Design and Synthesis of Cyclodextrin-Based Rotaxanes and Polyrotaxanes

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Abstract. Rotaxanes are compounds in which a ring is threaded by a chain having bulky terminal cap groups. In this article, we review the design, synthesis and characterization of rotaxanes and polyrotaxanes of cyclodextrins threaded by an alkyl chain or a poly(ethylene glycol) as well as the synthesis of a light-driven molecular shuttle based on a cyclodextrin-rotaxane.

Key words: rotaxane, polyrotaxane, cyclodextrin, molecular recognition, light-driven molecular shuttle, lipid, lipid bilayer, supramolecule, nanotube.

1. Introduction

The chemistry of topological supramolecules such as catenanes, rotaxanes, and knots is of considerable interest. Rotaxanes [1] are compounds in which a ring is threaded by a chain having bulky terminal cap groups so that the chain cannot be extruded from the ring. Considerable attention has recently been focused on these compounds from the viewpoints of the synthesis of unknown organic compounds and their potential applications for the construction of molecular devices. The α-, β- and γ-cyclodextrins (CyDs) are cyclic oligosaccharides consisting of six, seven or eight glucose units, respectively, and are known to form inclusion complexes with a variety of molecules which fit into their hydrophobic cylindrical cavities [2]. This article reviews the design, synthesis, and characterization of cyclodextrin-based rotaxanes and polyrotaxanes.

2. Rotaxanes and Polyrotaxanes of CyDs Threaded by an Alkyl Chain or a PoIy(ethylene glycol)

In 1981, Ogino [3] reported the synthesis of alkyl chain-threaded rotaxanes (**1**) with metalloorganic stoppers in which hydrophobic interaction between α, ω-diaminoalkanes and α-CyD was available (Scheme 1), which was the first report of a rotaxane synthesis with relatively high

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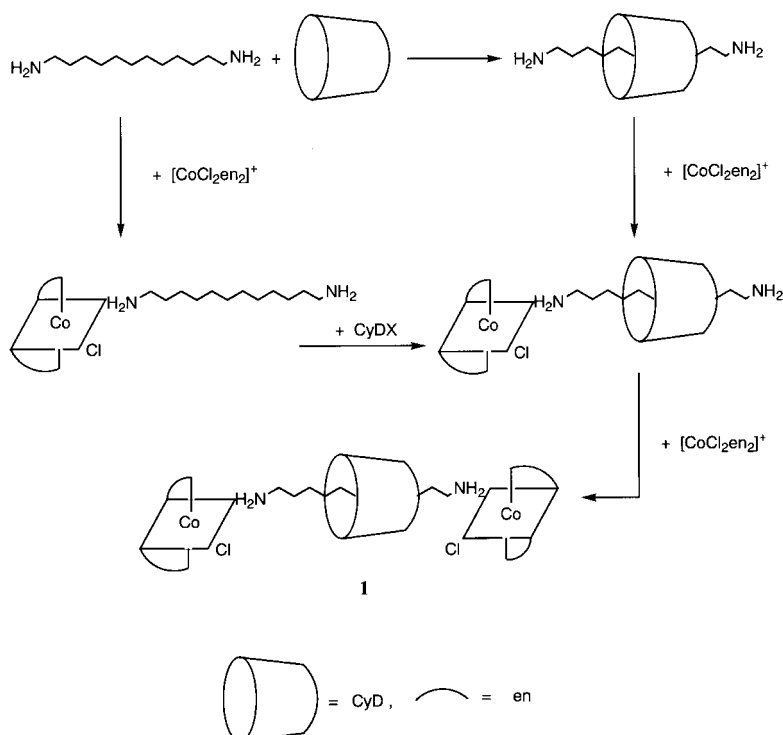
Scheme 1.

yield, utilizing the inclusion phenomenon. The best yield (19%) is obtained for the synthesis of $[2]$-$[[(en)_2ClCo(1,12$-diaminododecane$)CoCl(en)_2]Br_4]$-$[\alpha$-CyD]-rotaxane + $7H_2O$ (en = ethylenediamine) [3, 4]. Yamanari and Shimura [5] described the stereoselective formation of four possible diastereomers of $[2]$-$[[(en)_2$-Co$\{NH_2(CH_2)_2S(CH_2)_nS(CH_2)_2NH_2\}Co(en)_2]Cl_6]$-[CyD]-rotaxanes (**2**) composed of polymethylene-bridged dinuclear cobalt (III) complexes and α- or β-CyDs threaded by polymethylene chains (Figure 1).

