can be monitored by the position of a reflected laser light beam from the cantilever on a detector (figure 3.1). The cantilever deflection is measured by the optical beam deflection method.[12,13] In the "constant force contact mode" the deflection ($V_{A+B} - V_{C+D}$) is kept constant by changing the vertical position of the sample via a feed back system. The "corrections" in vertical position, executed by the system, can be translated directly to height differences i.e. the topography of the surface.

Since the invention of AFM new methods have been developed to determine the surface topography and to obtain details on the nature of the sample's surface. The most used technique for imaging surfaces nowadays is "Tapping Mode".

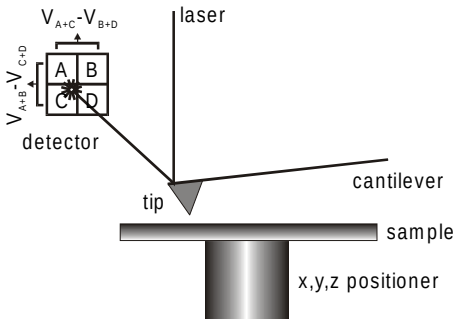

Figure 3.1. *Schematic representation of the principle of an Atomic Force Microscope.*

3.2.1.1 "Tapping Mode"

The principle disadvantage of the "contact mode" in which the tip is moved over the sample, is the physical contact of the tip with the surface. Especially when soft samples are studied, this can lead to severe damage of the sample. The result is poor images, due to the capillary forces between tip and sample. This problem can partially be circumvented, by measuring in a liquid, but this is not always practical or applicable. A better alternative is to measure the soft samples in the "Tapping Mode".

In this mode the cantilever is brought into resonance by a small piezo electric crystal and the amplitude of the oscillation is determined from the reflected laser beam on the detector. Far away from the surface the cantilever resonates freely. When the cantilever is lowered, the amplitude will decrease as soon as the tip interacts with the surface. Because the tip – surface contact time is strongly reduced, damaging of the sample surface can be neglected. Through a feedback system the height of the sample is continuously adapted to maintain the amplitude of the oscillation constant at an initial value (A_i). If while scanning, the tip approaches a feature on the surface higher than the surrounding area, the cantilever's oscillation will be damped (figure 3.2B). To compensate for the reduced amplitude the tip – sample distance will be increased ($h_i + \Delta h$) until the amplitude has reached its original value (figure 3.2C). An image of the surface topology is obtained, by plotting the height changes Δh as a function of the *x*,*y*-position.

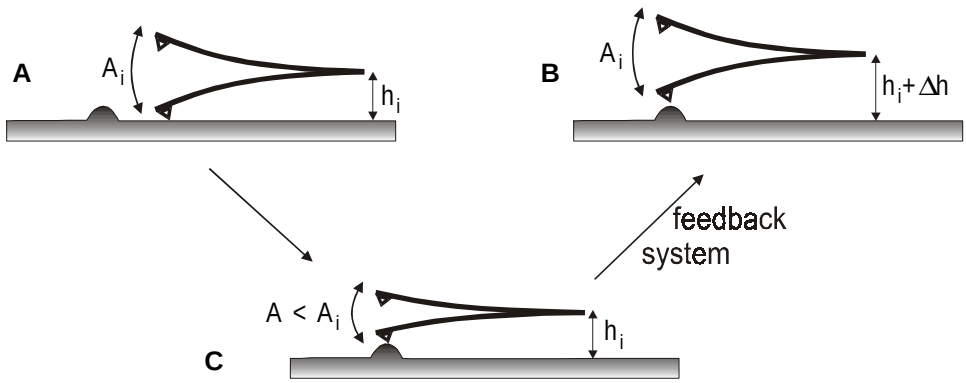

Figure 3.2. *Schematic representation of the feedback system used in "Tapping Mode".*

3.2.2 Small-angle Neutron Scattering

The scattering from dilute solutions of particles allows an analysis in terms of the shape and mass of the particles. Any non-uniformity of the population of particles, e.g. polydispersity, complicates such analysis and comes at the expense of the details to be reliably extracted. Good contrast between particles and medium (solvent) is most easily obtained by using a deuterated solvent. It relies on the large difference in scattering length for neutrons between H and D nuclei. A brief theory will be given here.[14,15] For a suspension of identical particles at low concentration, after removal of scattering contributions due to density fluctuations in the solvent and within the solute particles, the observed intensity $I(q)$ is proportional to the single-particle form factor, $P(q)$, the molar mass of the particle, M, its concentration, c (g.cm^{-3}), and the contrast factor K:

$$I(q) = KcMP(q)\ , \tag{1}$$

where $q = 4\pi\sin\theta/\lambda$, with the full scattering angle equal to 2θ, and λ the neutron wavelength. For particles of uniform density, constant K is conveniently expressed in the values of the scattering length densities ρ (in cm^{-2}) of solute (ρ_1) and solvent (ρ_0):

$$K = \frac{(\rho_1 - \rho_0)^2}{N_A d_1^{\ 2}}\ [\mathrm{cm}^2.\mathrm{mol.g}^{-2}], \tag{2}$$

where N_A is Avogadro's number and d_1 is the density of the solute in g.cm^{-3}. Note that with $\phi_1 = c/d_1$, these expressions can be converted to volume fraction ϕ_1. Values of ρ can be calculated for each substance (solvent, solute) from its atomic composition:

$$\rho = \frac{dN_A \sum_i b_i}{M}\ [\mathrm{cm}^{-2}], \tag{3}$$

where b_i are the atomic scattering lengths, widely tabulated.[16] Since the particle form factor $P(q)$ is normalized to $P(0) = 1$, extrapolation of the intensity to $q = 0$ furnishes the value of M. $P(q)$ itself contains the information about the shape of the solute particle.

The scattering from any uniformly dense particle can be described at smallest angles ($q << 2\pi/R_g$) by the Guinier approximation:

$$I(q) = I(0)e^{\left(\frac{-R_g{}^2 q^2}{3}\right)}. \quad (4)$$

The radius of gyration, R_g, is found from a plot of ln $I(q)$ vs. q^2.
For any rod-like particle with an aspect ratio $L/(2R) > 5$, a separation between length and cross-section scattering can be achieved. At $q > 2\pi/L$, the 1D-character introduces a factor $I_L = q^{-1}$ into the intensity:

$$I(q) = I_L(q)I_c(q) = \frac{I_c(q)}{q}. \quad (5)$$

The cross-section itself can therefore be characterized by R_c, its cross-sectional radius of gyration, in a range $2\pi/L < q < 2\pi/R_c$ via:

$$qI(q) = I_c(0)e^{\left(\frac{-R_c{}^2 q^2}{2}\right)}. \quad (6)$$

Table 3.2. *Number of cyclodextrins in the pseudo-polyrotaxanes depending on the threading procedure.*

Threading procedure		Number of cyclodextrins	Yield
Number	Description		
2	60 °C / 30 min	20	100 %
3	60 °C / 60 min	18	95 %
4	60 °C / 1 min	20	90 %
5	25 ° / 30 min	20	98 %
6	80 °C / 30 min	20	100 %
7	cyclodextrin added in 5 h	22	85 %

3.3 Characterization of α-cyclodextrin molecular tubes

Here the characterization, with several techniques, of the α-cyclodextrin molecular tubes obtained is described.

3.3.1 Determination of the number of cyclodextrins by Proton Nuclear Magnetic Resonance spectroscopy

The ^{1}H-NMR spectra of the pseudo-polyrotaxane, polyrotaxane, filled tube and empty tube are described in § 2.5 after the synthesis of the compounds.
From the ^{1}H-NMR spectra of the pseudo-polyrotaxanes, obtained after mixing poly(ethylene glycol) (2,000 g.mol^{-1}) with α-cyclodextrins, it can be calculated that there are approximately 20 α-cyclodextrins per polymer chain (compound 2 § 2.5) (figure 3.3 and figure 3.4). This leads to a value of 2.2 monomer units per cyclodextrin. The pseudo-polyrotaxanes obtained when using the different complexation procedures described in § 2.5 do not contain a significantly different number of cyclodextrins (table 3.2).

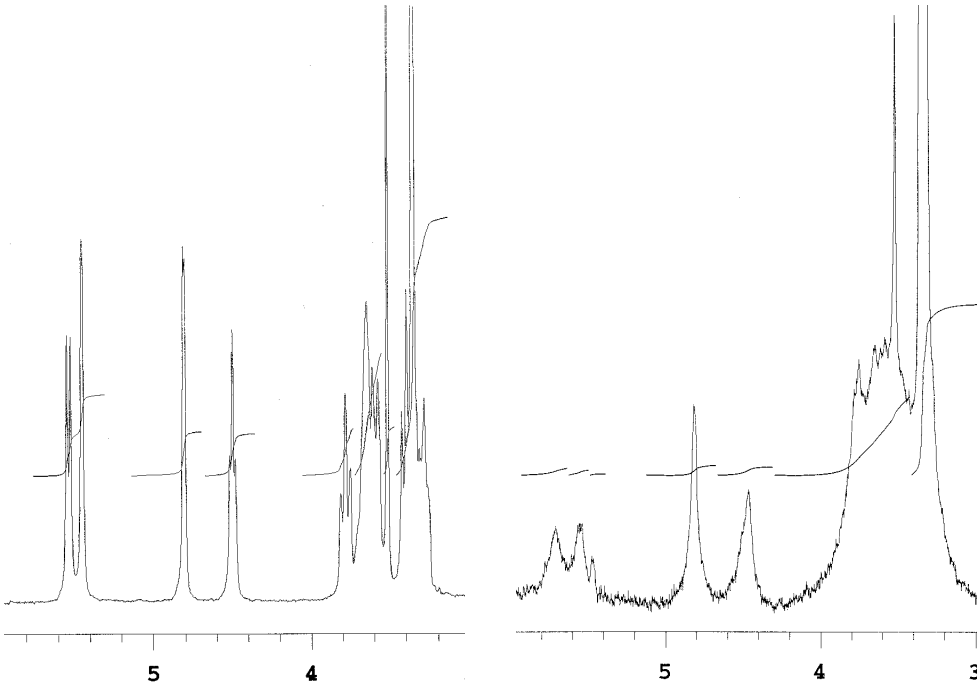

Figure 3.3. *Partial ^{1}H-NMR spectrum of pseudo-polyrotaxane (left) and polyrotaxane (right) both in DMSO-d_6.*

Figure 3.4. *Partial ^{1}H-NMR spectrum of pseudo-polyrotaxane (left), filled tube (middle) and empty tube (right) all in D_2O.*

It is difficult to determine the number of cyclodextrins in the obtained polyrotaxanes. ^{1}H-NMR spectra are broadened due to the rotaxane structure and the fact that the products obtained are polymeric products (figure 3.3). This causes substantial peak broadening which complicates the correct interpretation of the peak integrals. To solve the problem of peak broadening, the blocking groups were removed under basic reaction conditions from a sample of pure polyrotaxane and the mixture obtained was examined by ^{1}H-NMR. In this case the spectrum contains all the individual components and the ratio of the integrals of the cyclodextrin and polymer peaks was used to calculate the ratio of cyclodextrin to polymer. A value of 19 cyclodextrins/polymer chain was found for the α-cyclodextrin/poly(ethylene glycol) polyrotaxane **17** (§ 2.5). This corresponds to a value of 2.4 monomer

units/cyclodextrin in the polyrotaxane. So there is no significant evidence that cyclodextrins are unthreaded during the synthesis of the polyrotaxane.[7]
Since there is no possibility for the cyclodextrins to unthread during the crosslink reaction, this number of cyclodextrins will also be present in the filled tubes. Determination of the number of cyclodextrins in the filled tube was, however, difficult since there again is substantial peak broadening (figure 3.4). Removal of the blocking groups and taking a ^{1}H-NMR spectrum of the reaction mixture did not solve the problem in this case. The peaks were still broadened.
The ^{1}H-NMR spectra of the filled α-cyclodextrin molecular tubes show a peak at 5.22 ppm in D_2O. According to the literature the rigidity of the tube can be determined using this peak. According to this literature, this peak corresponds to the C^1H proton with a crosslink attached to a glucose unit.[2] A shift of the C^1H proton, however, can only be due to a crosslink on hydroxyl group 2 (OH_2), since a crosslink attached to OH_3 or OH_6 is too far away to cause a shift on C^1H (see figure 1.1 for the numbering of the carbon atoms in the glucose unit).[7] The assertion in the literature that it is possible to determine the number of crosslinks between the cyclodextrins out of the ratio of the peak due to C^1H and the shifted peak (C^1H') is probably incorrect. Most likely C^1H' is only due to a crosslink attached to OH_2. If there is a crosslink attached to OH_3 or OH_6, probably there will also be a shift for the protons of C^3H and C^6H, respectively. These shifted peaks, however, can not be distinguished from the non-shifted peaks for C^3H and C^6H, since they are underneath the large multiplet between 3.8 and 4.2 ppm (compound **21** § 2.5).
The ^{1}H-NMR spectrum of the empty cyclodextrin molecular tubes resembles that of the filled tubes although there are some small shifts (figure 3.4). As expected, one difference is the absence of the peak due to poly(ethylene glycol).

3.3.2 Detection of the "template polymer" by mass spectroscopy

Using Matrix Assisted Laser Desorption Ionization Time-of-Flight mass spectroscopy (MALI-TOF) it was possible to identify the "template polymer" in polyrotaxane **17** and in filled tube **25** (figure 3.5). In the MALDI-TOF spectrum of the empty tubes (figure 3.6) there are no "template polymer" peaks.
These results indicate the poly(ethylene glycol) "template polymer" is present in polyrotaxane **17** and in filled tube **25**. However, the poly(ethylene glycol) "template polymer" is removed out of the cyclodextrin molecular tube in the last step (the removal of the blocking groups) of scheme 2.2. This means that cyclodextrin molecular tube **25** is an empty tube.

The molecular weight of the compounds themselves could not be determined by MALDI-TOF, probably due to fragmentation of the cyclodextrins in the MALDI procedure. So MALDI-TOF can not be used to determine the number of cyclodextrins in the compounds. It can only be used to proof that the "template polymer" is removed upon going from the filled- to the empty tube.

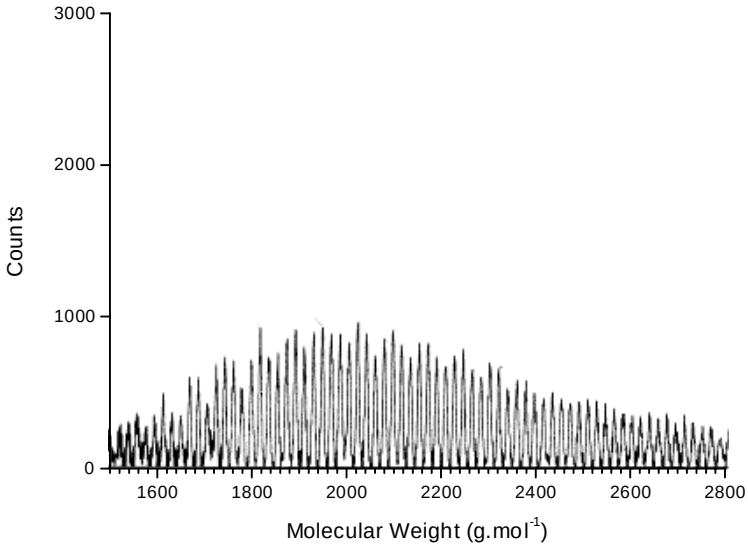

Figure 3.5. *MALDI-TOF spectrum of the filled α-cyclodextrin molecular tube showing the Gaussian distribution of the "template polymer".*

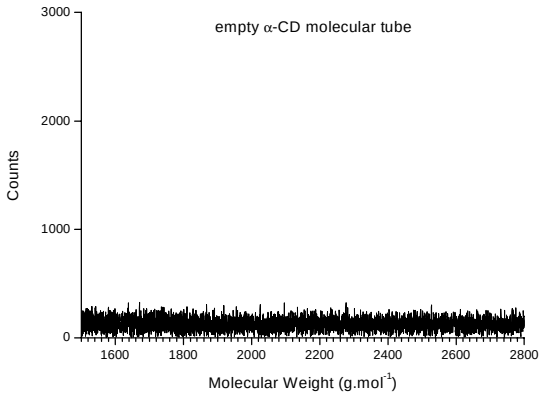

Figure 3.6. *MALDI-TOF spectrum of empty α-cyclodextrin molecular tube showing the absence of the "template polymer".*

3.3.3 Detection of the blocking groups by Ultra-Violet and Visible light spectroscopy

The presence of 2,4-dinitrophenyl groups in the products can be easily identified by UV−Vis spectroscopy. The UV−Vis spectra of the polyrotaxane and the filled tube in spectroscopic grade DMF show a peak at 342 nm due to the 2,4-dinitrophenyl blocking groups (figure 3.7).

The peak is also present in the empty tubes if the synthesis of the polyrotaxane is performed at 80 °C. This seems to be inconsistent with the removal of the "template polymer".[7] The peak is probably due to a reaction of the hydroxyls of the α-cyclodextrins with 2,4-dinitrofluorobenzene. Model reactions showed, that the α-cyclodextrins could react with 2,4-dinitrofluorobenzene at 80 °C, but this reaction was not observed at room temperature (see § 2.3.2.1). If the polyrotaxanes are synthesized using procedure **17** (§ 2.5) (so at room temperature instead of at 80 °C) no peak at 342 nm is observed in the UV−Vis spectra of samples of the empty tubes. This reveals, that the 2,4-dinitrophenyl groups are completely absent in the final empty α-cyclodextrin molecular tubes. No 2,4-dinitrophenyl is attached to the cyclodextrins and the blocking groups have been removed.

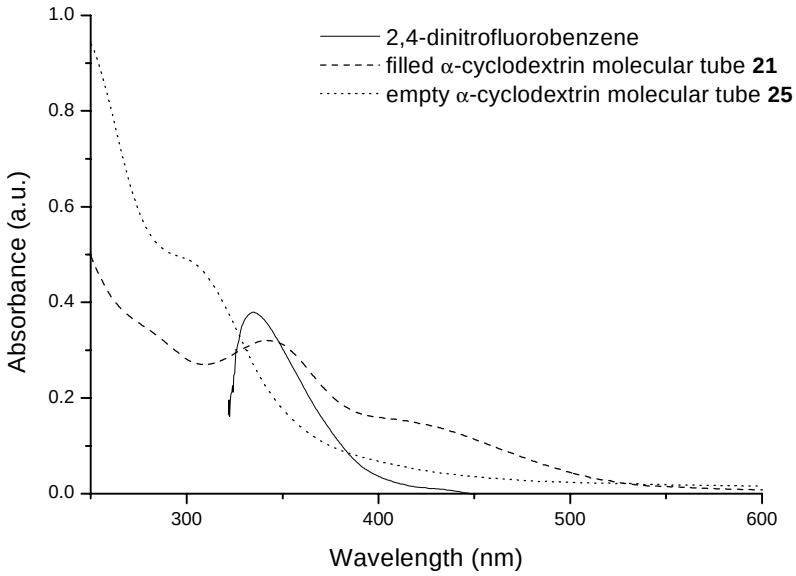

Figure 3.7. *UV−Vis absorption spectrum of 2,4-dinitrofluorbenzene (−), filled cyclodextrin molecular tube **21** (---) and empty cyclodextrin molecular tube **25** (···). All spectra were recorded in DMF.*

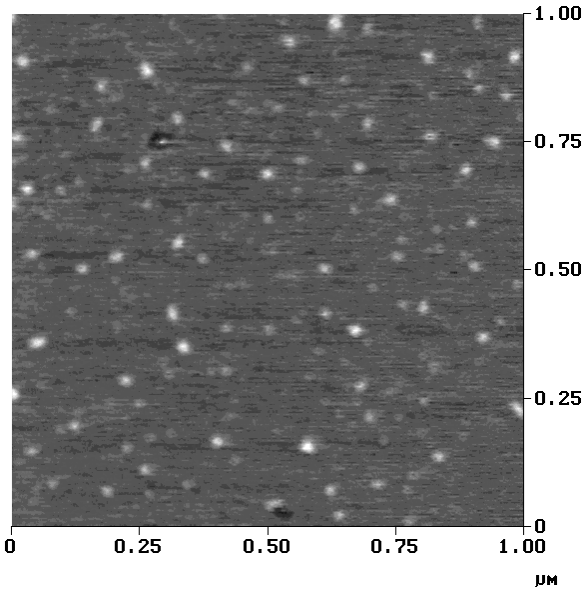

Figure 3.8. *AFM image of multiple isolated filled α-cyclodextrin molecular tubes on mica.*

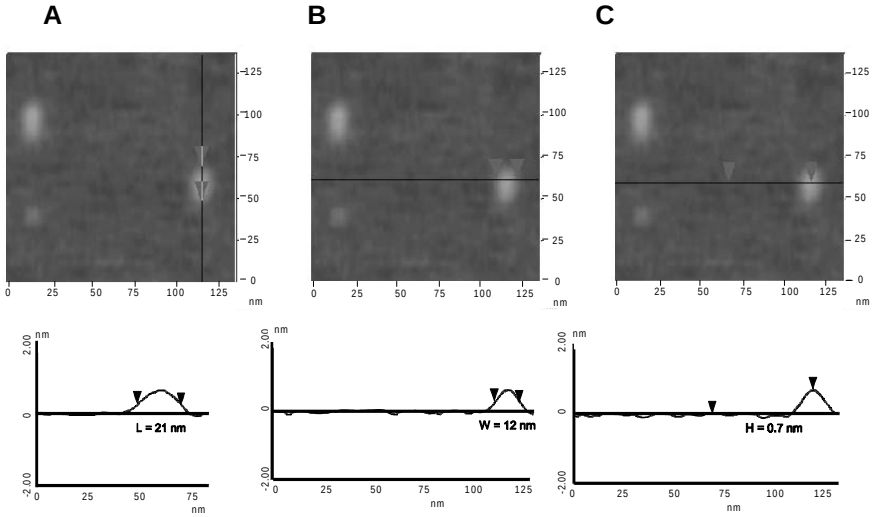

Figure 3.9. *AFM height profiles of one filled α-cyclodextrin molecular tube, showing its length (A), its width (B) and its height (C).*

3.3.4 Visualization of the α-cyclodextrin molecular tubes by Atomic Force Microscopy

Using the previously described characterization techniques it was possible to determine the number of cyclodextrins in the polyrotaxanes and in the filled tubes, it was also possible to determine that the "template polymer" and the blocking groups are present in the filled tube and that they are not present anymore in the empty tube. To obtain information on the shape of the compounds AFM was used.

As surface for the visualization of the compounds by AFM, mica was used. Mica has a polar surface and the compounds adhere to the surface.

Visualization of the polyrotaxanes always showed aggregates on the mica surface. Attempts to break down this aggregation, e.g. by the addition of NMP or urea, ultrasonic agitation and elevation of the sample solution temperature were not successful.

The visualization of the filled tubes (scheme 2.2) is possible. The addition of 0.7 (v/v) % NMP is necessary to break down aggregation. Due to this addition images showing isolated filled α-cyclodextrin molecular tubes (figure 3.8) can be obtained. The features observed are elongated (figure 3.9). According to the traces in the height profiles, the filled α-cyclodextrin molecular tubes are approximately 21 nm long, the width is approximately 12 nm and the height is 0.7 nm (figure 3.9A, B and C respectively). The larger then expected width can be explained by a tip effect. Ultra sharp tips are used with a diameter of less then 10 nm. The results obtained correspond nicely with the expected dimensions when this tip effect is taken into account (figure 2.4).

When the visualization of single empty α-cyclodextrin molecular tubes is attempted again aggregation is observed. These aggregates are present both in pure water and in DMSO samples. Again the addition of a small amount of NMP (0.7 (v/v) %) breaks down aggregation. However, no features are observed at all on the surface anymore.

3.3.5 Determination of the size and shape by Small-Angle Neutron Scattering

Since the empty α-cyclodextrin molecular tubes could not be visualized by AFM a different technique was attempted in order to determine the dimensions of the empty α-cyclodextrin molecular tubes, however, also the α-cyclodextrin/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxanes synthesized according to procedure **17** (§ 2.5) and all the filled α-cyclodextrin molecular tubes were measured. All these compounds give optically clear solutions in DMSO, while filled- and empty α-cyclodextrin molecular tubes are soluble in water as well.

Polyrotaxanes

Dissolution of polyrotaxane **17** in H_2O was found to be impossible.[6,17] For the SANS measurements of polyrotaxane **17**, DMSO-d_6 was used as solvent. Dissolution in DMSO does produce optically clear solutions. SANS experiments, however, showed the presence of very large aggregates in DMSO-d_6. The same result was found before by AFM. Even after filtration through a 0.2 μm filter the scattering rose steeply at the smallest angles, indicating aggregation of **17**, which is probably due to hydrogen bonding between polyrotaxanes. Various treatments, such as heating, ultrasonic agitation and the addition of hydrogen-bond breaking agents (urea, NMP) were attempted to reduce the aggregation.[18] SANS curves from all those samples were not amenable for meaningful evaluation. It was obvious from a comparison with the results obtained on tubes that a single-molecule solution could not be achieved for the polyrotaxane. The SANS results of the polyrotaxanes indicate, the aggregates have the shape of a prolate ellipsoid.

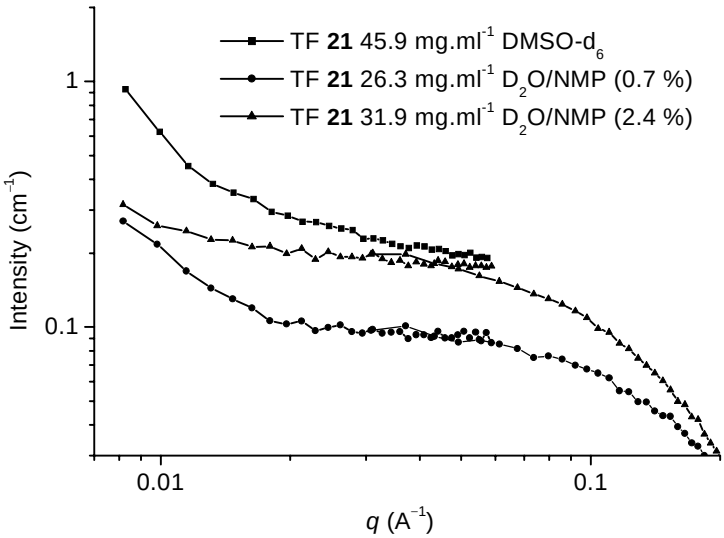

Figure 3.10. *Small-angle neutron scattering data (log−log) of filled tube **21** in DMSO-d_6 (−■−), in D_2O/NMP 0.7 (v/v) % NMP (−●−) and D_2O/NMP 2.4 (v/v) % NMP (−▲−).*

Filled α-cyclodextrin molecular tubes

The tubes obtained after the crosslinking of the α-cyclodextrins in the polyrotaxanes appeared to be soluble in DMSO as well as H_2O.[2] Though optically clear solutions are obtained in both solvents, aggregate formation is obvious from the SANS curves of samples of **21** (§ 2.5 and table 2.2) dissolved in DMSO-d_6 or D_2O.

