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Unidirectional α-cyclodextrin-based [2]rotaxanes bearing viologen unit on axle

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Abstract—1-(2-Carboxyethyl)-1′-(10-carbazole-9-yl-decyl)-4,4′-bipyridinium dibromide **2** forms a unidirectional [2]pseudorotaxane with α-cyclodextrin (α-CD) in water. Condensation of **2**/α-CD [2]pseudorotaxane with 4-amino-1-naphthalenesulfonate or 6-amino-β-CD provided the unidirectional [2]rotaxanes **3** and **4**, in which the secondary face of α-CD is oriented toward the viologen moiety. The structures were elucidated from two-dimensional ROESY and circular dichroism spectra.

A [2]rotaxane is a supramolecular assembly in which a linear rod (axle) threads a macrocycle (wheel) and is capped with bulky end groups. Rotaxanes are attracting much attention for the construction of molecular machines.[1,2] Cyclodextrins (CDs) have been widely used as wheels for the supramolecular assemblies.[2–9] Movement of the wheel along the axle by an external stimuli is one of the desired performances of rotaxanes.[4,8] As CDs are nonsymmetric macrocycles, [2]rotaxanes composed of a CD and a nonsymmetric rod usually give two isomers that differ in the orientation of CD with respect to the rod's end.[5–7] The two isomeric [2]rotaxanes having CD as a wheel were shown to exhibit quite contrasting physicochemical properties.[6,7] Thus it is highly desirable to prepare unidirectional rotaxanes for well-defined structure and characteristics of well-programmed performances, such as the unidirectional movement of a wheel along the axle. However, there is a paucity of reports on the preparation of unidirectional rotaxanes.

A common strategy for the preparation of [2]rotaxanes is the capping of [2]pseudorotaxanes formed from a wheel and a rod component. In this case, the formation of a unidirectional [2]pseudorotaxane is pre-requisite for the preparation of an oriented [2]rotaxane. Secchi and co-workers reported the synthesis of the oriented [2]rotaxanes via the capping of a unidirectional [2]pseudorotaxane obtained from a calix[6]arene derivative and a rod having a viologen unit.[10,11] Craig et al. obtained a unidirectional hexakis(2,3,6-tri-*O*-methyl)-α-CD-based azo dye [2]rotaxane.[9] Recently, Tian and co-workers reported the preparation of the oriented α-CD-based [2]rotaxanes having azobenzene and/or stilbene unit on axles and unidirectional shuttling of the α-CD wheel along the axles upon light irradiation.[8]

4,4′-Bipyridinium dication, commonly known as viologen, has been widely incorporated into rod components of rotaxanes or pseudorotaxanes, presumably due to its unique redox characteristics.[5,7,10–12] Yonemura et al.[12] and we[7] showed that the aliphatic chain-linked carbazole-viologen compounds form unidirectional [2]pseudorotaxanes with α-CD, in which the wider secondary hydroxyl side of α-CD faces the viologen moiety in aqueous media. This prompted us to utilize the characteristics of the formation of the unidirectional [2]pseudorotaxane for the synthesis of the unidirectional [2]rotaxanes. In this letter, we report the preparation of **2**, which is an aliphatic chain-linked carbazole-viologen compound having a terminal carboxylic group, the formation of a unidirectional [2]pseudorotaxane between **2** and α-CD, and the synthesis of the unidirectional [2]rotaxanes via condensation reactions of **2**/α-CD [2]pseudorotaxanes with bulky amines in aqueous media.