Isnin and Kaifer [6] reported the synthesis of α-CyD-based asymmetric zwitterionic rotaxanes (**3a**, **3b**, **4a**, **4b**, Scheme 2) in 15% yield, where carboxyalkyldimethyl(ferrocenylmethyl)ammonium compounds were treated with 2 equiv. of α-CyD, 1 equiv. of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) as a condensation reagent, and 1 equiv. of potassium 5-amino-2-naphthalenesulfonate in water. The NOESY 2D NMR spectrum of **4** clearly shows that the low-field amidic proton signal at 9.6 ppm correlates with the resonance of the secondary hydroxy groups of CyD. On the other hand, the high-field amidic proton signal at 9.5 ppm correlates with the resonance of the primary hydroxy groups of CyD. This provides compelling evidence for the proposed rotaxane structures and existence of the CyD-positional isomers **4a** and **4b**. This is the first report on the synthesis of isomers based on the orientation of the CyD.
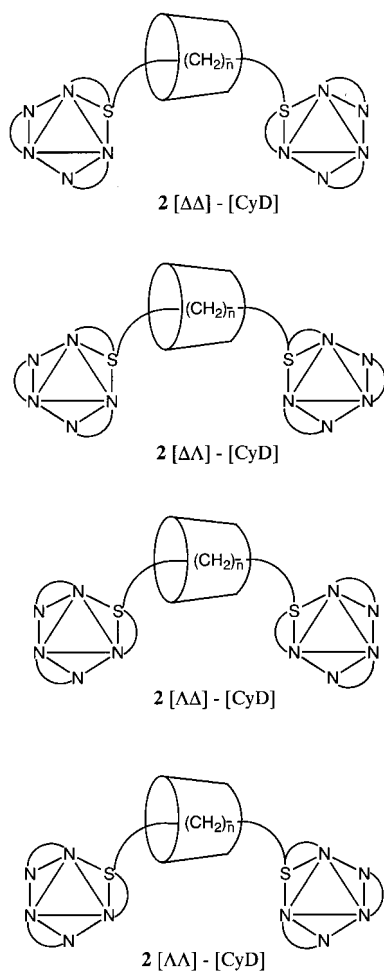
2 [ΔΔ] - [CyD]

2 [ΔΛ] - [CyD]

2 [ΛΔ] - [CyD]

2 [ΛΛ] - [CyD]

Figure 1. Four possible diastereomers of **2**.