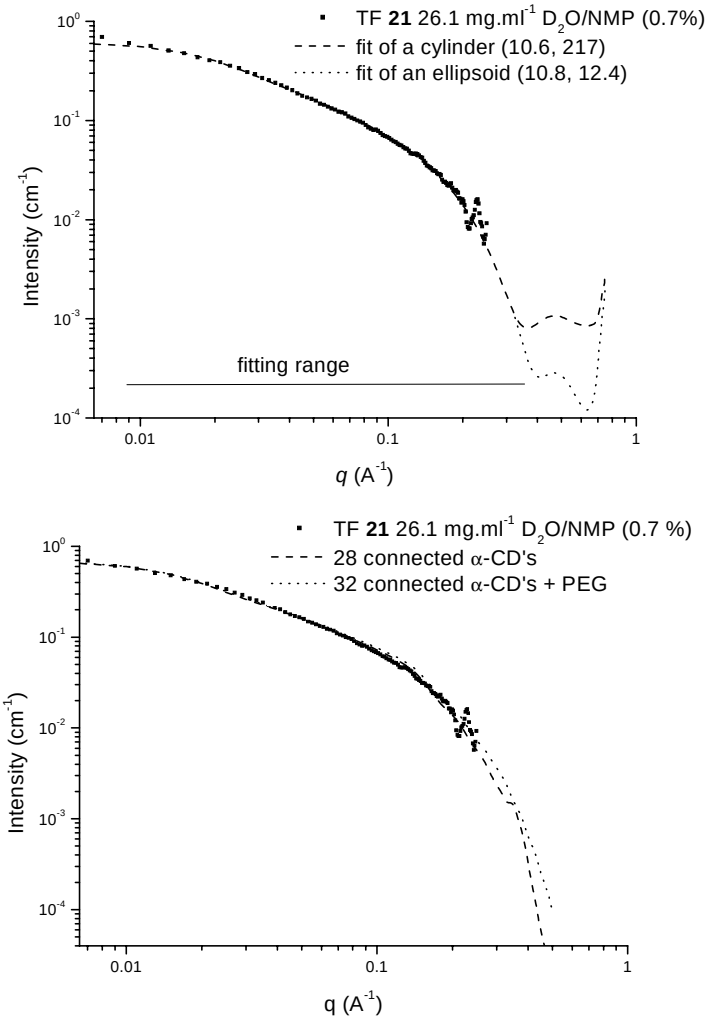

Figure 3.11. *Small-angle neutron scattering data (log−log) of filled tube 21 in D_2O/NMP 0.7 (v/v) % NMP (■); solid model fits (top) and molecular model fits (bottom).*

Several attempts were made to reduce aggregation. Addition of urea had little effect, just like ultrasonic agitation and elevation of the measuring temperature. Figure 3.10 shows the important result of increased single-particle character (horizontal curve at small angles) going from pure D_2O to D_2O containing 0.7 (v/v) % NMP to D_2O containing 2.4 (v/v) % NMP. This is evidence of aggregate suppression by NMP, though some polydispersity

persists. To each sample solution of filled tubes measured 0.7, 1.4 or 2.4 (v/v) % of NMP was added to reduce the aggregation tendency.

The SANS results of filtered solutions of filled tube **21** are shown in figure 3.10. Filled tube **21** is obtained from pseudo-polyrotaxanes prepared using the standard threading conditions and the cyclodextrins are connected using the standard method for synthesizing the filled tubes (see **2** and **21** § 2.5 and table 2.2).

The SANS results have been compared to two kinds of models (figure 3.11). First of all the results are compared to so-called solid models. In this case the dimensions of a solid model are computed out of the experimental data by using the FISH program.[19] Secondly, the experimental data have been compared to molecular models. In this case first a molecular model is built using the MSI-program Cerius[2], and then SANS data are calculated for this model by means of CRYSON.[20]

FISH-fits positively indicate very elongated particles. Since the statistics does not allow a meaningful fitting beyond q = 0.3 $Å^{-1}$, and no side maxima were involved, both solid cylinders and prolate ellipsoids give very good fits. For **21** fitted as a solid rod the results are L = 217 Å, R = 10.6 Å. This length is in good agreement with the AFM and ^{1}H-NMR data and with the expectations (figure 2.4).

An example of a molecular model built using Cerius[2] is later shown for the empty tube (figure 3.17). For simplicity of drawing units of 4 cyclodextrins were connected with each other and multiple units were laid straight in a line without any degree of freedom to move. The fitting indicated that 7 of these units next to each other fitted best with the experimental data of filled tube **21**. Since the fit depends primarily on the overall shape, the number of cyclodextrins found depends on how tightly they are packed in the model. A second type of molecular model containing poly(ethylene glycol) was built. In this case a model consisting of 32 cyclodextrins containing poly(ethylene glycol) fitted best.

The radius of gyration, determined from the Guinier plot, of filled tube **21** gives a value of 79 Å (figure 3.12). This value is in good agreement with the models.

Cross-section data are plotted in figure 3.13. The R_c for **21** is 7.0 Å.

The molecular weight of the compound can be derived from the extrapolation of the experimental data to q = 0 Å in the log−log plot. This gives a value of 30.10^3 g.mol^{-1}. The expected filled α-cyclodextrin molecular tube consisting of 21 threaded cyclodextrins on a poly(ethylene glycol) chain of molecular weight 2,000 g.mol^{-1} containing two 2,4-dinitrophenyl groups, would have a mass of approximately 20.10^3 g.mol^{-1}. The higher than expected molecular weight might be explained by the small amount of aggregation still present.

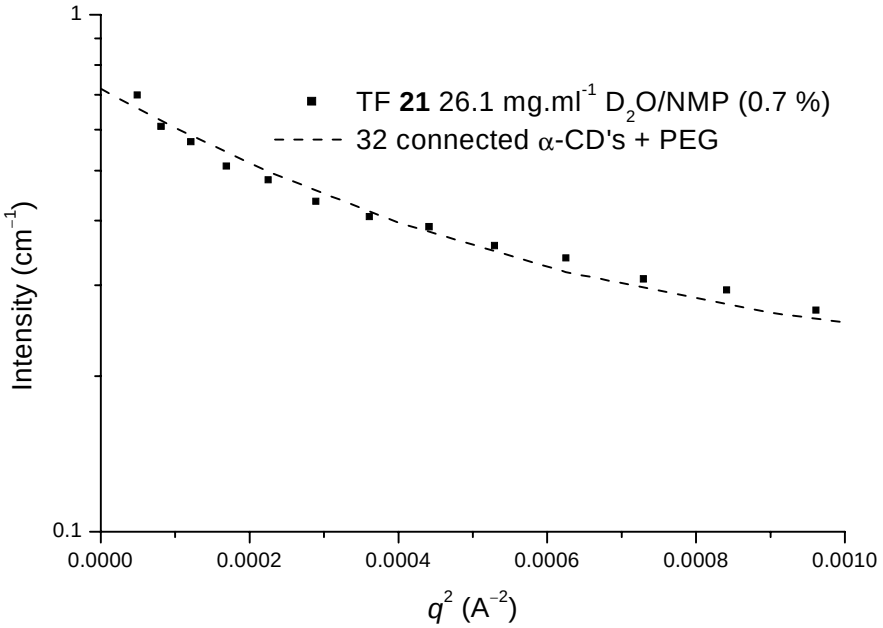

Figure 3.12. *Guinier plot of filled α-cyclodextrin molecular tube* ***21***.

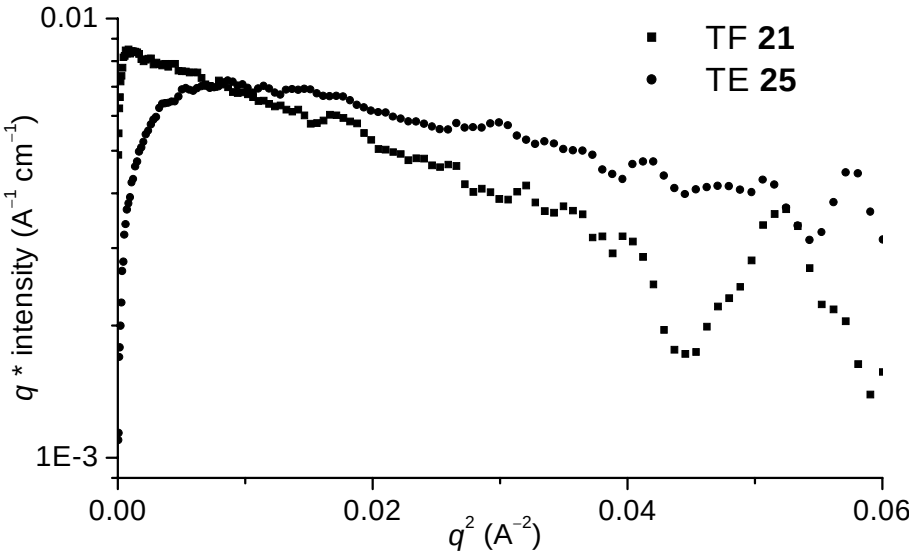

Figure 3.13. *Cross-section-factor Guinier plots.*

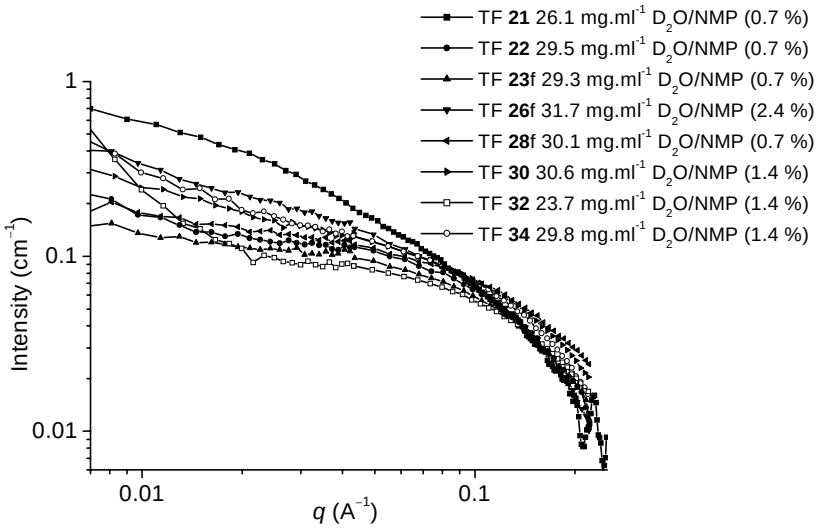

Figure 3.14. *Small-angle neutron scattering data (log−log) of filled tubes* ***21*** *(−■−),* ***22*** *(−●−),* ***23*** *(−▲−),* ***26*** *(−▼−),* ***28*** *(−◀−),* ***30*** *(−▶−),* ***32*** *(−□−) and* ***34*** *(−○−) in D_2O/NMP 0.7, 1.4 or 2.4 (v/v) % NMP.*

Table 3.3. *Result of FISH-fits for poly(ethylene glycol) filled α-cyclodextrin molecular tubes: ellipsoid (*R,R,XR*) + solid cylinder (*L *= 217 Å,* R *= 9 Å).*[a]

Compound	Ellipsoid *R* (Å)	Axial ratio *X*	σ^b	Φ_{recov} [%][c] total	Φ_{recov} [%][d] cylinders
21	19.9	2.6	53	0.094 [51]	0.0089 [49]
22	9.4	3.1	71	0.010 [50]	0.0005 [3]
23	8.6	3.3	92	0.011 [54]	0.0006 [3]
26f[e]	11.1	2.6	105	0.009 [41]	0.0043 [19]
28f	6.2	4.1	58	0.024 [115]	0.0013 [6]
30	7.3	3.5	31	0.017 [81]	0.0025 [12]
32	7.6	3.2	56	0.013 [80]	0.0009 [5]
34	9.0	2.7	42	0.012 [59]	0.0030 [14]

[a] cylinder fixed at L = 217 Å, R = 9 Å

[b] least-squares goodness of fit

[c] volume fraction of particles recovered by the fit; [recovered percentage of weighed-in volume fraction based on partial specific volume of 0.7 $ml.g^{-1}$]

[d] volume fraction of cylinders recovered by the fit; [recovered percentage of weighed-in volume fraction based on partial specific volume of 0.7 $ml.g^{-1}$]

[e] contains 2.4 (v/v) % NMP

The results for the other filled tubes that differ from filled tube **21** in some details of the preparation procedure (table 2.2) are shown in figure 3.14. For some of these samples a contribution of aggregates was found at very small angles, in spite of the presence of NMP. Some of the samples are filtered before measurement. The results for these tubes do indicate these compounds are rigid cylinders, however, they all show some deviation from the results obtained for filled tube **21**.

For the filled tubes, we now hypothesize the following situation which can rationalize the results: The solution contains various particles of connected cyclodextrins in addition to well-defined filled tubes with "proper" dimensions (L = 217 Å, R = 9 Å). The additional compounds have a polydisperse population and their scattering will be described by an ellipsoid of revolution table 3.3.

The radius of the ellipsoid and the axial ratio determine the shape of the ellipsoid needed together with the solid cylinder to fit the experimental data. The least-squares goodness of fit, σ, values shown in table 3.3 indicate how good the hypothesized situation corresponds with the SANS results obtained on the corresponding sample. The last column, the volume fraction of cylinders recovered by the fit, is the most important. It shows in percentages how many tubes are present in the sample solution, that have the dimensions used in the fit.

The differences look significant. Filled tube sample **21** is composed mainly of long tubes (the volume fraction of cylinders recovered by the fit is high). All other samples, except sample **26**, contain a minor amount of tubes. Sample **26** contains a substantial fraction of tubes.

The volume fraction of dissolved particles calculated from the fit parameters is for most samples approximately half of the amount weighted in experimentally. The cause of this discrepancy is unclear. One exception is sample **28**, which according to the fit contains a much larger amount of small particles, a result of the relatively slow decay towards large angles. Samples **30** and **32** come close to the expected amount.

Empty α-cyclodextrin molecular tubes

The results for the empty α-cyclodextrin molecular tubes indicate that the solute particles are rather heterogeneous and ill defined in D_2O and DMSO-d_6. Most probably they are aggregated and this dominates the scattering. Compared to the filled tubes, the aggregates of the empty ones look more polydisperse.

Addition of urea had little effect on the aggregates, just like ultrasonic agitation and elevation of the measuring temperature. Addition of NMP did reduce the aggregation tendency. Figure 3.15 shows an increased single-particle character (horizontal curve at small angles) going from pure DMSO-d_6 to D_2O containing 0.7 (v/v) % NMP. This is evidence of suppression by NMP of aggregate formation, though some polydispersity persists. The results of dissolution in D_2O/NMP instead of DMSO-d_6 are even more

convincing than for filled α-cyclodextrin molecular tubes (figure 3.10). To all empty α-cyclodextrin molecular tube sample solutions measured 0.7, 1.4 or 2.4 (v/v) % of NMP was added to reduce the aggregation tendency.

The SANS experimental data obtained for empty tube **25** have been compared to: 1) Curve-fits for solid models computed using the FISH program;[19] 2) Curves for molecular models built with the MSI-program Cerius[2] for which SANS data were calculated by means of CRYSON.[20]

Fitting a hollow cylinder to the data of sample **25** yields L = 46.4 Å, R = 7.5 Å; and t = 1.6 Å, where t is the cylinder wall thickness. The length found for this compound is much lower than for the filled tubes. This difference in the two compounds could already be observed from the comparison of the experimental data of the compounds (figure 3.16).

Also molecular models were built. The same kind of models was used as for the filled tubes. When it was attempted to fit the molecular models to the experimental data it was found that empty tubes **25** fitted well with a model consisting of 6 cyclodextrins (figure 3.17). The fit could be improved by using a mixture of 4 α-cyclodextrins connected to each other and 6 α-cyclodextrins connected to each other in a ratio of 20/80 (figure 3.18). Also in this case the fit depends primarily on the overall shape. Since SANS determines the shape of the compound the number of cyclodextrins found depends on how tightly the cyclodextrins are packed in the model.

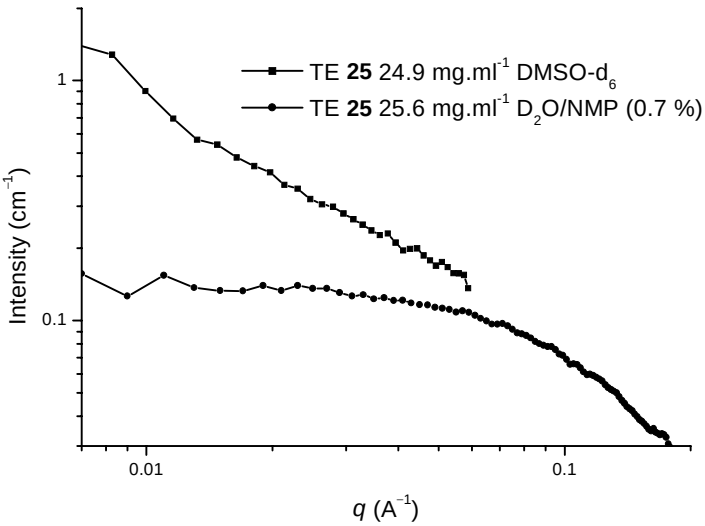

Figure 3.15. *Small-angle neutron scattering data (log−log) of empty tube* ***25*** *in DMSO-d_6 (−■−) and in D_2O/NMP 0.7 (v/v) % NMP (−●−).*

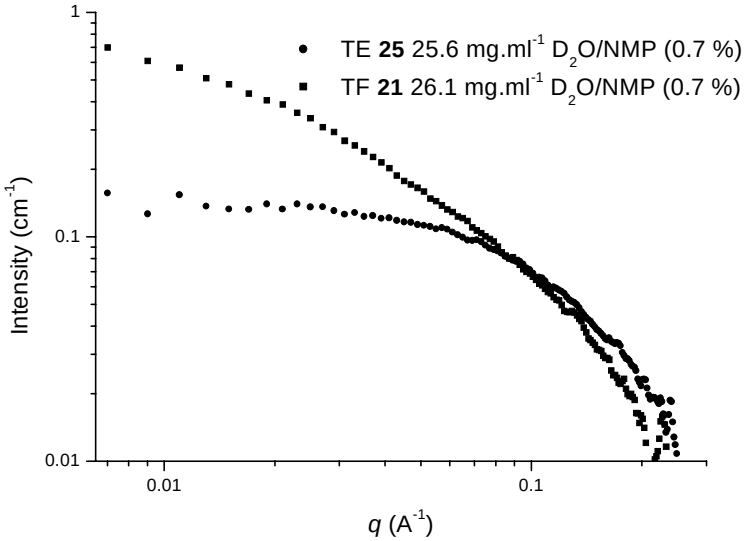

Figure 3.16. *Comparison between empty tube **25** and filled tube **21**. Empty tube **25** is obtained from filled tube **21**.*

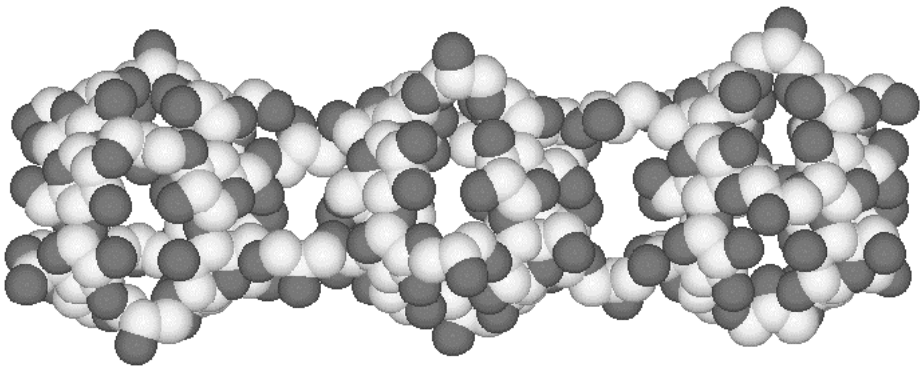

Figure 3.17. *Example of a model built using the Cerius[2] program suite. This model consists of 6 α-cyclodextrins connected to each other.*

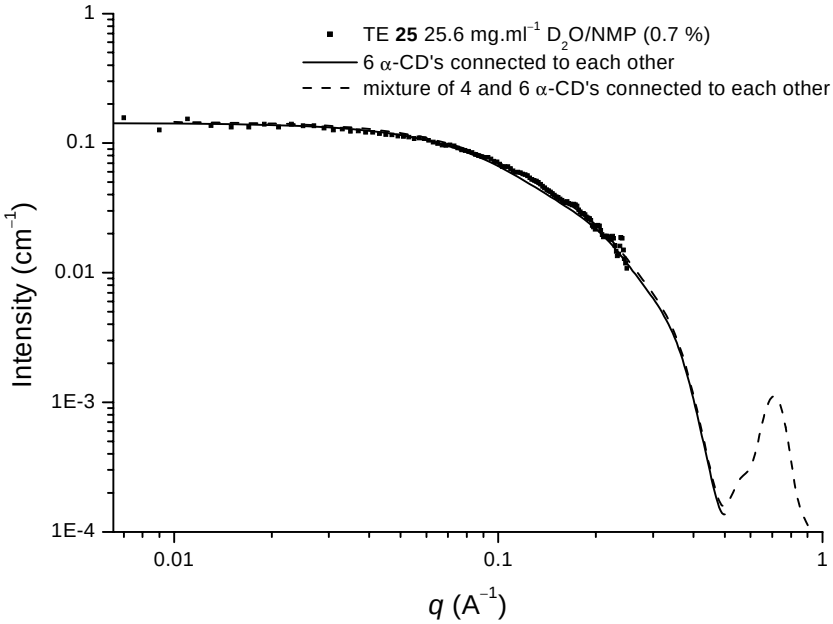

Figure 3.18. *Small-angle neutron scattering data (log−log) of empty tube* ***25*** *in D_2O/NMP 0.7 (v/v) % NMP (■) and molecular models.*

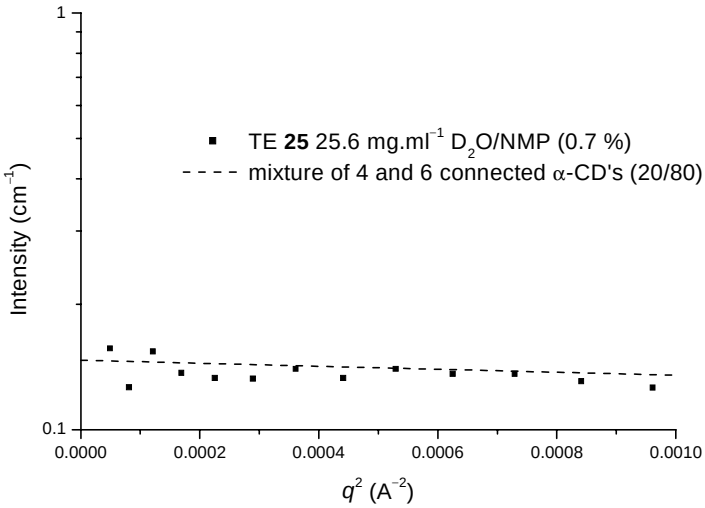

Figure 3.19. *Guinier plot of empty α-cyclodextrin molecular tube* ***25****.*

The radius of gyration of **25** according to the Guinier plot is 17 Å (figure 3.19). This value is in good agreement with the models.

Cross-section data of empty tube **25** are plotted in figure 3.13. R_c for **25** is 5.6 Å. This is low compared to the cross-sectional radius of gyration of the filled tube, especially when it is considered the central chain is absent in the latter.

The limiting intensity values, for q going to zero, imply that the molecular weight of the empty tubes is only about ¼ of the filled tubes (compare **21** and **25** in figure 3.16). The molecular weight found for the empty tube is $8.0.10^3$ g.mol^{-1}. This is much lower than expected, but in good agreement with the independently found results for the models.

The results for the other empty α-cyclodextrin molecular tubes that differ from **25** in some details of the preparation procedure (table 2.2) are shown in figure 3.20. For some of these samples a contribution of aggregates was found at very small angles, in spite of the presence of NMP. Some of the samples are filtered before measurement. All empty tubes show the same plateau in the range of $0.02 < q < 0.03$ Å^{-1} just as empty tube **25**.

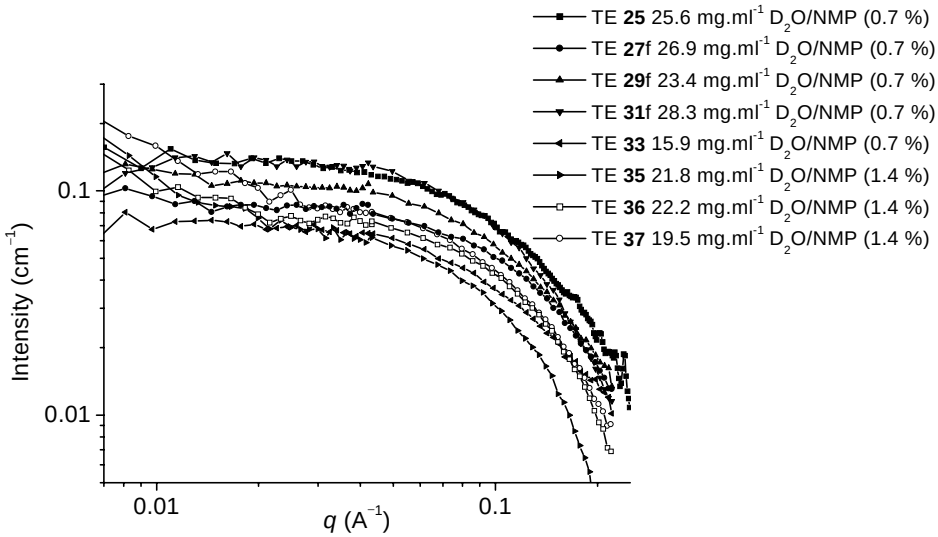

Figure 3.20. *Small-angle neutron scattering data (log−log) of empty tubes* ***25*** *(−■−),* ***27*** *(−●−),* ***29*** *(−▲−),* ***31*** *(−▼−),* ***33*** *(−◄−),* ***35*** *(−►−),* ***36*** *(−□−) and* ***37*** *(−○−) in D_2O/NMP 0.7 or 1.4 (v/v) % NMP.*

Table 3.4. Results of FISH-fits for empty α-cyclodextrin molecular tubes.

	Solid cylinder			Hollow cylinder, d*t* = 3		
	L	*R*	σ[a]	*L*	R_{out}	σ
25	49.1	7.4	34	49.2	6.5	33
27f	47.9	8.1	80	48.1	6.9	80
29f	40.8	8.0	101	40.9	6.9	100
31	43.7	12.6	74	44.9	10.0	68
33	40.7	10.0	32	41.1	8.3	30
35	48.3	9.3	43	48.6	7.8	41
36f	45.1	9.5	107	45.5	7.9	108
37	50.2	6.9	52	50.3	6.1	52

[a] least-squares goodness of fit

The empty tubes were fitted to solid- and to hollow cylinders. Hollow cylinders fit equally well (table 3.4). Since no side maxima were observed, there is little information about the wall thickness (d*t*), and d*t* is strongly correlated to the outer radius of the cylinder (R_{out}) via the radius of gyration. Hence, d*t* was fixed at 3 Å.
The differences between the empty tubes are smaller than between the filled tubes. The obtained results show that the length obtained is insensitive to the cylinder being hollow or not. The values for the radius, *R*, are not so reliable, since they are sensitive to the background level. They cannot be taken to be significantly different from each other. Most importantly, there does not seem to be a relation in the radius with the corresponding filled tube samples.

3.4 Discussion and conclusion

All α-cyclodextrin/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxanes are insoluble in H_2O. Dissolution in DMSO does produce optically clear solutions. However, no molecular solutions are obtained. This can be concluded both from the AFM and SANS measurements. Both techniques show aggregates. The insolubility is attributed to the inaccessibility of the hydroxyl groups at the rims of the densely threaded α-cyclodextrin cones. The filled- and empty tubes are well soluble in H_2O and DMSO. However, in pure solvent these compounds are not molecularly dissolved, as can be concluded from the AFM and SANS measurements on pure solutions.
^{1}H-NMR shows that the pseudo-polyrotaxane and polyrotaxane both contain approximately 20 α-cyclodextrins. Since there is no possibility for the cyclodextrins to unthread from the polymer chain in the filled tube, the filled tube should also contain 20 cyclodextrins.

According to AFM, the filled tubes have a length of approximately 20 nm, a width of approximately 12 nm and a height of approximately 1 nm. This is close to the expected dimensions for a rigid filled tube based on the "template polymer" having a molecular weight of 2,000 $g.mol^{-1}$. The larger than expected width can be explained by a tip effect. The empty tubes are smaller than the filled tubes according to AFM.

