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Flexible Cyclooligosaccharides: Guest-Binding and Regio-selective Modification

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Abstract

Modified β-cyclodextrin in which one glucopyranose unit is converted into an altropyranose unit showed a guest-induced fit behavior in the inclusion of globular or planar-shaped guests and brought about, as the result, the regioselective sulfonylation on 2-OH of the altropyranose unit.

Introduction

Cyclodextrins (CDs) are known to have a closed-up belt-shape structure that allows a 'lock and key' type binding of various guests. However, the rather rigid cavity hardly changes its conformation to enable an induced-fit binding which often plays a very important role in natural enzymes. In addition, its C_n-symmetry allows the bound guest to be located in various directions, but the orientation of bound guest should be properly controlled in order to develop more sophisticated receptors or enzyme mimics. Hence, if cyclodextrins are to be realistic enzyme models, flexibility has to be introduced into their macrocycles. According to these considerations, we have undertaken a study of the guest-binding properties of modified cyclodextrins in which one [1], two [2], or all [3] glucopyranose units have been converted into conformationally flexible altropyranose [4] residues (Scheme 1). We report here the example of guest-induced fit through the inclusion of globular [5] or planar [6] guests into mono-altro-β-cyclodextrin (MACD) **1** and a success on the regioselective modification [7] of MACD **1** as the result of the restriction of guest rotation by the induced-fit [6].

Results and discussion

*Inclusion of 1-adamantanecarboxylate or 2-naphthalene sulfonate into MACD **1***

As soon as one glucopyranose unit of β-CD is converted to an altropyranose unit (Scheme 1), the whole molecule becomes conformationally flexible and all the seven glucopyranose units become different from each other. ^{1}H-NMR spectroscopic technique allows the picking up signals of the altropyranose unit from the complicated spectrum and the obtained coupling constants prove that the altropyranose unit adapts mainly the $^4C_1$, $^0S_2$ and $^1C_4$ conformers equilibrating at a composition of 8% $^4C_1$, 31% $^0S_2$ and 61% $^1C_4$ in the D_2O solution (Scheme 2 and Table I). The $^0S_2$ conformer allows the whole molecule to keep the basic cavity shape of β-CD. The $^4C_1$ one, though compatible with this same cavity shape, extends its *altro*-3-OH deeply to the cavity. Unlike the former two, the $^1C_4$ conformer deforms the cavity to a mussel-shaped ellipse.

Upon binding guests, MACD **1** shows distinct conformational change which was determined by the ^{1}H-NMR spectra. The globular guest 1-adamantanecarboxylate causes the conformational equilibrium of the host shifted to 12% $^4C_1$, 80% $^0S_2$ and 8% $^1C_4$ (Figures 1–3 and Table I). In contrast, a planar guest such as 2-naphthalenesulfonate induces a conformational change of the host to the ellipse-shaped geometry which, in return, significantly restricts the orientation of the guest bound in (Figures 3–5).

*Regioselective sulfonylation of MACD **1** with 2-naphthalenesulfonyl chloride*

The reaction of MACD **1** with 2-naphthalenesulfonyl chloride in water gave only one sulfonate **2** (Scheme 3). The position of sulfonylation was determined to be the 2-OH of the altropyranose unit by the assignment of the ^{13}C-NMR signals (Table II). The 2-C signal of the altropyranose residue is significantly shifted downfield and signals of the adjacent carbons 1-C and 3-C are moderately shifted upfield, suggesting that the 2-OH of the altropyranose residue is sulfonylated. The structure determination was confirmed through the chemical conversion of **2** to the known 2,3-alloepoxy-β-CD which is prepared from 3-*O*-(2-naphthalenesulfonyl)-β-CD by the method reported by us [8]. In consistent with this unique mode of guest accommodation mentioned above, the sulfonylation of MACD **1** with 2-naphthalenesulfonyl chloride selectively picks the 2-OH of the altropyranose unit among the 21 different hydroxyl groups. The α-CD analogue of MACD **1** failed to show any regioselectivity in the sulfonylation reaction with 2-naphthalenesulfonyl chloride whose shape is too big to be bound into the cavity. These results demonstrate the