The self-assembly of an α-CyD-based [2] rotaxane (**5**) from $[Fe(CN)_5OH_2]^{3-}$ and $1,1'$-(α, ω-alkanediyl)bis(4,4-bipyridinium) ion was described by Wylie and Macartney [7]. Born and Ritter described the syntheses of comb-like rotaxanes containing 2,6-dimethyl-β-CyD in the side chain [8a] and of a polyrotaxane (**6**) with a tandem structure [8b]. The tandem polyrotaxane was synthesized by the condensation of the free acid groups of copolymer, which was radical copolymerized with 5-[(11-methacryloylamino)undecanoylamino]isophthaloylbis(12-azaundecanoic acid) and methylmethacrylate in a ratio of 1 : 4.1, and the free amino groups of semirotaxane, which were prepared from 2,6-dimethyl-β-CyD and 4-amino-N-[4-(triphenylmethyl)phenyl]butanamide. The semirotaxane used is similar to a low molecular weight rotaxane, which has only one bulky end cap and one reactive group, and is relatively stable. Elemental analysis proves that almost
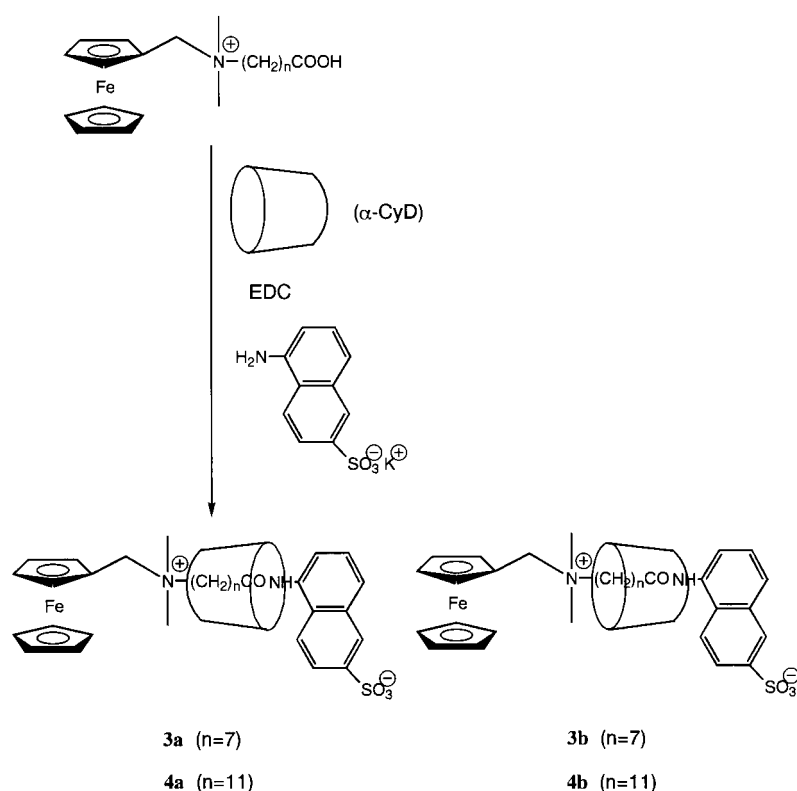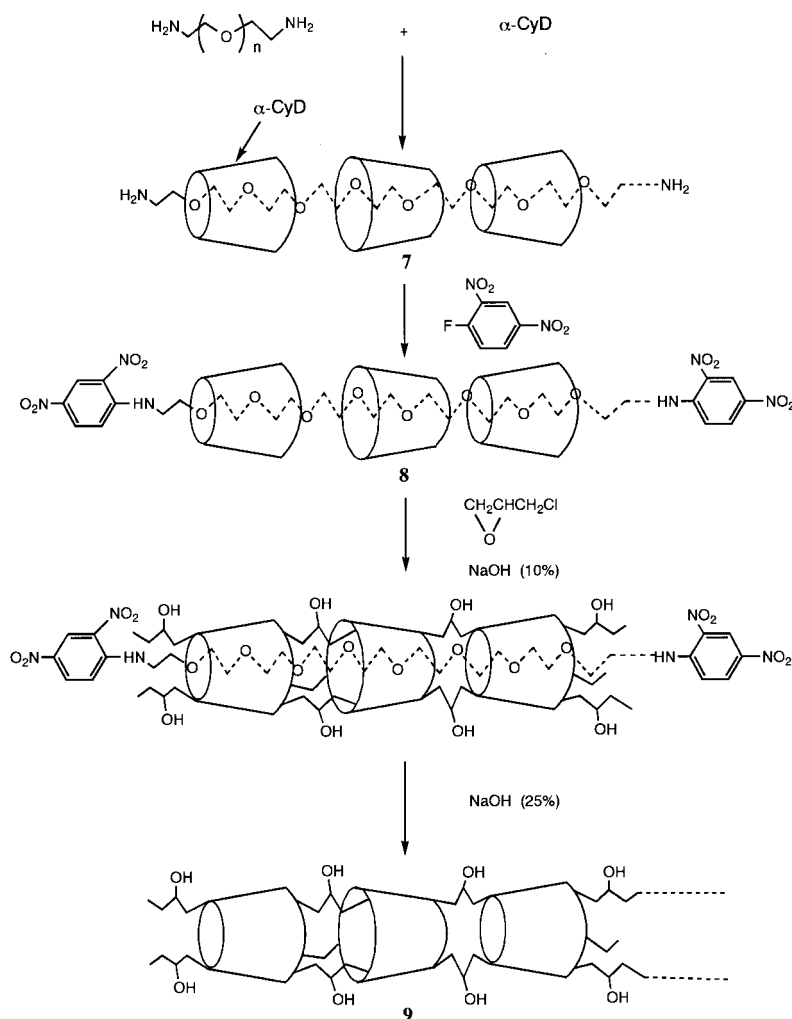
Scheme 2.

all of the side chains are occupied according to the proposed structure (**6**). The rotaxane structure of **6** was characterized by ^{1}H NMR spectroscopy. The chemical shifts at $\delta = 7.41$–7.43, corresponding to the anilide segment in the 2,6-position (H_a and H_b in **6**), are markedly broadened and shifted downfield by roughly $\Delta\delta = 0.05$. This indicates that the CyDs move readily along the aliphatic side chains at room temperature. In contrast, at $-10\,^\circ$C the CyDs are located preferentially near the anilide end groups, according to the NMR spectra.