SANS measurements show, that the filled tubes have an elongated shape. The shape of the curve cannot be explained exclusively by a rod-like shape of the particles, since the slope of the log−log curves at small angles is weaker than −1 (Here, $I_c(q)$ = constant, so that $I(q) \sim I_L = q^{-1}$ (see eq. 5)). A possible explanation is that the solutions contain diverse types of particles, long rods as well as smaller particles. If a solid cylinder is fitted to the data obtained on the filled tube synthesized using the standard threading- and crosslink conditions the cylinder has dimensions of 217 Å × 11 Å for length and radius, respectively. This is again consistent with the expectations for a rigid filled tube having a poly(ethylene glycol) "template polymer" of molecular weight 2,000 $g.mol^{-1}$. When molecular models are fitted, models consisting of 7 × 4 connected α-cyclodextrins or 8 × 4 connected α-cyclodextrins + poly(ethylene glycol) fitted best. The molecular weight of this filled tube is 30.10^3 $g.mol^{-1}$. The amount of long rigid tubes varies dramatically depending on the sample (table 3.3).

The shape of the curve of the empty α-cyclodextrin molecular tubes is very different. The curves for the empty tubes level off to small angles, those for the filled tubes do not. When a hollow cylinder is to be fitted, this cylinder should have a length of 46 Å and a radius of 7 Å. Molecular models fit best when a model of 6 connected α-cyclodextrins is used or even better when a mixture of 4 and 6 connected α-cyclodextrins in a ratio of 20/80 is used. The molecular weight of the empty tubes is $8.0.10^3$ $g.mol^{-1}$, much less than expected. Different complexation- or crosslink conditions do not result in larger empty tubes.

A remarkable result is the value found for R_c of the filled α-cyclodextrin molecular tubes (7.0 Å) which is larger than for the empty tubes (5.6 Å), in spite of the absence of the central chain in the latter. This is attributed to a combination of effects: 1) Tighter packing of cyclodextrins in the filled tube which causes the crosslinks to bulge out; 2) Higher scattering contrast for the crosslinks. It is suggested that the high content of CH_2 groups in the crosslinks provides contrast over the cyclodextrin rings themselves, and this is due to hydrogen atoms in the remaining hydroxyls being exchanged for deuterium. Such an exchange is general for biomacromolecules.[20] This suggestion is supported by the fact that the particle size based on absolute intensity data agrees with geometry: 21 cyclodextrin units in **21** and 6 units in **25**, only when this exchange is taken into account. (In this calculation, a partial specific volume of 0.7 $cm^3.g^{-1}$ was used.)

The results found with ^{1}H-NMR, UV−Vis, AFM and SANS are consistent with each other. Most important conclusion is that the empty α-cyclodextrin molecular tubes are smaller

than expected and that different complexation- or crosslink conditions do not produce larger α-cyclodextrin molecular tubes.
The difference in length between the filled- and empty α-cyclodextrin molecular tubes can not be explained by a difference in flexibility between the filled- and empty α-cyclodextrin molecular tubes, but must be due to insufficient crosslinking between the cyclodextrins on the polyrotaxane.
It is most likely that deficiencies in the polyrotaxane, cause defects in the filled tubes. These deficiencies prevent some cyclodextrins to be crosslinked with their neighbor. When the blocking groups are removed and the "template polymer" chain is released, multiple smaller α-cyclodextrin molecular tubes are liberated instead of one long α-cyclodextrin molecular tube. An example of a deficiency might be that the distance between the cyclodextrins is too large to be crosslinked due to non close-packing of the cyclodextrins on the "template polymer" chain. This defect can be excluded, since the ^{1}H-NMR data show the cyclodextrins are close-packed on the polymer. A further deficiency in the polyrotaxane might be a non-strictly alternating orientation of the α-cyclodextrin cones (figure 3.21). This causes a larger distance between the hydroxyl groups of the cyclodextrins which makes it more difficult to crosslink the cyclodextrin.
In summary it can be stated, that α-cyclodextrin molecular tubes have been obtained through the synthetic route chosen. However, the empty α-cyclodextrin molecular tubes obtained do not contain the number of cyclodextrins present in the polyrotaxane or the filled tube. The empty tubes are elongated particles having a length of 45−50 Å. No detectable amount of longer tubes remains. A reduction of the overall particle size upon removal of the central poly(ethylene glycol) chain implies that not all cyclodextrins are connected on both sides during the crosslinking of the polyrotaxane, and suggests that the crosslinking proceeds inhomogeneously. This is most likely due to deficiencies in the pseudo-polyrotaxane, primarily a non-strictly alternating orientation of the α-cyclodextrin cones during complexation.

3.5 Experimental

Measurements
^{1}H-NMR spectra were recorded on a 300 MHz Varian (VXR 300) spectrometer. Deuterated solvent was used as internal standard. All chemical shifts are denoted in δ-units (ppm) and converted to TMS scale. MALDI-TOF spectra were taken on a Micromass TofSpec E mass spectrometer using 2,4-dihydroxybenzoic acid (DHB) as matrix; pulse voltage: 1400 V. UV−Vis spectra were recorded on a SLM Aminco 3000 Array. Spectroscopic grade DMF was used as solvent.

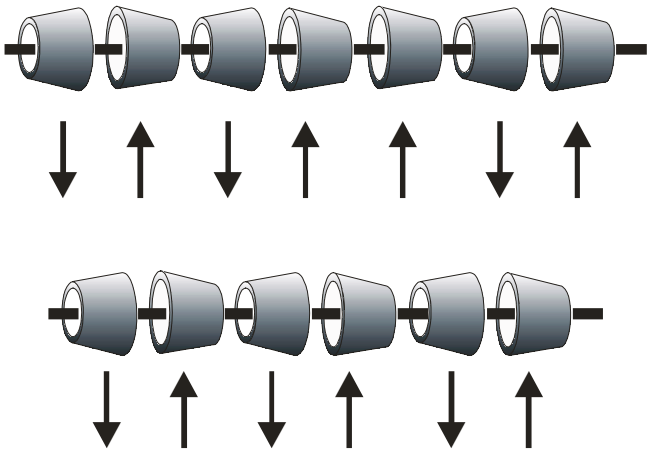

Figure 3.21. *Schematic representation of a possible defect in the α-cyclodextrin/poly(ethylene glycol) pseudo-polyrotaxane (top) compared to a pseudo-polyrotaxane without defect (bottom).*

Materials and methods

The synthesis of all pseudo-polyrotaxanes, polyrotaxanes, filled- and empty tubes is described in chapter 2. Urea was purchased form Merck. *N*-methyl-2-pyrolidinone (NMP) was purchased from ACROS. Spectroscopic grade *N*,*N*-dimethylformamide, dimethyl sulfoxide (DMSO), deuterated dimethyl sulfoxide (DMSO-d_6) and deuterated water (D_2O) were purchased from Aldrich. 18 MΩ ultra pure water obtained from an Elga Maxima water purification system was used as solvent in the AFM measurements and as reference material in the SANS measurements.

AFM sample preparation

AFM images were recorded with a NanoScope IIIa (Digital Instruments, Inc., Santa Barbara (US)), equipped with NT-MDT ultra-sharp silicon cantilever tips (NSC 21 series). Topographic images were taken in air in "Tapping Mode". Solutions of 2 (w/w) % of the α-cyclodextrin molecular tubes in H_2O/NMP = 150/1 (v/v) were drop-cast on freshly cleaved muscovite mica (grade 2, obtained from Mica New York Corporation (US)).

SANS

SANS Experiments were carried out at ISIS (Rutherford Appleton Laboratory, Didcot (UK)) and at the Laboratoire Léon Brillouin (LLB)(CEA, Saclay (F)). At ISIS, the LOQ instrument installed at the pulsed neutron source was used, with λ ranging from 2.2–10 Å. Time of flight and position of a neutron arriving at the 2D-detector (at 4.05 m) are

converted to λ and q. The data correction procedure takes into account the wavelength distribution, detector sensitivity, and sample transmission and furnishes intensity in absolute units (cm^{-1}) over a q-range of 0.009–0.25 $Å^{-1}$ (low-angle bank) and 0.2–1.5 $Å^{-1}$ (high-angle bank).

At CEA–LLB, the PAXY instrument was employed. Two equipment settings were used: 1) Sample-to-detector distance (D_{ED}) of 3.20 m with λ = 12 Å (q-range of 0.008–0.057 $Å^{-1}$), and 2) D_{ED} = 2.00 m with λ = 5.0 Å (q-range 0.03–0.22 $Å^{-1}$). For this instrument, Δλ/λ = 0.1. Absolute intensities corrected for detector sensitivity, were obtained by normalization to the scattering from H_2O (at D_{ED} = 3.20 m) or Plexiglas (at D_{ED} = 2.00 m), with reference to the direct beam.

Samples were contained in 2 mm path length quartz cells at 25 °C (LOQ-ISIS) or 22 ± 2 °C (PAXY-LLB). Typical counting times amounted to three hours. The scattering of solvent (including NMP, see below) was subtracted as background. An additional correction (subtraction) for incoherent scattering was based on a measurement of the excess intensity of solvent mixtures (D_2O/H_2O 98/2 (v/v) or DMSO-d_6/DMSO 98/2 (v/v)) over pure solvent (D_2O or DMSO-d_6) and subsequent scaling to the specific hydrogen content of each sample. This correction was a constant over the angular range covered. (For ISIS data, we used the difference between DMSO-d_6/DMSO 97/3 (v/v) and DMSO-d_6, each with 0.7 (v/v) % NMP added.)

Filtration of some samples was found necessary because of a sharp intensity upturn at low q, in spite of the presence of NMP. These samples have an “f” after their designation. The filters used had a pore diameter of 0.2 μm (Sartorius Minisart SRP 15 or Whatman Anotop 10). Empty tube samples were additionally filtrated using a 0.02 μm Whatman Anotop 10. Loss of material due to filtration was determined afterwards for each sample from the recovered solution. In some cases the loss was around 10 %, but in other cases it was much less.

Curve fitting to corrected data was performed by means of the FISH program (by R.K. Heenan).[19] The first four data points were omitted in all fits, in order to suppress contributions from any remnants of aggregates. Fits started at q = 0.0146 $Å^{-1}$. Molecular models of α-cyclodextrin tubes were constructed using the Cerius^2 program (Cerius^2 version 3.5, Molecular Simulations Inc., San Diego (US)). The corresponding scattering curves were calculated, by means of CRYSON, a program developed by and offered by Svergun and Barberato (EMBL, Hamburg (D)).[20]

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Chapter 4

Modeling

Abstract

The complexation of cyclodextrins on the "template polymer" is modeled in order to find a way to improve the possibilities for obtaining longer empty α-cyclodextrin molecular tubes. In order to study the thermodynamic equilibrium, an antiferromagnetic model was constructed, able to describe the complexation phenomenon.
When the complexation was completely random, no spin is favored. In such a random model the average length obtained is small. Thus the hypothesis that the interactions between the cyclodextrins played a role was obvious from the beginning. So the most important effect on the threading had to come from the structure of the cyclodextrins themselves, which gave rise to different interaction energies ε_0, ε_1, ε_2. *The hydrogen-bonds formed between the cyclodextrins have energies in the order of* k_BT. *Cyclodextrins have six possibilities to form hydrogen-bonds at their narrow side and twelve hydrogen-bonds at their large side. Every interaction is worth 2 units* k_BT *and it was assumed that bonds were formed between each side in contact with its neighbor. It was concluded that the thermodynamic equilibrium is not yet reached during complexation.*
The question that remained was why the thermodynamic equilibrium is not reached during complexation. According to the model the results could be improved by increasing the temperature. However, no significant difference was observed in the empty tubes, for which the pseudo-polyrotaxane was prepared at 80 °C instead of at room temperature (§ 3.3.5). Also gradual addition of cyclodextrin could help, to attain the thermodynamic equilibrium, although also in this case no significant difference was observed when the pseudo-polyrotaxane was prepared using this condition (§ 3.3.5).

The work presented in this Chapter is the undergraduate work of E. Collé.

4.1 Introduction

According to the characterization, of the α-cyclodextrin molecular tubes described in chapter 3 the empty tubes synthesized in chapter 2 are smaller than expected. Although the filled α-cyclodextrin molecular tubes do contain the right number of close-packed cyclodextrins, the empty α-cyclodextrin molecular tubes consist, according to the SANS measurements, of maximally 6 cyclodextrins. In the discussion and conclusion of chapter 3 it was already mentioned, that some kind of defect in the threading process or in the crosslinking must have caused this reduction in the number of cyclodextrins present in the empty tubes compared to the filled tubes. A possible defect is insufficient crosslinking, possibly due to not completely alternating orientation of the cyclodextrins on the "template polymer" chains. This introduces head-to-tail packed cyclodextrins, which are more difficult to crosslink due to longer distances between the hydroxyl groups (§ 2.2.3).
The threading of cyclodextrins on polymer chains was studied before by Lo Nostro *et. al*. Their research is based on the hydrophobic forces acting between the linear guest chain and the cyclodextrins. In other words, water molecules push the long hydrophobic chain toward the hydrophobic cavity, so that the formation of the resulting pseudo-polyrotaxane will lead to a consistent stabilization of the entire system.[1] In their research it is assumed that all cyclodextrins arrange head-to-head and tail-to tail since this is energetically most favorable.[2] However, this could was not verified. What was measured was the absorbance at 400 nm as a function of time and it was assumed that the threading process is finished at the moment the pseudo-polyrotaxane precipitate out.[1,3] According to their results the threading process is favored by low temperatures.
To obtain more insight in the threading process, in this chapter models were built in order to find explanations for possible defects. The model introduced describes the orientation of the cyclodextrins on the "template polymer". The insights obtained might direct towards threading conditions able to produce longer empty α-cyclodextrin molecular tubes. The model is also used for comparison, with the experimentally obtained results.

4.2 The model

When a cyclodextrin is threaded on a polymer chain there are two possible orientations for this cyclodextrin (figure 4.1). For simplicity here we distinguish the two orientations by an arrow.
When two cyclodextrins are threaded on a polymer chain, there can be four different situations (two of these situations (ε_0) can not be distinguished in a symmetrical polymer chain) (figure 4.2).

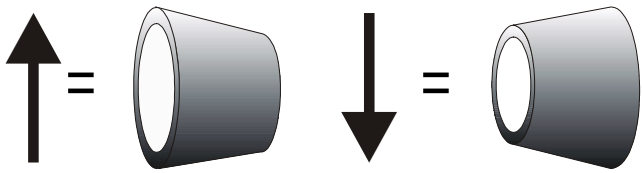

Figure 4.1. *Spin up (left) and spin down (right).*

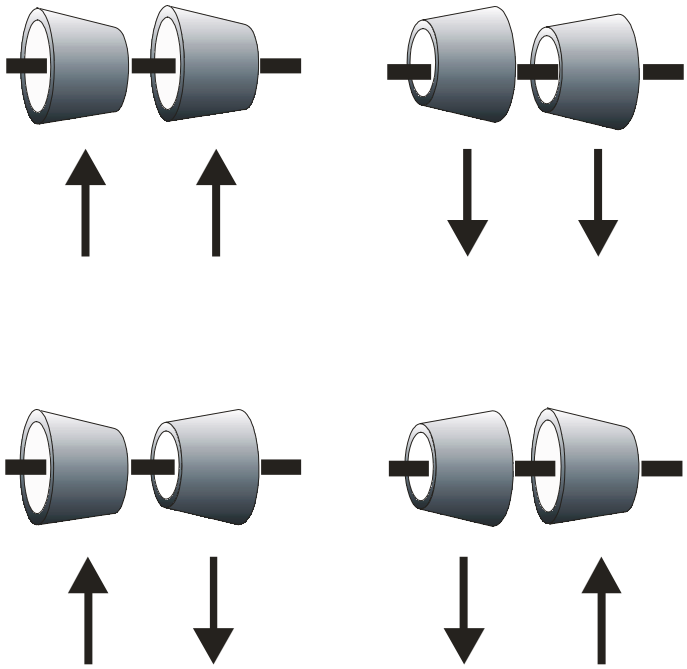

Figure 4.2. *Interaction energy* ε_0 *(top left); Interaction energy* ε_0 *(top right); Interaction energy* ε_1 *(bottom left); Interaction energy* ε_2 *(bottom right).*

For modeling the interactions of cyclodextrins threaded onto a polymer, a one-dimensional Ising system is considered, where the sign of the spins (+1 and −1) represents the orientation of the cyclodextrins (figure 4.1). In the case there are no cyclodextrins on the polymer chain, so when the cyclodextrins are not close-packed, there is a gap in the Ising system. The situation is considered in which a thermodynamic equilibrium is attained, meaning there is enough time for threading and dethreading of the cyclodextrins to be eventually threaded in their thermodynamically most favorable orientation. The consequences and limitations of this model are discussed in the discussion and conclusion (§ 4.4).

For the construction of a Hamiltonian, three energies can be identified: ε_0 represents the cases, in which two cyclodextrins are oriented head-to-tail, ε_1 is the case, in which the small sides are oriented towards each other (tail-to-tail) and ε_2 when the large sides are oriented towards each other (head-to-head) (figure 4.2). For a system in which the cyclodextrins are not close-packed, so a system containing gaps, the Hamiltonian can be written as shown in equation 1.

$$H = -\frac{1}{4}\sum_i [(2\varepsilon_0 + \varepsilon_1 + \varepsilon_2)S_i S_{i+1} + (\varepsilon_2 - \varepsilon_1)(S_i S_{i+1}^2 - S_i^2 S_{i+1}) + 2(\varepsilon_0 - \varepsilon_1 - \varepsilon_2)S_i^2 S_{i+1}^2] - \sum_i \mu_i S_i^2 \quad . (1)$$

Since each cyclodextrin can be oriented in two directions and there is the possibility of the absence of a cyclodextrin the spins can have three values $S_i = \{-1,0,1\}$. This Hamiltonian resembles the one obtained by Mukamel and Blume.[4]

In the experiment considered the polymer has N sites (approximately 20) all covered by cyclodextrins (close-packed pseudo-polyrotaxane), so there are no gaps. Thus the spins can have only two values $S_i = \{-1,1\}$ and the Hamiltonian can be written as:

$$H = -\frac{1}{4}\sum_i [(2\varepsilon_0 - \varepsilon_1 - \varepsilon_2)S_i S_{i+1} + (\varepsilon_2 - \varepsilon_1)(S_{i+1} - S_i) + 2(\varepsilon_0 + \varepsilon_1 + \varepsilon_2)] . \quad (2)$$

This may be simplified by the elimination of a constant and the summation of the second term:

$$H = J\sum_i S_i S_{i+1} - h(S_N - S_1) \text{ with } J = \frac{1}{4}(\varepsilon_1 + \varepsilon_2 - 2\varepsilon_0) \text{ and } h = \frac{1}{4}(\varepsilon_2 - \varepsilon_1) . \quad (3)$$

The threading of the cyclodextrins on the polymer chain now resembles an antiferromagnet. The desired quantity is the average length of the alternating part of the pseudo-polyrotaxane, since this has to be improved to obtain longer empty α-cyclodextrin molecular tubes. To calculate this quantity an operator $\tilde{f}(i,l)$ is introduced. This operator takes the value of 1 for a pseudo-polyrotaxane containing alternating cyclodextrins over a length l, beginning at site i or 0:

$$\tilde{f}(i,l) = \frac{(1+S_{i-1}S_i)}{2}\frac{(1-S_i S_{i+1})}{2}\ldots\ldots\ldots\ldots\frac{(1-S_{i+l-2}S_{i+l-1})}{2}\frac{(1+S_{i+l-1}S_{i+l})}{2} . \quad (4)$$

The first and last term in equation 4 indicate the spins before and after the alternating cyclodextrins in the pseudo-polyrotaxane have to have a non alternating orientation, compared to the alternating cyclodextrins. The cyclodextrins in between the cyclodextrins represented by the first and last term are alternating. This explains the difference in sign of the first and last term compared to the others. However, this operator is not valid in case the alternately ordered part touches the ends of the polymer chain, since there is no cyclodextrin and so no spin before or after the last site. In that case the exact expression is:

If the alternating part of the pseudo-polyrotaxanes touches the left end of the polymer chain:

$$\tilde{f}(1,l) = \frac{(1 - S_i S_{i+1})}{2} \cdots\cdots\cdots \frac{(1 - S_{i+l-2} S_{i+l-1})}{2} \frac{(1 + S_{i+l-1} S_{i+l})}{2}, \qquad (5)$$

If the alternating part of the pseudo-polyrotaxanes touches the right end of the polymer chain:

$$\tilde{f}(N - l + 1, l) = \frac{(1 + S_{i-1} S_i)}{2} \frac{(1 - S_i S_{i+1})}{2} \cdots\cdots\cdots\cdots\cdots \frac{(1 - S_{i+l-2} S_{i+l-1})}{2}, \qquad (6)$$

and in the case all the cyclodextrins are alternating along the whole polymer chain, there is no first and last term:

$$\tilde{f}(1, N) = \frac{(1 - S_i S_{i+1})}{2} \cdots\cdots\cdots\cdots\cdots \frac{(1 - S_{i+l-2} S_{i+l-1})}{2}. \qquad (7)$$

As a function of these quantities the fraction of the well ordered part of the pseudo-polyrotaxanes having a length, *l*, is written as:

$$f(l) = \sum_i f(i,l) = \begin{cases} f(1,l) + \sum_{i=2}^{N-l} f(i,l) + f(N - l + 1, l) & \text{for } 1 \le l \le N\text{-}2 \\ f(1, N-1) + f(2, N-1) & \text{for } l = N\text{-}1 \\ f(1, N) & \text{for } l = N \end{cases}, \qquad (8)$$

using average statistics: $f(i,l) = < \tilde{f}(i,l) >$.

It is possible, by using the distribution functions *f(l)*, to calculate multiple average lengths of the alternating part of the pseudo-polyrotaxanes, for example the average length in numbers is written as:

$$< l >= \frac{\sum_{l=1}^{N} l f(l)}{\sum_{l=1}^{N} f(l)}. \tag{9}$$

4.3 Length of the antiferromagnetic domains in the pseudo-polyrotaxane

4.3.1 Partition function

In the system without gaps so with close-packed cyclodextrins the Hamiltonian is comparable to an antiferromagnetic system with field effects at the ends (§ 4.2):

$$H = J\sum_i S_i S_{i+1} - h(S_N - S_1) \text{ with } J = \frac{1}{4}(\varepsilon_1 + \varepsilon_2 - 2\varepsilon_0) \text{ and } h = \frac{1}{4}(\varepsilon_2 - \varepsilon_1). \tag{3}$$

Thus the partition function in energy units, where $k_B T = 1$, is equal to:

$$Z = \sum_{\{S_i\}} \exp\left[-J\sum_i S_i S_{i+1} + h(S_N - S_1)\right]. \tag{10}$$

The partition function can be calculated using transfer matrixes. For a pseudo-polyrotaxane containing of two spins, the result is:

$$Z_2 = \left(e^h e^{-h}\right)\begin{pmatrix} e^{-J} & e^{J} \\ e^{J} & e^{-J} \end{pmatrix}\begin{pmatrix} e^{-h} \\ e^{h} \end{pmatrix}. \tag{11}$$

For a pseudo-polyrotaxane containing of three spins, the result is:

$$Z_3 = \left(e^h e^{-h}\right)\begin{pmatrix} e^{-J} & e^{J} \\ e^{J} & e^{-J} \end{pmatrix}^2\begin{pmatrix} e^{-h} \\ e^{h} \end{pmatrix}. \tag{12}$$

So finally the result for a pseudo-polyrotaxane containing N sites:

$$Z_N = \left(e^h e^{-h}\right)\begin{pmatrix} e^{-J} & e^J \\ e^J & e^{-J} \end{pmatrix}^{N-1}\begin{pmatrix} e^{-h} \\ e^h \end{pmatrix}. \tag{13}$$

To simplify the problem the following notations are used:

$$T_0 = \begin{pmatrix} e^{-J} & e^J \\ e^J & e^{-J} \end{pmatrix} \quad B = \begin{pmatrix} -1 & 1 \\ 1 & 1 \end{pmatrix} \quad B^{-1} = \begin{pmatrix} -\frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}. \tag{14}$$

The matrices B and B^{-1}can diagonalize T_0:

$$B^{-1}T_0B = \begin{pmatrix} e^{-J} - e^J & 0 \\ 0 & e^J + e^{-J} \end{pmatrix}, \tag{15}$$

as the relation is:

$$BB^{-1} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}. \tag{16}$$

It is possible to write equation (13) in the following way:

$$Z_N = \left(e^h e^{-h}\right)BB^{-1}T_0BB^{-1}.....BB^{-1}T_0BB^{-1}\begin{pmatrix} e^{-h} \\ e^h \end{pmatrix}. \tag{17}$$

After diagonalisation the result is:

$$Z_N = \left(e^h e^{-h}\right)B\begin{pmatrix} e^{-J} - e^J & 0 \\ 0 & e^J + e^{-J} \end{pmatrix}^{N-1} B^{-1}\begin{pmatrix} e^{-h} \\ e^h \end{pmatrix}. \tag{18}$$

Using the relations for B and B^{-1}:

$$Z_N = -2^N \sinh^2(h)\sinh^{N-1}(-J) + 2^N \cosh^2(h)\cosh^{N-1}(J). \tag{19}$$

4.3.2 Calculation of the operators

For calculation of the average length of the well ordered part of the pseudo-polyrotaxane the following value has to be found:

$$f(i,l) = < \tilde{f}(i,l) > = < \frac{(1+S_{i-1}S_i)}{2}\frac{(1-S_iS_{i+1})}{2}.....\frac{(1-S_{i+l-2}S_{i+l-1})}{2}\frac{(1+S_{i+l-1}S_{i+l})}{2} > . \tag{20}$$

For determining the length, *l*, of the alternating part of the pseudo-polyrotaxane, beginning at site *i*, using average statistics, it is necessary to calculate the following chain of transfer matrices:

$$f(i,l) = \frac{1}{Z}\begin{pmatrix} e^{h} & e^{-h} \end{pmatrix} T_{N-1}T_{N-2}.....T_{i+l}T_{i+l-1}T_{i+l-2}....T_iT_{i-1}T_{i-2}....T_1\begin{pmatrix} e^{-h} \\ e^{h} \end{pmatrix}. \tag{21}$$

T_i Represents the transfer matrix between the spins S_i and S_{i+1}. The matrices between T_i and T_{i+l-2} are the matrices of the spins of the complex themselves. The neighboring spins are well organized, i.e., they are alternating, so they have opposite values. So:

$$T_i = T_{i+1} = T_{i+2} = ... = T_{i+l-2} = \begin{pmatrix} 0 & e^{J} \\ e^{J} & 0 \end{pmatrix} = T_{tub} . \tag{22}$$

The first and last cyclodextrin of the well ordered part of the pseudo-polyrotaxane and their neighbors have to have the same direction. So these matrices have the form:

$$T_{i-1} = T_{i+l-1} = \begin{pmatrix} e^{-J} & 0 \\ 0 & e^{-J} \end{pmatrix} = T_{ex} . \tag{23}$$

Finally, the spins of the other cyclodextrins are able to have both values, the matrices are of the type:

$$T_1 = T_2 = ... = T_{i-2} = \begin{pmatrix} e^{-J} & e^{J} \\ e^{J} & e^{-J} \end{pmatrix} = T_0 , \tag{24}$$

$$T_{i+l} = T_{i+l+1} = ... = T_{N-1} = \begin{pmatrix} e^{-J} & e^{J} \\ e^{J} & e^{-J} \end{pmatrix} = T_0 . \tag{25}$$

Equation (21) can be written as:

$$f(i,l)=\frac{1}{Z}\begin{pmatrix}e^{h} & e^{-h}\end{pmatrix}T_0^{N-i-l}T_{ex}T_{tub}^{l-1}T_{ex}T_0^{i-2}\begin{pmatrix}e^{-h}\\ e^{h}\end{pmatrix}. \tag{26}$$

