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Design on head-to-tail directly linked homogeneous and heterogeneous cyclodextrin dimers and their evaluation of hydrophobic cavity

Yoshihiro Isihimaru *, Yasunori Kojo, Taich Masuda, Syunsuke Saito, Yu Yue, Yu Fujisaki

Division of Material Science, Graduate School of Science and Engineering, Saitama University, 255 Shimo-ohkubo, Sakura-ku, Saitama, Saitama 338-8570, Japan

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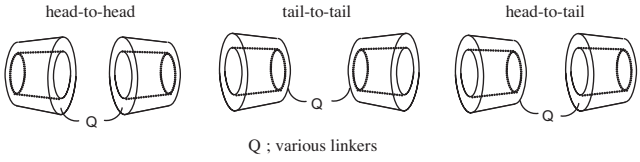
ABSTRACT

Covalent directly head-to-tail linked homogeneous and heterogeneous cyclodextrin (CD) dimers were synthesized, and that the reaction of 6-tosylated α-, β-, or γ-CD with a β-CD mono-oxyanion linked the second CD to the secondary hydroxyl side of β-CD was demonstrated. Moreover, deprotonation of α- and γ-CD using NaOH gave corresponding mono-oxyanions, which reacted with the 6-tosylated CDs to produce the CD dimers. The binding of the dimers to sodium 6-(4-*tert*-butylaniline)-2-naphthalenesulfonate (BNS) was investigated. The binding constant of the ^{6}β–^{2}β-CD dimer with BNS was estimated as $3.2 \times 10^{6}\ M^{-1}$, about 10^{2} times larger than that of β-CD monomer.

Cyclodextrin (CD) dimers have attracted considerable attention because their highly hydrophobic cavity serves as a host for various guest molecules and plays an important role in the modeling of enzymatic reactions in water. Numerous studies have addressed synthetic methods for these CD dimers and their unique properties.[1] Based on their linkage positions, these CD dimers are typically classified as head-to-head[2,3] or tail-to-tail.[4,5] As a consequence of the monomer conformation, 'head-to-tail'[6,7] CD dimers can be added to these two categories (Scheme 1). Moreover, based on these monomer types, the above three categories are subdivided into homogeneous and heterogeneous CD dimers. Especially, there are a few examples of syntheses of heterogeneous CD dimers[3,5,7] in three categories.

Despite considerable research efforts, few reports have described the synthesis of homogeneous and heterogeneous head-to-tail CD dimers directly linked through an ether linkage, prompting the development of a synthetic methodology for such CD dimers. The reaction of a 2,2′-bis(bromomethyl)benzene with a β-CD mono-oxyanion produced a head-to-head CD dimer,[2a] clearly depicting β-CD mono-oxyanion as a nucleophile. This result suggested that a 6-tosylated CD may react with a β-CD mono-oxyanion to form homogeneous and heterogeneous CD dimers linked through direct ether linkage. However, the reaction of a 6-tosylated CD with a nucleophile has proven difficult under basic conditions because 6-tosylated CDs were converted to their corresponding (3,6-anhydro)CD derivatives by intramolecular reaction under these conditions (Scheme 2).[8]



Scheme 1. Classification of CD dimers based on linkage position.

Therefore, alkylation of 6-hydroxyl groups cannot be achieved from 6-tosylated CDs, making head-to-tail CD dimers difficult to synthesize. Consequently, the primary hydroxyl group needs to be functionalized with a moderate protecting group to generate alkyl-type linkers for CD dimers. Herein, a simple method based on the reaction of a 6-tosylated CD monomer with a CD mono-oxyanion (Scheme 3) was developed for the preparation of homogeneous and heterogeneous CD dimers directly head-to-tail linked through ether linkages. In addition, differences between the hydrophobic cavities of the obtained homogeneous and heterogeneous head-to-tail CD dimers were successfully evaluated using sodium 6-(4-*tert*-butylaniline)-2-naphthalenesulfonate (BNS) as a guest molecule, which is known to present polarity sensitive properties.[9] Notably, the reaction of α- and γ-CD with NaOH gave the corresponding mono-oxyanions, enabling the formation of directly head-to-tail linked homogeneous and heterogeneous CD dimers.

