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COMMUNICATION

Flexibly Crown Ether-Capped β-Cyclodextrin

Our synthetic host molecules having two diverse recognition sites included guest molecules such as sodium *p*-nitrophenolate. The flexible linkage induced a more stable complex and increased the association constant.

The behaviors of artificial hosts having two diverse recognition sites in the host–guest chemistry have provoked considerable research for the past decade (*1*). These attempts to construct a multiple recognition element onto the host molecules gave a new strategy for hosts that mimic the sophisticated receptor and enzyme functions. At the recognition of substrates by receptor and enzyme, however, the induced fit plays an important role; namely, although receptor and enzyme prepare for their specific pockets, they are not fixed perfectly, the conformation of recognition sites is changeable according to bind substrates, and the induced fit produces a more stable complexation and catalytic function.

We now report the host compounds consisting of a crown ether coupled to β-cyclodextrin through the flexible linkage.

Synthesis of crown ether-capped β-CD was accomplished according to Scheme 1. The aldehyde of benzocrown ether **(1),** whose synthesis was previously described (*2*), was reduced ($NaBH_4$, EtOH) in the 98% yield. The alcohol **(2)** was converted to thioester **(3)** by the Mitsunobu method (Ph_3P, DIAD, CH_3COSH) (*3*) in 75% yield. Further reductive cleavage ($LiAlH_4$, ether) of the thioester **(3)** gave an air-sensitive thiol **(4)** in the 95% yield.

The azacrown ether-capped β-CD was prepared as following. Reaction of the benzyl-protected diethanolamine **(5)** with tetraethyleneglycol ditosylate **(6)** by the high dilution method (NaH, DMF) afforded the monoazacrown ether **(7)** (*4*) in the 58% yield. Hydrogenolysis of **7** afforded pure monoazacrown ether **(8)** in the quantitative yield. Acylation of **8** with bromoacethyl bromide (Et_3N, $CHCl_3$) followed by treatment with potassium thioacetate furnished a thioester **(9)** in the 71% total yield. Finally, hydrolysis of **9** afforded an air-sensitive thiol **(10)** in the 86% yield.

Each thiol moiety of crown ether reacted with 6-*O*-tosyl-β-CD and methyl tosylate under the same condition (DMF, NaH) afforded the crown ether-capped β-CDs **11** (62%) and **12** (69%) and methyl sulfides **13** (77%) and **14** (68%), respectively. The crude products of β-CD derivative were purified by reserved-phase column chromatography (Lobar column LiChroprep RP-18, 25 × 310 mm, Merck Ltd.). The structural assignments of **11** and **12** were made by FABMS[1] spectra and elemental analysis (Scheme 2).

[1] FABMS, fast atom bombardment mass spectrometry. **11:** FABMS *m/z* 1475 $(M + H)^+$; *Anal.* Calcd. for $C_{59}H_{94}O_{40}S/4H_2O$: C, 45.79; H, 6.64. Found: C, 45.77; H, 6.46. **12:** FABMS *m/z* 1454 $(M + H)^+$; *Anal.* Calcd. for $C_{56}H_{95}O_{40}NS/6H_2O$: C, 43.05; H, 6.90; N, 0.90. Found: C, 43.13; H, 6.59; N, 0.85.