T_1 can be diagonalized, using the same matrices as for T_0, B and B^{-1}:

$$B^{-1}T_{tub}B=\begin{pmatrix}-e^{J} & 0\\ 0 & e^{J}\end{pmatrix}. \tag{27}$$

Upon introduction of BB^{-1} in expression (26):

$$f(i,l)=\frac{1}{Z}\begin{pmatrix}e^{h} & e^{-h}\end{pmatrix}BB^{-1}T_0^{N-i-l}BB^{-1}T_{ex}BB^{-1}T_{tub}^{l-1}BB^{-1}T_{ex}BB^{-1}T_0^{i-2}BB^{-1}\begin{pmatrix}e^{-h}\\ e^{h}\end{pmatrix}. \tag{28}$$

It follows that:

$$f(i,l)=\frac{1}{Z}\begin{pmatrix}e^{h} & e^{-h}\end{pmatrix}B\begin{pmatrix}e^{-J}-e^{J} & 0\\ 0 & e^{J}+e^{-J}\end{pmatrix}^{N-i-l}\begin{pmatrix}e^{-J} & 0\\ 0 & e^{-J}\end{pmatrix}\begin{pmatrix}-e^{J} & 0\\ 0 & e^{J}\end{pmatrix}^{l-1}\begin{pmatrix}e^{-J} & 0\\ 0 & e^{-J}\end{pmatrix}\cdots$$
$$\cdots\begin{pmatrix}e^{-J}-e^{J} & 0\\ 0 & e^{J}+e^{-J}\end{pmatrix}^{i-2}B^{-1}\begin{pmatrix}e^{-h}\\ e^{h}\end{pmatrix} \tag{29}$$

$$f(i,l)=\frac{1}{Z}(-1)^{N-2}e^{(l-3)J}\left(2\sinh(J)\right)^{N-l-2}\sinh(h)^2+e^{(l-3)J}\left(2\cosh(J)\right)^{N-l-2}\cosh(h)^2. \tag{30}$$

As Z is calculated, the final result is:

$$f(i,l)=\frac{e^{(l-3)J}\left[(-1)^{N-2}\left(\sinh(J)\right)^{N-l-2}\sinh(h)^2+\left(\cosh(J)\right)^{N-l-2}\cosh(h)^2\right]}{2^{l+1}\left[(-1)^{N}\left(\sinh(J)\right)^{N-1}\sinh(h)^2+\left(\cosh(J)\right)^{N-1}\cosh(h)^2\right]}. \tag{31}$$

For the alternately ordered part of the pseudo-polyrotaxane touching one of the ends of the polymer chain, the operator is:

$$f(1,l)=f(N-l+1,l)=\frac{e^{(l-2)J}\left[(-1)^{N-1}\left(\sinh(J)\right)^{N-l-1}\sinh(h)^2+\left(\cosh(J)\right)^{N-l-1}\cosh(h)^2\right]}{2^{l}\left[(-1)^{N}\left(\sinh(J)\right)^{N-1}\sinh(h)^2+\left(\cosh(J)\right)^{N-1}\cosh(h)^2\right]}. \tag{32}$$

If the pseudo-polyrotaxane is well ordered over the whole length of the polymer chain, the operator is:

$$f(1,N)=\frac{e^{(N-1)J}\left[(-1)^N\sinh(h)^2+\cosh(h)^2\right]}{2^{N-1}\left[(-1)^N(\sinh(J))^{N-1}\sinh(h)^2+(\cosh(J))^{N-1}\cosh(h)^2\right]}. \tag{33}$$

4.3.3 Average length of the empty α-cyclodextrin molecular tubes for a system without end effects

Assume that the interaction energies, ε_1 and ε_2, are equal and that there are no field effects at the ends of the included polymer chain, then the Hamiltonian can be written as:

$$H=J\sum_i S_i S_{i+1}\ . \tag{34}$$

The operators calculated before can then be written as:

$$f(i,l)=\frac{e^{(l-3)J}}{(\cosh(J))^{l+1}2^{l+1}}, \tag{35}$$

$$f(1,l)=f(N-l+1,l)=\frac{e^{(l-2)J}}{(\cosh(J))^{l}2^{l}}, \tag{36}$$

$$f(1,N)=\frac{e^{(N-1)J}}{2^{N-1}(\cosh(J))^{N-1}}. \tag{37}$$

This can be written in an exponential form by the introduction of a decreasing length, $\bar{l}$:

$$\bar{l}=\frac{1}{\ln\left(1+e^{-2J}\right)}. \tag{38}$$

So the operators are:

$$
\begin{array}{ll}
1 \le l \le N-2 & \begin{cases} f(i,l) = \left(1 - e^{-1/\bar{l}}\right)^2 e^{-(l-1)/\bar{l}} & 1 < i < N-l-1 \\ f(1,l) = f(N-l+1,l) = \left(1 - e^{-1/\bar{l}}\right) e^{-(l-1)/\bar{l}} & i = 1 \text{ and } i = N-l+1 \end{cases} \\
l = N-1 & f(1,N-1) = f(2,N-1) = \left(1 - e^{-1/\bar{l}}\right) e^{-(N-2)/\bar{l}} \\
l = N & f(1,N) = e^{-(N-1)/\bar{l}}
\end{array}
\quad , \quad (39)
$$

Note the decreasing length, $\bar{l}$, is close to the correlation length ξ, which is:

$$\xi = \frac{1}{\ln \coth J} \, . \qquad (40)$$

In figure 4.3 the top curve represents two times the correlation length (2ξ) and the lower one represents the value of $\bar{l}$ both as a function of the interaction between the cyclodextrins (J). When the interaction between the cyclodextrins (J) becomes large, the two curves join. Thus $\bar{l}$ is a value, closely related to twice the correlation function ξ.

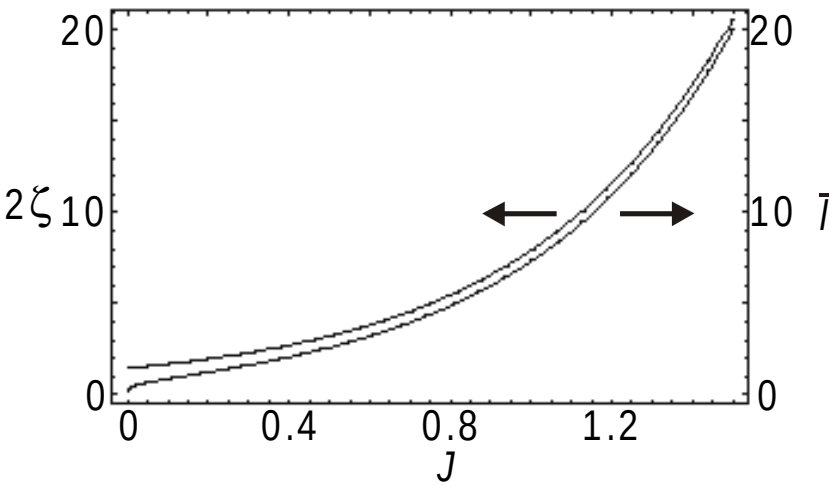

Figure 4.3. *Twice the correlation length (2ξ) (top curve) and the decreasing length ($\bar{l}$) versus interaction parameter* (J).

It is now possible, to calculate the distribution of the parts of the pseudo-polyrotaxanes well ordered over a length, l:

$$f(l)=\sum_i f(i,l)=\begin{cases}2f(1,l)+(N-l-1)f(i,l) & \text{for } 1\leq l\leq N-2\\ 2f(1,l) & \text{for } l=N-1\\ f(1,N) & \text{for } l=N\end{cases}. \quad (41)$$

The distribution of the lengths of the well ordered parts of the pseudo-polyrotaxanes is decreasing with a typical length $\bar{l}$. This gives the opportunity to calculate the average length of the well ordered part of the pseudo-polyrotaxane, which is written as:

$$<l>=\frac{\sum_{l=1}^{N} lf(l)}{\sum_{l=1}^{N} f(l)}=\frac{N}{N\left(1-e^{-\frac{1}{\bar{l}}}\right)+e^{-\frac{1}{\bar{l}}}}. \quad (42)$$

In the graph shown in figure 4.4, it is possible to follow the average length of the well ordered parts of the pseudo-polyrotaxanes <l> as function of the value of $\bar{l}$. Note the length saturates as the interaction between the cyclodextrins is strong. In that case the cyclodextrins in the pseudo-polyrotaxane are alternating over the whole length of the polymer. This variation as function of parameter J is also shown in figure 4.5

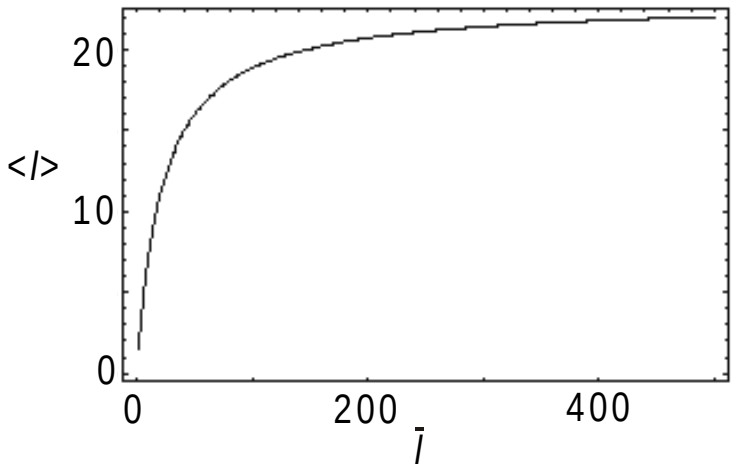

Figure 4.4. *Average length of alternating cyclodextrins (*<l>*) versus* $\bar{l}$.

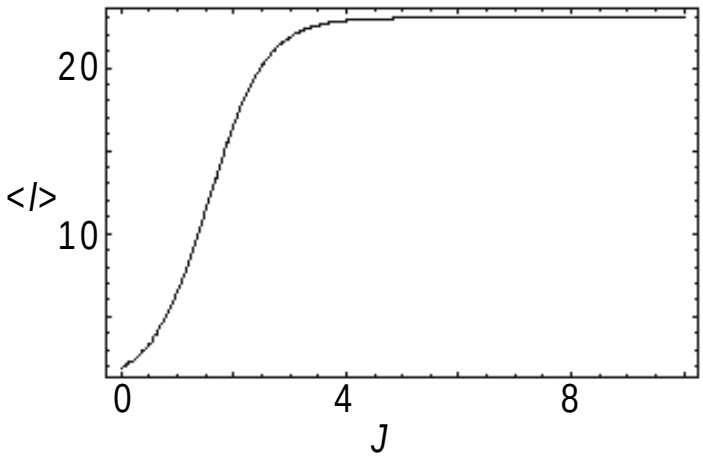

Figure 4.5. *Average length of alternating cyclodextrins (<l>) versus interaction parameter (J).*

Finally, three typical length distributions are shown for $\bar{l}$ «*N* (figure 4.6), $\bar{l} \cong N$ (figure 4.7), $\bar{l}$ »*N* (figure 4.8). Note a slope in the curve means, that there is a mixture of lengths since an average length is considered and further note that the possibility of a pseudo-polyrotaxane well ordered over the whole length of the polymer, is much larger when the interaction is average, than of obtaining a shorter alternating part (figure 4.7).

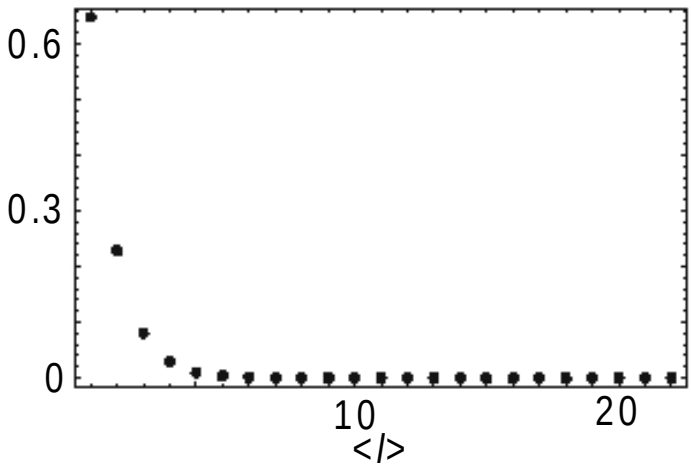

Figure 4.6. *Length distribution for* $\bar{l}$ «N.

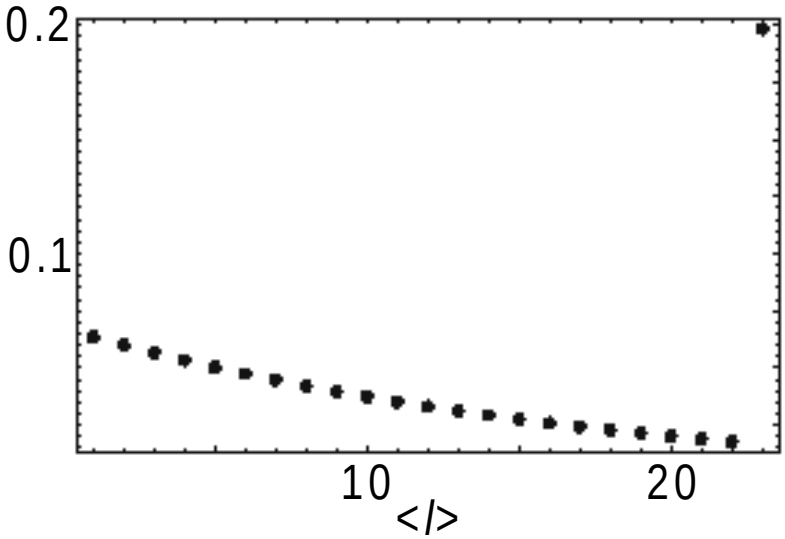

Figure 4.7. *Length distribution for* $\bar{l} \cong N$.

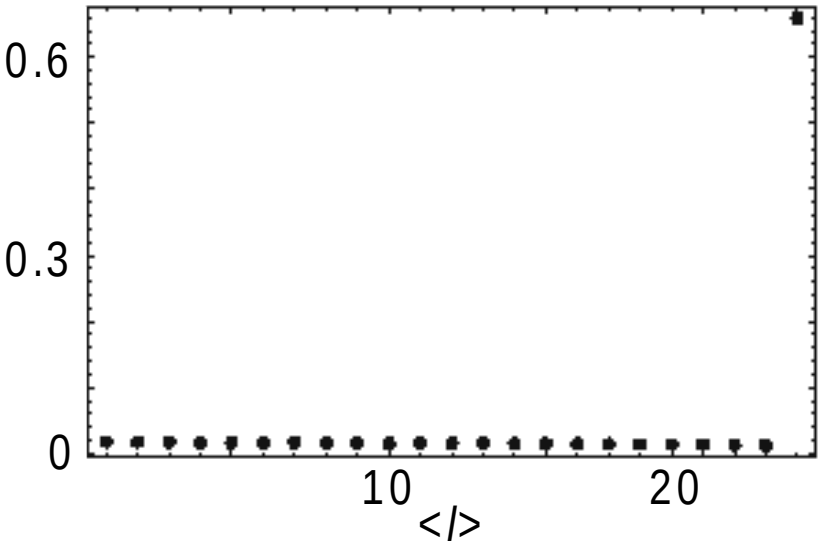

Figure 4.8. *Length distribution for* $\bar{l}$ »N.

4.3.4 Average length of the empty α-cyclodextrin molecular tubes for a system with end effects

Since the interactions (ε) between the cyclodextrins threaded on the polymer chain, are not the same when the large sides are oriented towards each other and when the small sides are oriented towards each other, a field effect occurs at the ends. Due to this field effect, formulas (31), (32) and (33) have to be used entirely (§ 4.3.2). Just as before, the formulas in the exponential form are used, however, this time two specific lengths have to be introduced:

$$\bar{l}_1 = \frac{1}{\ln\left(1+e^{-2J}\right)} \text{ and } \bar{l}_2 = \frac{1}{\ln\left(1-e^{-2J}\right)}. \tag{43}$$

The equations can be written as:

$$f(i,l) = \frac{(-1)^N \tanh^{N-1}(J)\tanh^2(h)\left(e^{1/\bar{l}_2}-1\right)^2 e^{(l-1)/\bar{l}_2} + \left(1-e^{-1/\bar{l}_1}\right)^2 e^{-(l-1)/\bar{l}_1}}{(-1)^N\left(\tanh^{N-1}(J)\right)\tanh^2(h)+1}, \tag{44}$$

$$f(1,l) = f(N-l+1,l) = \frac{(-1)^{N-1} \tanh^{N-1}(J)\tanh^2(h)\left(e^{1/\bar{l}_2}-1\right)^2 e^{(l-1)/\bar{l}_2} + \left(1-e^{-1/\bar{l}_1}\right) e^{-(l-1)/\bar{l}_1}}{(-1)^N\left(\tanh^{N-1}(J)\right)\tanh^2(h)+1}, \tag{45}$$

$$f(1,N) = \frac{(-1)^N \tanh^{N-1}(J)\tanh^2(h) e^{(N-1)/\bar{l}_2} + e^{-(N-1)/\bar{l}_1}}{(-1)^N\left(\tanh^{N-1}(J)\right)\tanh^2(h)+1}, \tag{46}$$

$$f(l) = \sum_i f(i,l) = \begin{cases} 2f(1,l) + (N-l-1)f(i,l) & \text{for } 1 \le l \le N-2 \\ 2f(1,l) & \text{for } l = N-1 \\ f(1,N) & \text{for } l = N \end{cases} \tag{47}$$

Finally, an average length can be obtained from:

$$< l >= \frac{\sum_{l=1}^{N} l f(l)}{\sum_{l=1}^{N} f(l)} = \frac{f_N(h,J)+1}{N\left(1-e^{-1/l_1}\right)+e^{-1/l_1}+f_N(h,J)e^{1/l_2}+N\left(1-e^{1/l_2}\right)}, \quad (48)$$

with:

$$f_N(h,J) = (-1)^N \tanh^{N-1}(J)\tanh^2(h). \quad (49)$$

It is possible to follow the curves for <*l*> as function of *J*, for different pseudo-polyrotaxanes consisting of 23 and 24 cyclodextrins for different values of *h* (figure 4.9, figure 4.10, figure 4.11, and figure 4.12). Note again average lengths are considered and thus a slope in the curves means a mixture in lengths. Note further the average value of a chain formed by an odd number of cyclodextrins, is half the value of a chain consisting of an even number of cyclodextrins for high values of *h* and *J* average. When *J* increases further, the tube length saturates to the maximum value for both types of chains. When *J* decreases, multiple defects are introduced into the complex.

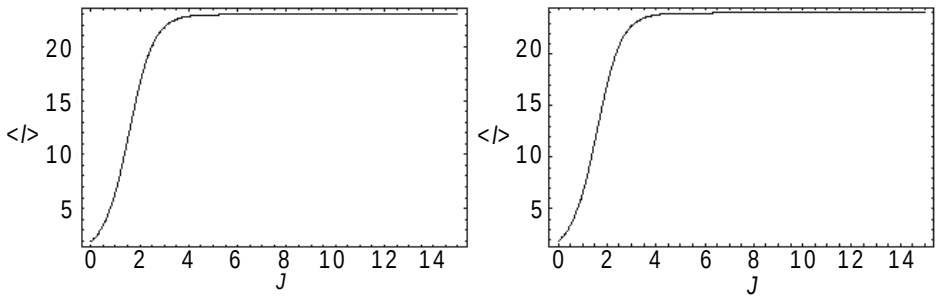

Figure 4.9. *Average length of the alternating part of the pseudo-polyrotaxane (*<l>*) versus interaction parameter (*J*) with* h *= 0; for a pseudo-polyrotaxane consisting of 23 cyclodextrins (left) and for a pseudo-polyrotaxane consisting of 24 cyclodextrins (right).*

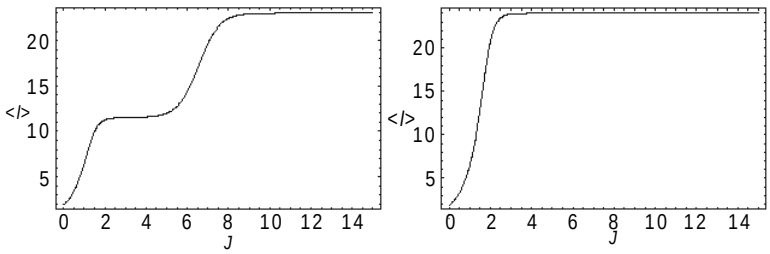

Figure 4.10. *Average length of the alternating part of the pseudo-polyrotaxane (<l>) versus interaction parameter (J) with* h *= 5; for a pseudo-polyrotaxane consisting of 23 cyclodextrins (left) and for a pseudo-polyrotaxane consisting of 24 cyclodextrins (right).*

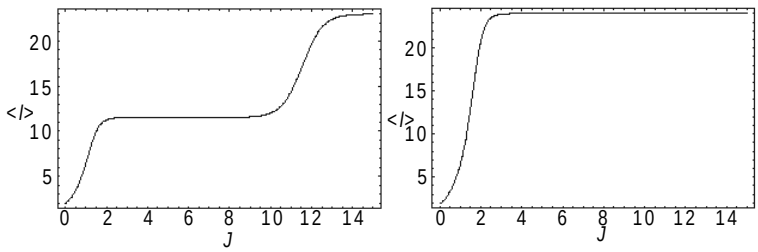

Figure 4.11. *Average length of the alternating part of the pseudo-polyrotaxane (<l>) versus interaction parameter (J) with* h *= 10; for a pseudo-polyrotaxane consisting of 23 cyclodextrins (left) and for a pseudo-polyrotaxane consisting of 24 cyclodextrins (right).*

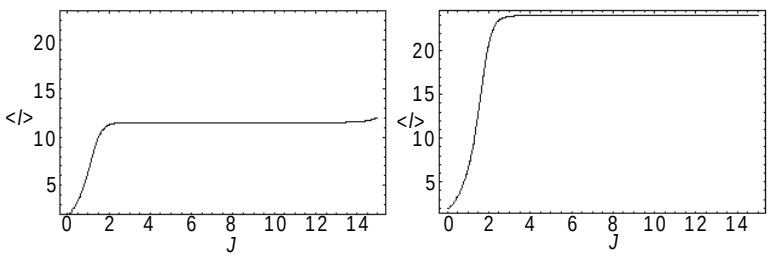

Figure 4.12. *Average length of the alternating part of the pseudo-polyrotaxane (<l>) versus interaction parameter (J) with* h *= 15; for a pseudo-polyrotaxane consisting of 23 cyclodextrins (left) and for a pseudo-polyrotaxane consisting of 24 cyclodextrins (right).*

The reason is, that when *h* is not 0, one interaction energy is larger than the other, $\varepsilon_2 > \varepsilon_1$, since the large sides can form more hydrogen-bonds with each other than the small sides. Consequently, the cyclodextrins are oriented in such a way to have as many as possible hydrogen-bonds and the cyclodextrins situated at the ends of the chains, have the tendency to have the narrow sides towards the ends in order to have more large sides oriented towards each other inside the complex. What makes the difference, between pseudo-polyrotaxanes containing of an odd number of cyclodextrins, contrary to pseudo-polyrotaxanes containing of an even number of cyclodextrins, is the always existing asymmetric interaction between two cyclodextrins (figure 4.13). This causes an average length of half the number of the cyclodextrins. When *J* is large enough, the system orients in such a way all cyclodextrins alter in direction. So one of the two cyclodextrins at the end has its large side oriented to the exterior.

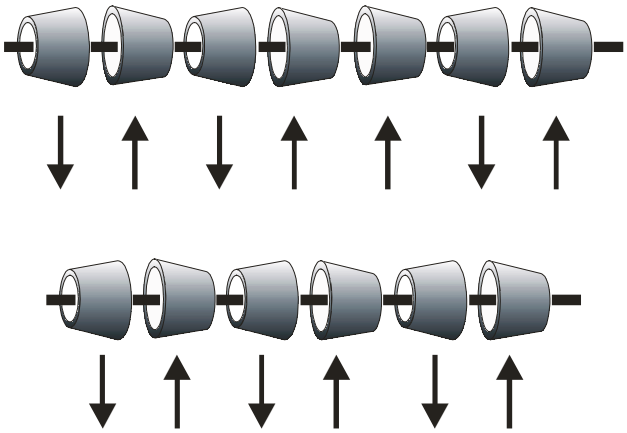

Figure 4.13. *Pseudo-polyrotaxane containing an odd number of cyclodextrins (top) and an even number of cyclodextrins.*

4.4 Discussion and conclusion

In this study, a chemical phenomenon is modeled in order to find a way to improve the possibilities for obtaining longer empty α-cyclodextrin molecular tubes, by studying the orientation of the cyclodextrins on the polymer chain. In order to study the thermodynamic equilibrium, a one dimensional Ising model is constructed, able to describe the complexation phenomenon. The next problem is to compare the obtained results, while leaving behind the molecular phenomenon, and draw the consequences from the parameters introduced.

The most important effect on the threading comes from the structure of the cyclodextrins themselves, which gives rise to different interaction energies ε_0, ε_1, ε_2. The bonds, formed between the cyclodextrins, are hydrogen-bonds having energy in the order of k_BT. Cyclodextrins have six possibilities to form hydrogen-bonds at their narrow side and twelve hydrogen-bonds at their large side. Every interaction is worth 2 units k_BT and it is assumed that bonds are formed between each side in contact with their neighbor. In that case $\varepsilon_0 = \varepsilon_1 = 12$ and $\varepsilon_2 = 24$, this gives a value of $J = 3$ (eq. 3). This value of J is in the order of J necessary for obtaining a length of 6 cyclodextrins per tube (≈ 1) as found experimentally by SANS experiments. The difference can be due to the following fact: The interactions are not forced effectively after the positioning of the bonds between those. This means, the thermodynamic equilibrium is not yet reached.

On the other hand in the case of end effects it appears the interaction energies cause a large difference between J and h, in favor of J, so the end effects will have much influence on the average length of the empty α-cyclodextrin molecular tubes eventually obtained. An example is the pseudo-polyrotaxane, containing 23 cyclodextrins, described.

The important point is the question, why the thermodynamic equilibrium is not yet reached. The exploration of all possible configurations depends on the kinetics of the complexation of the cyclodextrins on the "template polymer". When the speed is increased, the cyclodextrins thread very fast and there is no time to change positions anymore. In that case the phenomenon is completely random ($J = 0$), there is no effect of the cyclodextrin structure and no spin is favored. In such a random model the average length obtained is small. Thus the hypothesis the interactions between the cyclodextrins play a role, is visible from the start.

According to this model J can be increased by increasing the temperature (T). According to figure 4.10, figure 4.11 and figure 4.12 a higher value of J will yield pseudo-polyrotaxanes containing cyclodextrins that are alternating over a longer distance and thus result in longer empty α-cyclodextrin molecular tubes. However, no significant difference was observed in the empty tubes, for which the pseudo-polyrotaxane was synthesized at 80 °C instead of at room temperature (§ 3.3.5). This result is contrary to the result found for the threading process itself which is favored at low temperatures.[3] However, as found here a lower temperature would increase the number of defects. This might imply that is impossible to obtain a long cyclodextrin molecular tube when only the temperature is the only parameter varied. By adding cations or anions in the threading process, it might be possible to find an optimum temperature.[1]

Gradual addition of cyclodextrin could help, to attain the thermodynamic equilibrium, although again no significant difference was observed when the pseudo-polyrotaxane was synthesized using this procedure (§ 3.3.5).