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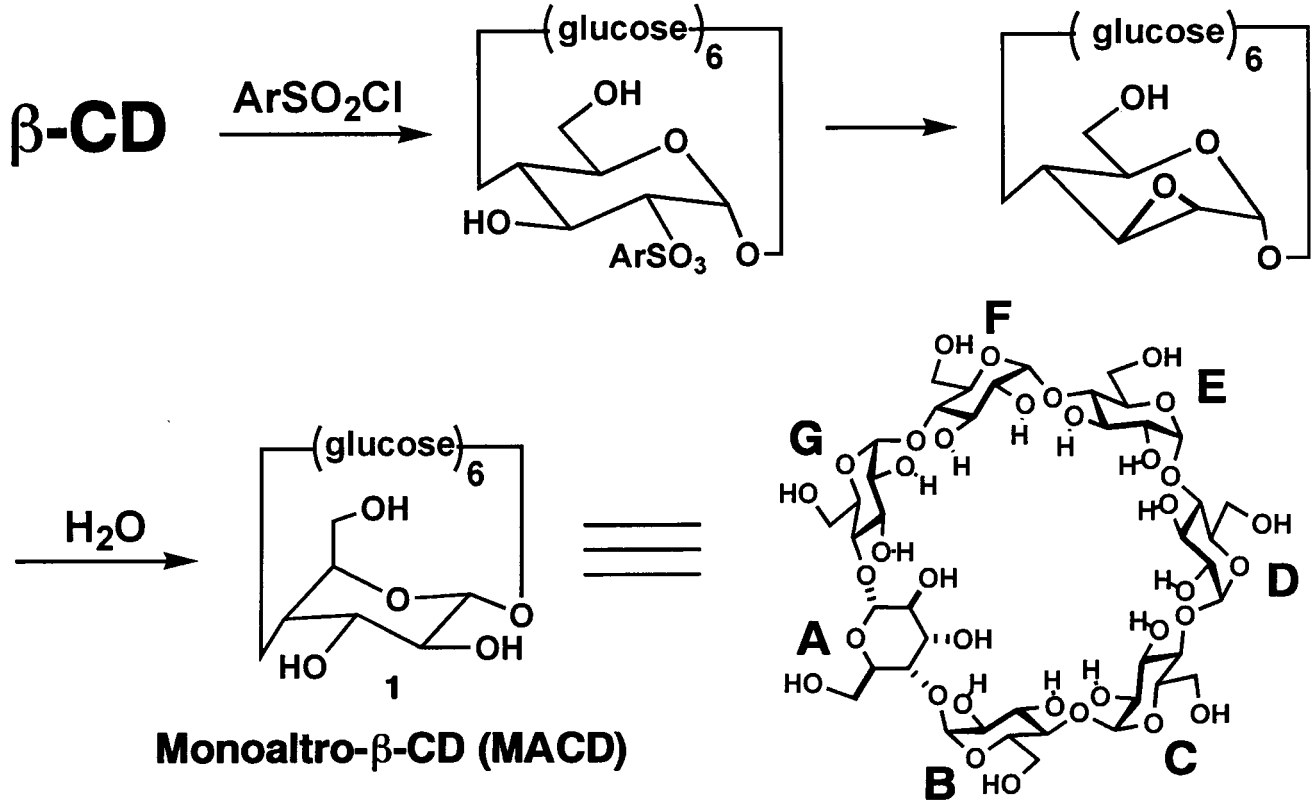
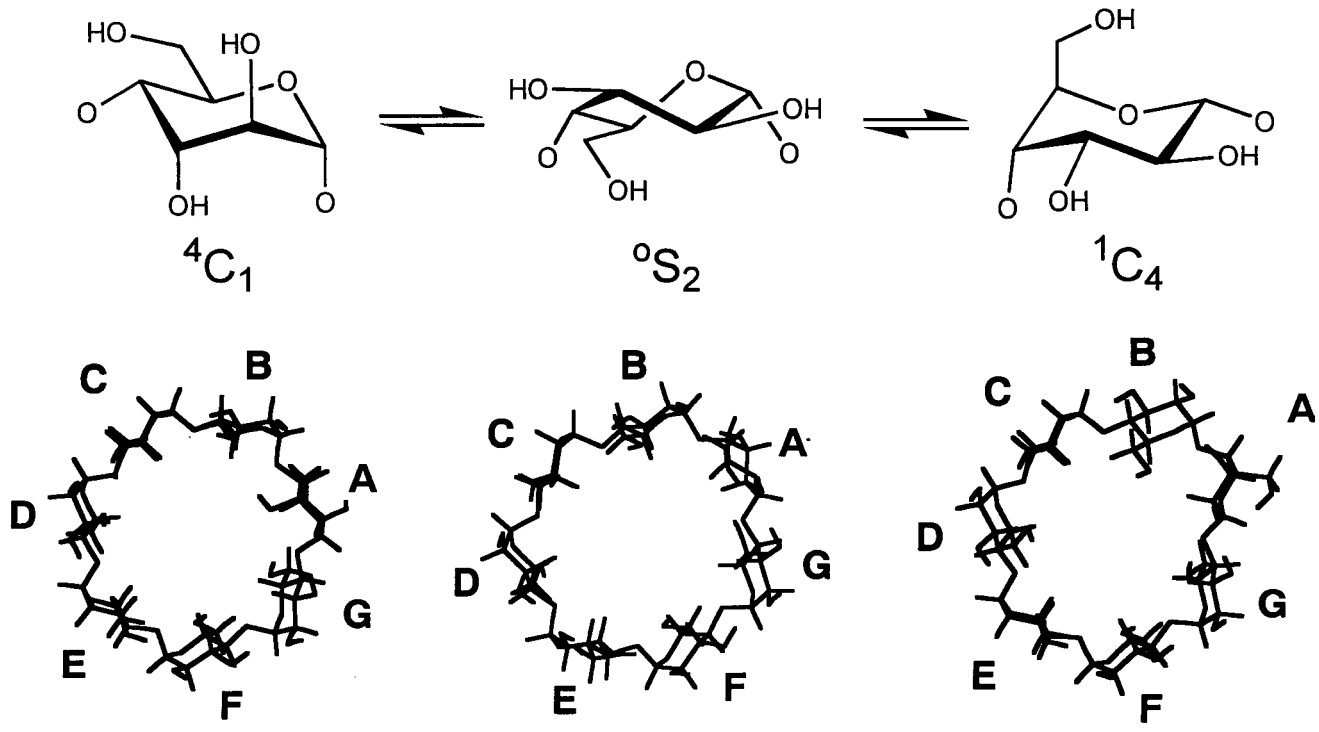