Since the first report [9] in 1990 on the synthesis of the crystalline inclusion complexes (**7**) of α-CyD with poly(ethylene glycol) (PEG) (the stoichiometry of the complexes is 2 : 1, two ethylene glycol units and one α-CyD) in high yield, Harada and Kamachi have developed a unique CyD chemistry [10]. They have succeeded in the synthesis of the molecular necklace: a rotaxane (**8**) containing many threaded α-CyD [11] by capping the chain of the complexes with bulky end groups. They then produced a nanotube: a tubular polymer (**9**) [12] by the crosslinking of adjacent CyD units in the necklace, followed by removing the bulky ends and the polymer thread (Scheme 3). Recently, they showed by a single crystal X-ray study that in a crystalline complex of hexa(ethylene glycol) with α-CyD, α-CyD forms columns in a head-to-head and tail-to-tail fashion [13].
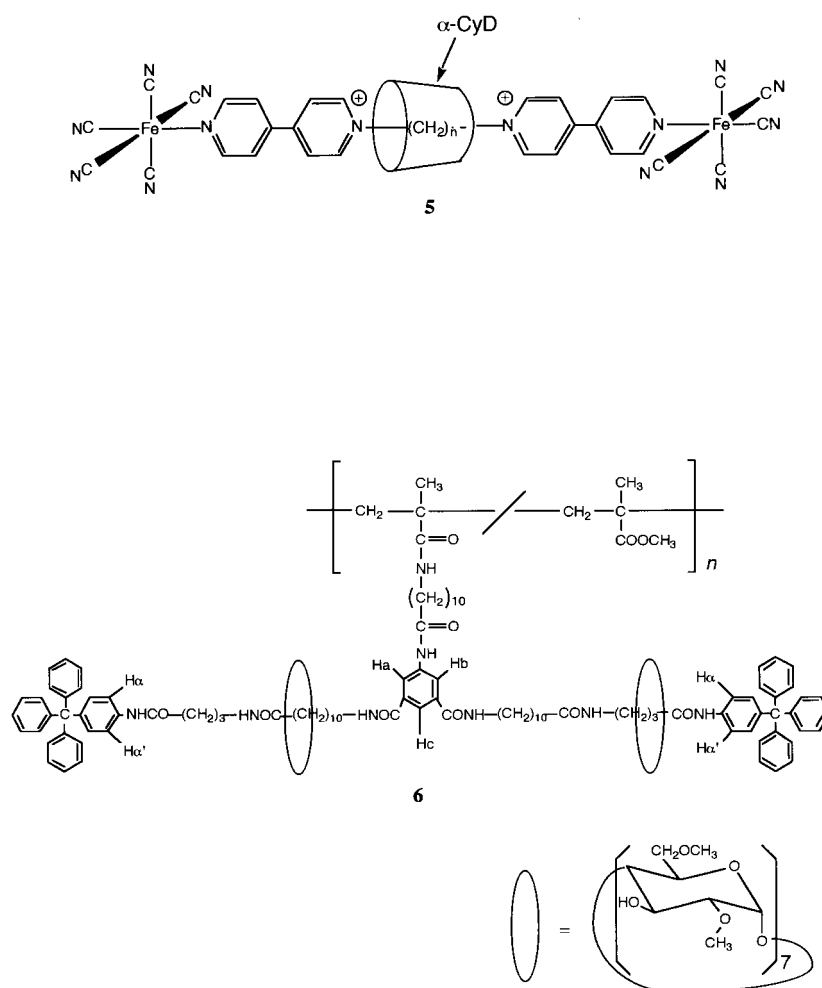
Compounds **5** and **6**.

