

Clockwise–counterclockwise differentiation on the upper rim of a monofunctional γ -cyclodextrin: efficient topological control in the syntheses of capped cyclodextrins

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Intramolecular condensation of 6^A-(*N*-dansyl-L-cysteine)- γ -cyclodextrin occurred only at 6^B-OH of the many OH groups to afford the corresponding lactone with an *exo*-topology.

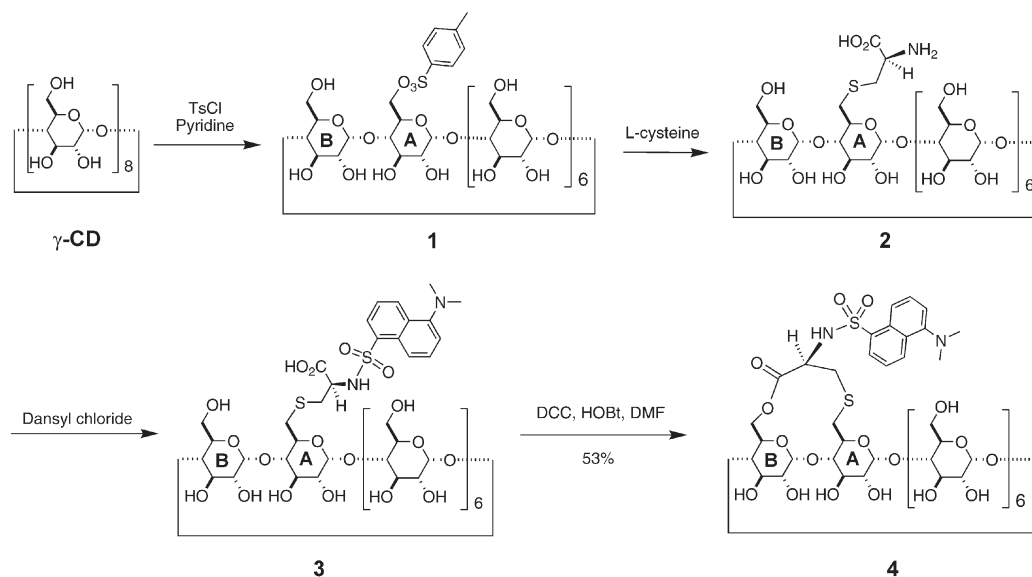
Cyclodextrins (CDs) are frequently employed as the guest-binding elements to develop artificial receptors, supramolecular catalysts, drug carriers, and so forth.¹ With the aim of improving their existing features as well as creating novel functions, profound investigations on the modification of CDs have been carried out.² The functionalities are usually connected to the CD rims *via* flexible spacers. However, such functional CDs can adopt many conformations, most of which do not favor cooperation between the functionality and the CD cavity or even prevent the functional CDs from performing with the desired selectivity. The capping technique in which one organic segment links two glucose units on the same rim,³ and it was proved efficient in controlling the geometry of functional groups above the cavity entrance.⁴ Reaction of 6^A,6^B-diiodo- β -CD with pyridoxamine-bearing

ethanedithiol generated two pairs (*endo*- and *exo*-, with the pyridoxamino group located near the A or B glucose unit) of 6^A,6^B-capped CDs, and the rigid *exo*-pair displayed much higher selectivity than the *endo*-pair or the flexibly suspended analog in the transamination reaction of pyruvic acids.⁴ Although such restriction of the geometry proved efficient in inducing selectivity, it was not addressed further because of the lack of selective methods to access the desired geometry. Herein we describe the first example of topologically controlled syntheses of capped CDs.

γ -CD was subjected to tosylation of one 6-OH (Scheme 1), subsequent substitution with L-cysteine and final reaction with dansyl chloride to afford 6^A-(*N*-dansyl-L-cysteine)- γ -CD (**3**). Condensation in DMF gave the corresponding lactone **4** in 53% yield.[†] The TOF-MS spectrum of **4** displayed the expected pseudomolecular ions at *m/z* 1637 (*M* + Na) and 1653 (*M* + K). Its structure and purity were confirmed by NMR (Fig. 1). The aromatic protons resonated as 4 doublets and one triplet at δ 8.53 (d, 1H), 8.29 (d, 2H), 8.13 (d, 1H), 7.32 (d, 1H) and δ 7.64 (t, 2H), respectively. The cysteine segment demonstrated 3 doublets of doublets at δ 3.90 (1H, α -H), 2.79 (1H) and 2.66 (1H, β -H) while the two geminal protons of S-substituted 6^A appeared at δ 2.53 (t, 1H), 3.11 (overlapped, 1H). Another pair of geminal protons were observed at δ 4.33 (d, 1H) and 4.03 (overlapped with HDO), much larger than the chemical shifts of normal 6-Hs. Such a downfield