Scheme 1. Preparation of MACD **1** through three-step transformation of a glucose unit to an altrose unit.



Scheme 2. The flexible altrose unit making the cavity shape of MACD **1** alterable.

Table 1. Coupling constants for the altrose unit of MACD **1** and its complex with 1-adamantanecarboxylate

J (Hz)	Calculated[a]			Found (in D_2O, 35 °)		
	$^4C_1$	$^1C_4$	$^0S_2$	Host[b]	90% Complex +10% Host	Complex[c]
$J_{1,2}$	2.2	8.0	4.0	6.4	5.2	5.1
$J_{2,3}$	2.7	10.2	10.2	9.5	9.3	9.3
$J_{3,4}$	3.4	2.4	4.5	3.5	4.5	4.6
$J_{4,5}$	9.7	1.4	6.4	3.5	6.7	7.0

[a]Calculated according to the generalized Haasnoot-equation.
[b]Host: MACD, Complex: adamantanecarboxylate@MACD.
[c]Calculated for the 100% inclusion complex based on the experimental data for MACD and those for the equilibrium of 90% complex and 10% MACD.

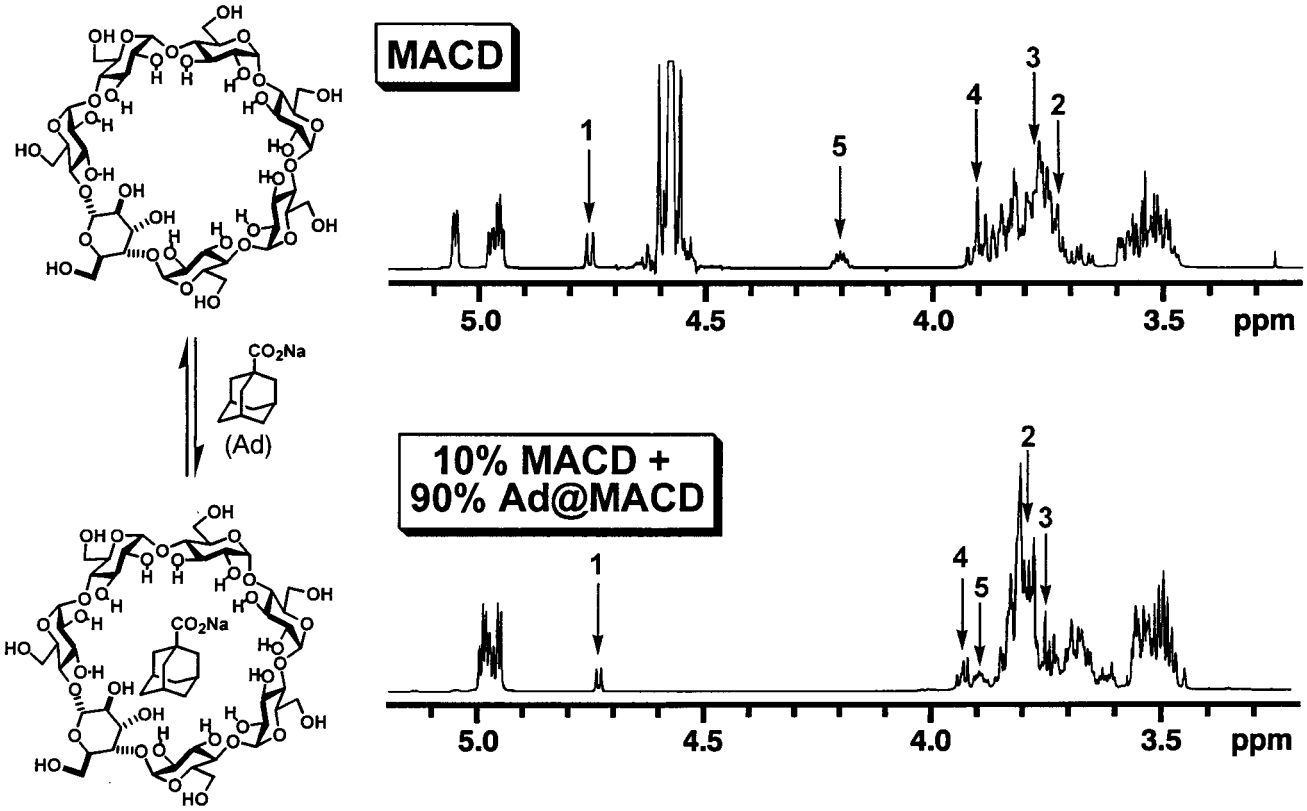


Figure 1. ^{1}H-NMR spectra of MACD **1** (top) and its inclusion complex with 1-adamantanecarboxylate (Ad) (bottom) in D_2O.

Table 2. Chemical shifts (ppm) of C1–C4 of MACD 1 and its sulfonylation product 2

	Altrose residue A			
	C1	C2	C3	C4
MACD	104.2	~72	70.7	79.9
Sulfonylation product	99.1	80.4	68.1	81.2
	Glucose residues B–G			
	C1	C2	C3	C4
MACD	101.9–102.6	72.0–74.0	73.7–74.0	71.3–81.9
Sulfonylation product	100.8–103.5	72.5–74.3	71.0–74.3	81.4–82.8[a]

[a]The signal relating to the C4 carbon of pyranose G was found at δ 73.6.

