Dansyl-modified β-Cyclodextrin with a Monensin Residue as a Hydrophobic, Metal Responsive Cap

Michiei Nakamura, Akira Ikeda, Nobuyuki Ise, Tsukasa Ikeda, Hiroshi Ikeda, Fujio Toda and Akihiko Ueno*

Department of Bioengineering, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Ngatsuta-cho, Midori-ku, Yokohama 226, Japan

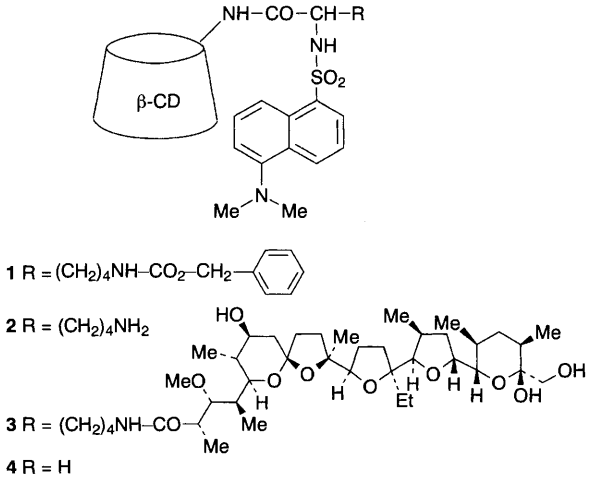
The guest-binding abilities of the monensin–dansyl–β-cyclodextrin triad system **3** are enhanced by the presence of the hydrophobic monensin residue as well as by sodium ions which may interact with monensin.

Cyclodextrins (CDs) form inclusion complexes with various compounds in aqueous solution.[1,2] Although CDs are spectroscopically inert, detection of organic guests in aqueous solution can be achieved by using modifications of CDs with chromophores.[3–6] For example, dansylglycine-modified β-CD has been shown to exhibit remarkable decreases in the dansyl fluorescence upon complexation with many organic compounds. On the other hand, monensin is an ionophore that converts its structure from the open form to a macrocycle-like form when it binds a sodium ion. In this study, we prepared the monensin–dansyl–cyclodextrin triad system **3** and we report the effects of monensin as a hydrophobic cap and metal-binding ionophore on the guest accommodation of **3**.

Compound **3** was prepared by the following route. First, **1** was prepared by condensation of 6-*O*-deoxy-6-amino-β-cyclodextrin with N_ε-Z-dansyl-L-lysine. Removal of the benzyloxy carbonyl (Z) unit from **1** was achieved by treatment with hydrogen gas on a palladium–carbon catalyst, yielding **2**. The reaction from **1** to **2** is not successful in aqueous 20% methanol solution but proceeds in the presence of an excess of (−)-borneol as a guest. This result suggests that the Z group is included in the cavity of β-CD and the reaction was prohibited, whereas the reaction was allowed by the presence of an added guest species because of exclusion of the Z group from the cavity. Compound **2** was treated with monensin in DMF, yielding crude **3**, which was then purified by column chromatography with Sephadex LH-20. Compound **3** was identified by TLC (R_f 0.64, butanol–ethanol–water 5:4:3), ^{1}H NMR† and elemental analysis.

Compound **3** exhibits a fluorescence peak at *ca.* 543 nm in aqueous solution, and the intensity decreases upon addition of organic guest compounds, for example, adamantan-1-ol (50 μmol dm^{-3}) caused a 39.5% decrease of the fluorescence intensity of a solution of **3** (2 μmol dm^{-3}). This observation indicates that the dansyl moiety is excluded from the hydrophobic β-CD cavity to water environment associated with the guest binding. The result is consistent with the fact that the monensin is too large to be included in the cavity of β-CD and acts only as an environmental factor. From such guest-induced fluorescence variation, we obtained binding constants for various guests by a curve-fitting analysis based on 1:1 stoichiometry using the Benesi–Hildebrand type equation. The results obtained in the absence and presence of 1 mol dm^{-3} sodium chloride are summarized in Table 1 together with the data of dansylglycine-modified β-CD **4**. All six alcohols examined here gave larger binding constants for **3** than for **4**. In particular, **3** exhibits markedly improved binding for acyclic compounds such as nerol (64-fold) and geraniol (92-fold). This observation contrasts with the smaller improvement observed for cyclic compounds (*ca.* fourfold or less). The result demonstrates that the monensin residue acts as a hydrophobic cap, which enhances guest accommodation.[7,8] The strengthened binding of nerol and geraniol with **3** may be related to the flexibility of the guests, which enables the guests to assume the structures which lead to a larger contact area with the monensin residue in the complex. Our fluorescent indicators or sensors for molecules so far prepared have only fluorophores as pendants. This is the first example of fluorescent CDs that have another moiety in addition to the fluorophore. The induced-fit guest binding of this type is shown in Fig. 1.