Scheme 1 illustrates the synthetic pathways for the [2]rotaxanes **3** and **4** in *aqueous media*: the reaction for two isomeric [2]rotaxanes **5a** and **5b** in DMF was

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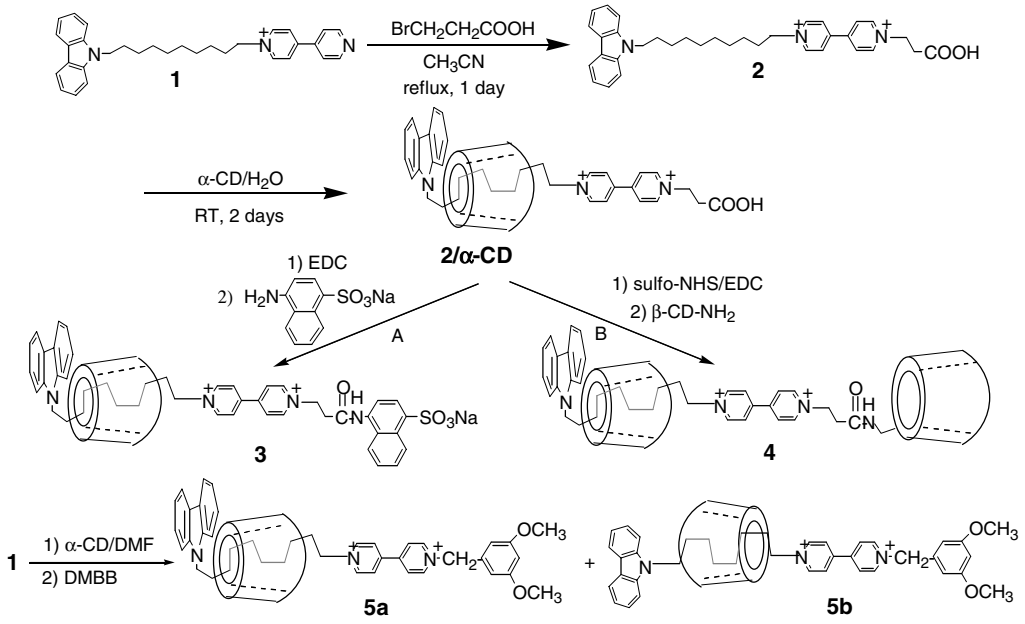

Scheme 1. Synthetic pathways for the unidirectional α-cyclodextrin-based [2]rotaxanes **3** and **4** bearing viologen moiety on the axle. The formation of two isomeric [2]rotaxanes **5a** and **5b** (in 9:7 ratio) from the capping of **1**/α-CD [2]pseudorotaxanes with 3,5-dimethoxybenzyl bromide (DMBB) in DMF is shown for comparison (from Ref. 7). The counter ions, which are bromide for **1** and **2** and chloride for the purified **3**–**5**, are omitted.

included for comparison. The compound **2** was prepared by the reaction of 1-(*N*-carbazole)-10-[4-(4-pyridino)-1-pyridinio]decane **1**[7] with 3-bromopropionic acid.[13] Stirring of a solution of **2** and 5-molar excess of α-CD for 2 days gave the unidirectional **2**/α-CD [2]pseudorotaxane: at the early stage of the stirring, a precipitate was formed, but further stirring resulted in a clear solution. We reported that the isomeric [2]rotaxanes composed of α-CD and an aliphatic chain linked carbazole-viologen compound, **5a** and **5b**, exhibit widely different solubility in water: the **5a** isomer in which the secondary side of α-CD faces the viologen moiety is more soluble than the other isomer.[7] Also, with an aliphatic chain linked carbazole-viologen compound (an analogue of **2** having a terminal methyl group instead of carboxyethyl), it has been shown that, in aqueous media, the threading rates of viologen unit through either the primary side or the secondary side of α-CD are not much different, but the dethreading rate of a [2]pseudorotaxane isomer in which the secondary side of α-CD faces the viologen (as **2**/α-CD in Scheme 1) is much slower than that of the other isomer, giving mostly the slower dethreading, that is, the thermodynamically stable [2]pseudorotaxane isomer after a long period of time.[7] Thus it is certain that the precipitate formed at the early stage is the [2]pseudorotaxane isomer having the α-CD orientation as in **5b**, and the component in the clear solution after stirring for 2 days is mostly the unidirectional [2]pseudorotaxane having the α-CD orientation as **2**/α-CD as depicted in Scheme 1. The ^{1}H NMR (not shown) and circular dichroism (vide infra) spectra confirmed the orientation of α-CD in the pseudorotaxanes. The orientation of α-CD in [2]pseudorotaxane agrees well with the observations of the preference of the secondary face of CDs for viologen moiety in inclusion complexes of viologen compounds with CDs.[14] The [2]pseudorotaxane **2**/α-CD was subjected to coupling reaction with either 4-amino-1-naphthalenesulfonate or 6-NH_2-β-CD in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC)[15] or sulfo-NHS/EDC,[16] respectively, as catalyst to obtain [2]rotaxanes **3** and **4**. Purification by cation exchange chromatography and membrane filtration gave analytically pure [2]rotaxanes in 22% (for **3**) and 8% (for **4**) yields.[17,18]