4.5 References

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Chapter 5

Inclusion of polyaniline by α-cyclodextrin molecular tubes

Abstract

Inclusion of polyaniline, which is a conducting polymer once doped, by α-cyclodextrin molecular tubes is described. The inclusion compounds formed might be used as insulated single-chain conducting polymer wires. These insulated single-chain conducting polymer wires might open the way to the technology of the molecular electronics of the near future. The formation of inclusion compounds could be detected by UV−Vis. The UV−Vis absorption of the mixture of polyaniline and α-cyclodextrin molecular tubes in water/NMP is decreased and shifted to lower wavelengths compared to pure polyaniline in water/NMP. Using AFM it was possible to visualize the complexes formed. This showed that there were two types of inclusion compounds obtained. One type of inclusion compound was composed of one polyaniline chain and multiple α-cyclodextrin molecular tubes. The other complex was like a kind of molecular necklace composed of multiple polyaniline chains and multiple α-cyclodextrin molecular tubes. The length of these molecular necklaces increased with time. The longest molecular necklaces observed had a length of more than 1 μm. At some point the molecular weight of the molecular necklace became so high they precipitated out.

5.1 Introduction

The discovery of the metallic properties of doped polyacetylene in 1977 by MacDiarmid, Heeger and Shirakawa was a major breakthrough in organic (semi-)conducting materials and their applications.[1] Since then remarkable progress has been achieved in the synthesis of conjugated polymers, and the understanding of their properties.

In the field of electronic engineering, miniaturization is one of the prime focal points. This will reach a limit in the near future due to physical limitations. The chemical approach of which the work described in this chapter is one example, may offer a solution to this challenge. A molecular wire, the simplest and also smallest possible electronic component can be represented by a one-dimensional molecule that can transport charge carriers between its ends. Research on these electronic components has been focused primarily on the synthesis of conducting molecules and the evaluation of their ability to transport charge.[2,3,4,5] The actual incorporation of such conducting molecules in an insulating environment has been much less studied until now.

Solubility is a prime requirement for the application of any conjugated polymer in molecular electronics. The substitution of pendant groups to the conjugated backbone is one of the most used strategies for obtaining soluble conjugated polymers. Depending on the type of conjugated backbone and type of substituents, the electronic properties are affected to a greater or lesser extent. An unfavorable example is polyacetylene, which loses its conjugation and conductivity when substituents are added.[6]

Instead of modifying the polymer backbone with substituents, here a different strategy is described for obtaining soluble conjugated polymers. This strategy is the use of complex formation with a conjugated polymer as guest and cyclodextrins as hosts.

The synthesis of the α-cyclodextrin molecular tubes used for this purpose is described in chapter 2. The α-cyclodextrin molecular tubes obtained have an inside diameter of approximately 0.5 nm (see figure 2.4). The characterization of the empty α-cyclodextrin molecular tubes showed the tubes obtained are much smaller than expected. According to the models fitted to the SANS data, the empty α-cyclodextrin molecular tubes are composed of only 5 to 6 cyclodextrins and so have a length of only 5 to 6 nm.

Despite the shorter than expected length of the empty α-cyclodextrin molecular tubes, it is expected that the α-cyclodextrin molecular tubes obtained are able to included various kinds of guests, just as predicted for long α-cyclodextrin molecular tubes.[7] Recently the complexation of sodium dodecyl sulfate in α-cyclodextrin molecular tubes was reported.[8] In this chapter the complexation of polyaniline, a conjugated polymer, in α-cyclodextrin molecular tubes is described.

In this chapter inclusion compounds are obtained by mixing the α-cyclodextrin molecular tubes in water with polyaniline in *N*-methyl-2-pyrrolidinone (NMP) at room temperature.

The inclusion compounds were visualized by AFM. The formation of inclusion compounds is also studied by UV−Vis spectroscopy.
Figure 5.1A shows the structural formula of polyaniline. Figure 5.1B shows a 3D image of one repeating unit. Using this molecular model it can be found that the maximum diameter of a polyaniline chain is 0.4 nm. Polyaniline is a conducting polymer when doped.[9,10]

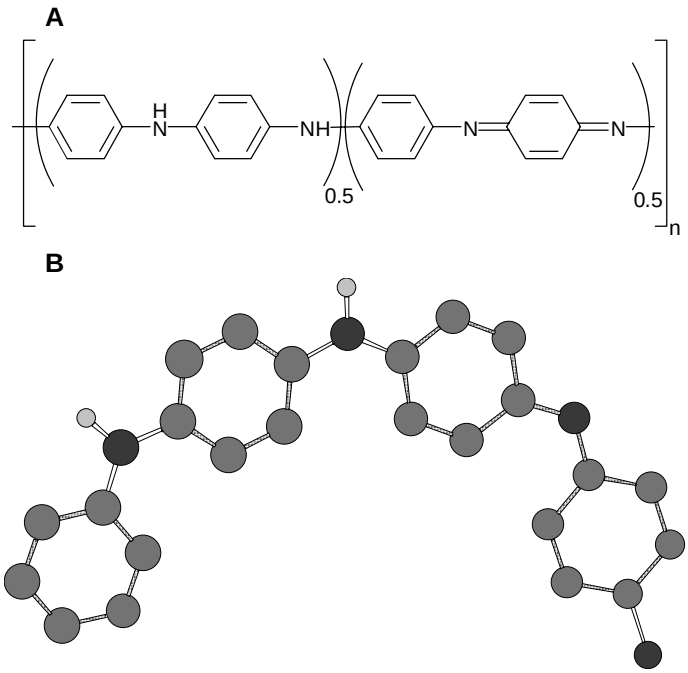


Figure 5.1. *A) Structural formula of polyaniline emeraldine base. B) Molecular model of one repeating unit of polyaniline emeraldine base.*

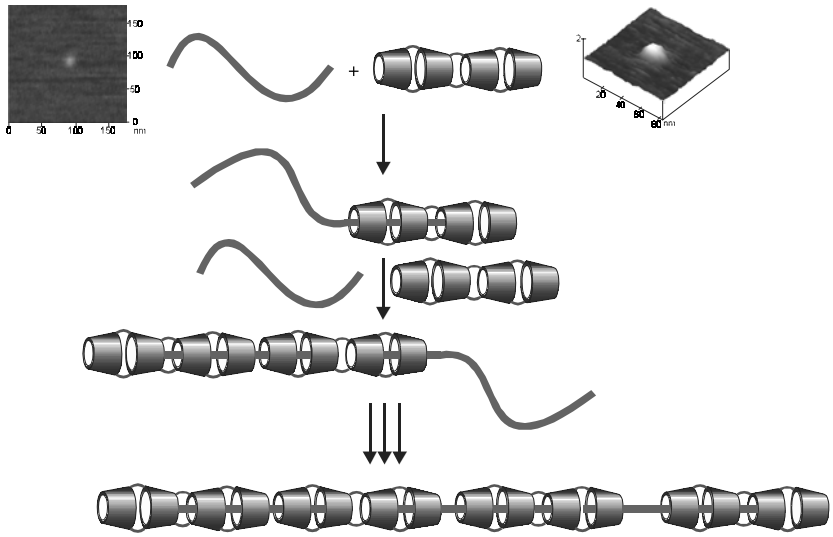
Previously it was reported that β-cyclodextrin could thread on polyaniline.[11,12] On the other hand polyaniline could not form inclusion compounds with α-cyclodextrins. This illustrates the complexation properties of the α-cyclodextrin molecular tube is different from the α-cyclodextrin building blocks. The pseudo-polyrotaxanes consisting of polyaniline and β-cyclodextrin dissociated at elevated temperatures.[11,12] This pseudo-polyrotaxane was proposed to be an insulated molecular wire.
Recently the polymerization of monomer units included by cyclodextrins was described. This yielded a pseudo-polyrotaxane having a conjugated polymer as thread and cyclodextrins as rings. The pseudo-polyrotaxane obtained was proposed to be an insulated molecular wire as well.[13]

5.1.1 Insulated molecular wires

In the literature the polymerization of polymers inside zeolites was published.[14] The zeolite might acts as the insulator.[15] Thiophene monomer was introduced into the pore system of different types of zeolite hosts. The zeolites varied in pore size. Oxidized polythiophene was obtained in zeolites with a pore size of about 0.7 nm. However, no polymerization was observed in the pores of zeolites with pore-openings of about 0.4 nm since the small pore openings did not allow monomer diffusion into the zeolite pores.
Provided that structural features and control of electronic transport properties is achieved at a molecular level, low-dimensional conductors can be obtained. These offer the potential of reducing electronic circuitry to molecular dimensions.
Carbon nanotubes can be used as “nano-wires”.[16,17] Also organic molecules with long conjugated π systems can be regarded as “molecular wires” because they have mobile electrons.[18] These conjugated polymers have many potential applications, for example in non-linear optics, in organic electroluminescent display devices and as organic semiconductors, but the small HOMO−LUMO energy gaps responsible for their special electronic properties often lead to chemical reactivity and instability, which can limit their usefulness.[19] By encapsulation of the conjugated chain the stability of the insulated molecular wire is increased. The encapsulation of conducting polymers has been explored by many other groups in a variety of ways. Molecular wires have been insulated by threading them through zeolite frameworks,[20] and by using ligand shells.[21] Since doped polyaniline is a semi-conducting polymer, the inclusion complex consisting of polyaniline inside α-cyclodextrin molecular tubes can be considered to be an insulated molecular wire.

5.2 Results

Polyaniline was synthesized according to a procedure described in the literature.[22] The molecular weight of the synthesized polyaniline was difficult to determine.[22] However, according Cao *et al.*, the molecular weight of polyaniline synthesized according to this procedure, is approximately 6.10^3 $g.mol^{-1}$.[23] Using chemical models it can be calculated that the contour length of this molecular weight of polyaniline is approximately 30 nm.



Scheme 5.1. *Formation of molecular necklace composed of polyaniline and α-cyclodextrin molecular tubes. The AFM images on the top display a polyaniline blob (top left) and an isolated α-cyclodextrin molecular tube (top right) on mica.*

Solutions of polyaniline in NMP and α-cyclodextrin molecular tubes in water are mixed at room temperature (scheme 5.1). Upon mixing the dark blue solution of polyaniline in NMP with the colorless solution of α-cyclodextrin molecular tubes in water a light blue solution is obtained. This solution is stable for about one week. After about one week a blue precipitate is formed. When the polyaniline is added to the same amount of pure water, so without α-cyclodextrin molecular tubes, a blue precipitate is formed within 5 minutes. The solutions obtained after mixing polyaniline and α-cyclodextrin molecular tubes were studied by AFM and UV−Vis.

5.2.1 Study of the threading by Ultra-Violet and Visible light spectroscopy

Inclusion complex formation could be observed by UV−Vis spectroscopy. The dashed line in figure 5.2 shows polyaniline in NMP/water. Upon mixing polyaniline and α-cyclodextrin molecular tubes, there is a blue shift (lower wavelengths) for the polyaniline absorption and the intensity of the absorption decreases (figure 5.2). This absorption is stable in time. A decrease in intensity is observed more often upon complexation in a macrocycle.[18,24,25,26,27] Also shifts in the absorption maximum are observed more often upon inclusion in cyclodextrins and can be attributed to sometimes competing factors. Both a change in the

dielectric constant of the chain's surroundings and a deformation of the chain backbone may cause such changes in the spectrum. The observed differences in the spectrum then might be due to the fact that the included molecule is in a different environment compared to the molecule in pure solution.[28,29,30] The polyaniline chain is in a less polar environment, compared to the free polyaniline chains in H_2O/NMP and pure NMP. This also explains the difference in absorption maximum between polyaniline dissolved in NMP and in H_2O/NMP, or more general the difference in absorption maximum due to a different solvent.[26,31] As mentioned differences can also be caused by conformational changes of the included molecule compared to the free molecule. It might be expected, that the included polyaniline chain is more planar than the free polyaniline chain. In the literature it was predicted by using theoretical calculations that a more planar, better-conjugated conformer would absorb at lower wave lengths than a twisted conformer.[32] However, it was found that in the case of several modified 1,4-pentadien-3-one the more planar, better-conjugated conformer absorbed at higher wavelength.[33] This indicates results concerning planar and twisted conformers are not directly transposable.

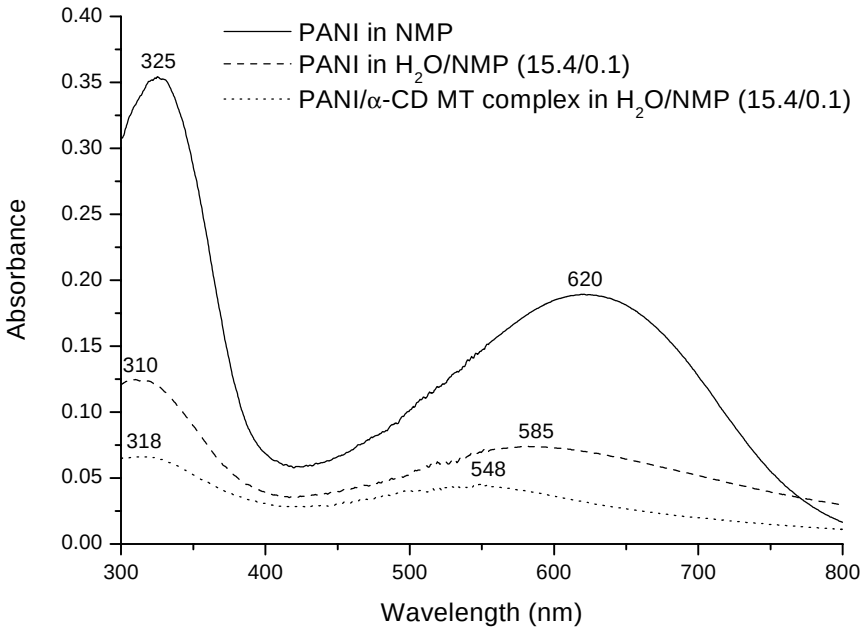


Figure 5.2. *UV−Vis spectra of polyaniline in NMP (solid line), of polyaniline in H_2O/NMP (15.4/0.1) (dashed line) and of the mixture of polyaniline and α-cyclodextrin molecular tubes (dotted line).*

5.2.2 Visualization of the polyaniline inclusion compounds by Atomic Force Microscopy

Using UV−Vis it was possible to identify inclusion compounds were formed. To determine the size and shape of these inclusion compounds AFM was used.
First of all the polyaniline chains were visualized by AFM on mica. When polyaniline is dissolved in NMP and added to the same amount of water in the absence of α-cyclodextrin molecular tubes and the solution is immediately drop-cast on mica, blobs are observed (top left AFM image in scheme 5.1). As mentioned before in the absence of α-cyclodextrin molecular tubes a blue precipitate is formed within 5 minutes.
The solutions containing polyaniline and α-cyclodextrin molecular tubes were drop-cast on mica and graphite. On mica elongated features were observed. No features were observed on the graphite surfaces.

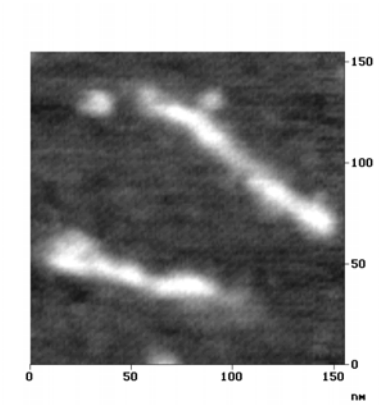


Figure 5.3. *AFM image of inclusion compounds composed of polyaniline and α-cyclodextrin molecular tubes on mica: Small pseudo-polyrotaxanes (top left feature) and long molecular necklaces.*

Surprisingly, AFM images showed two kinds of elongated features. First of all there were features with a length of approximately 30 nm (figure 5.3 and figure 5.4). This length corresponds to the contour length of one polyaniline chain. These features should be pseudo-polyrotaxanes composed of one polyaniline chain and multiple α-cyclodextrin molecular tubes. As mentioned in § 3.3.4 the empty α-cyclodextrin molecular tubes are too small to be observed by AFM. The height of the pseudo-polyrotaxanes is approximately 1 nm. This is close to the external diameter of an α-cyclodextrin and an α-cyclodextrin molecular tube (see table 1.1 and figure 2.4). The height profile is shown in figure 5.4B.

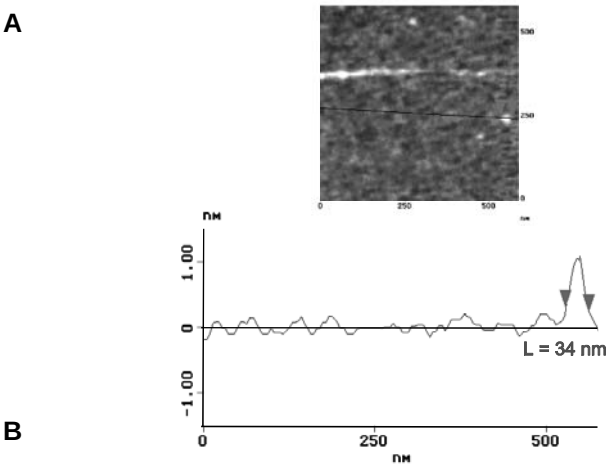


Figure 5.4. *A) AFM images showing large (top) and small inclusion compounds composed of polyaniline and cyclodextrin molecular tubes. B) Height profile of the pseudo-polyrotaxane.*

Elongated features with a length larger than 30 nm were also observed. Figure 5.3 shows an AFM image containing two of these features on freshly cleaved mica. The features have a length of approximately 100 nm. Since 100 nm is longer than the contour length of the polyaniline chains and the length of the α-cyclodextrin molecular tubes, the features are most likely molecular necklaces composed of multiple polymer chains linked by multiple α-cyclodextrin molecular tubes. Linking the polyaniline chains together by α-cyclodextrin molecular tubes can be depicted as shown in scheme 5.1. The height of these molecular necklaces is also approximately 1 nm (figure 5.5B). The trace of the height profile shows that there is some space between some α-cyclodextrin molecular tubes (figure 5.5B). The minimum distance found between gaps is approximately 5-6 nm, so this corresponds to 1 α-cyclodextrin molecular tube.

The length of the molecular necklaces obtained depends on time, although no real correlation could be determined. In general the longer the time between the formation of the molecular necklace and the drop-casting on mica the longer the molecular necklaces are. The number of long molecular necklaces is limited. Of the two types of inclusion compounds observed, pseudo-polyrotaxanes are always the most numerous. The longest molecular necklaces observed have a length of more than 1 μm (figure 5.6).

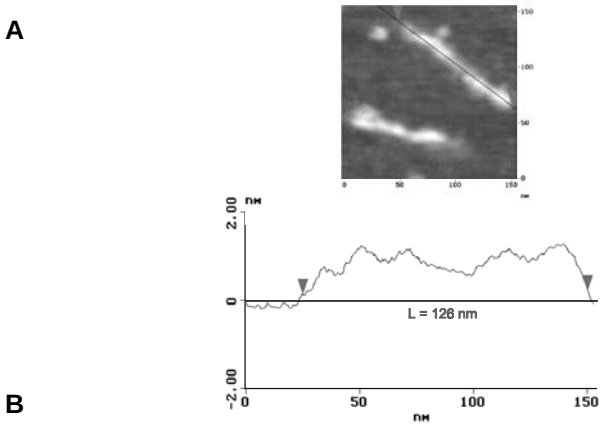


Figure 5.5. *A) AFM image showing two molecular necklaces composed of multiple polyaniline chains and multiple α-cyclodextrin molecular tubes, B) Height profile of one of the molecular necklaces.*

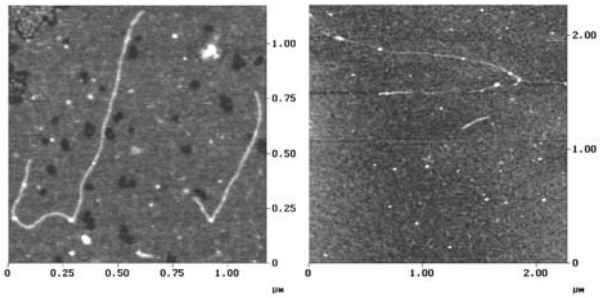


Figure 5.6. *Some molecular necklaces composed of polyaniline and α-cyclodextrin molecular tubes are more than 1 μm long.*

5.3 Discussion and conclusion

Inclusion compounds consisting of polyaniline, which is a conducting polymer once doped, and α-cyclodextrin molecular tubes have been observed by AFM. AFM showed two types of inclusion compounds composed of polyaniline and α-cyclodextrin molecular tubes. One type of inclusion compound is composed of one polyaniline chain and multiple α-cyclodextrin molecular tubes. The other inclusion compound is a kind of molecular necklace that is composed of multiple polyaniline chains and multiple α-cyclodextrin

molecular tubes. For both types, the α-cyclodextrin molecular tubes cover the polyaniline chain almost completely. The length of the molecular necklaces increases with time. The longest molecular necklaces observed have a length of more than 1 μm. At some point the molecular weight of the molecular necklace becomes so high that they precipitate out.
The intensity of the UV−Vis absorption of the mixture of polyaniline and α-cyclodextrin molecular tubes in water/NMP is decreased and shifted to lower wavelengths compared to pure polyaniline in water/NMP.
A possible reason for the formation of the inclusion compounds is that dissolution of polyaniline in water would result in a strong decrease in entropy as a result of hydration. Rather than precipitating from solution, the polyaniline chains form inclusion compounds with the α-cyclodextrin molecular tubes, due to a substantial enthalpic interaction on binding to the tube interior.
As described polyaniline chains can be threaded by α-cyclodextrin molecular tubes. However, polyaniline can not be threaded by α-cyclodextrins.[11,12] This suggests the structure of the cyclodextrin rings in the α-cyclodextrin molecular tubes is modified by the process of cross-linking of the adjacent cyclodextrins.
The inclusion compounds might be used as insulated single-chain conducting polymer wires. Because the polyaniline is included inside α-cyclodextrin molecular tubes the shielding of the polyaniline from the environment will be better than in the case of the insulated molecular wires based on β-cyclodextrin, reported in the literature[11,12] since the number of openings between the cyclodextrins is reduced. The pseudo-polyrotaxane composed of one polyaniline chain and multiple α-cyclodextrin molecular tubes might ultimately enable one to measure the conductivity of one single polyaniline chain. The molecular necklace consisting of multiple polyaniline chains and multiple α-cyclodextrin molecular tubes might eventually enable one to study the charge transport ("hopping") between the ends of two polyaniline chains. Besides for studying these fundamental properties, these insulated single-chain conducting polymer wires might open the way to the technology of the molecular electronics of the future.

5.4 Experimental

Materials and methods

The synthesis of α-cyclodextrin molecular tubes is described in chapter 2. Polyaniline was synthesized according to a procedure described in the literature.[22] According to Cao *et al.*, the molecular weight of polyaniline synthesized according to this procedure, is approximately 6.10^3 $g.mol^{-1}$.[23] *N*-methyl-2-pyrrolidinone (NMP) was purchased from ACROS. The water used was 18 MΩ ultra pure water obtained from an Elga Maxima water purification system.

Measurements
UV−Vis spectra were recorded on a SLM Aminco 3000 Array.

AFM sample preparation
AFM images were recorded with a NanoScope IIIa (Digital Instruments, Inc., Santa Barbara (US)), equipped with NT-MDT ultra-sharp silicon cantilever tips (NSC 21 series). Topographic images were taken in air in "Tapping Mode". Solutions were drop-cast on freshly cleaved muscovite mica (grade 2, obtained from Mica New York Corporation).

Inclusion of polyaniline by α-cyclodextrin molecular tubes
PANI (6 μg) was dissolved in 0.10 ml NMP. α-CD molecular tube **25** (1.70 mg) was dissolved in 15.4 ml H_2O. The two solutions were mixed at room temperature and the mixture was ultrasonically agitated at room temperature for 10 min.

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Chapter 6

Synthesis of polyrotaxanes based on polythiophene and β-cyclodextrin

Abstract

An insulated single-chain conducting polymer wire would give the opportunity to measure the conductivity of a single polymer chain. The synthesis of a soluble high molecular weight conjugated polymer opens the way to both the technology of the molecular electronics of the future and to fundamental studies of polymer conductivity at a molecular level.
A stable polyrotaxane consisting of polythiophene and β-cyclodextrins was synthesized. Using MALDI-TOF it was possible to determine the molecular weight of the polythiophene polymer inside the polyrotaxane. It was found that this polymer consisted of 12 bithiophene repeating units and contained two anthracene blocking groups. Each bithiophene repeating unit can be included by one β-cyclodextrin having a height of 0.79 nm and an inside diameter of approximately 0.74 nm (table 1.1). Therefore an average length of 10-12 nm and a width and height of maximally 1 nm was expected on the basis of the MALDI-TOF results.
Using SANS it was found the polyrotaxane consisted of 12 ± 4 bithiophene units and a molecular weight of 2000 ± 650 $g.mol^{-1}$ was found for the polyrotaxane. This molecular weight indicated the cyclodextrins are not close-packed on the polythiophene polymer chain.
This polyrotaxane was soluble in DMSO and water. A polythiophene with this molecular weight normally is insoluble in any solvent.

The work presented in this Chapter is the undergraduate work of P. van ‘t Hof.

6.1 Introduction

In chapter 5 a route for obtaining insulated molecular wires is described. The insulated molecular wires obtained are complexes of polyaniline and α-cyclodextrin molecular tubes. Due to the absence of blocking groups the α-cyclodextrin molecular tubes can be unthreaded from the polyaniline chains. This means that the insulated molecular wires obtained are not stable and it is difficult to manipulate the compound and to be eventually able to measure the conductivity through the chain. In this chapter a different route towards insulated molecular wires is described in which eventually stable products are obtained.

Maciejewski was the first, to describe the polymerization of monomers included by cyclodextrins.[1,2] Stable polymeric products containing β-cyclodextrin threaded onto vinylidene chloride polymer chains were obtained. Also other monomer/cyclodextrin inclusion compounds were polymerized. However, the products obtained after polymerization were unstable and dissociated when purified with hot water.[1] More groups studied this kind of polymerizations.[3] The group of Anderson described the polymerization of biphenyl/β-cyclodextrin inclusion compounds for obtaining conjugated pseudo-polyrotaxanes.[4,5]

The synthesis of insulated molecular wire has been the subject of earlier work in our group.[6] Insulated single-chain conducting polymer wires composed of polyaniline threaded by α-cyclodextrin molecular tubes were obtained.

The group of Lacaze used cyclodextrins to increase the solubility of a thiophene monomer. They studied the electrochemical polymerization of thiophene monomers in water. Usually thiophene monomers do not polymerize in aqueous solution because the monomers are insoluble in water and because the oxidation potential is higher than that of water decomposition. There are some reports on the polymerization of bithiophene in water using acidic solutions or anionic micellar solutions.[7,8] Another strategy for polymerization of hydrophobic heterocyclic compounds in water consists of employing cyclodextrins in order to improve the solubility of the thiophenes in water, just as Maciejewski performed his polymerizations. Several inclusion compounds were prepared. Among these inclusion compounds were inclusion compounds consisting of bithiophene and β-cyclodextrin and inclusion compounds consisting of bithiophene and terthiophene and hydroxypropyl-β-cyclodextrin. The dimensions of bithiophene molecules correspond well to the size of the cavity of β-cyclodextrin, so these were used to form stable 1:1 host-guest inclusion compounds, cyclodextrin being the host and bithiophene being the guest.[9,10,11,12] The inclusion compounds were then polymerized electrochemically. Polythiophene films were obtained on platinum electrodes. These films showed increased solubility in common solvents and spectrometric measurements indicated the presence of cyclodextrin molecules in the film even after extensive rinsing. Partial encapsulation of the polymer chains by

cyclodextrins was suspected. However, it was concluded that the films did contain cyclodextrin, but the polymer itself was not encapsulated by cyclodextrins anymore.[9,10,11,12] In the case of the polymerization of bithiophene encapsulated inside hydroxypropyl-β-cyclodextrin the polymer chains in the thin films contained approximately one hydroxypropyl-β-cyclodextrin molecule per 10 bithiophene monomers, so the cyclodextrins are not close-packed on the polymer chains. It was concluded that the polymerization occurs outside the cyclodextrin cavity and cyclodextrin might be included in between the polymers. The enhanced solubility of the films is due to low conversion. In the case of terthiophene complexed by β-cyclodextrin the polymer obtained was mainly sexithiophene. Also other monomers were included and then polymerized.[9]

Instead of modifying the polymer backbone with substituents, here a different strategy is described for obtaining soluble conjugated polymers. This strategy is the use of polyrotaxane formation with a conjugated backbone and cyclodextrins as rings.