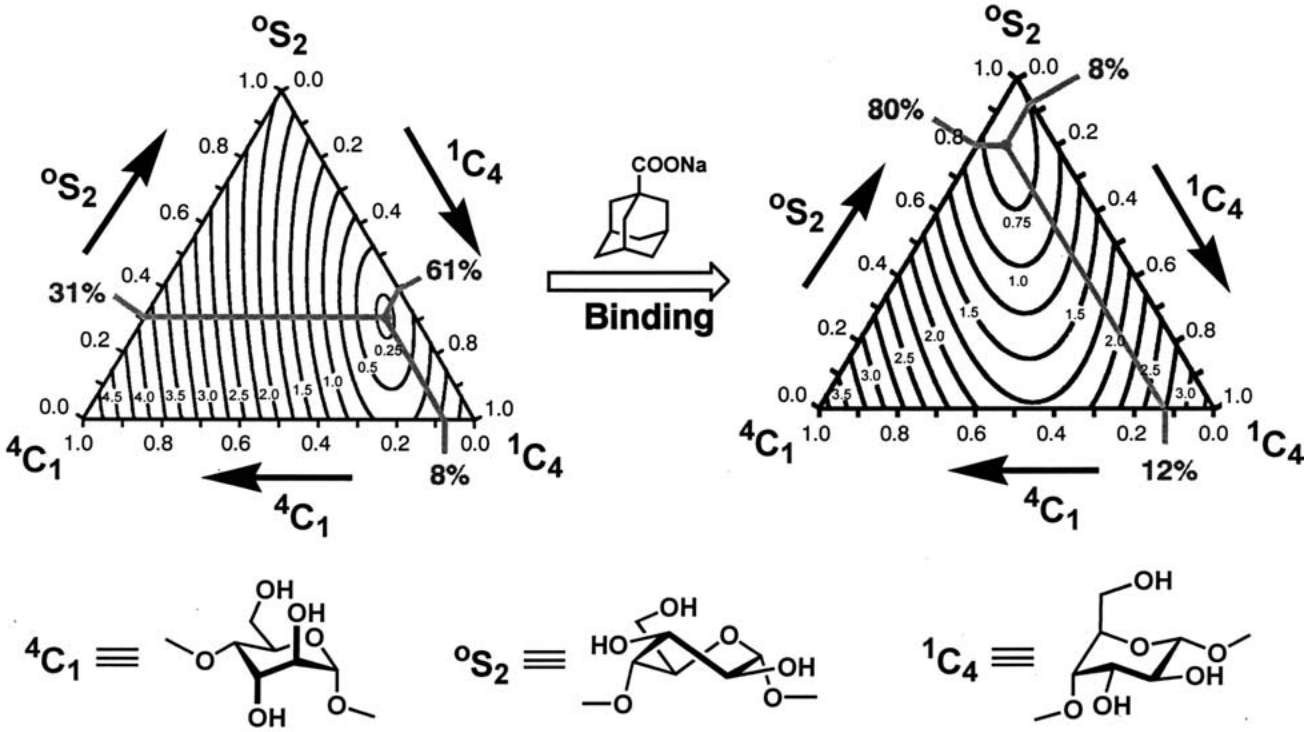


Figure 2. Change of the equilibrated conformer-composition of the altrose unit in MACD **1** upon inclusion of 1-adamantanecarboxylate.