* Corresponding author. Tel./fax: +81 48 858 3537.
E-mail address: ishimaru@fms.saitama-u.ac.jp (Y. Isihimaru).

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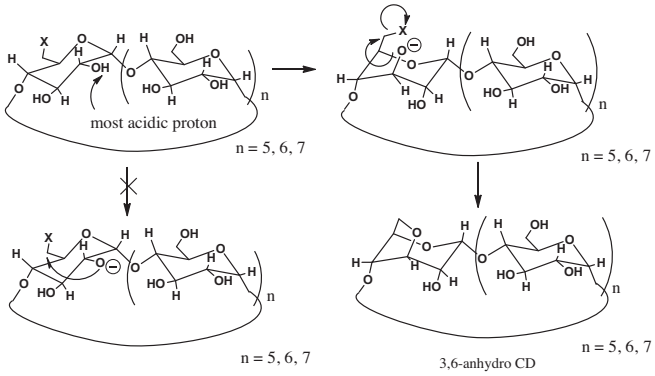
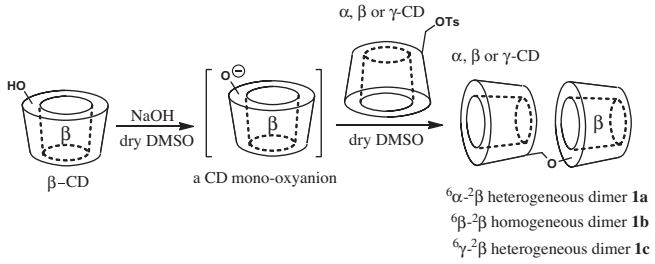


Scheme 2. Conversion of a 6-tosylated CD into a (3,6-anhydro)CD under basic conditions.



Scheme 3. Syntheses of heterogeneous and homogeneous CD dimers **1a**–**1c**.

In this synthetic approach, the combination of β-CD with 6-tosylated α-, γ-, and β-CD gave heterogeneous (**1a** and **1c**) and homogeneous (**1b**) CD dimers, respectively. After extensive purification, the desired products **1a**–**1c** were isolated in 5.2%, 7.3%, and 4.3% yield, respectively. The MALDI-TOF MS spectra showed an *m*/*z* peak at 2111.968, 2274.049, and 2435.849 corresponding to $[M+Na]^+$ for **1a**, **1b**, and **1c** [calculated *m*/*z* for $C_{78}H_{128}O_{64}Na$ (**1a**) = 2111.665, $C_{84}H_{138}O_{69}Na$ (**1b**) = 2273.718, and $C_{90}H_{148}O_{74}Na$ (**1c**) = 2435.771], respectively, in agreement with the proposed structures. The (3,6-anhydro)CD monomer or dimer derivatives were detected by MALDI-TOF MS measurement as by-products. Further synthetic details are shown in the experimental section.[10]

^{13}C NMR analysis of the prepared compounds was conducted to obtain specific structural information at the substitution position. Dimer structures were established by ^{13}C NMR and DEPT 135 spectra (Fig. 1). The ^{13}C NMR spectrum of **1a** in D_2O at 303 K (Fig. 1a) showed signals at around 98 and 70 ppm, which were attributed to C1′- and C6″-positions, consistent with the DEPT 135 spectrum (Fig. 1b). On the other hand, C2′- and C3′-positions were not assigned because their corresponding peaks overlapped with the signals for C4′- and C5″-positions as a result of their respective downfield and upfield shifts. Generally, a downfield shift of the α-carbon signal and an upfield shift of the β-carbon signal result from the alkylation of a hydroxyl group at the C2′-position.[11] The integrated intensities from the ^1H NMR spectra were consistent with the number and type of protons in each cyclodextrin dimer. The NMR spectra of **1b** (Fig. 1c and d) and **1c** (Fig. 1e and f) also showed a pattern similar to **1a**. Therefore, the substitution unambiguously occurred at C2′- and C6″-positions of the CD glucose units in all three products. Microanalytical data of compounds **1a**–**1c** were consistent with the proposed structures.