The polyrotaxane obtained might be used as an insulated molecular wire (see § 5.1.1). The approach described here uses cyclodextrins as the insulator part of insulated molecular wires and polythiophene as the conducting polymer. The group of Anderson also described the use of cyclodextrin for obtaining soluble conducting polymers, but in their case poly(phenylene vinylene) was used as the conducting polymer.[4,5]

The goal of the research described in this chapter is to synthesize an insulated single-chain conducting polymer wire based on polythiophene and β-cyclodextrin. To obtain an insulated single-chain conducting polymer wire, first 2,2'-dibromo-5,5'-bithiophene monomer was included by β-cyclodextrin. This inclusion compound was then polymerized using a condensation polymerization and at the end of the reaction an anthracene blocking group was added to prevent the dethreading of the cyclodextrins from the polymer chain. The polymer was synthesized using a dehalogenation polycondensation. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$) was utilized as catalyst for the polycondensation of 2,2'-dibromo-5,5'-bithiophene in order to produce the π-conjugated polythiophene.

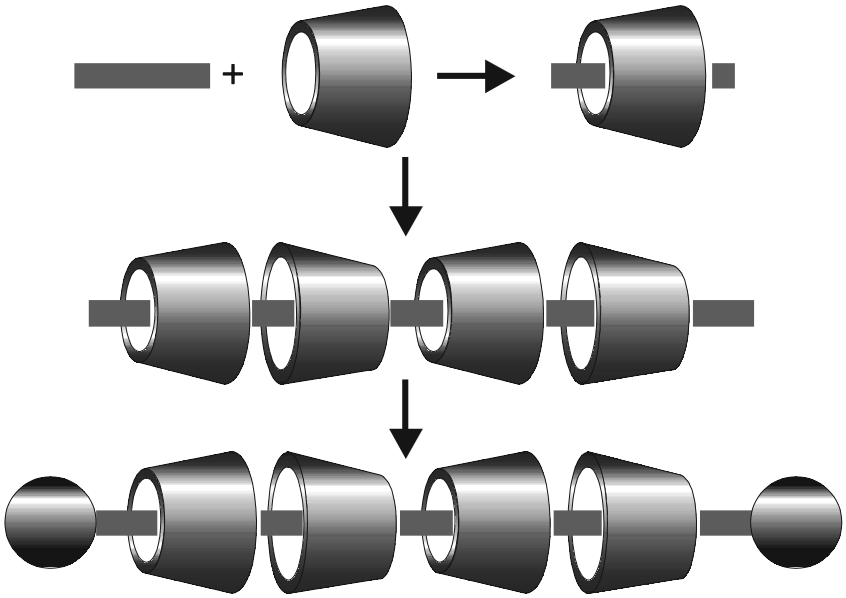
6.2 Synthesis of polythiophene polyrotaxanes

For the synthesis of the insulated single chain conducting polymer wires described in chapter 5 the first step is the synthesis of the α-cyclodextrin molecular tube. These were synthesized through a four-step procedure. Then the inclusion compounds consisting of α-cyclodextrin molecular tubes and polyaniline could be obtained. The synthesis of the insulated molecular wire consisting of polyaniline and α-cyclodextrin molecular tubes is a five-step procedure.

This raised the question, if it was possible to reduce the number of reaction steps. The solution was the complexation of the monomer inside a cyclodextrin and the

polymerization of this complex. Scheme 6.1 shows a schematic diagram of this synthetic approach.

This approach consists of three steps. The blocking groups are added after the polymerization by adding a bulky mono-functionalized monomer to prevent dethreading of the cyclodextrins from the polymer chain. This is depicted in the scheme as two steps. However, the blocking groups can be added to the reaction mixture directly after the polymerization reaction.



Scheme 6.1. *Schematic diagram for obtaining a polyrotaxane by the polymerization of an included monomer.*

6.2.1 Inclusion of 2,2'-dibromo-5,5'-bithiophene by β-cyclodextrin

As mentioned in § 6.1 the group of Lacaze reported about the inclusion of thiophene, bithiophene and terthiophene inside β-cyclodextrins.[9,10,11,12] The work described in this chapter aims to synthesize polythiophene polyrotaxanes. To be able to obtain a polyrotaxane a dibrominated thiophene monomer must first be included inside β-cyclodextrin. The thiophene monomer should be long enough so the catalyst can react with the carbons to which the bromines are connected. On the other side the thiophene monomer should not be to long, otherwise a less close-packed polyrotaxane will be obtained. The

2,2'-dibromo-5,5'-bithiophene (Br_2T_2)/β-cyclodextrin inclusion compounds are according to 3D models the best choice (figure 6.1). In the case of the dibrominated thiophene, the entire molecule is enclosed inside the β-cyclodextrin cavity, the carbon-bromine bond is inaccessible. The dibrominated terthiophene/β-cyclodextrin complex would result in less close-packed polyrotaxanes. A less close-packed polyrotaxane will probably result in a less well shielded polythiophene backbone.

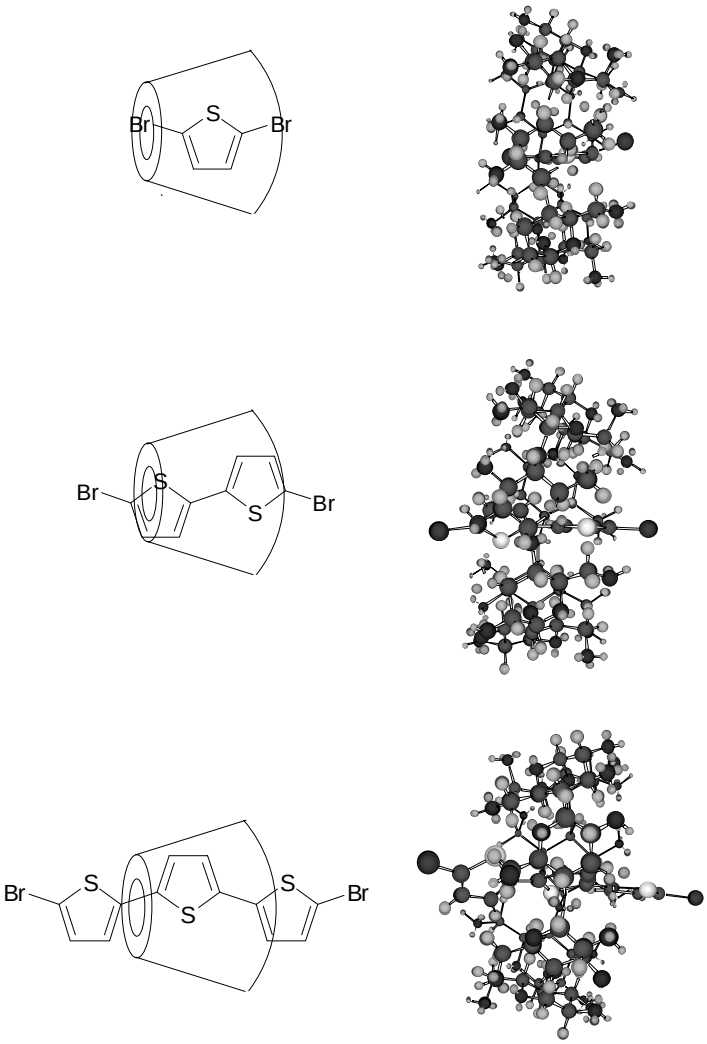


Figure 6.1. *Three different dibrominated oligothiophene/β-cyclodextrin inclusion compounds.*

Therefore it was planned to use the dibrominated bithiophene/β-cyclodextrin complex. Since in the case of the dibrominated bithiophene/β-cyclodextrin inclusion compound the carbon-bromine bond is accessible, and the polyrotaxane will have close-packed β-cyclodextrins around the polythiophene backbone. Figure 6.2 shows the inclusion compound in more detail. The space filling model shows that there is sufficient space for reaction.

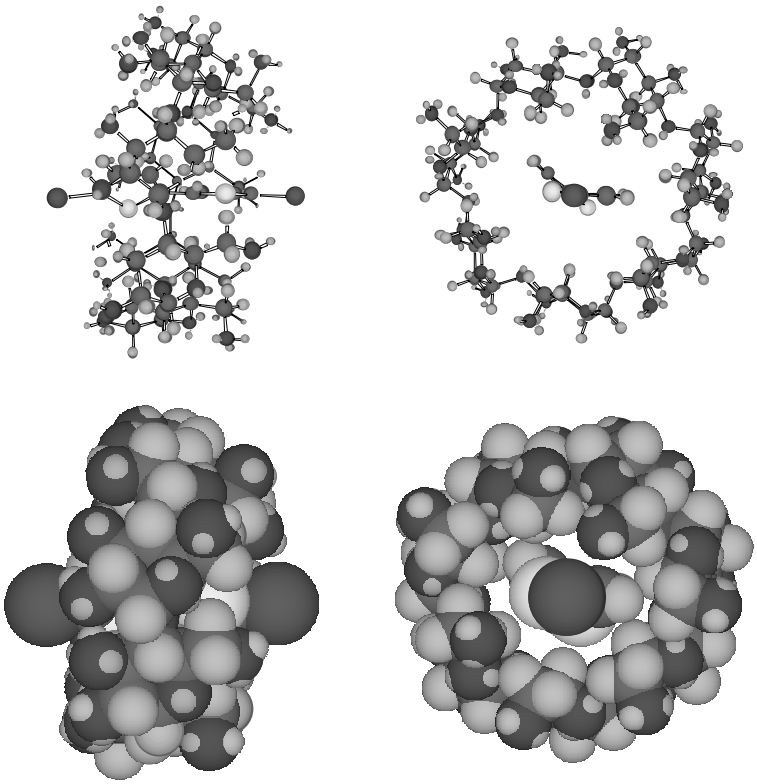


Figure 6.2. *A more detailed view of the model of the dibrominated bithiophene/β-cyclodextrin inclusion compound.*

The inclusion of dibrominated bithiophene inside β-cyclodextrin is performed according to the literature procedure described by the group of Lacaze for the inclusion of bithiophene inside β-cyclodextrin.[10] Except the monomer, two additional complexation parameters are changed. The first parameter changed, is the solvent for the monomer since the dibrominated bithiophene does not dissolve in methanol. Several solvents, like DMF, NMP and hexamethylphosphorous triamide (HMPT) were attempted. DMF was used eventually

because of multiple reasons. First of all, DMF gave the best ratio of dibrominated bithiophene:β-cyclodextrin. Secondly, DMF was the best solvent for dibrominated bithiophene. The advantage of this is that a smaller amount of solvent can be used and this is important in view of the ratio water/solvent.

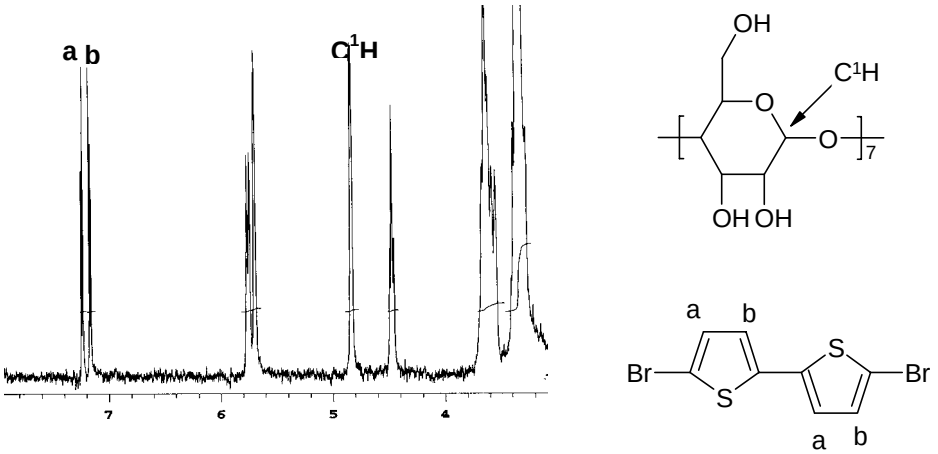


Figure 6.3. *Partial ^{1}H-NMR spectrum of the dibrominated bithiophene/β-cyclodextrin inclusion compound.*

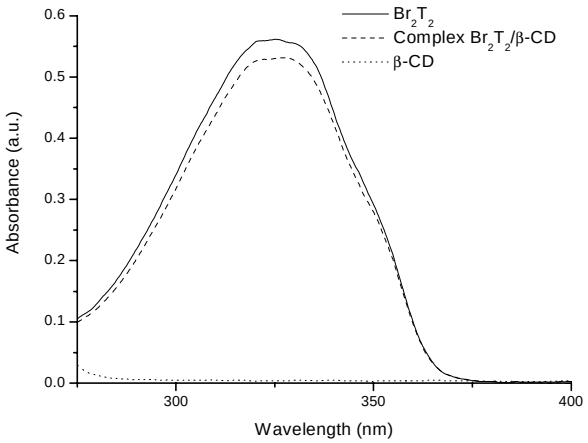


Figure 6.4. *UV−Vis spectra of 2,2'-dibromo-5,5'-bithiophene (solid line), the inclusion compound consisting of 2,2'-dibromo-5,5'-bithiophene and β-cyclodextrin (dashed line), and of β-cyclodextrin (dotted line). All spectra were recorded in DMF.*

The second parameter changed is the temperature. In the literature the inclusion of bithiophene by β-cyclodextrin is performed at 60 °C. When the inclusion of dibrominated bithiophene by β-cyclodextrin was performed at 60 °C, the yield was very low. Although both compounds are insoluble in water, a small amount of compound has to be dissolved in the water/DMF mixture, for obtaining a complex. Probably a temperature of 60 °C is too low for the dibrominated bithiophene to be at least partly soluble in the DMF/water mixture. The problem was solved by raising the temperature. Several different temperatures were attempted: 90, 110 and 150 °C. The inclusion at 110 °C gave the best results in both yield and ratio of thiophene to cyclodextrin. The solid obtained, consists of dibrominated bithiophene and β-cyclodextrin in a ratio of 1:1 (figure 6.3).
UV−Vis spectroscopy (figure 6.4) was performed to analyze the inclusion compound of 2,2'-dibromo-5,5'-bithiophene and β-cyclodextrin. UV−Vis spectroscopy showed a small decrease in absorbance of the inclusion compound compared to free dibrominated bithiophene (the same concentration 2,2'-dibromo-5,5'-bithiophene).

6.2.2 Polymerization of the 2,2'-dibromo-5,5'-bithiophene/β-cyclodextrin inclusion compound

A dehalogenation polymerization can be performed using a large number of polymerization procedures. Since in this case an inclusion compound has to be polymerized, the number of solvents that can be used for the polymerization is limited.[1,2] Dehalogenation polymerization techniques for obtaining conjugated polymers like the Glazer-[13] or Heck-[14,15,16,17,18] are normally not performed with water or DMF as solvent. Electrochemical polymerization is not possible for obtaining a polyrotaxane. First of all, a film is obtained on an electrode. This makes the isolation of single polymer chains difficult. Secondly, as already mentioned in § 6.1 the cyclodextrins unthread from the polymer chain in an electrochemical polymerization.[9,10,11,12] Another polymerization used for the synthesis of conjugated polymers is the Suzuki coupling.[19,20,21,22,23,24] This polymerization can be performed in water, however, a Suzuki coupling requires a boronic acid and our monomer only has bromine functional groups (figure 6.5).
Polythiophene can also be synthesized using the metal-catalyzed polymerization independently discovered by the group of Yamamoto and the group of Lin and Dudek. A slight modification of these polymerization techniques are the polymerizations catalyzed by zero valent Nickel:[25]

$$n\ X{-}Ar{-}X + n\ Ni(0)L_m \rightarrow -[-Ar-]_n- + n\ NiX_2L_m. \qquad (1)$$

One of the most used zero valent Nickel catalysts is bis(1,5-cyclooctadiene)nickel(0).[26,27] Bis(1,5-cyclooctadiene)nickel(0) needs an extra neutral ligand for polymerization. As neutral ligand, triphenyl phosphine is best suited for the polymerization of thiophene monomers. The ligand exchange reaction of bis(1,5-dicyclooctadiene)nickel(0) with triphenyl phosphine provides a convenient route for the preparation of the zero valent $Ni(cod)(PPh_3)_2$ complex. The mechanism of the reaction is depicted in figure 6.6.[25,26] DMF is a typical solvent for bis(1,5-cyclooctadiene)nickel(0) and so this polymerization can be performed in DMF.[28,29,30,31]

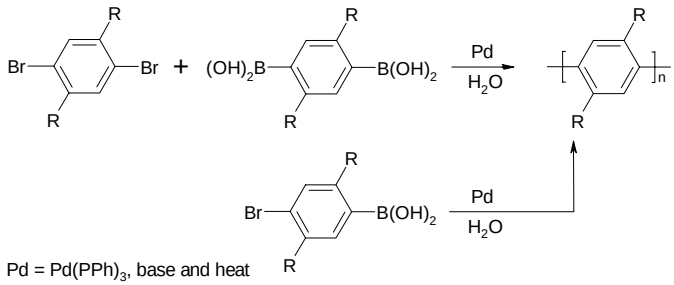


Figure 6.5. *Suzuki coupling of aryl halides and arylboronic acids.*

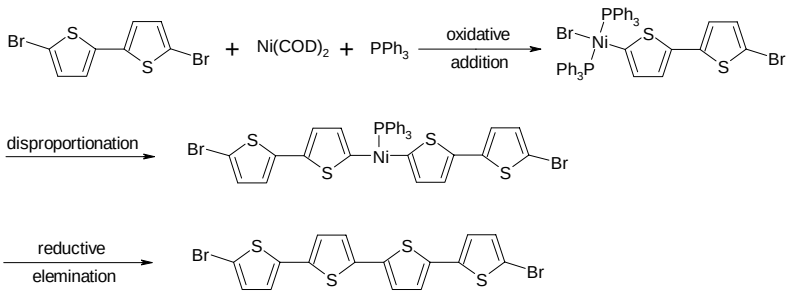
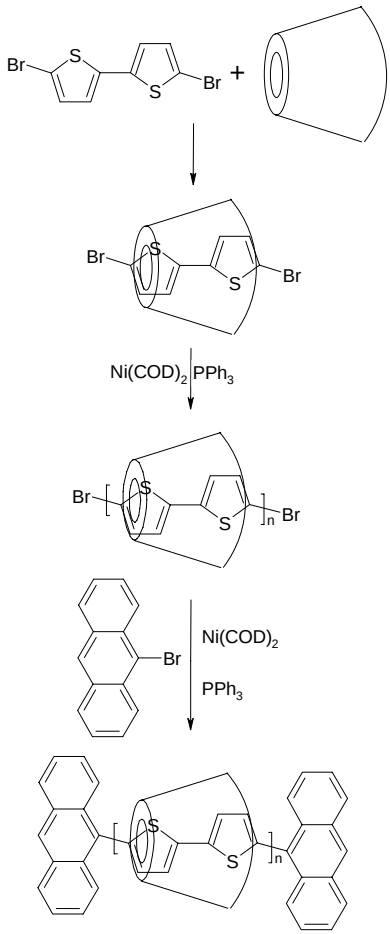


Figure 6.6. *Mechanism of the Kumada modified Yamamoto reaction.*[25,26]

During the polymerization of the 2,2'-dibromo-5,5'-bithiophene/β-cyclodextrin inclusion compound a beige/grey precipitate was formed. Polythiophene is a reddish polymer. In case of dethreading of the cyclodextrins from the polymer chain, during or after the polymerization a reddish polymer was expected to be obtained. Cyclodextrins are white, so when a pseudo-polyrotaxane is formed, a white color can be expected. A reddish polymer complexed by white cyclodextrins could very well yield such a beige/brownish color.

As stated before, during the polymerization 9-bromoanthacene was added as a blocking group. This yielded the desired polyrotaxane, which was subsequently purified by a series of dissolving and precipitation steps (see the experimental section § 6.5).
According to molecular models, anthracene is large enough to prevent the unthreading of the cyclodextrins from the polymer chain.
The polyrotaxane synthesized according to the procedure depicted in scheme 6.2 was characterized by ^{1}H-NMR, MALDI-TOF, UV−Vis, AFM, solubility measurements and SANS.



Scheme 6.2. *Synthetic procedure for obtaining polythiophene/β-cyclodextrin polyrotaxanes.*

6.3 Results

6.3.1 Study of the polythiophene polyrotaxane by Proton Nuclear Magnetic Resonance spectroscopy

The polyrotaxane obtained after the purification showed no peaks in the aromatic region. The absence of the anthracene peaks in the ^{1}H-NMR spectrum can be attributed to the ratio of anthracene protons in comparison to cyclodextrin and polymer protons. The absence of a signal due to polythiophene is more difficult to explain. From the MALDI-TOF spectra (§ 6.3.2) it is clear, the product has a high molecular weight. The absence, of a signal due to the polythiophene protons, can therefore only be attributed to shielding of the signal by the cyclodextrins. The absence of a polythiophene signal indicates a close packing of the cyclodextrins around the polythiophene.

As stated before the spectra obtained showed no aromatic peaks, however, the peaks in the spectrum look like cyclodextrin peaks with some peaks shifted 0.2 ppm down field (the $C^{2}H$ and OH_3 signal) but at the same time the original peaks are also present. Polyrotaxanes give broadened NMR signals. The splitting of signals in two peaks is difficult to explain. A possible explanation can be the presence of hydrogen-bonds between the cyclodextrins.

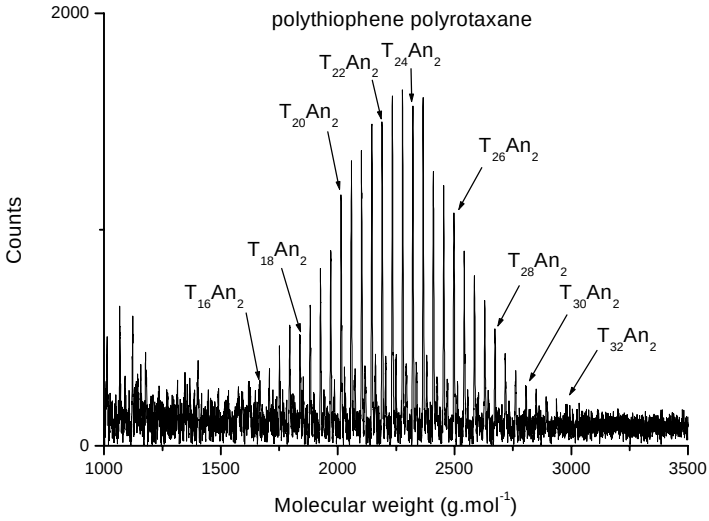


Figure 6.7. *MALDI-TOF spectrum of the polythiophene polyrotaxane.*

6.3.2 Detection of the polythiophene chain by mass spectroscopy

The presence of polythiophene in the polyrotaxane is confirmed by MALDI-TOF (figure 6.7). The molecular weight of the polymer in the polyrotaxane ranges from 1666 g.mol^{-1} ($T_{16}An_2$) to 2978 g.mol^{-1} ($T_{32}An_2$), with an average molecular weight of 2322 g.mol^{-1} ($T_{24}An_2$). In the case of $T_{24}An_2$ 12 bithiophene monomers are connected to each other together with two anthracene blocking groups. The difference between the peaks in the spectrum is 164 g.mol^{-1}. This corresponds to a bithiophene repeating unit. No peaks due to odd polythiophene chains were observed. This means, there is no fragmentation of the polythiophene chains in the MALDI procedure. Just as with the MALDI-TOF procedure of the compounds described in chapter 3 also here there is fragmentation of the cyclodextrins in the polyrotaxane. No peak due to the whole polyrotaxane could be observed.

The other peaks in the spectrum can be attributed to fragments of the polyrotaxane containing one or no stopper groups. Some peaks below 1500 g.mol^{-1} represent smaller oligothiophenes and fragments of the β-cyclodextrins.

The distribution is not completely Gaussian. It is cut off at the high molecular weight side. This is probably due to reduced solubility of the higher molecular weight polyrotaxanes. These precipitate out during polymerization.

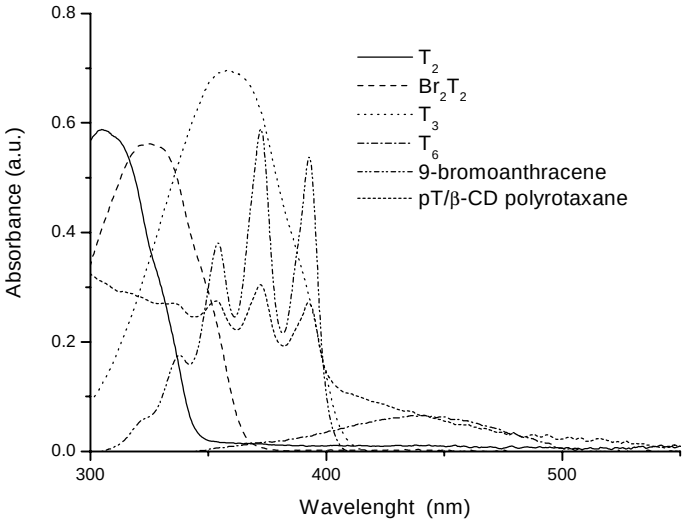


Figure 6.8. *UV−Vis spectra of 2,2'-bithiophene (T_2), 2,2'-dibromo-5,5'-bithiophene, terthiophene (T_3), sexithiophene (T_6), 9-bromoanthracene and the polythiophene/β-cyclodextrin polyrotaxane. All spectra were recorded in DMF.*

6.3.3 Detection of the polymer and the blocking groups by Ultra-Violet and Visible light spectroscopy

The UV−Vis spectra, depicted in figure 6.8, show the absorption of the polyrotaxane. The absorption curves of some oligothiophenes and anthracene are also depicted. From these UV−Vis spectra two conclusions can be drawn. The first conclusion is the anthracene stopper groups are still present in the polyrotaxane after purification. Secondly, the polyrotaxane absorption extents to higher wavelengths than the oligothiophene absorptions, indicating a higher molecular weight of the conjugated polymer inside the polyrotaxane compared to the oligothiophenes.