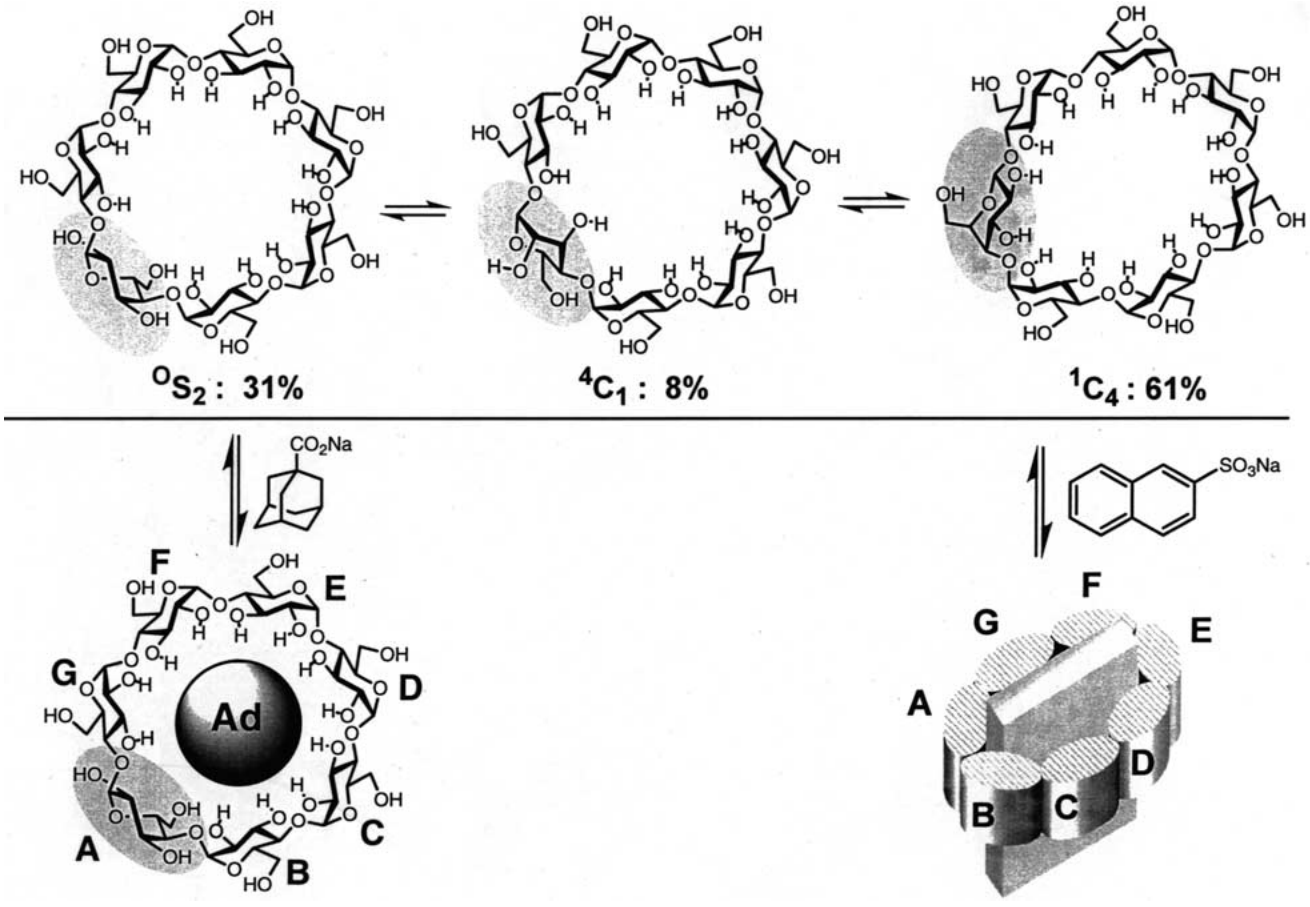


Figure 3. Induced-fit type conformational change of MACD **1** upon inclusion of 1-adamantanecarboxylate or 2-naphthalenesulfonate.

