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Dependence of Guest-Binding Ability on Cavity Shape of Deformed Cyclodextrins

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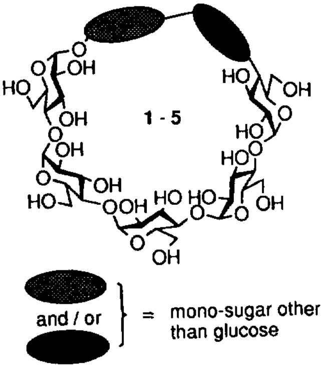
Abstract: Guest-binding ability of some β-cyclodextrin derivatives with deformed cavities were dependent on the cavity shapes, where 2,3'-anhydro-β-cyclodextrin 3 bound methyl orange about 2.8 times stronger than native β-cyclodextrin at 10°C.

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 1,4-linked D-(+)-glucopyranose units having $^4C_1$ chair conformation and have hydrophobic cavities in which a wide variety of substrates is included. The formation of inclusion complexes and the reactions constrained in the cavities have been studied extensively.[1] Molecular design of the guest molecule has attracted much attention for attaining optimum binding[2] and catalysis[3] by CDs and their derivatives. On the other hand, no attempt has been made to optimize the cavity shapes of the host molecules toward the guest-binding. These studies are important for obtaining the real tailor-made host molecule for a given guest molecule. Although many chemical modifications were carried out to change the structures and the properties of CDs, major part of such modification has not led to significant changes of the CD molecular structures.[1,4] We studied deformation of the CD cavity by chemical modification such as interglucosidic ether formation,[5] 2,3-anhydration,[6] or 3,6-anhydration[7] of one, two, or three glucose units. Recently, interesting cyclooligosaccharides[8] including per-3,6-anhydo-[9] and per-2,3-anhydro-CDs[10] have been prepared from monosugars or cyclodextrins.

In this circumstances, a study on the effect of the cavity shape of host CD molecule on its ability to bind guest is required. We describe here for the first time that the guest-binding ability of β-CD is dependent on the change of cavity shape brought about by replacement of a glucose unit by another sugar unit. All β-CD derivatives, mannoepoxy-β-CD 1,[6a] altro-β-CD 2,[11] 2,3'-anhydro-β-CD 3,[5] 3,6-anhydro-β-CD 4,[7a] and alloepoxy-β-CD 5[6b] employed here were prepared according to the reported methods.

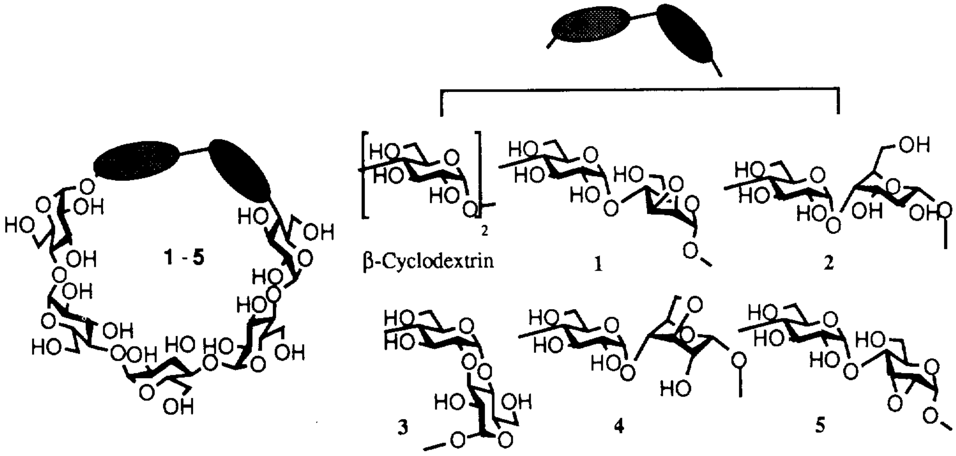


In contrast to the $^4C_1$ conformation of the glucose

Table 1. Association constants and thermodynamic parameters for inclusion of methyl orange by β-cyclodextrin and deformed β-cyclodextrins [a]

	β-CD	mannoepoxy-β-CD (**1**)	altro-β-CD (**2**)	2,3'-anhydro-β-CD (**3**)	3,6-anhydro-β-CD (**4**)	alloepoxy-β-CD (**5**)
Ka (M^{-1})						
10°C	2 600±31	1 650±3	1 550±12	7 140±120	962±4	
20°C	2 250±14	1 470±7	1 350± 7	5 950± 7	855±8	813±1
30°C	2 040±20	1 290±4	1 140± 9	4 930± 21	699±6	734±9
40°C	1 700±19	1 100±8	943± 8	3 830± 37	556±4	626±4
50°C						494±8
ΔG (kcal/mol)						
10°C	-4.42±0.05	-4.16±0.01	-4.13±0.03	-4.99±0.09	-3.86±0.02	
20°C	-4.49±0.03	-4.24±0.02	-4.20±0.02	-5.06±0.01	-3.93±0.04	-3.91±0.01
30°C	-4.59±0.05	-4.31±0.01	-4.24±0.03	-5.12±0.02	-3.94±0.03	-3.89±0.05
40°C	-4.64±0.05	-4.35±0.03	-4.26±0.04	-5.13±0.05	-3.93±0.03	-4.02±0.02
50°C						-3.99±0.06
ΔH (kcal/mol)						
	-2.38±0.02	-2.38±0.02	-2.94±0.01	-3.60±0.04	-3.24±0.05	-3.15±0.05
-TΔS (kcal/mol)						
10°C	-2.04±0.03	-1.78±0.02	-1.19±0.01	-1.39±0.03	-0.62±0.01	
20°C	-2.11±0.02	-1.86±0.02	-1.26±0.01	-1.46±0.02	-0.69±0.01	-0.76±0.01
30°C	-2.21±0.03	-1.93±0.02	-1.30±0.01	-1.52±0.02	-0.70±0.01	-0.74±0.02
40°C	-2.26±0.03	-1.97±0.02	-1.32±0.01	-1.53±0.02	-0.69±0.01	-0.87±0.01
50°C						-0.84±0.02