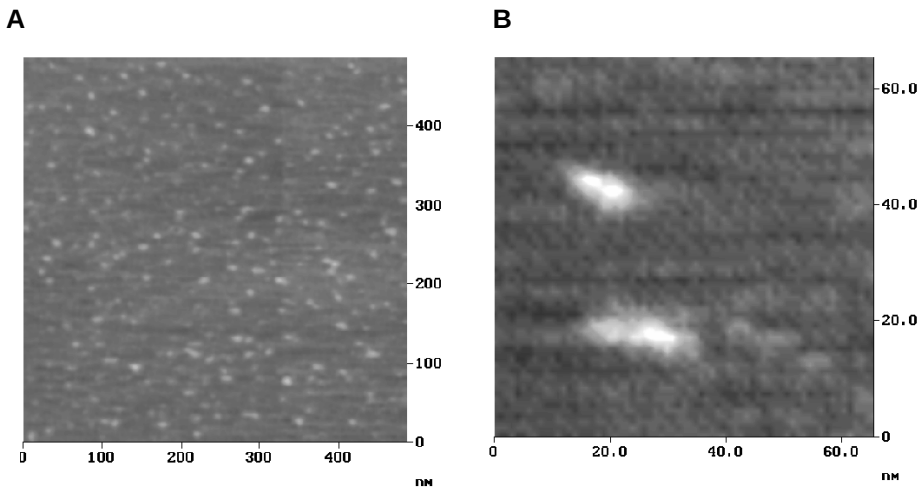


Figure 6.9. *AFM images of polythiophene polyrotaxanes. A) Surface showing multiple isolated polyrotaxanes; B) Zoom in showing two polyrotaxanes.*

6.3.4 Visualization of the polythiophene polyrotaxanes by Atomic Force Microscopy

AFM images show elongated structures. In figure 6.9B two of these structures are depicted. The structures depicted in figure 6.9B are part of a larger surface containing many individual polythiophene polyrotaxanes having the same dimensions (figure 6.9A).
To obtain such a sample it was necessary to add a small amount of NMP to the solution of polyrotaxane in DMSO, which was subsequently spin-coated on a mica substrate. The phenomenon of NMP breaking down aggregates was discovered before (§ 3.3.4).[6]

The dimensions of these elongated features were measured as shown in figure 6.10. The length of the features ranges from 10 to 20 nm. The height of the features is approximately 0.5 nm, which is lower than the 1.5 nm which is expected (table 1.1). But it has to be kept in mind, that 1.5 nm is the diameter of the widest side of the conically shaped cyclodextrin, the other diameter is narrower. Furthermore the polyrotaxane consists of a polymer backbone, threaded by cyclodextrins. When close packing of cyclodextrins along the backbone of the polymer is not achieved, there are openings between the cyclodextrins on the polymer chain. In between the cyclodextrins there is only the bare polythiophene, which is thinner.

According to the AFM image the width of the feature is approximately 6 nm. This can be attributed to a tip-effect. Although ultra-sharp tips are used, the diameter of these tips is still several nm, so the value found for the width of the polyrotaxane is acceptable.

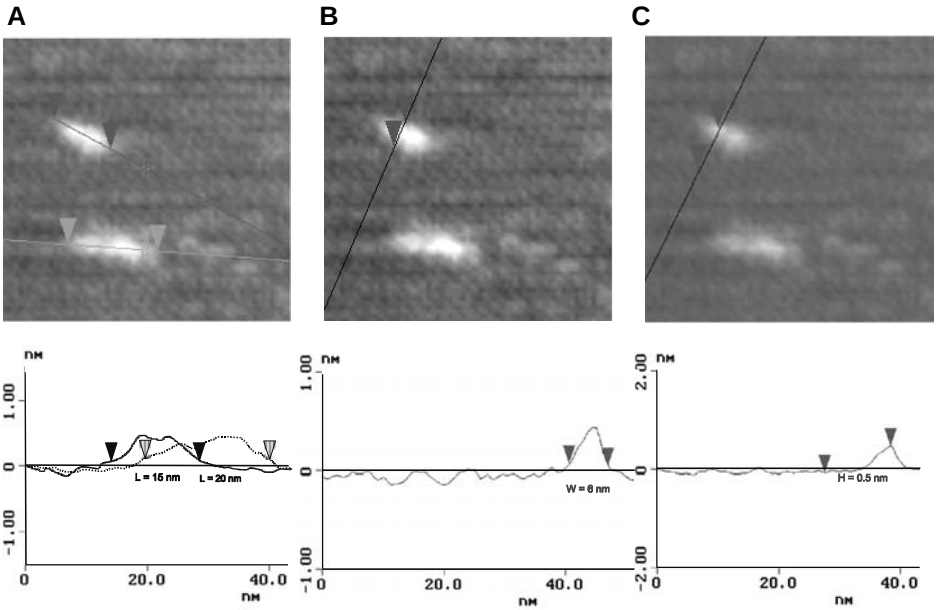


Figure 6.10. *AFM height profiles of polythiophene polyrotaxanes, showing its length (A), its width (B) and its height (C).*

6.3.5 Solubility measurements of the polythiophene polyrotaxanes

The polythiophene polyrotaxanes are very well soluble in DMSO (> 50 $mg.ml^{-1}$) and well soluble in water (± 40 $mg.ml^{-1}$). Polythiophene without cyclodextrins with a molecular weight as high as determined by MALDI-TOF would not be soluble in DMSO or water. This demonstrates the power of the complexation of cyclodextrins around the polythiophene backbone. Soluble polythiophenes can be obtained by the addition of pendant side groups along the backbone. However, to the best of our knowledge no side groups were published in the literature rendering a molecular weight as high as our polythiophene water soluble. Unsubstituted oligothiophenes with a molecular weight higher than sexithiophene are insoluble in any solvent.

6.3.6 Determination of the size and shape by Small-angle Neutron Scattering

The SANS results confirmed the observations by AFM indicating that the β-cyclodextrin polythiophene polyrotaxanes are aggregated. This is probably due to hydrogen bonding between polyrotaxanes. Addition of small amounts of NMP did reduce aggregation, but some aggregates were still present. After filtration through a 0.2 mm filter the intensity upturn at low q was gone, indicating that all aggregates of the polythiophene polyrotaxanes were removed.

The scattering curve of the filtered sample was fitted to a cylinder.[35] The cylinder fit is shown in figure 6.11. The length of the cylinder is 75 Å, its radius 8.3 Å.

The radius of gyration of the polythiophene polyrotaxane, determined from the Guinier plot, gives a value of 74 Å. This value is in good agreement with the models.

Cross-section data are plotted in figure 6.13. The cross sectional radius of gyration, R_c, of the polythiophene polyrotaxane is 6.8 Å.

The molecular weight of the compound can be derived from the extrapolation of the experimental data to q = 0 $Å^{-1}$ in the log−log plot. It is found that the molecular weight of the polythiophene polyrotaxane is 9.0×10^3 $g.mol^{-1}$. The weight-average molecular weight of the polythiophene part of the polyrotaxane is 2.3×10^3 $g.mol^{-1}$ according to the MALDI-TOF results. This corresponds to 24 thiophene units. When 12 cyclodextrins were threaded on this polymer chain, the molecular weight would be 14.10^3 $g.mol^{-1}$. So the molecular weight found is lower than expected on the basis of the weight-average molecular weight calculated from the MALDI-TOF results. It might be possible that some cyclodextrins are unthreaded during the polymerization process, yielding a polyrotaxane containing fewer cyclodextrins.

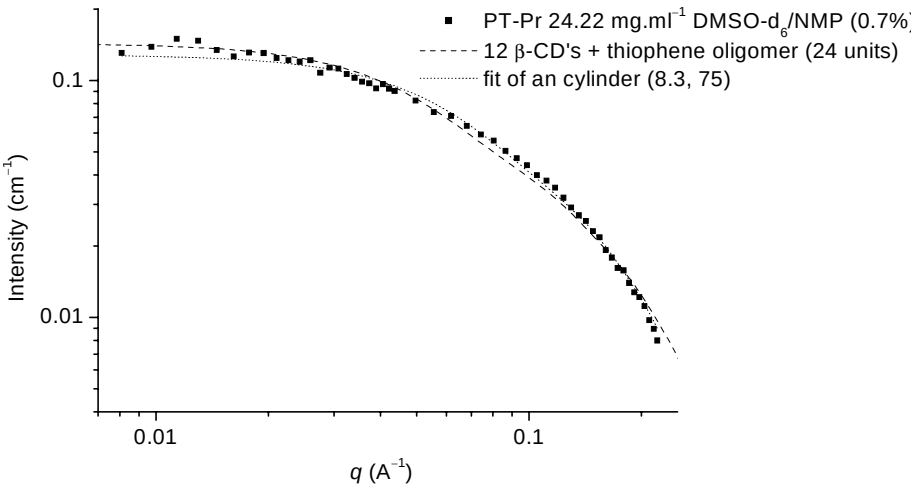


Figure 6.11. *Small-angle neutron scattering data (log-log) of polythiophene polyrotaxane in D_2O/NMP 0.7 (v/v) % NMP (■); cylinder fit (---) and molecular model fit (···).*

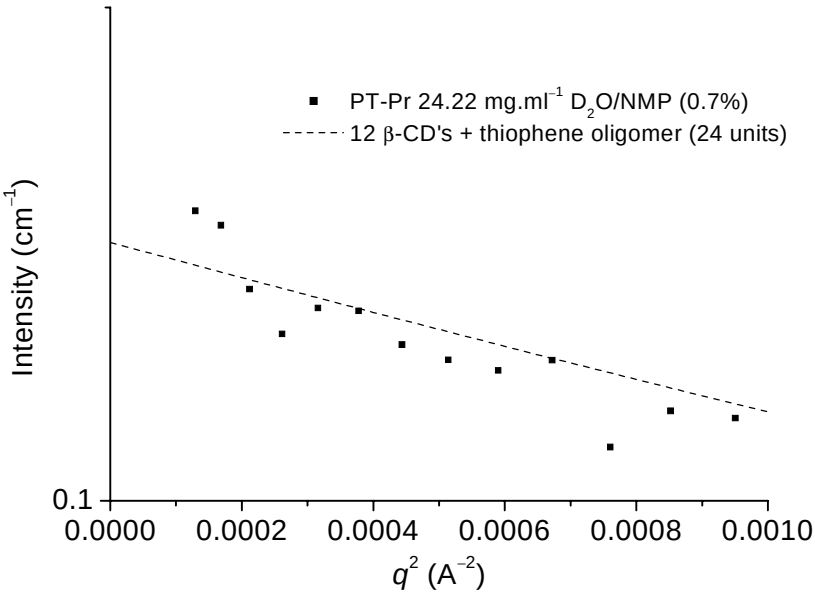


Figure 6.12. *Guinier plot of polythiophene polyrotaxane.*

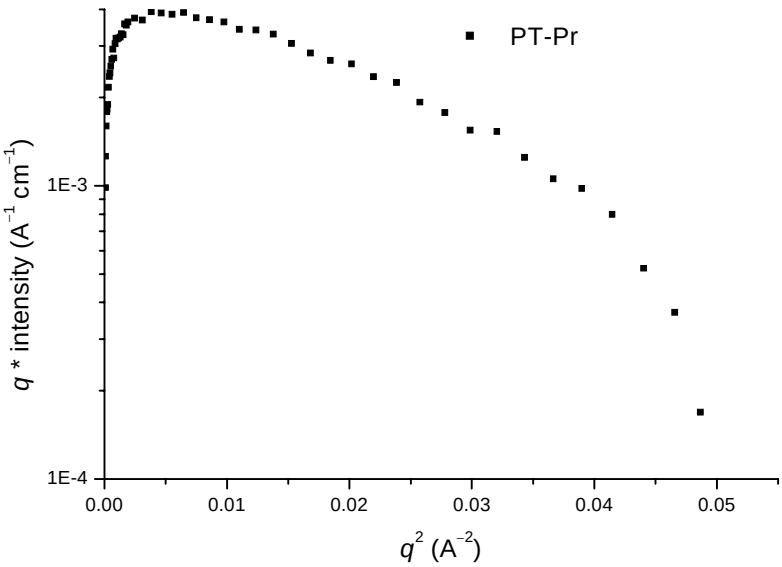


Figure 6.13. *Cross-section-factor Guinier plot.*

6.4 Discussion and conclusion

By synthesizing a polyrotaxane through the polymerization of bithiophene/β-cyclodextrin inclusion compounds it was possible to obtain a polythiophene that is soluble in DMSO and water. From the results obtained with MALDI-TOF it is possible to obtain dimensions of the polyrotaxanes obtained. The average polyrotaxane consists of 12 bithiophene monomers and two anthracene stopper groups. The polythiophene is included by β-cyclodextrins having a height of 0.79 nm and an inside diameter of approximately 0.74 nm (table 1.1). Therefore an average length of 10-12 nm and a width and height of maximally 1 nm is expected.

The polythiophene consists of 12 ± 4 bithiophene units and the molecular weight of the polythiophene is 2000 ± 650 g.mol^{-1}. A polythiophene with this molecular weight normally is insoluble in any solvent. The addition of pendant groups to render polythiophene of this molecular weight water-soluble is not described in the literature.

From the UV−Vis spectra of the polythiophene polyrotaxanes two conclusions can be drawn. The first conclusion is the anthracene stopper groups are present in the polyrotaxane after purification. Secondly, the polyrotaxane absorption extents to higher wavelengths than that of oligothiophenes, indicating a higher molecular weight of the conjugated polymer inside the polyrotaxane compared to oligothiophenes.

AFM images show elongated structures. The dimensions of these elongated features were measured using the traces in the height profiles. The length of the features ranges from 10 to 20 nm. The height of the features is approximately 0.5 nm, which is lower than the 1.5 nm which is expected. This might be an indication that the cyclodextrins are not close-packed on the polymer chain. According to AFM the width of the polyrotaxane is approximately 6 nm.
The polythiophene polyrotaxanes are very well soluble in DMSO (> 50 $mg.ml^{-1}$) and well soluble in water (± 40 $mg.ml^{-1}$).
The SANS data could be fitted with a cylinder having a length of 75 Å and a radius of 8.3 Å. The molecular weight found for the polythiophene polyrotaxane is $9.0.10^3$ $g.mol^{-1}$. This molecular weight is also an indication that the cyclodextrins are not close-packed on the polymer chain.
An insulated single-chain conducting polymer wire would give the opportunity to measure the conductivity of a single polymer chain. The synthesis of a soluble high molecular weight conjugated polymer opens the way both to the technology of the molecular electronics of the future and to fundamental studies of polymer conductivity at a molecular level.

6.5 Experimental

Measurements
^{1}H-NMR spectra were recorded on a 300 MHz Varian (VXR 300) spectrometer. Deuterated DMSO-d_6 was used as internal standard. All chemical shifts are denoted in δ-units (ppm) and converted to TMS scale. MALDI-TOF spectra were taken on a Micromass TofSpec E mass spectrometer using dithranol as matrix; pulse voltage: 1000 V. UV−Vis spectra were recorded on a SLM Aminco 3000 Array. SEC was performed using a Waters Associates chromatography pump (model 590), a Waters Associates differential refractometer R 401, as detector, Sephadex G25[32] as column material (dimensions of the column: length: 30 cm and diameter: 2.2 cm), degassed reversed-osmosis water as eluent (elution rate 1.4 $ml.min^{-1}$).

Materials and methods
9-Bromoanthracene, DMF and 1,5-cyclooctadiene (cod) were purchased from Aldrich. DMF was distilled over P_2O_5 before use. COD was distilled and stored under a dry nitrogen atmosphere. β-Cyclodextrin (β-CD) was purchased from ACROS. β-CD was dried at 80 °C under vacuum before use. Triphenylphosphine ($P(Ph)_3$) was purchased from Merck. 2,2'-dibromo-5,5'-bithiophene (Br_2T_2) was synthesized according to a literature procedure.[33]

Bis(1,5-cyclooctadiene)nickel(0) $Ni(cod)_2$ was synthesized according the Guerrieri and Salerno method.[34]
The water used for the inclusion experiments was 18 MΩ ultra pure water obtained from an Elga Maxima water purification system.

AFM sample preparation
AFM: NanoScope IIIa (Digital Instruments, Inc., Santa Barbara (US)), equipped with NT-MDT ultra-sharp silicon cantilever tips (NSC 21 series). Topographic images were taken in air in "Tapping Mode". Solutions containing $2.5.10^{-2}$ $mg.ml^{-1}$ sample in DMSO containing 5 µl $NMP.ml^{-1}$ were spin coated on freshly cleaved muscovite mica (grade 2, obtained from Mica New York Corporation (US)).

SANS
SANS Experiments were carried out at the Laboratoire Léon Brillouin (LLB)(CEA, Saclay (F)). The PAXY instrument was employed. Two equipment settings were used: 1) Sample-to-detector distance (D_{ED}) of 3.20 m with λ = 12 Å (q-range of 0.008–0.057 $Å^{-1}$), and 2) D_{ED} = 2.00 m with λ = 5.0 Å (q-range 0.03–0.22 $Å^{-1}$). For this instrument, $\Delta\lambda/\lambda$ = 0.1. Absolute intensities corrected for detector sensitivity, were obtained by normalization to the scattering from H_2O (at D_{ED} = 3.20 m) or Plexiglas (at D_{ED} = 2.00 m), with reference to the direct beam.
Samples were contained in 2 mm path length quartz cells at 22 ± 2 °C. Counting times amounted to three hours. The scattering of solvent (including NMP) was subtracted as background. An additional correction (subtraction) for incoherent scattering was based on a measurement of the excess intensity of solvent mixtures DMSO-d_6/DMSO 98/2 (v/v)) over pure solvent (D_2O or DMSO-d_6) and subsequent scaling to the specific hydrogen content of each sample. This correction was a constant over the angular range covered.
Filtration of the samples was found necessary because of a sharp intensity upturn at low q, in spite of the presence of NMP. For filtration a series of filters was used having pore diameters of 0.2 µm (Whatman Anotop 10) and 0.02 µm (Whatman Anotop 10). Loss of material due to filtration was determined afterwards for each sample from the recovered solution. The loss was around 30 %.
Curve fitting to corrected data was performed by means of the FISH program (by R.K. Heenan).[35] The first four data points were omitted, in order to suppress contributions from any remnants of aggregates. Fits started at q = 0.0146 $Å^{-1}$. Molecular models of β-cyclodextrin/polythiophene polyrotaxanes were constructed using the Cerius^2 program (Cerius^2 version 3.5, Molecular Simulations Inc., San Diego (US)). The corresponding scattering curves were calculated, by means of CRYSON, a program developed by and offered by Svergun and Barberato (EMBL, Hamburg (D)).[36]

Inclusion of Br_2T_2 by β-CD (1)

β-CD (0.310 g; 0.273 mmol) was weighed in a pressure tube. 7.7 ml Ultra pure water was added. The tube was placed in an oil bath and heated to 110 °C under continuous stirring. A solution of Br_2T_2 (10 mg; $3.4.10^{-2}$ mmol) in 0.3 ml DMF was added slowly. The solution was cooled to room temperature after 1 h. The dispersion was ultrasonically agitated for 20 min and the dispersion was left undisturbed at room temperature for 1h. The dispersion was centrifuged (10,000 rpm) and the supernatant was removed. The precipitated inclusion compound was dried under vacuum over P_2O_5. The inclusion compound was obtained as a white solid with a yield of 98 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 7.36 (d, 2 H, aromatic CH at positions 3 and 3' of Br_2T_2), 7.20 (d, 2 H, aromatic CH at positions 4 and 4' of Br_2T_2), 5.80 (d, 7 H, O^2H of β-CD), 5.71 (s, 7 H, O^3H of β-CD), 4.87 (d, 7H, C^1H of β-CD), 4.52 (s, 7 H, O^6H of β-CD), 3.56–3.78 (m, 21 H, C^3H, C^6H, C^5H of β-CD), 3.34–3.50 (m, 14 H, C^4H, C^2H of β-CD).

Synthesis of polyrotaxane (2)

Cod (30 µl; 26 mg; 0.24 mmol), $P(Ph)_3$ (77 mg; 0.29 mmol), Br_2T_2/β-CD inclusion compound **1** (0.140 g; $9.78.10^{-2}$ mmol) and $Ni(cod)_2$ (32 mg; 0.12 mmol) were dissolved in 1.3 ml DMF. The reaction mixture was stirred at 60 °C for 27 h. 9-bromo-anthracene (72 mg; 0.28 mmol) was added. The reaction mixture was centrifuged (10,000 rpm) after 16 h. The beige pellet was dissolved in DMSO and centrifuged (10,000 rpm) to remove insoluble compounds. The supernatant was precipitated with acetone and the solid was washed with acetone (3×). The solid was dried under vacuum. The solid was dissolved in DMSO and precipitated with water. The dispersion was centrifuged (10,000 rpm). The aqueous supernatant was concentrated, and acetone was added to the residue. The precipitated solid was washed with acetone. Finally the solid was dried under vacuum over P_2O_5 and further purified by SEC. The high molecular weight fraction was collected and evaporated. The yield was 25 mg of a beige/grey compound.

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Chapter 7

Sliding gels

Abstract

Topological networks consisting of α-cyclodextrin/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxanes, were synthesized using the same kind of chemistry as used for the synthesis of the α-cyclodextrin molecular tubes. The molecular weight of the "template polymer" used for these topological networks was 20,000 g.mol^{-1}. The polyrotaxanes in the topological network contained approximately 50 cyclodextrins. These cyclodextrins were not close-packed on the "template polymer" chain.

This material could be used as "sliding gel" by absorbing 30 times its dry weight of water or DMSO.

SANS is often used for studying gels. Unfortunately SANS experiments performed on the "sliding gel" did not show signs of anisotropy or other changes resulting from the shear imposed on the gel.

Possible explanations for the lower than expected swelling and the absence of anisotropy under shear suggested are the limited distance, the mechanical crosslink points were able to slide along the "template polymer" chain. 50 Cyclodextrins complexed on a polymer chain able to contain up to 228 cyclodextrins means, the cyclodextrins can in average only slide over a distance corresponding to 4.5 times their own length.

7.1 Introduction

A “sliding gel” is a polymeric material in which there are mechanical instead of covalent crosslinks between the polymer chains. The crosslink points of the topological network have the ability to slide over the polymer chains. Such a material was first described theoretically by de Gennes.[1] The “sliding gel” was based on DNA chains, which bound to organic cations. A number of these cations were linked to one metallic particle, which acted as a crosslink (figure 7.1).

Because the links between the chains are based on mobile connections instead of covalent bonding, these networks are expected to show special mechanical and rheological properties. In particular when the connections have significant freedom to slide along the polymer chain, this uncommon behavior is expected to appear (figure 7.2).[1]

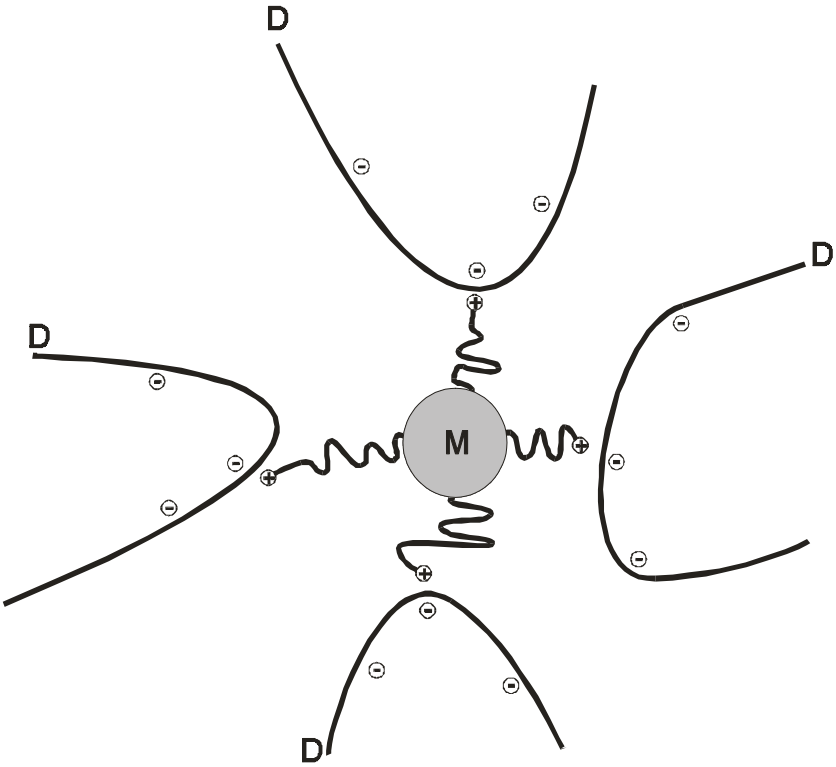

Figure 7.1. *Sliding bridges: A metal particle* M *carries a certain number of organic cations, which bind to DNA chains* D. *The chains can slip, but they must maintain the contact.*

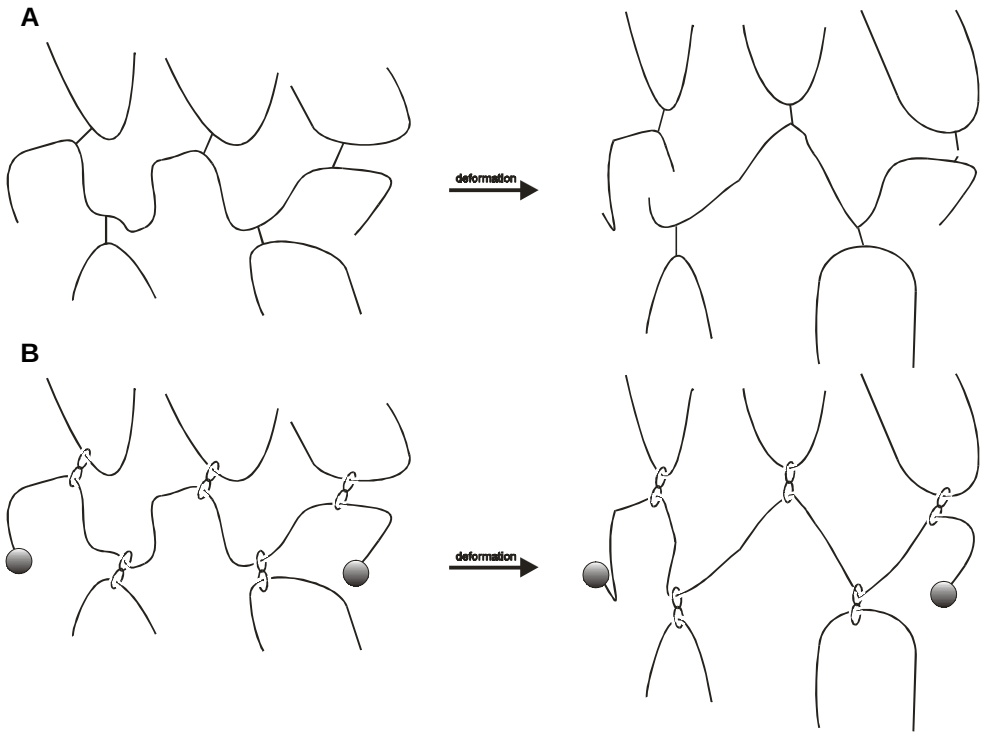

Figure 7.2. *Comparison of a covalently crosslinked gel and a "sliding gel" upon deformation. A) The covalently crosslinked gel is broken down. B) The "template polymer" in the "sliding gel" can pass through the crosslinks to avoid localizations of the stress.*

In this chapter the design and synthesis of "sliding gels", composed of the same building blocks as used for the synthesis of the α-cyclodextrin molecular tubes, is described. In this case, α-cyclodextrin is threaded on poly(ethylene glycol) of higher molecular weight than the polymer used for synthesizing the tubes. The α-cyclodextrins threaded on this high molecular weight poly(ethylene glycol) do not achieve close-packing. This gives the cyclodextrins the freedom to slide along the polymer chain. In the molecular structure synthesized, the cyclodextrins are prevented from unthreading by bulky blocking groups chemically attached to the polymer end-groups. The "sliding gel" is obtained by establishing intermolecular, rather than intramolecular, crosslinks between threaded cyclodextrins. Okumura *et al.* used cyanuric chloride as a linker to obtain a "sliding gel".[2] However, other linkers, varying in length and functionality might be used as well. So also the linker used in the case of the cyclodextrin molecular tubes, epichlorohydrin, might be used. The resulting "sliding gel" is depicted in figure 7.3.