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Scheme 1

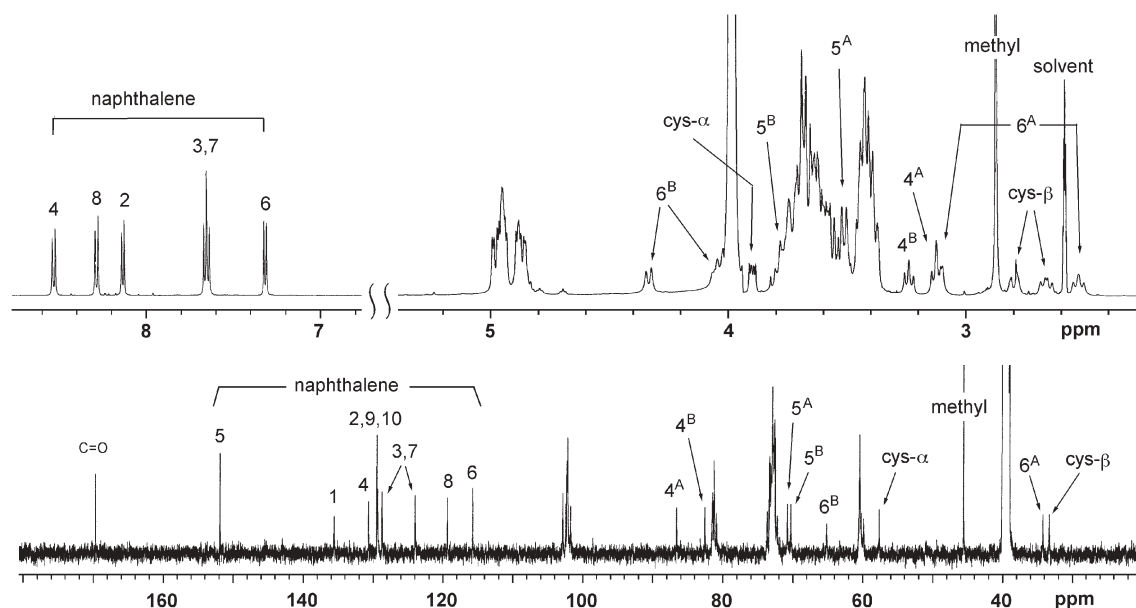


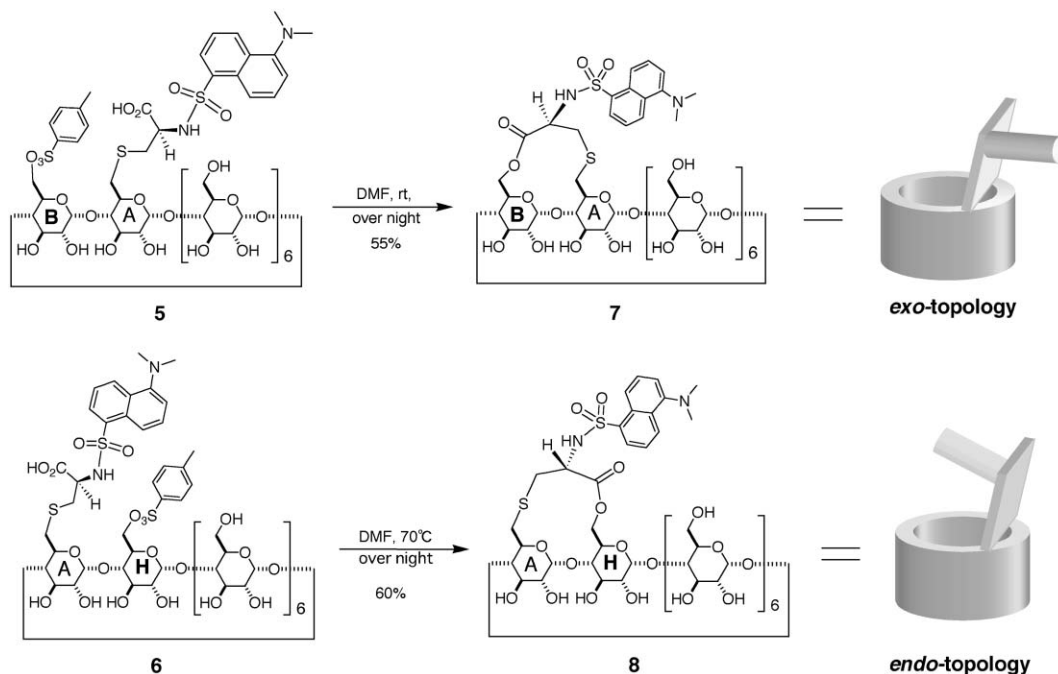
Fig. 1 ^1H and ^{13}C NMR spectra of lactone **4** in $\text{DMSO-d}_6/\text{D}_2\text{O}$ (6 : 1).

