Tetrahedron Letters, Vol.22, No.24, pp 2273 - 2276, 1981
Printed in Great Britain

0040-4039/81/242273-04$02.00/0

A,C; A',C'-DOUBLY CAPPED β-CYCLODEXTRIN. DIRECT EVIDENCE FOR THE CAPPING STRUCTURE

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Doubly capped β-cyclodextrin was firstly prepared in good yield by the treatment of β-cyclodextrin with an excess amount (2.6/1 mol/mol) of benzophenone-3,3'-disulfonyl chloride. This successful double capping demonstrates that benzophenone-3,3'-disulfonyl capping takes place on A,C rings. The present double cap is a useful key intermediate for the preparation of regiospecifically tetrasubstituted cyclodextrins.

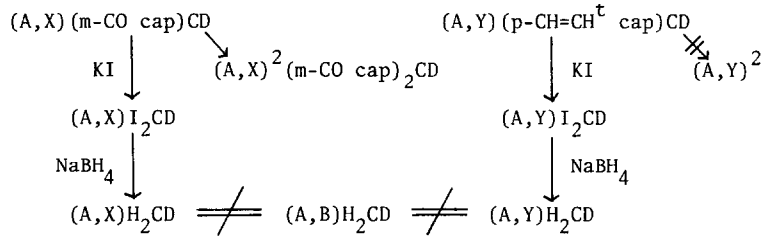
Enzymes or other biological molecules recognize the shapes of their specific substrates (or other counterparts) through the unique and strong multicentered interaction along the surface of their recognition sites (electrostatic, metal coordination, hydrogen bonding etc.). Recently enormous attention has been paid for designing and preparation of artificial host molecules which recognize their guest molecules (counterparts) by multiple interactions to gain insight into this biological multicentered interaction. Some typical examples of this multicentered recognition are shown in recent publications.[1-4]

This kind of chemistry is inevitably accompanied by many complexities which should be solved by developing new techniques and procedures. Thus, we have reported the transannular capping,[5,6] applicable to the preparation of organic catalysts[1-2,7,8,] of enzyme-like activities from cyclodextrins. However, the original capping is assumed to give a mixture of positional isomers substituted at A,C and A,D rings of β-cyclodextrin.[2] Even though the catalysis (or the energy transfer)[6] of this isomer mixture can be analyzed reasonably[7] but simple application of the capping to structural problems without careful consideration of this complexities may lead to uncertainties.

In these circumstances, strict determination of the structures of these isomers is necessary, although such common spectroscopic approaches as IR, ^{1}H-NMR are almost helpless for the purpose. Now we wish to report the successful structure determination via double capping.

The regiospecific capping was carried out for β-cyclodextrin with benzophenone-3,3'-disulfonyl chloride or stilbene-4,4'-disulfonyl chloride to afford AX and AY isomers, respectively, as shown in Scheme 1. These capped cyclodextrins were converted to the corresponding diiodide according to our reported procedure,[9] and these diiodides were further converted to the corresponding deoxy derivatives, β-CD-H_2 by the treatment with $NaBH_4$ in DMSO at room temperature for 3 hr. Analysis calculated for A,C-dideoxy trihydrate, $C_{42}H_{70}O_{33}$ $3H_2O$ are; C, 43.60, H, 6.62 and found, C, 43.51, H, 6.21; FD-Mass spectrum showed M^+ peak at 1102. Analysi

Scheme 1. Interconversion of Bifuctionalized β-cyclodextrins



m-CO cap = $-O_3S-C_6H_4^m-CO-C_6H_4^m-SO_3-$

p-CH=CH^t cap = $-SO_3-C_6H_4^p-CH=CH^t-C_6H_4^p-SO_3-$

found for A,D-dideoxy trihydrate are; C, 43.40, H, 6.78; FD-Mass spectrum showed $(M+Na)^+$ peak at m/e 1125. As a nmr standard, we also have prepared the monodeoxy β-cyclodextrin.

$$\beta\text{-CD-OTs(primary)} \xrightarrow{KI} \beta\text{-CD-I} \xrightarrow{NaBH_4} \beta\text{-CD-H}$$

In Table I are listed C^{13} chemical shifts observed for the deoxy derivatives. Apparently the chemical shifts of ring A carbons of AX and AY isomers are not influenced by another substituent on ring X or Y within experimental error, leading to a conclusion that neither AX nor AY is the A,B isomer, since a slight but appreciable remote (de)shielding effect of A substituent on ring B carbons should be observed according to Knowles' experiment.[10] It is most probable, then, to assume that AX is AC and AY is AD based on the CPK model, since the distance between two reacting sites of trans stilbene-4,4'-disulfonyl chloride (1.35 nm) is too long to link A and C rings (0.55—0.99 nm). But these structures were determined on firm chemical grounds of the formation of doubly capped cyclodextrin.

