

## A new approach to cyclodextrin-based rotaxanes

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### Abstract

A new synthetic strategy for the preparation of cyclodextrin-based rotaxanes is described. The method is essentially based on the formation of stable inclusion complexes between  $\alpha$ -CD and aliphatic chains. The interaction in aqueous media of compounds containing a long alkyl chain terminated in a bulky (ferrocenylmethyl)dimethylammonium group with  $\alpha$ -CD leads to inclusion complexes in which the cyclodextrin is threaded by the alkyl chain. Functionalization of the other chain terminus with a carboxylic acid group allows trapping of the chain-threaded CD receptor *via* amidation reactions of the carboxylic functional group with bulky amines. The rotaxane products are asymmetric since the two terminal groups are different. This feature allows, for the first time, the detection of isomeric rotaxanes exhibiting the two possible orientations of the trapped CD.

Rotaxanes are interesting supramolecular structures in which a cyclic component (the so-called *bead*) is threaded by a linear subunit (ref. 1). In order to prevent dissociation between the cyclic and linear components, the latter bears bulky terminal groups that act as stoppers for the cyclic bead, sterically preventing its dissociation or unthreading. A schematic representation of a rotaxane is shown below. Formally, the bead is bound to the linear thread and the equilibrium association constant ( $K$ ) is infinitely large because the kinetic rate of dissociation is zero and  $K = k_{\text{assoc}}/k_{\text{dissoc}}$ .

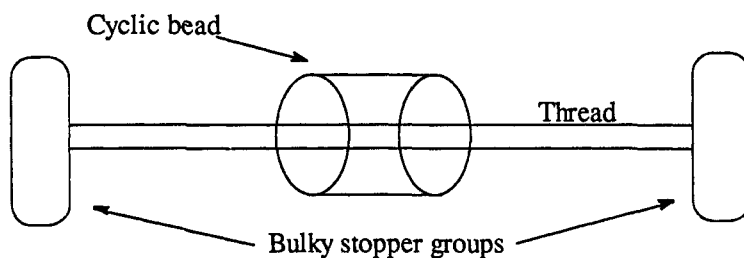


Figure 1. Structural components of a rotaxane.

The literature contains several classes of methods for the preparation of rotaxanes. Some methods are based on statistical approaches and usually generate rotaxane structures in which there is no sizable interaction between the *thread* and the *bead* components. However, higher yields can be obtained if the rotaxane structure is pre-organized using bead-thread interactions. If these interactions lead to the formation of covalent bonds between the thread and the bead component, the final step in the preparation of the rotaxane is the breaking up of these covalent bonds. However, the approach that has enjoyed substantial popularity during the last few years makes use of non-covalent bead-thread interactions. The advantage of this methodology is that these interactions pre-organize or *self-assemble* the rotaxane structure, allowing the appropriate chemical reactions to take place, and yielding the rotaxane without the final need to break any bonds. As a recent example of this methodology, Stoddart and collaborators have masterfully utilized electron

donor-acceptor interactions between aromatic subunits to synthesize a variety of complicated rotaxanes and catenanes (ref. 2).

Cyclodextrins (CD's) appear to be ideal as pre-formed beads for rotaxane chemistry because of their shape and binding properties. These natural receptors are cyclic glucopyranose oligomers with a well defined toroidal shape and a strong binding affinity for hydrophobic molecules in aqueous media (refs. 3 and 4). The inner surface of their molecular cavity is hydrophobic because it is lined by the glycosidic oxygen bridges. In contrast, the exterior surface of CD's is substantially hydrophilic due to the hydroxyl groups. An important characteristic of CD receptors is the size difference between the two cavity openings. The narrower opening is formed by the primary hydroxyl groups (those in C-6) while the wider opening contains the secondary hydroxyls on C-2 and C-3 of the glucopyranose rings.