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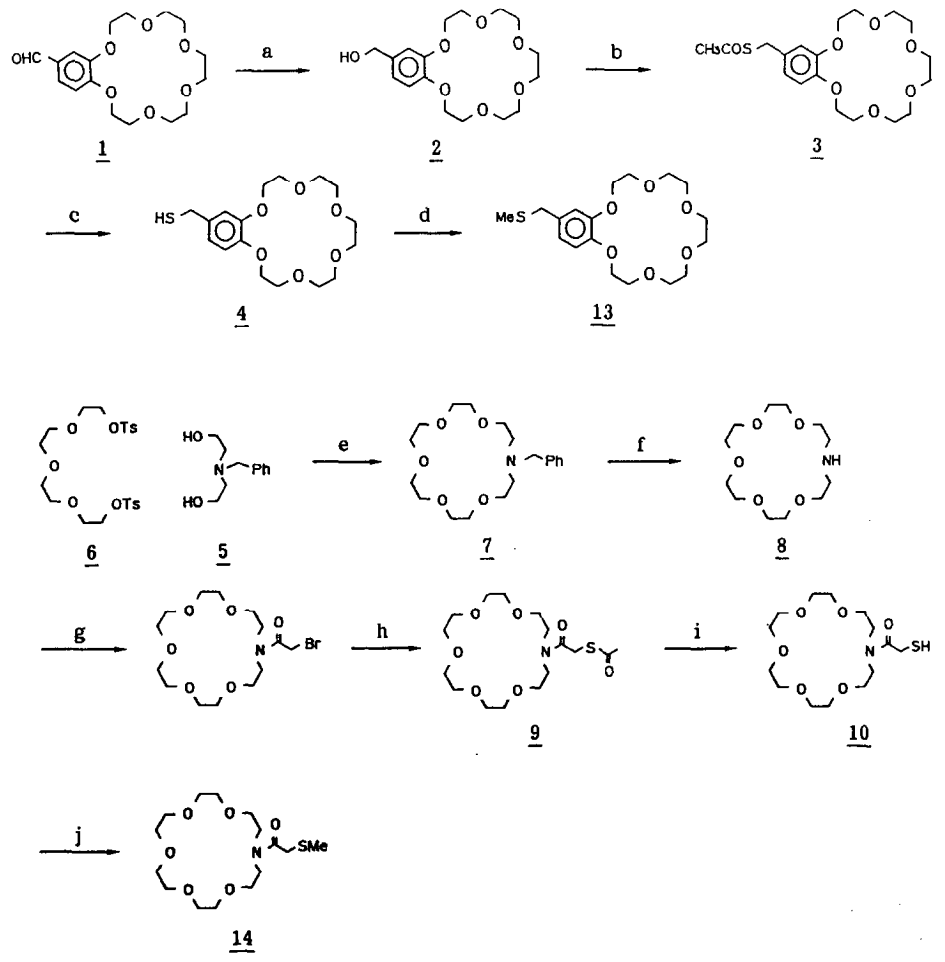
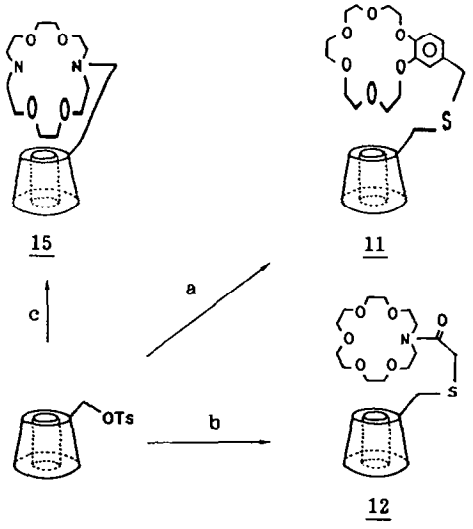


SCHEME 1. Preparation of crown moieties: (a) $NaBH_4$/EtOH/RT/98%; (b) PPh_3/DIAD/CH_3COSH/RT/75%; (c) $LiAlH_4/Et_2O$/RT/95%; (d) methyltosylate/NaH/DMF/RT/77%; (e) NaH/DMF/RT/58%; (f) 10% Pd–C/MeOH/H_2/RT/quant; (g) $BrCH_2COBr/Et_3N/CHCl_3$/RT; (h) CH_3COSK/DMF/RT/71%; (i) NaOH/MeOH/H_2O/RT/86%; (j) methyltosylate/NaH/DMF/RT/68%.

Complexation of sodium *p*-nitrophenolate and host molecules was examined spectroscopically by the ^1H NMR spectra and the uv spectra. On the basis of 270-MHz ^1H NMR spectra in d_6-DMSO, both signals of *ortho*- and *meta*-proton of sodium *p*-nitrophenolate decreased with an increase in the concentration of β-CD. Furthermore, the change in the *ortho*-proton's chemical shift was much greater than that of the *meta*-proton; therefore, the orientation of the guest molecule in the cavity of β-CD could be determined: it should be the *ortho*-position in a cavity deeper than that of the *meta*-position. In the benzocrown ether-capped β-CD **(11)** and the monoazacrown ether-capped β-CD **(12)**, the same result was also obtained (Fig. 1).



SCHEME 2. Synthesis of crown ether-capped β-cyclodextrins: (a) 4/NaH/DMF/RT/62%; (b) 10/NaH/DMF/FT/69%; (c) diaza[18-crown-6] ether/DMF/80°C/60%.

The association constants (K_a) of the substrates to the various hosts were calculated with uv spectra (*5*) and are summarized in Table 1. Spectroscopic experiments showed only 1 : 1 complex formation on the basis of observing two isosbestic points in all complexation studies.