[a] In phosphate buffer solution (pH 6.86)



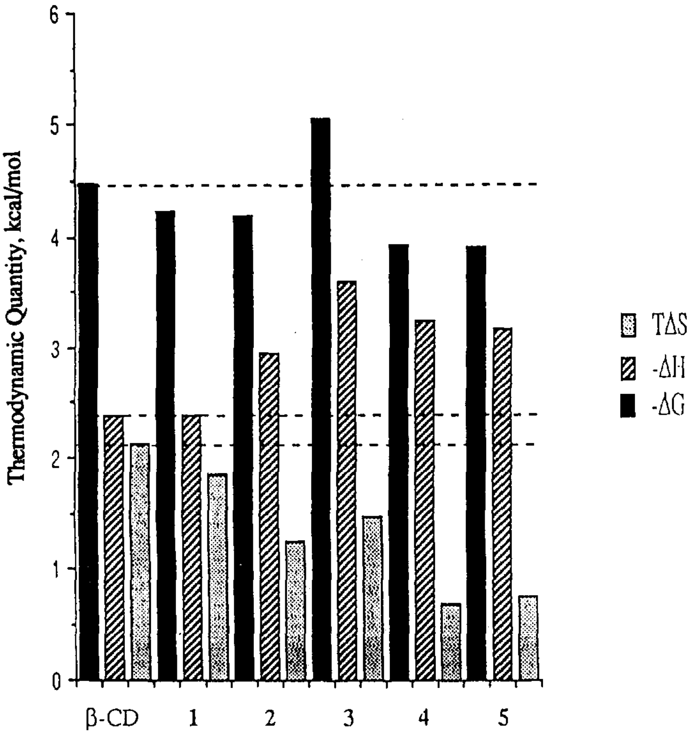


Figure 1. Changes in free energy (ΔG), enthalpy (ΔH), and entropy values (TΔS) for association of β-cyclodextrin and the deformed β-cyclodextrins with methyl orange in phosphate buffer solution (pH 6.86) at 20°C.

unit in CD, the conformation of the altrose unit in **2** is $^1C_4$ where 2- and 3-OHs are equatorial.[11] The conformation of the 3,6-anhydroglucose unit in **4** is also $^1C_4$ which has an axial 2-OH directed to the cavity center. The cyclic sugar **3** has an interglucosyl anhydride bridge which makes a tricyclic part composed of two $^4C_1$ chair glucose conformers and a chair conformer. The cyclic sugar **5** has an oxyrane oxygen directed to the cavity center, whereas the oxyrane oxygen of **1** is located outside the cavity.

The association constants between methyl orange and β-CD derivatives **1**-**5** were obtained by a usual method where spectral changes caused by addition of the β-CD derivatives to a methyl orange solution showed the existence of isosbestic points and were treated by a Scatchard method.[12] The results and the thermodynamic parameters are summarized in Table 1 and Figure 1.

Except for **3**, the association constants of the CD derivatives with deformed cavities are smaller than that of β-CD. The smallest association constants are obtained for **4** and **5** which have an axial 2-OH and an oxyrane-oxygen, respectively, directed to the inside of the cavities. Replacement of a constituent of β-CD by an altrose unit or a 2,3-anhydromannose unit as shown in the cases of **1** and **2** slightly decreases the binding ability. These results seem to be reasonable since that the structural perturbations caused by the replacements are small. The deformation of the β-CD cavity brought about decrease in both ΔH and ΔS, compared with the case of β-CD. Decrease in binding ability by deformation of the β-CD cavity except for the case of **3** is attributable to the decrease in ΔS which overcomes the decrease in ΔH, suggesting that tighter guest-binding causes more decrease in the degree of freedom of the guest. Interestingly, only **3** showed the enhancement (2.75 times at 10°C) of the binding ability. This is due to the decrease in ΔH which overcomes the decrease in ΔS compared with the case of β-CD. According to the consideration based on the CPK molecular model, the cavity of **3** are smaller than that of β-CD. Moderate and appropriate reduction in cavity size without extreme destruction of the symmetry of the cavity shape may be necessary for attainment of larger binding ability for methyl orange. On the other hand, the CD derivatives of unique cavity shapes will be useful for binding of appropriate unsymmetrical guest molecules.

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