We are interested in the design and construction of self-assembled lipid supramolecular structures based on the combination of lipid chemistry and host-guest chemistry. Aqueous bilayers of a triple-chain synthetic lipid bearing poly(ethylene glycol) (**10**) form a crystalline complex (**11**) with α-CyD which has been characterized by ^{1}H NMR and FT-IR spectroscopy and differential scanning calorimetry (DSC) [14]. The ^{1}H NMR spectra of the complex revealed that the 2.2 $\pm$ 0.1 ethylene glycol units of the lipid were captured in one α-CyD molecule. This crystalline complex retains the fundamental characteristics (phase transition) of the lipid bilayers. The synthesis of poly(rotaxanes) based on the complex is possible [15].
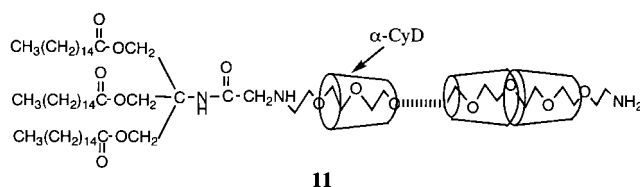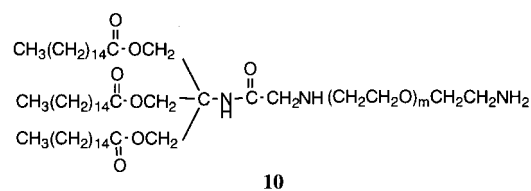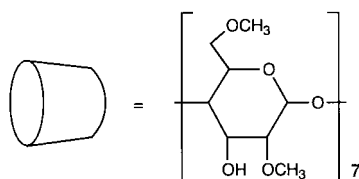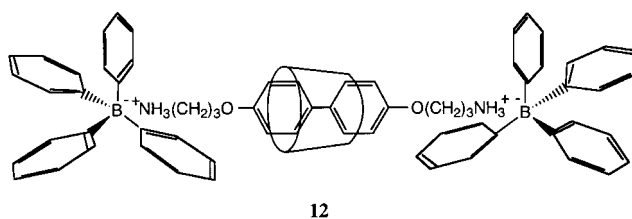
Scheme 3.

3. Aromatic Chromophore-Threaded Rotaxanes of CyDs

In 1990, Lawrence and co-workers described the synthesis of a rotaxane-like mole-
cule (**12**) which includes a biphenyl chromophore in the cavity of β-CyD [16] as
well as the synthesis of template-driven self-assembly of a porphyrin-containing
supramolecular complex (**13**) [17]. The formation of rigid molecular nanotube
aggregates (**14**) of β- and γ-CyDs through linkage by the rod-like molecules of
1,6-diphenyl-1,3,5-hexatriene was reported by Li and McGown [18]. They showed
an STM image of their aggregates.

One strategy for the tactical syntheses of rotaxanes is to utilize host/guest inter-
actions of aromatic compounds with CyDs [19]. Based on this idea, we designed
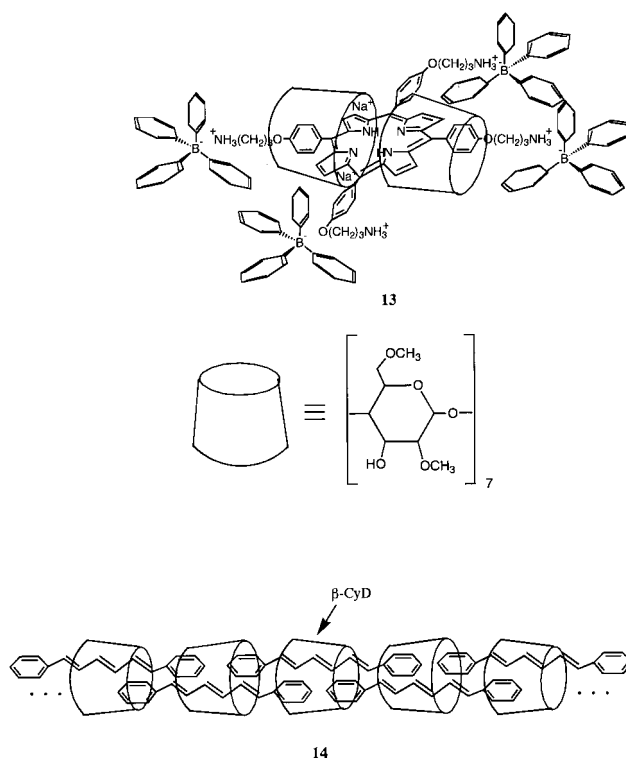
Compounds **10** and **11**.