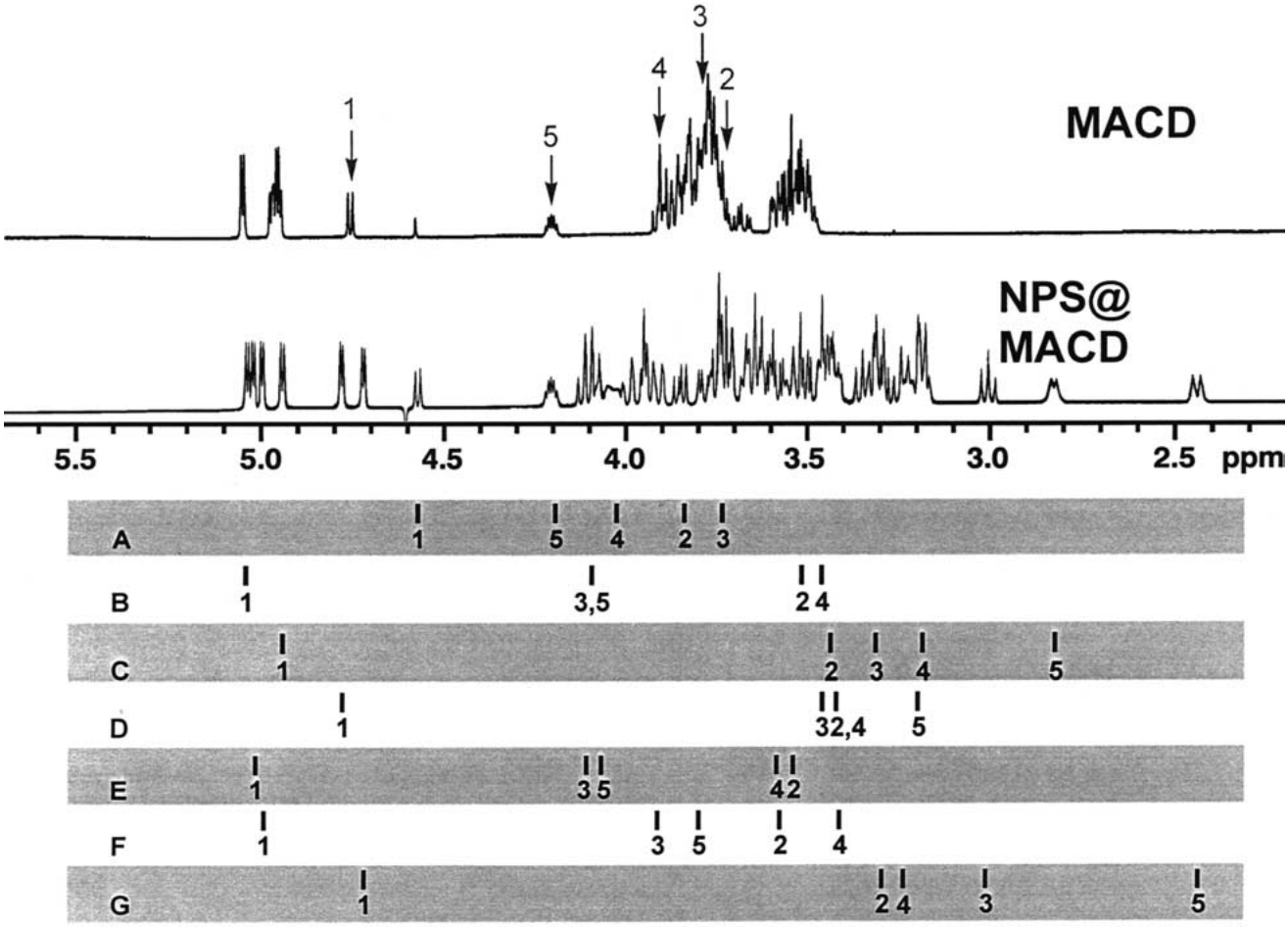


Figure 4. Assignment of the ^{1}H-NMR spectra of MACD **1** in the inclusion complex