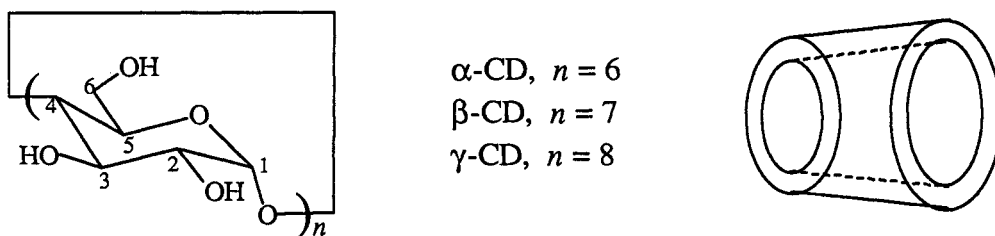
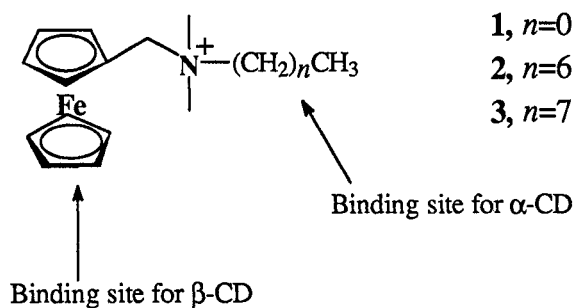


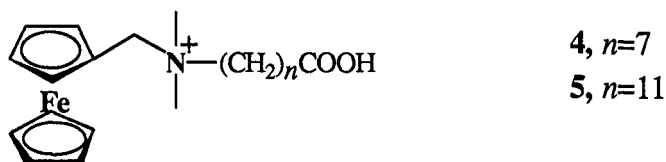
Figure 2. Molecular structure and shape of cyclodextrins.

CD complexes are usually of the inclusion type, that is, the whole guest or the molecular region bound is totally or, at least, partially engulfed by the CD cavity. In very simplistic terms, the major driving force for complex formation is the hydrophobic effect and, hence, CD-guest complexes lose stability in non-aqueous media. Our interest in cyclodextrin-based rotaxanes arose from CD complexation studies of a series of surfactant ferrocene derivatives. These alkyl dimethyl(ferrocenylmethyl)ammonium cations, 1-3, exhibit two different hydrophobic regions and, as a result of this, two types of binding interactions with CD's. We have previously demonstrated that  $\alpha$ -CD (with a cavity diameter range of 4.7-5.3 Å) binds preferentially to the alkyl chain while  $\beta$ -CD (cavity diameter from 6.0 to 6.5 Å) engulfs the ferrocene subunit (ref. 5). The selectivity in binding site results obviously from the optimization of the fit between the corresponding cavities and hydrophobic groups.



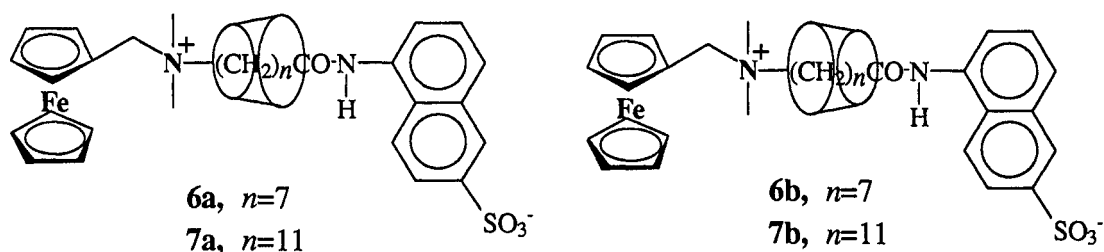
Regarding the binding of cations 2 and 3 by  $\alpha$ -CD, our spectroscopic data indicates that the receptor is threaded by the alkyl chain. In fact, one can exert some control on the number of  $\alpha$ -CD molecules that participate in the complex by changing the length of the aliphatic chain in the ferrocene derivative. Therefore, the  $\alpha$ -CD complexes of derivatives 2 and 3 can be considered *pre-rotaxane* structures. Since it is sterically impossible for the CD bead to unthread or dissociate from the chain through the end occupied by the bulky (ferrocenylmethyl)dimethylammonium group, capping of the other end is necessary in order to synthesize stable rotaxanes. This requires the

appropriate functionalization of this side of the chain. For reasons of synthetic accessibility, we selected the carboxylic acid functional group for this purpose and synthesized compounds **4** and **5**.