shift is indicative of the esterification of that glucose unit. Consistent with the acylation, a reasonable downfield shift of that methylene carbon (at δ 64.5) was confirmed. The clear one-to-one nuclei-signal correlations in the ^{13}C NMR spectrum relating the substituents and modified methylene groups strongly suggested that lactone **4** is a pure compound rather than a mixture of regio-isomers.

The above result is somewhat astonishing since the cysteine moiety is quite flexible and seven primary hydroxyl groups may compete in the esterification. Arene di(sulfonyl chloride)s are frequently used to cap CDs at two specific positions, but they

should be rigid enough to fix the distance between the two sulfonyl groups, otherwise all possible regio-isomers form with poor selectivity as in the case of benzophenone 3,3'-di(sulfonyl chloride).⁵ Even more interesting is that, in addition to the spatial differentiation, the flexible cysteine moiety can also differentiate hydroxyl groups in a clockwise-counterclockwise relationship, and thus ensures an efficient control of the topology of the product (high *endo-lexo*-selectivity). The bulky dansyl group is supposed to display an important role in controlling the regio-selectivity.

Considering the short length of the cysteine moiety, one of the OH groups adjacent to the cysteine moiety should be most



Scheme 2

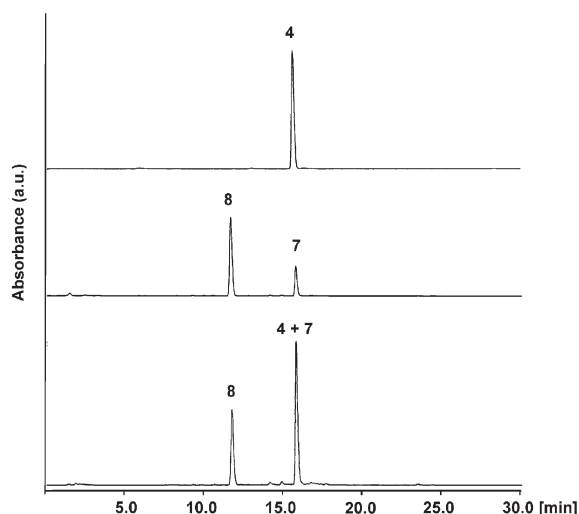


Fig. 2 HPLC chromatograms of lactone **4** (top), mixture of **7** and **8** (middle), and lactone **4** + mixture of **7** and **8** (bottom). A Cosmosil packed 5C18-AR-II column (4.6 × 150 mm) and a gradient elution of 5–60% aqueous acetonitrile at a flow rate of 0.8 ml min^{−1} were applied.

susceptible to esterification. Unfortunately, NMR experiments failed to afford useful information for the identification of that OH. To solve this problem, we developed another method to synthesize (*N*-dansyl cysteine)-capped γ -CDs from bifunctional CDs whose regio-chemistry is unambiguously determined. The 6^A-(*N*-dansyl-L-cysteine)-6^B or ^H-tosyl- γ -CDs **5** and **6**,⁶ stable enough in aqueous solution, readily underwent intramolecular substitution in DMF, generating the *exo*- and *endo*-topologies, respectively (Scheme 2). Just stirring **5** in DMF at rt overnight ensured a complete substitution of tosylate by carboxylate group and the lactone **7** was isolated in 55% yield.[†] The counterclockwise regio-isomer **6** is less reactive, and its conversion to the corresponding lactone **8** was realized by an overnight heating of the DMF solution at 70 °C.

Lactones **7** and **8** show the pseudomolecular ions at *m/z* 1637 (M + Na) and 1653 (M + K) in the TOF-MS spectra. Their NMR spectra are different from each other but very similar. Both the ¹H and ¹³C NMR spectra of **7** are superimposable on the corresponding spectra of **4**, indicating that the intramolecular condensation of **3** occurred at 6^B-OH and generated the *exo*-topology with a very high selectivity. This assignment was further confirmed by HPLC analysis.