with 2-naphthalenesulfonate (NPS) in D_2O.

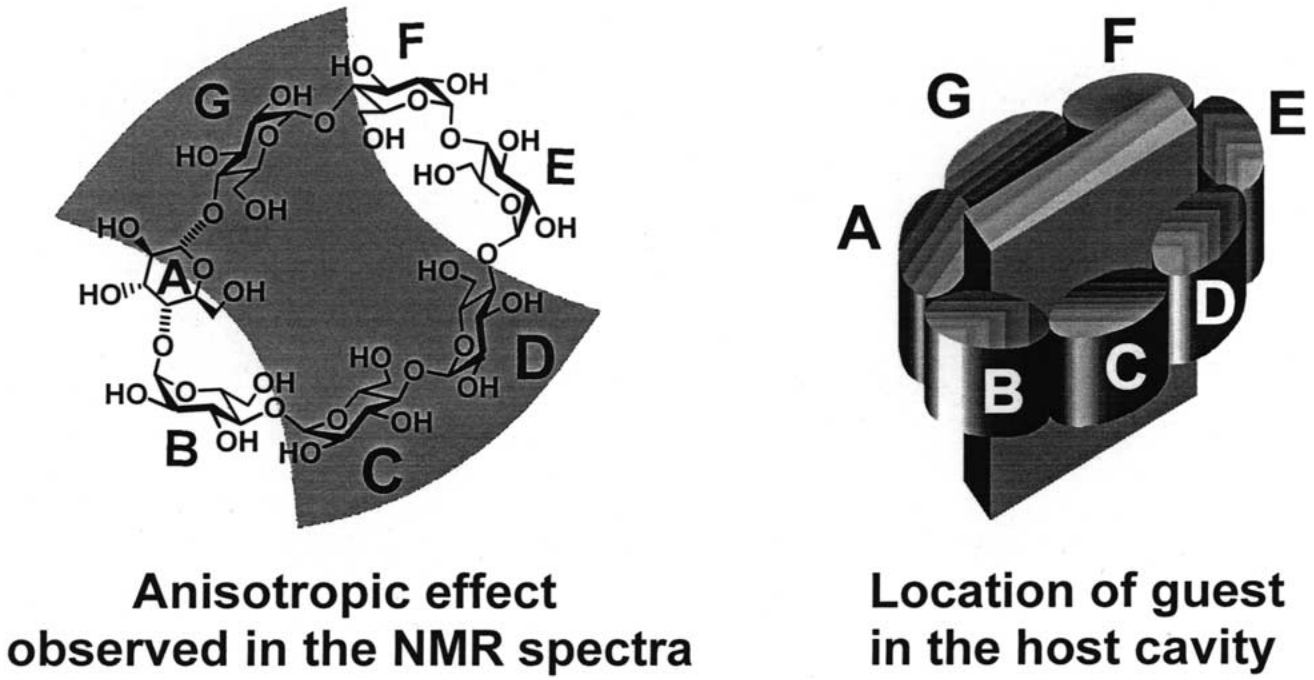
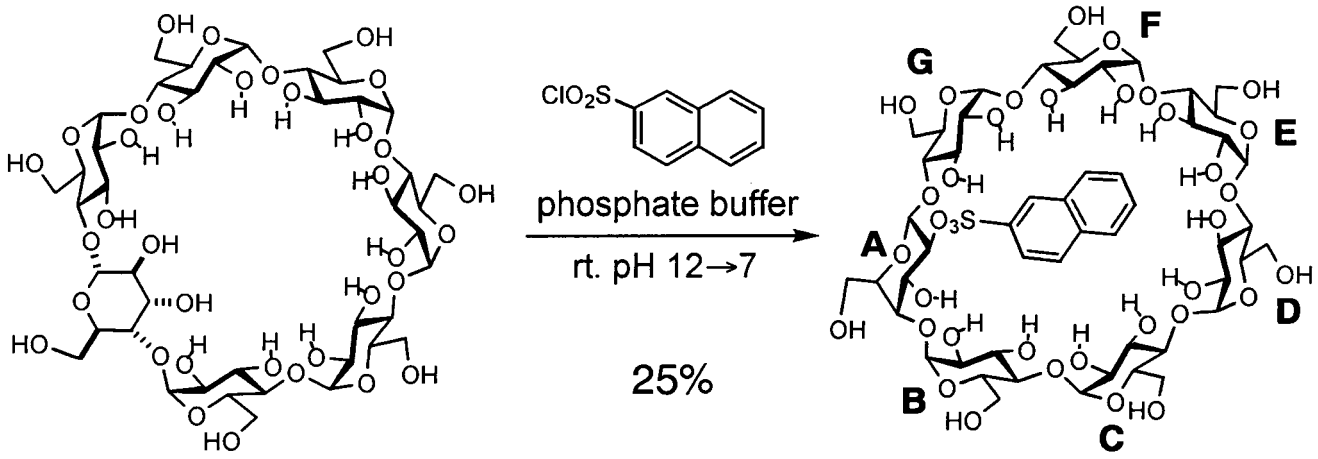