Apparently, synthetic host **12** bound sodium *p*-nitrophenolate 47 times stronger than parent β-CD: this association constant corresponded to 5.48 kcal of free energy change and thus the energy change is worth 88.4% of the sum of free energy change for parent β-CD (3.19 kcal) and benzocrown ether (3.01 kcal for **13**). In comparison, the free energy change for rigidly capped β-CD **(15)**, estimated at about 4.88 kcal, increased by 1.70 kcal against parent β-CD[2] (3.70 kcal is

TABLE 1

Association Constant of Host–Guest Complexes in DMSO

Entry	Host	$K_a(M^{-1})^a$	$K_a/K_{a_{CD}}$	$-\Delta G$(kcal)
1	β-CD	2.20×10^2	1.0	3.19
2	Benzocrown-CD(11)	1.04×10^4	47.3	5.48
3	Monoazacrown-CD(12)	1.55×10^2	0.7	2.99
4	Benzocrown-Me(13)	1.60×10^2	—	3.01
5	Monoazacrown-Me(14)	2.03×10^2	—	3.15
6	Diazacrown-CD(15)	3.76×10^3	17.1	4.88
7	Diazacrown	5.20×10^2	—	3.70

[a] Association constants were determined from the respective Scott's linear plots ([guest]$_0$ = 5.0×10^{-5} M, [host]$_0$ = $1.0 \times 10^{-4} - 1.0 \times 10^{-3}$ M).

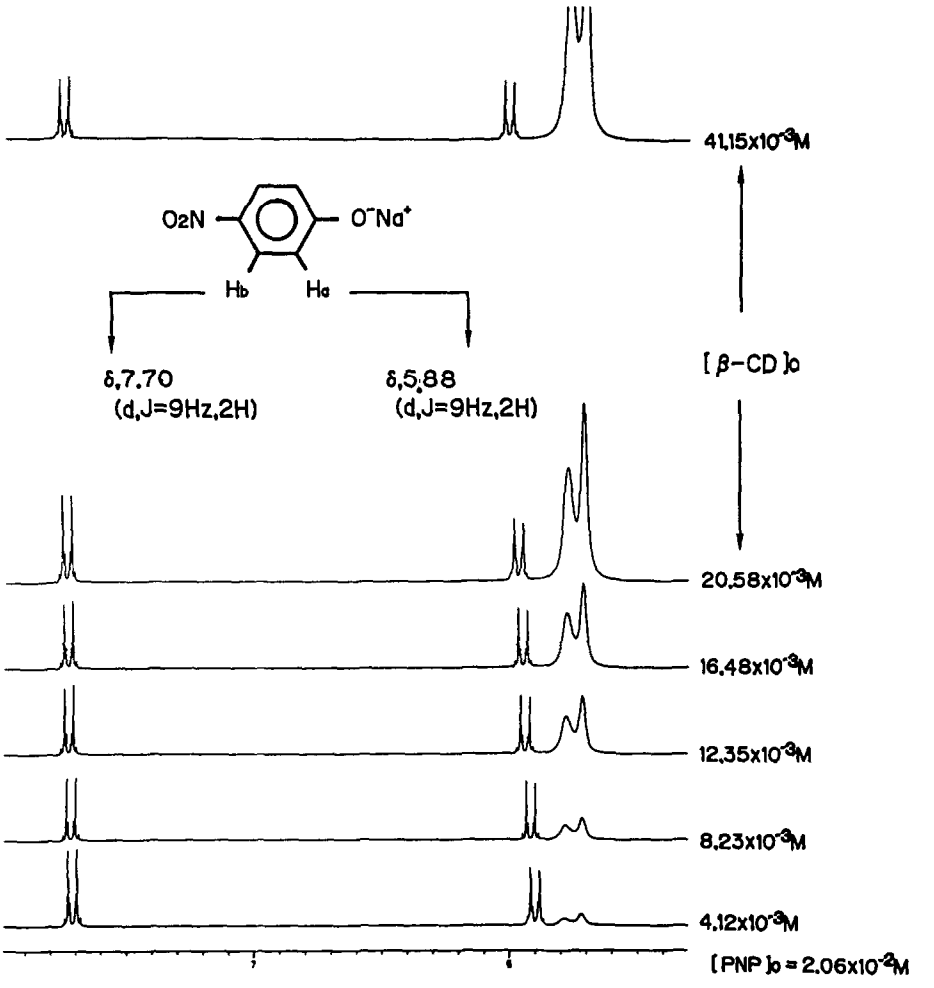


FIG. 1. The chemical shift changes of sodium *p*-nitrophenolate in the inclusion complex with β-cyclodextrin.

expected as increment by attachment of crown ether). Though monoazacrown CD **(12)** has a long linkage on a level with **11,** the observed increment of the stability was negligible, because they possibly cause rotational inhibition by the amide bond and steric disadvantages at inclusion.

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[2] The association constant was estimated 2.8 × 10^4 M^{-1} by Willner *et al.* (*1c*), but under our experimental condition, the value was not increased beyond 5.0 × 10^3 M^{-1} at a maximum.

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