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Kinetic Control of Threading of Cyclodextrins onto Axle Molecules

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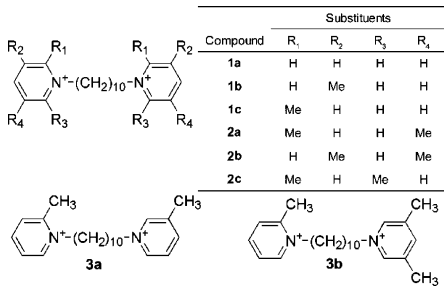
Rotaxanes are considered to be a typical prototype of molecular machines bearing a rotor and an axle in the molecule.[1,2] Crown ethers,[3] cyclodextrins (CDs),[4] calixarenes,[5] and cucurbituril[6] have been used as ring components of rotaxanes. CD has a rigid, well-defined "nonsymmetric" ring structure. Although there are a few reports on the isolation of unidirectional pseudo-[2]rotaxane composed CDs and axle molecules, there are no reports on the kinetic control of the face-direction of CDs in the complex formation step.[7] We report here, for the first time, the face-direction control of CD in the construction of a pseudo-rotaxane with an alkyl chain bearing pyridyl end caps without any purification procedure. The yields of complexes of CDs with guest alkyl derivatives were controlled by the simple change of the position and the number of methyl groups bound to the pyridyl moiety. A single-substituted pyridyl group attached to the ends of an alkyl chain regulated the rate for CDs passing them. Two methyl substituents could clearly govern the degree of complex formation of CD with guest molecules and resulted in the distinction of the face-direction of CD molecules entering the gates at guest ends.

Chart 1 shows structures of various kinds of guest molecules

Chart 1. Structures of Axle Molecules



used as a dumbbell in this study. Axle molecules have decamethylene units for the recognition site of CDs and pyridinyl units as the electric and steric trap moieties. Axle molecules were prepared by the reaction of α,ω-dihalodecane with pyridine derivatives.[8] Counteranions of the pyridinium cation in these compounds were changed to chloride to improve the solubility in water. Dicationic symmetrical axle molecules, **1a**−**c** and **2a**−**c**, were mixed with 4 molar excess of α-CD in D_2O. The ^1H NMR spectrum of **1a** in the presence of α-CD (4 molar excess) showed the split in all peaks of **1a** and no peaks of free **1a**. This result indicates that **1a** was included in α-CD completely. In the case of **1b**, with a methyl group at the 3-position of a pyridinium part, the complexation mode was similar to that of the α-CD−**1a** complex. This result indicates that α-CD could pass through the end caps with methyl groups at the 3-position of a pyridinium part. The complexation of **1c** with α-CD had the time dependency. The rate of the inclusion of **1c** to α-CD was extremely slow. The complexation between α-CD and **2a**, which has methyl groups at the 2- and 5-position of the pyridinium group, showed a similar behavior to that of α-CD with

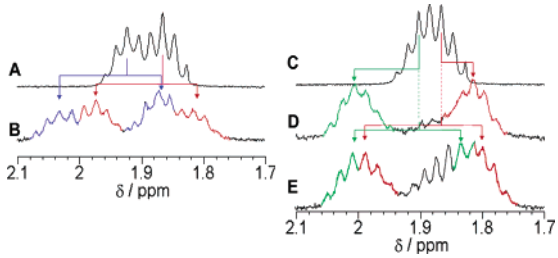


Figure 1. ^1H NMR spectra of axle molecules in D_2O. (A) **3a** in the absence of CDs, and (B) in the presence of α-CD after 1 day at 30 °C. (C) **3b** in the absence of CDs, (D) in the presence of α-CD after 70 days at 30 °C, and (E) in the presence of α-CD after 2 days at 70 °C. The arrows indicate splitting behaviors of each signal on the complexations.

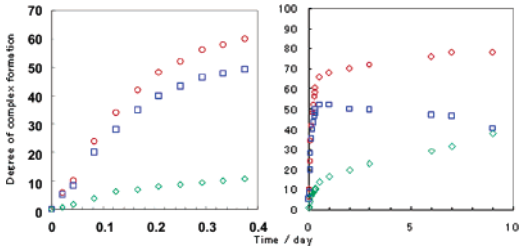


Figure 2. The correlation between time and degree of complex formations of α-CD with **3b** at 70 °C (complex that the primary hydroxyl groups in the α-CD face the 2-methylpyridine moiety (□) and 3,5-dimethylpyridine moiety (◇). The sum of two isomers (○)).

1c. These results show that the methyl group at the 2-position of the pyridinium part obviously plays an important role in controlling the rate of the complex formation. The methyl group at the 2-position of pyridinium part was found to retard the threading of α-CD. The ^1H NMR spectra of **2b** and **2c** showed no changes on mixing with α-CD, indicating that axle molecules **2b** and **2c** cannot form inclusion complexes with α-CD. The two methyl groups at the 3-, 5-positions or the 2-, 6-positions of the pyridinium part prevent α-CD from passing.