Figure 5. ^{1}H NMR anisotropic effect and location of 2-naphthalenesulfonate included in MACD **1**.



Scheme 3. Regioselective sulfonylation of MACD **1**.

importance of reactant-binding and the control of reactant-orientation in MACD **1** cavity.

Experimental

Assignments of ^{1}H- and ^{13}C-NMR signals

The signals in D_2O were assigned by DQFCOSY, HMQC, TOCSY, DDS, and ROEDS spectra.

*Preparation of MACD **1***

This compound was easily obtained through three steps from β-CD by the method reported elsewhere [1].

*Reaction of MACD **1** with 2-naphtahlenesulfonyl chloride in water*

Na_2HPO_4 (225 mg) was dissolved in water (5.1 mL) and the solution was adjusted to pH 12. To the solution, MACD **1** (600 mg, 0.58 mmol) was added and then powdered 2-naphthalenesulfonyl chloride (1.8 g, 7.9 mmol) was poured in at one portion. The pH of the reaction mixture was allowed to decrease during decomposition of sulfonate product in alkaline solution. Three hours later, the reaction mixture reached a neutral pH and the insoluble material was then removed by filtration. Chromatography of the filtrate on a reversed-phase Lobar column (Rp-18, size C, eluted with a gradient of 0–60% aq. CH3CN) afforded the only sulfonate **2** in 25% yield. The proton ^{1}H-NMR spectrum of 2 clearly exhibited seven doublet signals for the anomeric protons: δ 4.83 (1A, J = 7.0 Hz), 5.02 (1B, J = 4.0 Hz), 5.25 (1C, J = 4.0 Hz), 5.17 (1D, J = 3.5 Hz), 5.14 (1E, J = 3.5 Hz), 5.10 (1F, J = 3.5 Hz), 4.65 (1G, J = 3.5 Hz).

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