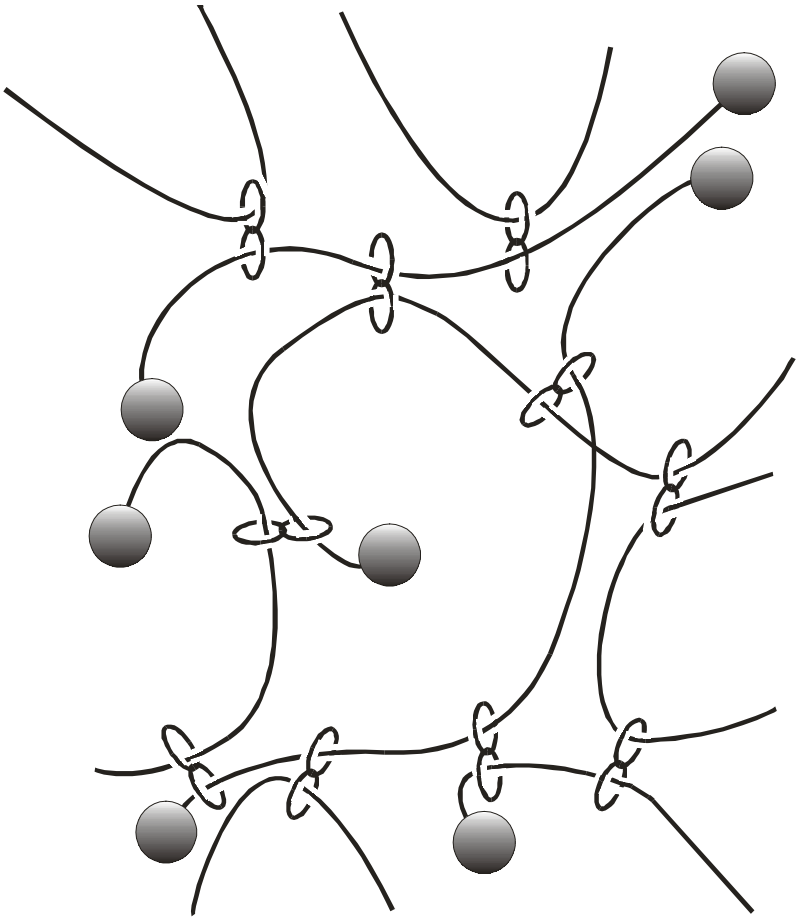

Figure 7.3. *Schematic diagram of the topological network prepared form the not close-packed polyrotaxanes by intermolecular crosslinking of the cyclodextrins.*

7.2 Design and synthesis of the sliding gels

As "template polymer" for the topological network poly(ethylene glycol) chains of $\overline{M}_n$ = 20,000 g.mol^{-1} was used. The polydispersity of the poly(ethylene glycol) used was 1.05. This high molecular weight poly(ethylene glycol) does form pseudo-polyrotaxanes with α-cyclodextrin, however, the cyclodextrins do not achieve close-packing on the polymer chains.[3]

Since the same kind of cyclodextrin has to be prevented from unthreading from the "template polymer" chains as in the synthesis of the cyclodextrin molecular tubes, the same

blocking groups, 2,4-dinitrophenyl, can be used. Of course the poly(ethylene glycol) should be amine terminated again to facilitate the connection of 2,4-dinitrofluorobenzene to the "template polymer".

To obtain polyrotaxanes in which the cyclodextrin are intermolecularly crosslinked the crosslink reaction should be performed under more concentrated conditions, than used for the intramolecular crosslinking of the cyclodextrins in the case of the synthesis of the α-cyclodextrin molecular tubes. To crosslink the cyclodextrins cyanuric chloride is used. This compound can be connected to the hydroxyls of cyclodextrins under basic reaction conditions (1.00 M (aq) NaOH) (figure 7.4). The basic reaction conditions turn the hydroxyl groups into the more reactive alkoxide groups and break down hydrogen bonds between cyclodextrins.

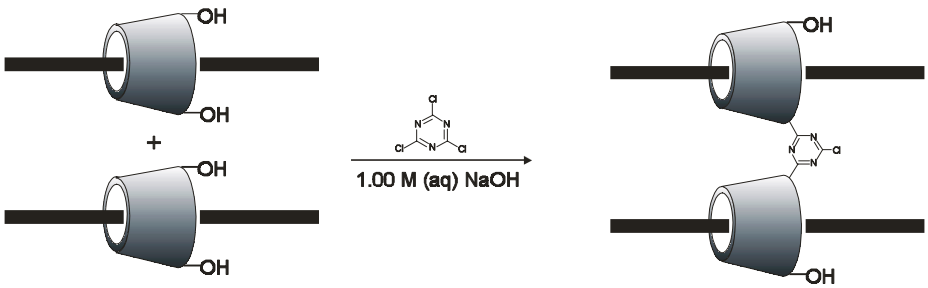

Figure 7.4. *Intermolecular crosslinking of cyclodextrins by cyanuric chloride The residual chlorine shown at the right hand side of the reaction might react with another cyclodextrin hydroxyl.*

7.3 Results

7.3.1 Determination of the number of cyclodextrins by Proton Nuclear Magnetic Resonance spectroscopy

The number of ethylene glycol repeating units in poly(ethylene glycol) of molecular weight 20,000 g.mol^{-1} is approximately 455. Since 2 ethylene glycol repeating units fit in one α-cyclodextrin a maximum of 228 α-cyclodextrins can be threaded on one poly(ethylene glycol) chain (figure 2.1).[4,5,6]

The ^{1}H-NMR spectra of the pseudo-polyrotaxane obtained from α-cyclodextrin and poly(ethylene glycol) showed that approximately 120 cyclodextrins were threaded on the polymer (figure 7.5). So indeed the α-cyclodextrins were not close-packed on the polymer chain.

Because the peaks in the ^{1}H-NMR spectrum of the polyrotaxane are broadened, the number of cyclodextrins in the polyrotaxane is determined in the same way as for the polyrotaxane used for synthesizing the α-cyclodextrin molecular tubes (§ 3.3.1). The blocking groups are removed from the polyrotaxane and a ^{1}H-NMR spectrum of the resulting reaction mixture is taken. The ^{1}H-NMR of the former polyrotaxane showed, that there are approximately 50 cyclodextrins in one polyrotaxane. This is less than in the starting α-cyclodextrin/poly(ethylene glycol) complex. The reason probably is that the reaction between the amine end-groups and 2,4-dinitrofluorobenzene is slower with this molecular weight of "template polymer" than with a lower molecular weight used in the synthesis of the tubes and this enables some cyclodextrins to unthread from the polymer chain.

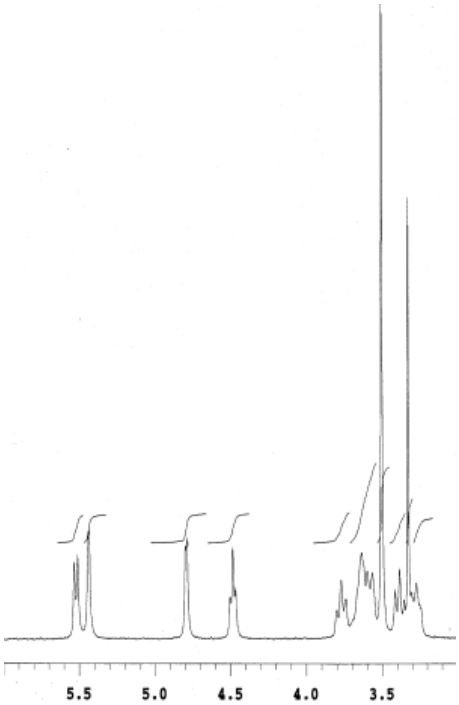

Figure 7.5. *Partial ^{1}H-NMR spectrum of the pseudo-polyrotaxane consisting of PEG with $\overline{M}_n$ = 20,000 g.mol^{-1} and α-cyclodextrin.*

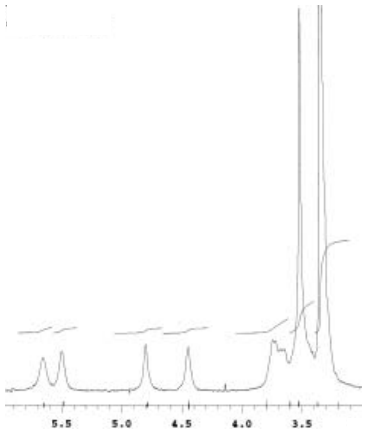

Figure 7.6. *Partial ^{1}H-NMR spectrum of the former polyrotaxane.*

7.3.2 Swelling of the "sliding gel"

A topological network is expected to have better swelling properties compared to conventional network since it is easier for the topological network to obtain a homogeneous distribution of the polymer chains though out the swollen material. To investigate if the material obtained indeed had such swelling capabilities, water and DMSO were added to the material.

It was found, that the topological network can absorb water or DMSO up to 30 times the dry weight of the topological network. These large amounts of solvent can be retained by the topological network for a long time. The volume changes are reversible.

7.3.3 Reference experiment to study the influence of the topological crosslinks

To verify the effect of the polyrotaxane topology on the gelation, a mixture of 2,4-dinitrophenyl terminated polymer and α-cyclodextrin was prepared in the same composition as in the polyrotaxane and the same crosslinking reaction in 1.00 M (aq) NaOH was performed. A solid was obtained. The ^{1}H-NMR spectrum of this solid only showed peaks due to cyclodextrin. When water or DMSO was added to the material it dissolved instead of swelled. This result indicates that the topological constrictions schematically shown in figure 7.3 are essential for swelling.

7.3.4 Study of the "sliding gel" by Small-angle Neutron Scattering

Scattering techniques have been applied successfully in the past to reveal the structure and the dynamic behavior of chemical and physical gels, i.e., polymer networks crosslinked by covalent permanent connections or by reversible bridges, respectively. The physics of swelling, polymer stretching, bond percolation and many other interesting phenomena in soft matter have been studied in gels. But the inability to make homogeneous gels, where the concentration of chains and crosslinks is distributed evenly, has tempered many of these efforts. In a gel built from a solution of almost monodisperse strands, connected by sliding crosslinks, the degree of disorder is expected to be reduced to its basic minimal form imposed by the topological constraints of connectivity. Although theoretical expectations for the shear modulus of these gels do not predict very soft structures at maximum swelling,[1] a non-trivial dependence of the scattering intensity with the degree of swelling is anticipated, because of the mass redistribution resulting from the sliding motion of the links. Also, the local sliding connectivity is expected to induce a different behavior of the scattering pattern under shear conditions. In particular, this behavior may provide information on if and how these gels retain their water while under shear, through sliding of the α-cyclodextrins on the polymer chain.
Unfortunately, in none of the preliminary SANS experiments performed on the topological network obtained, the scattering pattern observed showed signs of anisotropy or any other significant change resulting from the shear imposed on the solution.

7.4 Discussion and conclusion

Topological networks consisting of α-cyclodextrin/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxanes, in which the cyclodextrins are crosslinked by cyanuric chloride, are synthesized. The polyrotaxanes in the topological network contain approximately 50 cyclodextrins. The cyclodextrins are not close-packed on the "template polymer" chain.
By absorbing 30 times its dry weight of water or DMSO this material is a "sliding gel". The swelling is, however, not as high as described in the literature for such a material.[2]
SANS is often used for studying gels. Unfortunately SANS experiments performed on the "sliding gel" did not show signs of anisotropy or other changes resulting from the shear imposed on the gel.
Possible explanations for the lower than expected swelling and the absence of anisotropy under shear, might be the limited distance the mechanical crosslink points are able to slide along the "template polymer" chain. 50 Cyclodextrins on a polymer chain able to contain

up to 228 cyclodextrins means, that in average the cyclodextrins can only slide over a distance corresponding to 4.5 times their own length. If this is the explanation for the lower than expected swelling and the absence of anisotropy under shear, the material could be improved by reducing the number of threaded cyclodextrins in the polyrotaxane.

7.5 Experimental

Measurements

^{1}H-NMR spectra were recorded on a 300 MHz Varian (VXR 300) spectrometer. The deuterated solvent was used as internal standard. All chemical shifts are denoted in δ-units (ppm) and converted to TMS scale. Splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet).

SANS

SANS experiments were performed at Laboratoire Léon Brillouin (LLB) (CEA, Saclay (F)). The PAXY instrument was employed. Sample-to-detector distance (D_{ED}): 3.14 m; λ = 12.0 Å (q-range of 0.008–0.057 Å^{-1}). Samples were measured in a Couette apparatus installed on the beam line: $\varnothing_{int}$ = 43.5 mm, $\varnothing_{ext}$ = 47.0 mm. All measurements were performed at room temperature. At least 550×100 monitor counts were collected.

The solid material was dissolved in DMSO-d_6 or D_2O and the solution brought into the Couette apparatus. In the first experiment (4.8 (w/w) % gel in DMSO-d_6), the rotation speed was increased stepwise, almost logarithmically, up to an excess of 650 rpm. Measurements were performed at constant shear rate. Further experiments were conducted on 9.8 (w/w) % and 19.9 (w/w) % gels in DMSO-d_6 and on 3.0 (w/w) % gel in D_2O, all at 400 rpm.

Materials and methods

Poly(ethylene glycol) (PEG, $\overline{M}_n$ = 20,000 g.mol^{-1}) was purchased from Serva. PEG was dried by an azeotropic distillation from toluene before use. Triphenylphosphine and 2,4-dinitrofluorobenzene (DNFB) were purchased from Merck. α-cyclodextrin (α-CD), *N*,*N*-diisopropylethylamine (DIPEA) and tetrahydrofuran (THF) were purchased from ACROS. α-CD was dried at 80 °C under vacuum before use. THF was dried by distillation over sodium and benzophenone before use. Phthalimide, diethyl azodicarboxylate, cyanuric chloride, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), deuterated dimethyl sulfoxide (DMSO-d_6) and deuterated water (D_2O) were purchased from Aldrich. Phthalimide was recrystallized from ethanol before use. DMF was dried by distillation over P_2O_5 before use and DMSO was dried over 3 Å molecular sieves before use. Hydrazine

hydrate was purchased from Fluka. The water used, for the threading experiments, was 18 MΩ ultra pure water obtained from an Elga Maxima water purification system.

α,ω-Bis-amine-terminated poly(ethylene glycol) (1)

α,ω-Bis-amine-terminated poly(ethylene glycol) (PEG-BA) was synthesized from PEG ($\overline{M}_n$ = 20,000 g.mol^{-1}) using a procedure slightly different compared to procedure **1** described in § 2.5.[7] PEG (5.00 g; 0.250 mmol) was dissolved in 38 ml THF. Triphenylphosphine (655 mg; 2.50 mmol) and phthalimide (370 mg; 2.51 mmol) were added and the mixture stirred for 15 min under a dry nitrogen atmosphere. Diethyl azodicarboxylate (435 mg; 2.50 mmol) was dissolved in 12 ml THF. This solution was added drop-wise in 30 min to the reaction mixture, which was then refluxed for 72 h. The reaction mixture was evaporated. The residue was dissolved in 30 ml $CHCl_3$. The product was precipitated by ether and the solid washed with ether. The solid was dried on under vacuum. The product was dissolved in 29 ml H_2O and precipitated from solution by adding 10 g NaCl. The precipitate was collected by centrifugation (7,500 rpm) and the precipitate was washed with acetone. The acetone supernatant was evaporated (= product fraction 1 = 113 mg). 7.3 g KBr was added to the NaCl supernatant. The precipitate was collected by centrifugation (7,500 rpm) and the product was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was extracted with H_2O. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated (= product fraction 2 = 311 mg). The NaCl/KBr supernatant was evaporated and the residue was washed with CH_2Cl_2. The CH_2Cl_2 was evaporated (= product fraction 3 = 4.76 g). The three product fractions were combined (total amount of product = 5.18 g). The product is obtained as a white solid. This is used without further purification in the second step. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.57 (s, 4H × 455, CH_2's of PEG).

α,ω-Bis-phthalimide-terminated PEG (5.00 g), hydrazine hydrate (66 µl) and 66 ml absolute ethanol were refluxed for 26 h. Upon cooling to room temperature a precipitate was formed. The precipitate was removed by centrifugation (7,500 rpm). The supernatant was evaporated and the residue was dissolved in 26 ml $CHCl_3$. The product was precipitated by drop-wise addition of 21 ml ether. The precipitate was collected by centrifugation (7,500 rpm) and the solid was dried under vacuum to yield pure PEG-BA (4.27 g; 0.214 mmol) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.58 (s, 4H × 455, CH_2's of PEG). Overall yield of the synthesis of α,ω-bis-amine-terminated PEG is 89 %.

α-CD/α,ω-bis-amine-terminated poly(ethylene glycol) pseudo-polyrotaxane (2)

α-CD (4.00 g; 4.11 mmol) was dissolved in 28 ml H_2O at 80 °C. PEG-BA **1** (1.00 g; $5.00.10^{-2}$ mmol) was dissolved in 5.3 ml H_2O. The PEG-BA solution was added to the α-CD solution. Immediately a white precipitate formed. The dispersion was stirred at 80 °C

for 30 min and then stirred at 5 °C overnight. The dispersion was ultrasonically agitated at 5 °C for 10 min and the dispersion left undisturbed at 5 °C for 1 h. A white pellet was obtained after centrifugation (7,500 rpm) and the solid was dried over P_2O_5 under vacuum. The pseudo-polyrotaxane was obtained as a white powder with a yield of 71 %. ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.52 (d, 6H × 120, O^2H of α-CD), 5.42 (s, 6H × 120, O^3H of α-CD), 4.80 (d, 6H × 120, C^1H of α-CD), 4.48 (t, 6H × 120, O^6H of α-CD), 3.78 (t, 6H × 120, C^3H of α-CD), 3.55−3.69 (m, 12H × 120, C^6H, C^5H of α-CD), 3.52 (s, 4H × 455, CH_2's of PEG), 3.24−3.43 (m, 12H × 120, C^2H, C^4H of α-CD). The ratio of the peaks in the ^{1}H-NMR spectra corresponding to C^1H and the CH_2's of PEG revealed a number of approximately 120 CD's/polymer chain.

α-CD/poly(ethylene glycol)/2,4-dinitrophenyl polyrotaxane (3)

α-CD/PEG pseudo-polyrotaxane **2** (14.29 g; 0.1500 mmol), DNFB (8.00 g; 43.0 mmol) and DIPEA (0.11 ml; 80 mg; 0.62 mmol) in 34 ml DMF were stirred at room temperature overnight. The reaction mixture was dissolved in 50 ml DMSO. Adding 0.1 % NaCl (aq) precipitated the product. The solid was collected by centrifugation (7,500 rpm) and washed with H_2O and MeOH. The solid was dried under vacuum and the solid was dissolved in 107 ml DMSO. Adding ether precipitated the product. The precipitate was washed with ether. The pure polyrotaxane was obtained as a yellow solid (100 %). ^{1}H-NMR (300 MHz, DMSO-d_6, 25 °C): δ = 5.65 (s, 6H × 50, O^2H of α-CD), 5.50 (s, 6H × 50, O^3H of α-CD), 4.80 (d, 6H × 50, C^1H of α-CD), 4.45 (s, 6H × 50, O^6H of α-CD), 3.60−3.80 (m, 18H × 50, C^3H, C^6H, C^5H of α-CD), 3.53 (s, 4H × 455, CH_2's of PEG), 3.20−3.38 (m, 12H × 50, C^2H, C^4H of α-CD).

Topological network (4)

The topological network was synthesized according to a procedure reported by the group of Ito.[2] Some steps were slightly modified. Polyrotaxane **3** (2.00 g; $2.90.10^{-2}$ mmol) was dissolved in 6.1 ml 1.00 M (aq) NaOH and was cooled to 5 °C. Cyanuric chloride (0.12 g; 0.66 mmol) was dissolved in 6.1 ml 1.00 M (aq) NaOH and slowly added at 5 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was neutralized with 1.00 M (aq) HCl. The mixture was centrifuged (7,500 rpm) and the supernatant precipitated with acetone. The gel-like precipitate was washed with H_2O and MeOH. The gel-like solid was dried under vacuum. The product was obtained as yellow solid.

Swelling experiments

Some topological network particles **4** (20 mg) were mixed with 1 ml of H_2O or DMSO. The mixture was shaken at 700 osc/min for 2h. The swollen gel particles were separated from

the remaining liquid. The swollen gel particles had a weight of 700 mg in the case of H_2O and 500 mg in the case of DSMO. The water was removed from the water swollen gel particles by drying the gel particles over P_2O_5 under vacuum. This yielded dry gel particles (20 mg).

7.6 References

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Summary

Cyclodextrins are cyclic oligosaccharides composed of glucose. Cyclodextrins are used in literature to built relatively new and exciting supramolecular architectures that might find their application in molecular devices. Many of these supramolecular architectures are based on cyclodextrins threaded onto polymer chains.

In this thesis the synthesis of cyclodextrin-containing supramolecular structures, their characterization and possible applications of these supramolecular structures is presented.

In **chapter 1** an overview is given of cyclodextrins and of some possible cyclodextrin-containing supramolecular structures described in literature.

In **chapter 2**, the design and synthesis of a cyclodextrin molecular tube is described in detail. First, a pseudo-polyrotaxane in which the cyclodextrins are close-packed from end to end on a “template polymer” is prepared. This pseudo-polyrotaxane is converted to a polyrotaxane by the reaction of the ends of the template polymer with bulky blocking groups. The cyclodextrins are connected intramolecularly and in this way a cyclodextrin molecular tube is obtained, however, the “template polymer” is still inside the tube. When the blocking groups are removed, the polymer chain is released from the molecular tube and a cyclodextrin molecular tube is obtained.

The characterization of the α-cyclodextrin molecular tube is presented in **chapter 3**. Among others especially Atomic Force Microscopy and Small-angle Neutron Scattering are used to obtain information about the dimensions and rigidity of the synthesized cyclodextrin molecular tube. The characterization shows the α-cyclodextrin molecular tubes do not contain the number of cyclodextrins present in the parent polyrotaxane.

In order to find possible explanations for the shorter then expected empty α-cyclodextrin molecular tubes in c**hapter 4** models are discussed describing the cyclodextrin pseudo-polyrotaxanes.

Chapter 5 concerns a possible application of the empty α-cyclodextrin molecular tubes. Inclusion compounds are formed between the cyclodextrin molecular tubes and polyaniline. Polyaniline is a conjugated polymer and when doped electrically conducting. The inclusion compounds consisting of cyclodextrin molecular tubes and polyaniline chains might be regarded as insulated molecular wires. Surprisingly enough, two types of inclusion compounds are obtained. One inclusion compound consisted of one polyaniline chain threaded by multiple α-cyclodextrin molecular tubes. The other inclusion compound consisted of multiple polyaniline chains and multiple α-cyclodextrin molecular tubes.

The synthesis of a different type of potential insulated molecular wire is described in **chapter 6**. This potential insulated molecular wire is obtained by first including a monomer inside the cavity of a cyclodextrin. The polymer obtained after polymerization of this inclusion compound was a conjugated polymer. The polymer obtained was still threaded by

cyclodextrins so a pseudo-polyrotaxane was obtained. This pseudo-polyrotaxane was converted into a stable polyrotaxane by reaction of the ends of the polymer obtained with bulky blocking groups.

In **chapter 7**, a completely different material is described, for which the same kind of chemistry is used as that for obtaining the cyclodextrin molecular tubes. The only difference is the molecular weight of the poly(ethylene glycol) “template polymer”. In this case a higher molecular weight “template polymer” is used. Because of this higher molecular weight “template polymer” the cyclodextrins are not close packed along the polymer chain. If a polyrotaxane is synthesized anyway, the cyclodextrins have the ability to slide along the polymer chain. When the cyclodextrin rings are connected with each other intermolecularly, a new type of network is obtained. Due to the ability of the cyclodextrins to slide along the polymer chains this network is proposed as material, able to take up large amounts of solvent.

Samenvatting

Cyclodextrines zijn cyclische oligosaccharides, opgebouwd uit glucose eenheden. Cyclodextrines worden in de literatuur gebruikt om relatief nieuwe en spannende supramoleculaire architecturen te bouwen die gebruikt kunnen worden als moleculaire apparaten. Veel van deze supramoleculaire architecturen zijn gebaseerd op cyclodextrines die op polymeer ketens geregen zijn.

In dit proefschrift wordt de synthese van cyclodextrine bevattende supramoleculaire structuren alsmede hun karakterisatie en mogelijke toepassing gepresenteerd.

In **hoofdstuk 1** wordt een overzicht gegeven van cyclodextrines en enkele cyclodextrine bevattende supramoleculaire structuren zoals beschreven in de literatuur.

In **hoofdstuk 2** wordt in detail het ontwerp en de synthese van een moleculaire buis opgebouwd uit cyclodextrines beschreven. Eerst wordt er een pseudo-polyrotaxaan gesynthetiseerd, waarin de cyclodextrines zo zijn geregen, dat er geen ruimte tussen de cyclodextrines meer is. Deze pseudo-polyrotaxaan wordt omgezet in een polyrotaxaan door de reactie van de eindgroepen van het polymeer in de pseudo-polyrotaxaan met grote stopper groepen. De cyclodextrines worden intramoleculair verbonden en op deze manier wordt een moleculaire buis bestaande uit cyclodextrine eenheden verkregen. Het polymeer, dat gebruikt is om de cyclodextrines op te rijgen, is echter nog steeds aanwezig in de buis. Wanneer de stopper groepen worden verwijderd, wordt ook de polymeerketen uit de moleculaire buis bestaande uit cyclodextrine eenheden verwijderd en wordt een echte moleculaire buis verkregen.

De karakterisatie van de moleculaire buis bestaande uit cyclodextrines wordt gepresenteerd in **hoofdstuk 3**. Onder andere Atomic Force Microscopy en Small-angle Neutron Scattering worden gebruikt om informatie over de dimensies en starheid van de uit cyclodextrines bestaande moleculaire buis te verkrijgen. De karakterisatie laat zien dat de moleculaire α-cyclodextrine buizen niet het aantal cyclodextrines bevatten dat aanwezig is in de polyrotaxaan waaruit de buis is verkregen.

Om mogelijke verklaringen te vinden voor het feit dat de lege α-cyclodextrine moleculaire buizen korter zijn dan verwacht, worden in **hoofdstuk 4** modellen besproken die de pseudo-polyrotaxanen beschrijven.

Hoofdstuk 5 gaat over een mogelijke toepassing van de verkregen lege moleculaire α-cyclodextrine buizen. Een complex wordt gevormd uit de uit cyclodextrines bestaande moleculaire buizen en polyaniline. Polyaniline is een geconjugeerd polymeer en wordt halfgeleidend na doping. Het complex bestaande uit de moleculaire cyclodextrine buizen en polyaniline kan worden gezien als een geïsoleerde moleculaire spanningsdraad. Verrassend genoeg worden twee typen complexen verkregen. Namelijk een pseudo-polyrotaxaan

bestaande uit een polyaniline keten geregen door meerdere moleculaire α-cyclodextrine buizen en een moleculaire ketting bestaande uit meerdere polyaniline ketens en meerdere moleculaire α-cyclodextrine buizen.

De synthese van een ander type geïsoleerde moleculaire spanningsdraad is beschreven in **hoofdstuk 6**. Deze geïsoleerde moleculaire spanningsdraad is verkregen door eerst een monomeer in te sluiten in de holte van een cyclodextrine. Het polymeer, verkregen na de polymerisatie van het gecomplexeerde monomeer, is een geconjugeerd polymeer. Het polymeer bevat nog steeds cyclodextrines en dus is een pseudo-polyrotaxaan verkregen. Deze pseudo-polyrotaxaan is omgezet in een stabiele polyrotaxaan door de reactie van de eindgroepen van het verkregen polymeer met grote stopper groepen.

In **hoofdstuk 7** wordt een compleet ander materiaal beschreven, hoewel dezelfde soort chemie is gebruikt als voor de synthese van de moleculaire cyclodextrine buizen. Het enige verschil is het molecuulgewicht van het poly(ethyleen glycol) polymeer dat gebruikt is als mal om de cyclodextrines op te rijgen. Vanwege het hogere molecuulgewicht is er ruimte tussen de cyclodextrines geregen op de polymeerketen. Wanneer toch een polyrotaxaan wordt gesynthetiseerd, hebben de cyclodextrines de mogelijkheid om te bewegen over de polymeerketen. Wanneer de cyclodextrine ringen intermoleculair met elkaar verbonden worden, wordt een nieuw type netwerk verkregen. Vanwege de vrijheid van de cyclodextrines om over de polymeerketen te glijden, kan dit materiaal misschien grote hoeveelheden oplosmiddel opnemen.