Compound **3** exhibits further enhancement to its guest binding ability by the addition of sodium ions, as shown by



β-CD-NH_2 $\xrightarrow{i}$ **1** $\xrightarrow{ii}$ **2** $\xrightarrow{iii}$ **3**

Scheme 1 i, N_ε-Z-dansyl-L-lysine, DCC, 1-hydroxybenzotriazole, DMF; ii, H_2, Pd–C, (−)-borneol, 20% aq MeOH; iii, monensin, DCC, 1-hydroxybenzotriazole, DMF

Table 1 Binding constants of the monensin–dansyl–β-cyclodextrin triad **3** and dansylglycine-modified β-CD **4** in aqueous solution at 25 °C[a]

	K/dm^3 mol^{-1}		
Guests	**3**	**3** + Na^+ (1 mol dm^{-3})	**4**
Nerol	5370	10300	83.3
Geraniol	6320	11900	68.4
Cyclohexanol	2250	15800	540
Cyclooctanol	3310	9010	1700
(−)-Borneol	15100	19700	4020
Adamantan-1-ol	38200	43000	8910

[a] Binding constants of 1:1 stoichiometry obtained by curve-fitting analysis based on a Benesi–Hildebrand type equation. Excitation and emission wavelengths are 370 and 543 nm, respectively.

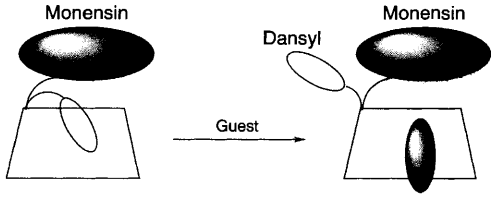


Fig. 1 Induced-fit type of complexation of **3**

comparison of the binding constants in the presence and absence of sodium ions. The degrees of the enhancement are *sevenfold* or less depending on the guest species. For comparison, we checked the effects of sodium ion on the guest binding with **2** under the same conditions, when no such enhancement with sodium ion was observed. So the enhancement observed with **3** may be induced by a structural change from the acyclic form to the macrocyclic one, the latter having a sodium ion in the centre of monensin residue. This result is consistent with the strengthened hydrophobic nature around the cavity, which is caused by the compactly folded monensin residue. It is noted that native monensin binds sodium ions by forming a macrocyclic form through hydrogen bonding between a carboxy group at one end of the molecule and a hydroxy group at the other end, but it has been reported that even when the carboxy group is converted to ester or amide form, monensin retains the ability to bind cations.[9] So it is reasonable that **3**, in which one end of monensin molecule is an amide form, is responsive to sodium ions.

This research was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

Received, 21st September 1994; Com. 4/05751A

Footnote

† *Selected data NMR* for **3**: δ_H (500 MHz, D_2O) 8.64 (1H, d, dansyl); 8.30 (2H, d, dansyl); 7.68 (1H, t, dansyl); 7.56 (1H, t, dansyl); 7.38 (1H, d, dansyl); 5.18 (1H, d, H-1); 5.15 (1H, d, H-1); 5.09 (1H, d, H-1); 5.04 (1H, d, H-1); 4.94 (1H, d, H-1); 4.88 (1H, d, H-1); 4.83 (1H, d, H-1); 2.94 (6H, s, NMe_2). The signals of the other CD protons overlap with those of the monensin residue.

References

1 M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag, Berlin, 1978.
2 J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
3 A. Ueno, I. Suzuki and T. Osa, *Anal. Chem.*, 1990, **62**, 2461.
4 A. Ueno, T. Kuwabara, A. Nakamura and F. Toda, *Nature*, 1992, **356**, 136.
5 K. Hamasaki, H. Ikeda, A. Nakamura, A. Ueno, F. Toda, I. Suzuki and T. Osa, *J. Am. Chem. Soc.*, 1993, **115**, 5035.
6 *Fluorescent Chemosensors for Ion and Molecule Recognition*, ed. A. W. Czarnik, ACS Symp. Ser. 538, ACS, Washington, DC, 1992.
7 J. Emert and R. Breslow, *J. Am. Chem. Soc.*, 1975, **97**, 670.
8 I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, *J. Am. Chem. Soc.*, 1976, **98**, 7855.
9 K. Maruyama, H. Sohmiya and H. Tsukube, *Tetrahedron*, 1992, **48**, 805.