Due to the topological effect, the two lactones also behave quite differently on the reversed phase HPLC column. The *exo*-lactone **7** eluted much slower than the *endo*-lactone **8**, affording the possibility of making an unambiguous identification of the lactone **4** by HPLC. As shown in Fig. 2, lactone **4** displayed a single peak at *R_f* = *ca.* 16 min, and this peak was superimposed on the one with longer retention time of the mixture of lactones **7** and **8**, suggesting that lactones **4** and **7** are identical. This result is consistent with that obtained by NMR spectral analyses and confirmed the structural assignment of lactone **4**.

In conclusion, we have described for the first time how a functionality at the primary rim of a CD, even one as flexible as a cysteine moiety, may differentiate hydroxyl groups of the CD in a clockwise-counterclockwise relationship, and thus afford the possibility of building a specific topology on the CD rim in a controlled manner.

Notes and references

[†] Compound **2** (1.44 g) and Na₂CO₃ (0.33 g) were dissolved in water (15 ml), and an acetonitrile solution (15 ml) containing 0.53 g dansyl chloride was added. After being stirred at rt for 3 h, the reaction mixture was adjusted to pH 3 and added to acetone. The precipitates were collected and chromatographed on a reversed phase Lobar column to afford compound **3** (1.17 g, 70%). TOF-MS, *m/z* 1655 (M + Na); ¹H NMR (DMSO-*d*₆), δ 8.43 (d, 1H), 8.24 (d, 1H), 8.18 (d, 1H), 7.58 (t, 2H), 7.23 (d, 1H), 5.90–5.73 (m, 18H), 4.88–4.50 (m, 17H), 3.72–3.21 (m, overlapped with HDO), 2.88–2.80 (m, 9H), 2.57 (dd, 1H) ppm; ¹³C NMR (DMSO-*d*₆), δ 170.9, 151.1, 136.3, 129.1, 128.9, 127.6, 123.2, 119.2, 114.8, 102.1, 101.7, 101.5, 101.2, 84.2, 81.3, 81.2, 80.9, 80.8, 80.7, 72.9, 72.8, 72.6, 72.4, 72.3, 72.2, 72.0, 71.9, 60.0, 59.9, 59.7, 45.0, 37.3, 33.7 ppm.

Compound **3** (100 mg), DCC (110 mg), and 1-hydroxybenzotriazole (66 mg) were dissolved in DMF (2 ml), and the resulting solution was stirred overnight at rt. The reaction mixture was then added to acetone and the precipitates were collected and chromatographed on a reversed phase Lobar column to afford lactone **4** (52 mg, 53%). TOF-MS, *m/z* 1637 (M + Na) and 1653 (M + K); NMR, Fig. 1.

The intramolecular displacement reactions of **5** and **6** were carried out simply by stirring the bifunctional γ -CDs overnight in DMF at rt (for **5**) or at 70 °C (for **6**). Work-up of the reaction mixtures by a procedure similar to that described for lactone **4** afforded lactones **7** and **8** in 55% and 60% yields, respectively. Lactone **7**: TOF-MS and NMR spectra are identical to those of lactone **4**. Lactone **7**: TOF-MS, *m/z* 1637 (M + Na) and 1653 (M + K); ¹³C NMR (DMSO-*d*₆), δ 169.7, 150.9, 135.6, 129.4, 128.7, 128.1, 127.6, 123.2, 119.1, 114.8, 102.0, 101.9, 101.7, 101.5, 101.4, 101.1, 100.3, 99.8, 85.5, 81.5, 80.7, 80.5, 80.2, 80.1, 79.4, 79.2, 75.8, 73.9, 73.1, 72.8, 72.7, 72.6, 72.5, 72.4, 72.2, 72.1, 72.0, 71.9, 71.8, 71.7, 71.5, 67.3, 64.0, 60.1, 60.0, 59.6, 59.5, 59.3, 55.5, 44.9, 35.0, 31.8 ppm.

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- Y. Yu, Y. Makino, M. Fukudome, R.-G. Xie, D.-Q. Yuan and K. Fujita, to be published. Compounds **5** and **6** were prepared from 6^A,6^B-ditosyl- γ -CD by treatment with equimolar L-cysteine and then dansyl chloride. Their regio-chemistry was unambiguously determined by enzymatic conversion of **5** and **6** to the corresponding linear trioses and subsequent sequence determination of the trioses by NMR and PSD-MS.