Except in the region of the capped groups, the ^{1}H NMR, ^{1}H–^{1}H COSY, and two-dimensional ROESY spectra of the [2]rotaxanes **3** and **4** (Supplementary data) were almost identical to that of the oriented rotaxane **5a** reported in an earlier letter,[7] and showed no hint of the presence of the **5b**-type isomer.[19] The orientation of α-CD in the rotaxanes was clearly revealed in the two-dimensional ROSEY spectra (see Fig. 1 for **4**). The *i* and *j* protons of carbazole moiety show NOE cross-peaks with H-6 protons of α-CD. The β- and γ-methylene protons exhibit cross-peaks with H-5, but not with H-3 protons of α-CD. In contrast to this, the ι-methylene protons show a cross-peak only with H-3 protons. The δ- to θ-methylene protons exhibit NOE cross-peaks with both H-3 and H-5 protons of α-CD. However, the intensities of the cross-peaks of δ- and ε-protons with H-5 are much stronger than those with H-3 protons, while the ζ- to θ-protons show stronger cross peaks with H-3 than with H-5 protons. The ^{1}H 2D ROESY NMR spectrum of **3** showed essentially the same pattern of NOE cross-peaks. These are clear evidences that the secondary side of α-CD is adjacent to the viologen unit in the [2]rotaxanes, as represented in Scheme 1.

Circular dichroism spectra of [2]rotaxanes **3** and **4**, and the [2]pseudorotaxane **2**/α-CD also confirm the

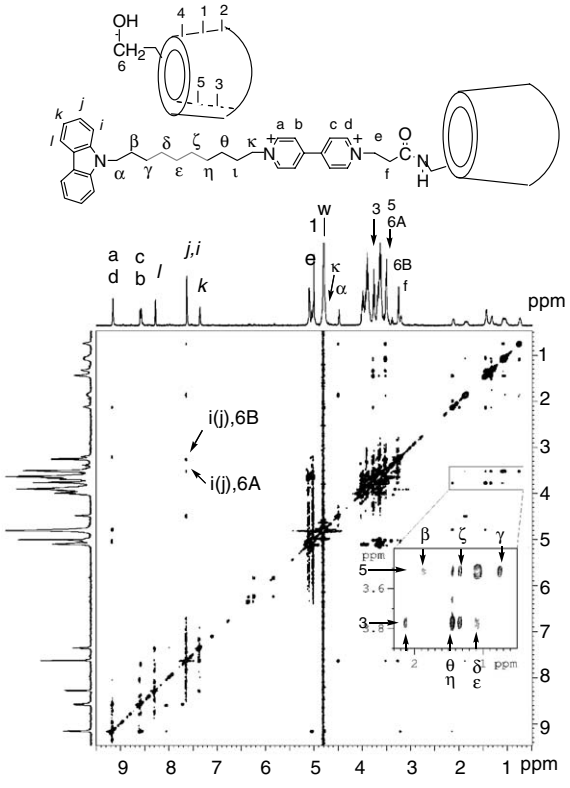

Figure 1. ^{1}H two-dimensional ROESY NMR (600 MHz) spectrum of **4** in D_2O. The assignments of peaks were made by ^{1}H–^{1}H COSY and the ROESY spectra. The wheel α-CD, which encircles the aliphatic linkage, is shown above the linkage for clarity.