The cavity properties of different dimers were investigated using BNS by fluorescence spectroscopy (Fig. 2). After addition of **1b** to BNS (0.1 μM) in 100 μM phosphate buffer solution (0.1 M, pH 6.9) at 298 K, the fluorescence intensity of BNS at 448 nm

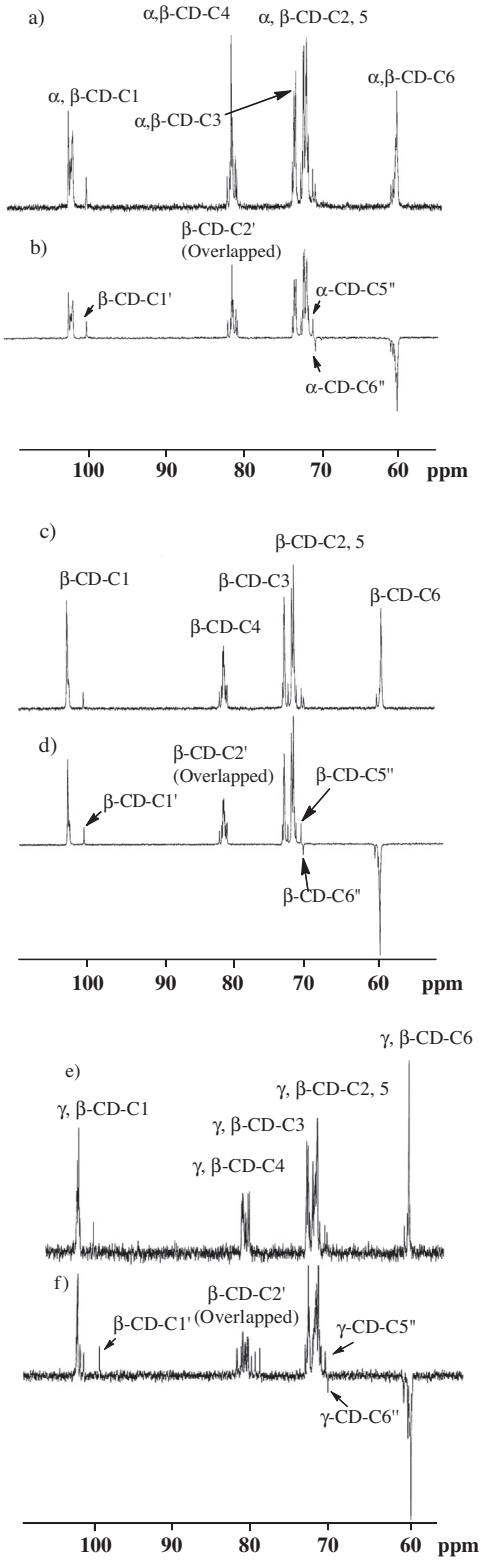


Figure 1. ^{13}C NMR and DEP T135 spectra of **1a**, **b**, and **c** in D_2O at 303 K, respectively (a); ^{13}C NMR spectrum of **1a**, (b); DEPT 135 spectrum of **1a**, (c); ^{13}C NMR spectrum of **1b**, (d); DEPT 135 spectrum of **1b**, (e); ^{13}C NMR spectrum of **1c**, (f); DEPT 135 spectrum of **1c**.

(λ_{ex} = 320 nm) significantly increased, suggesting a strong host–guest binding (Fig. 2b). This increase in fluorescence intensity was less pronounced upon addition of **1a** or **1c**, showing that these CD dimers exhibited much lower binding affinities to BNS than **1b** (Fig. 2a and c).