Compound **12**.

a rotaxane in which an aromatic chromophore is threaded in the cavity of β-CyD (Figure 2). Scheme 4 shows the synthetic route to a rotaxane (**15**) and a reference compound (**16**). 4,4′-Diaminostilbene + 2HCl and an excess of β-CyD were dissolved in aqueous sodium carbonate solution to give a complex, which was capped with 1-amino-3,6,8-naphthalene trisulfonic acid-substituted trichloro-*s*-triazine at 25 °C. The remaining chloro function was treated with aniline at 90 °C to produce a rotaxane **15** in 28% yield. The structure of **15** was characterized by UV-visible and circular dichroism (CD) spectra; CD experiments in particular provide strong proof for the formation of the rotaxane structure; i.e., an aqueous solution of **15** gave a distinct induced CD spectrum, in the 300–400 nm region which corresponds to the absorption band of the stilbene moiety, indicating that the π–π^* transition of the stilbene chromophore is perturbed from the chiral environment of β-CyD. No such

Compounds **13** and **14**.

ICD spectrum is observed for compound **16** in the presence of a large excess of β-CyD.

Wenz and co-workers have described that the Menschutkin reaction of 1-[4-(7,7,7-triphenylheptyloxy)benzyl]-4,4′-bipyridinium complexed in heptakis(2,6-di-*O*-butyl-3-*O*-acetyl)-β-CyD with 4-(7,7,7-triphenylheptyloxy)benzyl bromide gives a rotaxane (**17b**) in 36% yield [20].

4. A Light-Driven Molecular Shuttle Based on a Rotaxane

The construction of stimuli-responsive molecular devices and molecular machines is a great challenge. The construction of molecular shuttles in which a ring moves back and forth like a shuttle between two or more 'stations' in response to external stimuli is one such target [21]. Recently, Stoddart and coworkers reported the synthesis of temperature-controlled (-140 to 50 °C) molecular shuttles using rotaxanes [22]. Ballardini and co-workers described the idea of a light-driven molecular shuttle in the last part of their paper [23].