Thus, an excess amount (2.6 times) of benzophenone-3,3'-disulfonyl chloride was used to functionalize β-cyclodextrin where after 1 hrs' heating at 60°C followed by usual work up and separation through the flash column chromatography, doubly capped cyclodextrin, $(A,X)^2(m\text{-CO cap})_2CD$, was obtained in 35 % yield together with a small amount of monocap AX. Double cap; H^1NMR, 8.0—7.2 (aromatic, 16H), 4.7 (C_1-H, 7H), 2.7—4.2 (other H); IR 1650 and 1190 cm^{-1} showed a very large R_f value for common eluents, quite different from polymeric materials (R_f, ca 0). A typical example was, double cap 0.6, mono cap 0.5, β-CD 0.2, polymeric material 0 (n-PrOH : H_2O : AcOEt : 25 % NH_4OH = 5 : 3 : 2 : 1). Double cap was converted to the corresponding tetraiodo derivative by treatment with a large excess KI in DMF at 80° for 2 hrs. Crude product was obtained in 73 % on precipitation with tetrachloroethylene. The tetraiodo derivative was further converted to the tetradeoxy derivative in 64 % H^1NMR of tetradeoxy-β-cyclodextrin (d_6-DMSO) showed signals centered at 1.21 δ (12.0H, CH_3), at 4.76 and 4.85 (6.8H combined, C_1-H), and other protons (59H). FD-Mass spectrum showed M^+

Scheme 2 Possible Doubly Capping at A,C;D,F(-·-) of A,C;E,G(---)

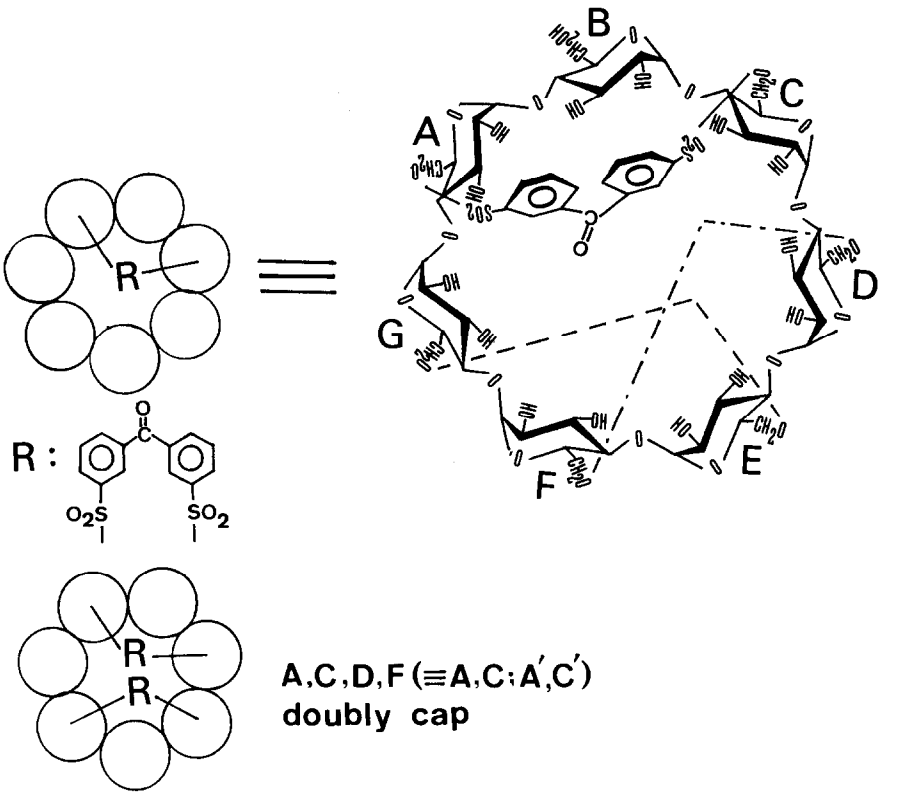


Table I. C^{13} NMR Chemical Shift of Deoxycyclodextrins, δ in ppm[a]

Carbon Compds.	C_1	C_2, C_3, C_5	C_4	C_4'	C_5'	C_6	C_6'
A,C — H_2	101.88	71.98, 72.47, 72.98	81.60	88.15	66.65	59.93	17.41
A,D — H_2	101.86	72.03, 72.43, 72.96	81.60	88.15	66.55	59.93	17.38
A — H (monodeoxy-cyclodextrin)	102.17	72.39, 72.66, 73.31	81.85	88.37	66.97	60.32	17.75
A,C:A',C'— H_4	102.02	72.41, 72.80 (70.42, 71.28)[b]	81.60, 83.16	87.98[c]	66.56[c]	59.80	17.32[c]

[a] Average is taken if necessary; internal stardard, d_6-DMSO (39.60 ppm).

[b] Shoulder. [c] Thin multiplet.

peak at m/e 1070. Analysis. Calcd. for $C_{42}H_{70}O_{30}$ $7H_2O$: C, 42.14; H, 7.07. Found: C, 42.63; H, 6.57.

Under similar conditions, formation of doubly capped cyclodextrin was negligible for the A,Y capping. Therefore, it is evident that AX is AC, capable of further capping leading either to A,C; D,F or A,C; E,G and that AY is AD, not capable of further capping.

As a conclusion, we now present excellent procedure of the regiospecific capping at the A,C positions as well as that at the A,C; A',C' positions, which promises versatile application to the regiospecific bi- and tetra-functionalization of cyclodextrin.

Acknowledgements: Authors are very grateful to Dr. K. Fujita of Kyushu University for his kind taking FD-Mass spectra and for his helpful discussions.

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(Received in Japan 28 February 1981)