orientation of α-CD in the supramolecular assemblies. It has been shown that, in the carbazole absorption region of 310–360 nm, **5a** shows the positive circular dichroism band, whereas **5b** exhibits the negative one with similar ellipticity.[7] This was ascribed to the difference in the orientation of carbazole ring with respect to CD axis, as represented in Scheme 1. The positive circular dichroism bands of **3**, **4**, and **2**/α-CD, and the similar molar ellipticity values of these species to that of **5a** are unequivocal evidences for the unidirectionality of α-CD wheel on axles and the same bent conformation of the carbazole ring in these systems: the larger ellipticity of **3** in 300–335 nm region, compared to others, are ascribed to the contribution from the aminonaphthalene sulfonate moiety used as a stopper (Fig. 2).

It is obvious that the formation of unidirectional [2]rotaxanes **3** and **4** arises from the unidirectionality of the precursor, **2**/α-CD [2]pseudorotaxanes in aqueous media. Such orientation specificity was not observed in the **1**/α-CD [2]pseudorotaxane in DMF, as two isomeric [2]rotaxanes **5a** and **5b** are obtained with almost 1:1 ratio from **1**/α-CD [2]pseudorotaxane.[7] Though it appears to be clear that in aqueous media, the viologen unit prefers the secondary side of CDs in its complexation with CDs,[14] and the orientation specificity of **2**/α-CD [2]pseudorotaxane is a consequence of the slower dethreading rate of the isomer, the detailed origin of the thermodynamic stability of the isomer is not clear at this point and is beyond the scope of this work.

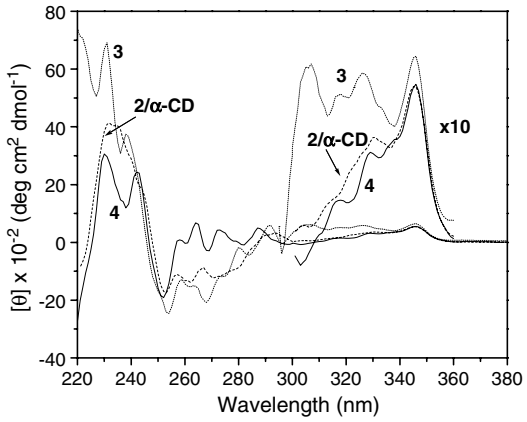

Figure 2. Circular dichroism spectra of **2**/α-CD, **3**, and **4**. The spectrum of **2**/α-CD was taken with a mixture of **2** (0.50 mM) and α-CD (8.0 mM) after stirring for a day. The 300–360 nm regions were expanded 10-fold and overlaid.

In conclusion, we have demonstrated the synthesis of unidirectional α-CD-based [2]rotaxanes **3** and **4**. This work can be extended for the construction of oriented polyrotaxanes having axles of alternating energetically favored portions (station) and disfavored portions (bumper), and for one-way movement of a wheel along an axle. The [2]rotaxane **4** has an unoccupied β-CD moiety, which can be utilized to assemble supramolecular architectures with molecules having appropriate guest unit. Works in these directions as well as the kinetic studies on the directional threading/dethreading processes are underway.

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Supplementary data

^{1}H NMR, ^{1}H–^{1}H COSY, and two-dimensional ROESY spectra of the [2]rotaxanes **3** and **4**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.187.