We recently described the design, synthesis, and characterization of a rotaxane (**18**) which functions as a light-driven molecular shuttle [24]. Compound (**18**), which consists of a ring, a threading chain molecule, and bulky terminal caps of α-
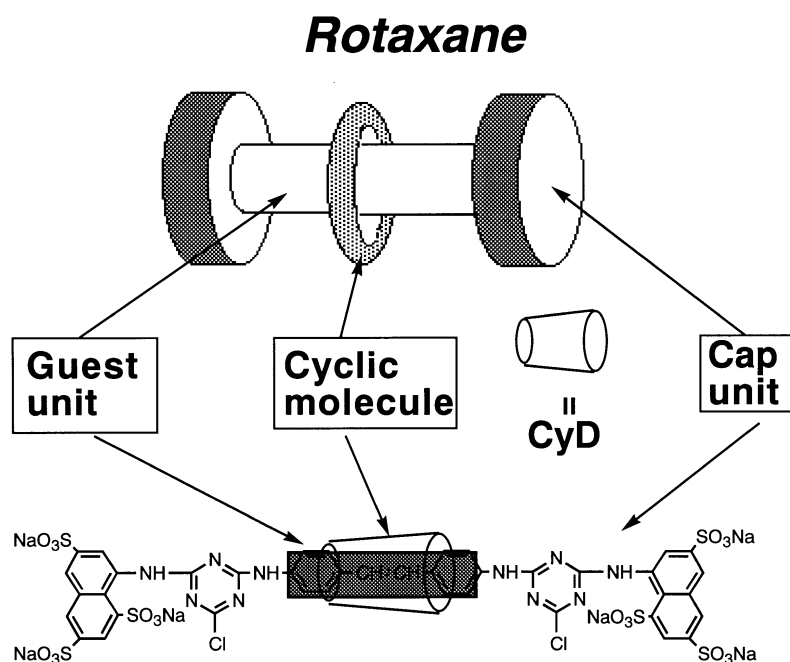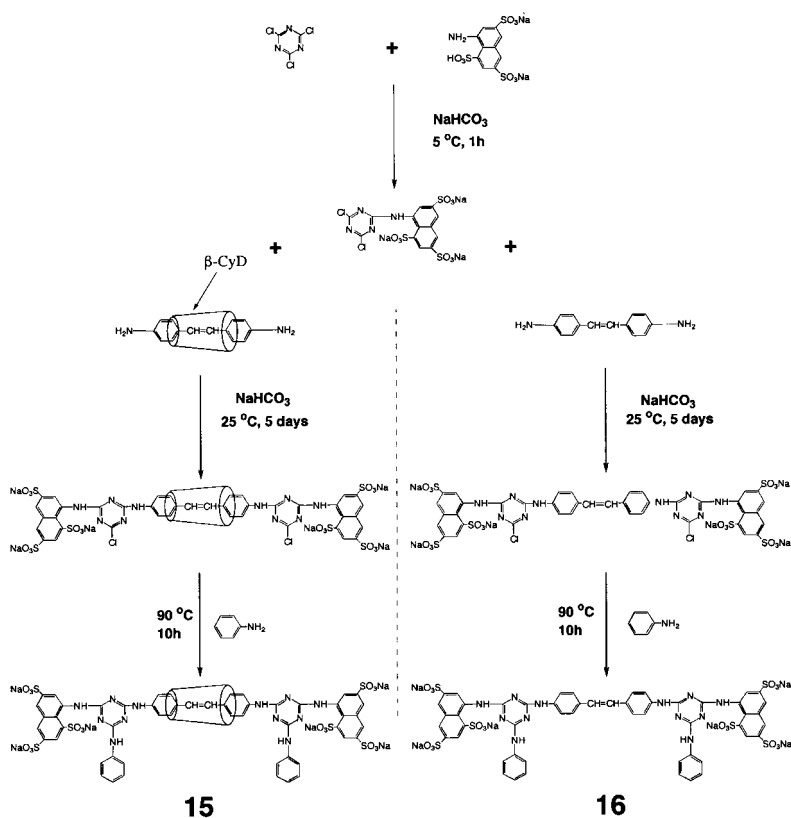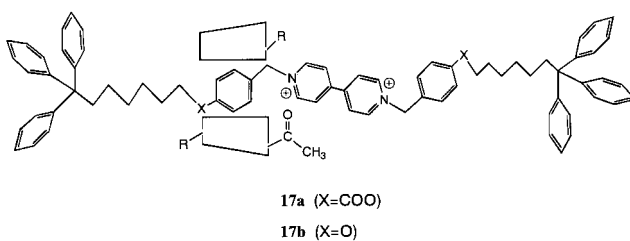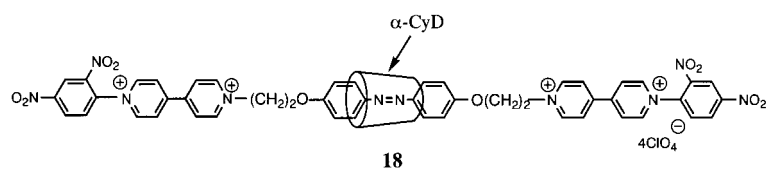
Rotaxane

Figure 2. An aromatic chromophore-threaded CyD-based rotaxane.

CyD, azobenzene, and 2,4-dinitrobenzene moieties, respectively, was synthesized as follows. 4,4′-Bis(2-bromoethoxy)azobenzene and 4,4′-bipyridine were reacted in DMF at 85 °C. A precipitate produced was filtered and washed with DMF and then diethyl ether to yield 4,4′-bis[4-(4′-pyridyl)pyridinium-2-ethoxy]azobenzene dibromide, which was treated with 2,4-dinitrofluorobenzene in water containing excess α-CyD at 25 °C to yield **18** (30.3%).

The rotaxane structure was confirmed by ^{1}H NMR spectroscopy. UV-light irradiation at 360 nm in an aqueous solution of **18** causes the photoisomerization from *trans-* to *cis*-configuration of the azobenzene unit, reverting to the *trans-*configuration by irradiation at 430 nm. The UV-light irradiation causes the positive induced CD (ICD) band at 360 nm to decrease together with the increase in the positive and negative ICD bands at 312 nm and 430 nm, respectively, which are reversed *via* irradiation with visible light. Alternating photoirradiation with UV and visible light reveals that the photoswitching process is reversible. This study might afford the opportunity to design and develop nanoscale switching devices based on light-driven molecular shuttles.

Scheme 4.

17a (X=COO)

17b (X=O)

Compounds **17a** and **17b**.

Compound **18**.

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