Not unexpectedly, the interaction of compound **4** with  $\alpha$ -CD is highly pH-dependent. If the pH is above the  $pK_a$  of the acid group (which was found to be 4.4), deprotonation takes place, generating a negative charge at the end of the chain. This terminal negative charge hinders the binding (threading) of the CD receptor, decreasing the observed value of the binding constant. At a pH of 2.6, at which the carboxylic acid is completely protonated, the binding constant was found to be  $425\text{ M}^{-1}$  while the corresponding value at pH=8.0, at which the acid group is ionized, is  $71\text{ M}^{-1}$ . Therefore, the carboxylic acid can be seen as a *pH-dependent gate*, controlling the complexation reaction between  $\alpha$ -CD and the aliphatic chain within the limits established by the binding constant values given above.

In spite of the pH-dependent binding characteristics introduced by the carboxylic acid group, we accomplished our primary goal, that is, to utilize its reactivity to trap the CD receptor threaded by the alkyl chain. We used standard amidation chemistry, reacting the carboxylic acids **4** and **5** with a bulky water-soluble amine, potassium 5-amino-2-naphthalenesulfonate, in the presence of  $\alpha$ -CD and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) as a catalyst. These reactions were conducted in aqueous media to enhance the interactions leading to CD threading. From the resulting reaction mixtures, we isolated (in 15% yield) the zwitterionic asymmetric rotaxanes represented below (ref. 6).



Compound **4** produced a mixture of the isomeric rotaxanes **6a** and **6b** in 6:4 ratio. Similarly, the longer chain analog **5** yielded **7a** and **7b** in 4:6 ratio. The presence of isomers was clearly detected in the 400 MHz  $^1\text{H}$  NMR spectra recorded in  $\text{DMSO-d}_6$  (ref. 6). For instance, the rotaxane product isolated from **4**, exhibits split resonances for both the amidic protons and the methyl groups on the quaternary nitrogen. NOESY 2D NMR experiments clearly showed that this splitting is related to the two possible orientations of the threaded CD receptor. Thus, the low-field amidic proton (9.6 ppm) correlates with the secondary hydroxyls on the wider opening of the CD (isomer **6a**) while the other amidic proton (9.5 ppm) exhibits a clear correlation with the primary hydroxyl groups that populate the narrower CD opening (isomer **6b**).

We have successfully separated these isomeric rotaxanes using reversed phase TLC. In fact, the separation was surprisingly easy using  $\text{C}_{18}$ -bonded silica plates and a water:methanol (70:30 v/v) solvent mixture. Under these conditions, the observed  $R_f$  values were: **6a**, 0.57; **6b**, 0.74; **7a**, 0.36; and **7b**, 0.50. These values indicate that the rotaxanes derived from the longer-chain precursor (compound **5**) are less polar, as expected, than those synthesized from the shorter-chain parent

compound, **4**. Not so easy to rationalize are the polarity differences related to CD orientation. For instance, the quoted  $R_f$  values indicate that the rotaxanes having the threaded CD oriented with the wide opening away from the ferrocene terminal group (**6a** and **7a**) are correspondingly less polar than those in which the CD has the wide opening facing this group (**6b** and **7b**).

Another interesting observation is that isomers **6a** and **7a** undergo *slow unthreading*. The rate of this process seems to be highly dependent on solvent nature. In strong contrast to this, rotaxane isomers **6b** and **7b** are completely stable against unthreading. However, this difference can be rationalized by inspection of CPK models. In rotaxanes **6a** and **7a**, it is possible to release the CD bead by pushing it over the naphthalenesulfonate capping group. This is completely impossible with models of rotaxanes **6b** and **7b**.

This work has provided the first examples of truly asymmetric CD-based rotaxanes. The positive charge on the (ferrocenylmethyl)dimethylammonium group and the negative charge on the naphthalenesulfonate capping group confer zwitterionic character to these rotaxane structures. Furthermore, the asymmetric nature of the structures allows the detection, for the first time, of isomers resulting from the two possible orientations of the chain-threaded CD receptor. This finding is quite relevant to those interested in CD inclusion complexation.

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