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13. CH_3CN (30 mL) solution of **1** (0.60 g, 1.1 mmol) and 3-bromopropionic acid (1.7 g, 11 mol) was refluxed for 24 h. The precipitate was filtered and washed with hot acetonitrile, and then recrystallized from 9:1 acetonitrile–methanol to afford **2** (0.67 g, 87% yield) as a yellow solid. UV/vis (H_2O) λ_{max}/nm ($\log\varepsilon$) 260 (4.59), 333 (3.49), 347 (3.51). ^{1}H NMR (250 MHz, D_2O): δ 9.07 (d, 2H, $J = 6.6$), 8.87 (d, 2H, $J = 6.7$), 8.30 (d, 4H, $J = 6.6$), 7.78 (d, 2H, $J = 7.6$), 7.24–718 (m, 2H), 7.07–6.93 (m, 4H), 4.97 (t, 2H, $J = 6.0$), 4.49 (6, 2H, $J = 7.2$), 3.79 (br (t), 2H), 3.18 (t, 2H, $J = 6.3$), 1.89–1.65 (m, 2H), 1.47–1.18 (m, 2H), 1.16–0.60 (m, 12H). Anal. Calcd for $C_{35}H_{41}Br_2N_3O_2$: C, 60.44; H, 5.94; N, 6.04. Found: C, 60.43, H, 5.99; N, 6.01.
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17. To a solution of **2**/α-CD prepared from **2** (0.25 g, 0.36 mmol) and α-CD (1.75 g, 1.79 mmol) in water (25 mL), EDC (0.069 g, 0.36 mmol) in water (2 mL) was added and the reaction mixture was stirred for 30 min. Then sodium 4-amino-1-naphthalenesulfonate (0.088 g, 0.36 mmol) in water (3 mL) was added and stirred for 48 h at room temperature: two subsequent additions (1 equiv of EDC each) were made after 18 and 34 h. Acetone (250 mL) was added to the reaction mixture. The precipitate was filtered, dissolved in hot water (30 mL) and then applied on a Sephadex CM C-25 column. The loaded column was washed with water and then eluted with 0.1 M NaCl. The fractions active in UV/vis and optical rotation were collected and evaporated to dryness. The product was recovered by selective solubilization in DMF. After evaporating off the DMF at reduced pressure, the residue was suspended in water, and desalted by membrane filtration through MW cut-off 1000 celluose membrane. The product **3** (145 mg, 22% yield) was precipitated by the addition of acetone. UV/vis (H_2O) λ_{max}/nm ($\log\varepsilon$) 262 (4.69) 292 (4.49) 3.45 (3.60). ^{1}H NMR (600 MHz, D_2O, $\delta_{HDO} = 4.800$): δ 9.23 (d, 2H, $J = 6.6$, H-d), 9.10 (d, 2H, $J = 6.6$, H-a), 8.66 (d, 1H, $J = 8.4$, Nap), 8.56 (d, 2H, $J = 6.6$, H-c), 8.51 (d, 2H, $J = 6.6$, H-b), 8.26 (d, 2H, $J = 7.8$, H-l), 8.10 (d, 1H, $J = 7.8$, Nap), 7.86 (d, 1H, $J = 8.4$, Nap), 7.72 (t, 1H, $J = 7.8$, Nap), 7.58–7.62 (m, 5H, H-i, H-j, Nap), 7.50 (d, 1H, $J = 7.8$, Nap), 7.32–7.36 (m, 2H, H-k), 5.17 (t, 2H, $J = 6.0$, H-e), 4.96 (d, 6H, $J = 3.6$, H-1 of α-CD), 4.74 (t, 2H, $J = 7.2$, H-κ), 4.43 (t, 2H, $J = 6.0$, H-α), 3.73 (t, 6H, $J = 9.3$, H-3), 3.73 (t, 