In the ^1H NMR spectrum of the nonsymmetric axle molecule (**3a**), whose 2-position of one pyridyl end and 3-position of the other end was substituted by a methyl group, both signals of methylene groups in the vicinity of the 2-methylpyridine side and the 3-methylpyridine side of **3a** in the complex with α-CD shifted to upfield and downfield (Figure 1B), indicating that each end group was located in an asymmetric environment; that is, α-CD formed a complex with **3a** in the random direction (Figure 4A). The ^1H NMR spectrum of **3b** in the presence of α-CD in D_2O showed the upfield split on the methylene groups in the vicinity of the 2-methylpyridine side and downfield split on the signals in the vicinity of the 3,5-dimethylpyridine side, respectively (Figure 1D). Even after 70 days, the complex formation of **3b** with α-CD did not reach an equilibrium state completely. α-CD was found to form complexes with **3b** only from the 2-methylpyridine side and to give a unique supramolecular structure. The number and position of the

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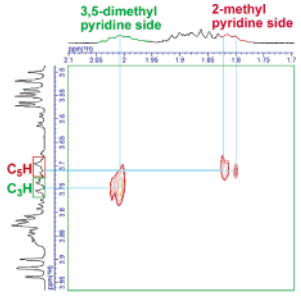

Figure 3. The 2D ROESY NMR spectrum of **3b**−α-CD after 21 days in D_2O, at 30 °C.

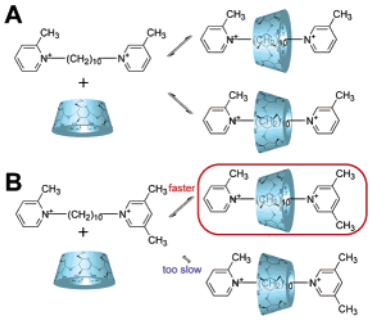

Figure 4. Proposed structures of pseudo-[2]rotaxane **3a**−α-CD (A) and **3b**−α-CD (B) at room temperature.

methyl groups in the end group of the axle obviously contribute to the complexation of α-CDs with axle molecules.

The 2D ROESY spectrum of axle molecule **3b** with α-CD in D_2O showed a negative ROE correlation between 3-position protons of α-CD and downfield-shifted methylene protons of 3,5-dimethylpyridine (Figure 3). A similar correlation was observed on the protons of the 5-position in α-CD. In addition, the ^{1}H spin−lattice relaxation time (T_1) of the methylene moiety in **3b**−α-CD decreases more than those of the pyridinium moiety in the free axle molecule. The T_1 values of upfield-shifted methylene protons of inclusion complexes decrease more than downfield-shifted signals. This result shows that the mobility of the upfield-shifted methylene proton was restricted by α-CD. The cavity size of the primary hydroxyl group side of α-CD is narrower than the secondary hydroxyl group side, so the primary hydroxyl side could strongly restrict mobility of guest molecules. These results indicate that α-CD formed an inclusion complex with **3b** in a unique direction, where the primary hydroxyl groups in the α-CD face the 2-methylpyridine moiety and the secondary side faces the 3,5-dimethylpyridine moiety. Figure 4B shows the proposed structures of the **3b**−α-CD complex with the face selectivity.

Axle molecule **3b** and 4 molar equiv of α-CD were mixed in D_2O solutions at 70 °C. The ^{1}H NMR showed new resonances (Figure 1E). These signals are derived from α-CD facing an opposite direction shown in Figure 4B. After many days, signals of the two isomers had almost the same intensity. This result shows that the face selectivity of CD in the complex disappeared at high temperature. This phenomenon can be explained by the following: at lower temperature, α-CD threads from the 2-methylpyridinium side of **3b** only from the secondary hydroxyl group side of itself because of comparatively slow molecular dynamics. On the other hand, α-CD can thread from the terminal group from both hydroxyl sides of itself because molecular dynamics and equilibrium rate are faster at high temperature. The complexation of **3b** with α-CD was controlled kinetically at low temperature and dominated by thermostatics at high temperature. These results mean that the rate of complexation differs significantly between two isomers.

In conclusion, pseudo-[2]rotaxane was obtained with α-CD located in a unique direction at a recognition site of dicationic axle molecule **3b**. The methyl group at the 2-position of a pyridinium group on the end cap of the axle molecule was found to control the rates of threading of α-CD. This is the first observation that the terminal group of axle molecules controls the direction of faces of plural ring components in the rotaxane structure kinetically. The controlling face of the ring component is expected to be efficient enough to realize the unidirectional movement in the rotaxane due to its nonsymmetric structure. We are now studying the dynamics of α-CD on the axle compounds with multi-stations in detail.

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Supporting Information Available: Synthesis and characterization of axle molecules and T_1 measurement. This material is available free of charge via the Internet at http://pubs.acs.org.

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