6H, $J = 9.3$, H-3), 3.61 (t, 6H, $J = 9.6$, H-4), 3.59 (dd, 6H, $J = 9.9$, 3.3, H-2), 3.56 (t, 2H, $J = 6.0$, H-f), 3.73 (t, 6H, $J = 9.3$, H-3), 3.51–3.46 (m, 12H, H-5 and H-6_A), 3.22 (d, 6H, $J = 10.8$, H-6_B), 2.09 (m, 2H, H-ι), 2.09 (m, 2H, H-ι), 1.89–1.77 (m, 2H, H-β), 1.44–1.36 (m, 4H, H-θ and H-η), 1.33–1.26 (m, 2H, H-ζ), 1.11–0.98 (m, 4H, H-δ and H-ε), 0.71 (quintet, 2H, $J = 7.0$, H-γ). Anal. Calcd for $C_{81}H_{107}Cl_2N_4NaO_{34}S{\cdot}4H_2O$ (with 8.1 wt. % NaCl): C. 47.59; H, 5.67; N, 2.74. Found: C, 47,58; H, 5.68; N, 2.74. MALDI TOF MS: calcd for $[M-Na^+-2Cl^-]^+$ 1711.65, found 1711.42. (For labeling of protons, see Fig. 1.)
18. A solution containing **2** (0.39 g, 0.56 mmol) and α-CD (2.73 g, 2.8 mmol) in water (25 mL) was stirred for 2 days at room temperature. After cooling the solution to 4 °C, sulfo-NHS (122 mg, 0.56 mmol) in water (2 mL) was added, and then EDC (320 mg, 1.7 mmol) in water (6 mL) was added dropwise for 1 h. After stirring for 1 h, the temperature was raised to 25 °C, β-CD-NH_2 (635 mg, 0.56 mmol) was added, and pH of the solution was adjusted to 7.5 with 0.1 M triethylamine. After stirring for 20 h, acetone (200 mL) was added to obtain 3.6 g of the precipitate. The procedure for the purification of **4** from the acetone precipitate is essentially the same as that utilized for **3**. Yield of **4**, 120 mg (8% yield). λ_{max}/nm ($\log\varepsilon$) 260 (4.45), 333 (3.51), 3.47 (3.55). ^{1}H NMR (600 MHz, D_2O, $\delta_{HDO} = 4.800$): δ 9.16 (d + d, 4H, $J = 6.6$, H-d and H-a), 8.59 (d, 2H, $J = 6.6$, H-b or c), 8.57 (d, 2H, $J = 6.6$, H-b or c), 8.28 (d, 2H, $J = 7.8$, H-l), 7.65–7.61 (m, 4H, H-i, and H-j), 7.37–7.34 (m, 2H, H-k), 5.11–5.04 (7H, H-1 of β-CD), 5.09 (t, 2H, $J = 6.0$, H-e), 5.00 (d, 6H, $J = 3.0$, H-1 of α-CD), 4.77 (t, overlapped with HDO peak, 2H, $J = 7.2$, H-κ), 4.48 (t, 2H, $J = 6.0$, H-α), 4.03–3.83 (m, 28H of β-CD), 3.76 (t, 6H, $J = 9.3$, H-3), 3.71–3.54 (m, 29H, H2 and H4 of α-CD, 14H of β-CD), 3.53–3.48 (m, 12H, H-5 and H-$6_A$of α-CD), 3.25 (d, 6H, $J = 10.8$, H-6_B of α-CD), 3.20 (3H, H-f), 2.15–2.09 (m, 2H, H-ι), 1.90–1.80 (m, 2H, H-β), 1.47–1.40 (m, 4H, H-θ and H-η), 1.35–1.29 (m, 2H, H-ζ), 1.12–0.98 (m, 4H, H-δ and H-ε), 0.78–0.71 (m, 2H, H-γ). Anal. Calcd for $C_{113}H_{170}Cl_2N_4O_{65}{\cdot}5H_2O$ (with 5% salt): C. 46.26; H, 6.18; N, 1.91. Found C, 46.35; H, 6.21, N; 1.85. MALDI TOF MS: calcd for $[M-2Cl^--H^+]^+$ 2622.01, found 2621.99.
19. The 1D and 2D ROESY ^{1}H NMR patterns of **5a** and **5b** are considerably different from each other in α-CD and decamethylene linkage regions (see Ref. 7 for spectra).