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Specific Bifunctionalization on Cyclodextrin

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Cyclodextrins have attracted increasing attention of chemists since its striking characteristics of specific binding and catalysis modeling simple enzymes have been found in many examples[1]. However, a possible approach to better (or more sophisticated) enzyme models by use of ideally bifunctionalized or polyfunctionalized cyclodextrins is experiencing a serious barrier to be overcome in that the bifunctionalization at given (appropriate) positions among 6-8 (identical) primary and 12-16 secondary positions of α,β or γ-cyclodextrin is extremely difficult using ordinary techniques of organic chemistry.

Very recently, the authors reported[2] the synthesis of very useful key compounds, rigidly capped β-cyclodextrins[3], Ia, which is activated at the bridgehead positions of the capping group toward the nucleophilic displacement, and is apt for the specific bifunctionalization.

Significant advantage of the capping lies in the remarkable facilitation of isolation of these specifically bifunctionalized cyclodextrins, Ia and Ib, due to their enhanced binding of some special guest molecules to form the host-guest inclusions of much reduced (or enhanced, in some limitted cases) solubilities.

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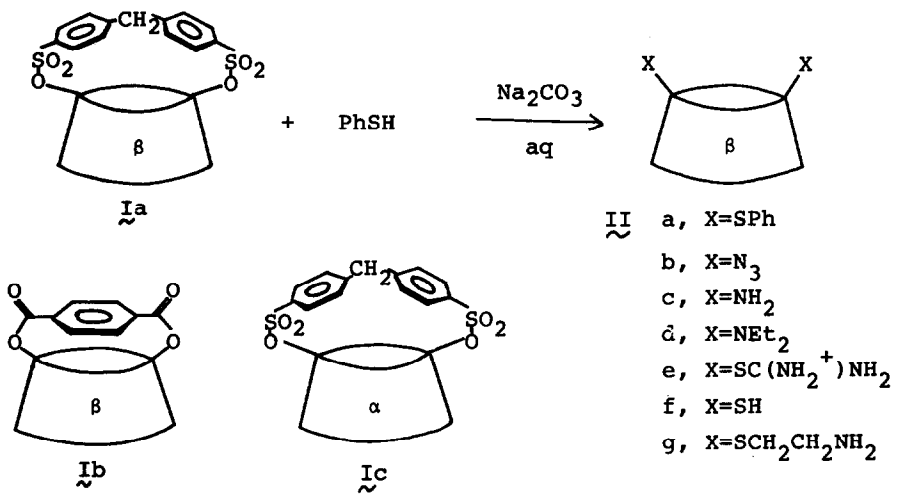
Now the authors wish to report the successful preparation of several specifically disubstituted cyclodextrins. Capped β-cyclodextrin, Ia[2], was used as a starting material for the specific bifunctionalization of β-cyclodextrin and for the specific bifunctionalization



of α-cyclodextrin, capped α-cyclodextrin similarly prepared from diphenylmethane-p,p'-disulfonyl chloride, Ic, (in 40% yield) was used. The disubstituted β-cyclodextrins, IIa-g, were prepared from Ia via double nucleophilic displacement, a typical example of which is described below.

Thus, 100 mg of Ia (0.07 mmol) and 100 mg of thiophenol (0.91 mmol) were dissolved in 20 ml of aqueous sodium carbonate to adjust pH 10 and the solution was stirred for 24 hrs at 50°. A solid obtained on evaporation of water was dissolved in dimethylformamide and reprecipitated by addition of chloroform. Recrystallization of the precipitate gave 18.5 mg of practically pure IIa (20% yield). Silica gel tlc eluted with water-ethyl acetate-isopropanol (5:7:7) shows single round spot at Rf 0.8; mp 190°-195°(decomp.); characteristic absorptions at 1580, 1480, 1440 cm^{-1}; NMR absorptions (DMSO-d_6) cen-

tered at δ 7.24 (aromatic), 4.90 (C_1 protons) and 3.32 (others); elemental analyses, C found 49.14 (calculated 49.15), H found 5.96 (5.51%).

Similar double nucleophilic displacements gave IIb (50%), IId (80%), IIe (80%) or IIg (80%). From 100 mg of IIb was obtained IIc by the hydrogenation at 50 atm H_2 for 4 days in the presence of 100 mg of platinum oxide at room temperature. Resultant diamine IIc was practically pure after filtration off the platinum and was obtained in 80% yield through condensation and precipitation by addition of methanol. Decomposition of IIe in 10% NaOH aqueous solution at 50° for 5 hrs followed by acidification afforded crude IIf, considerably contaminated with the corresponding (telomeric) disulfides. Treatment of the crude mixture with sodium borohydride followed by acidification (HCl) to adjust pH 3 gave crude IIf which

Table 1

compound	characteristic IR absorption (cm^{-1})	^{1}H NMR absorption solvent	δ, ppm[a] (No. of protons)
IIa	1580, 1480, 1440	DMSO-d_6	7.24(10), 4.90(7), 3.3(42)
IIb	2100, 1300	D_2O	5.13(7), 3.8(42)
IIc	1510, 1450, 1380	D_2O	5.13(7), 3.9(38), 3.00(4)
IId	1590, 1355, 1180, 810	D_2O	5.17(7), 3.9(38), 3.00(12)[b], 1.2(12)
IIe	1490, 1410, 1180	D_2O	5.20(7), 4.0(42)
IIf	1380, 1300	D_2O	5.20(7), 3.9(38), 3.15(4)
IIg	1565, 1490, 1220	D_2O	5.20(7), 3.8(38), 2.9(12)[c]

a) The center of the broad absorption. b) Superposition of the absorptions of all protons α to N. c) Superposition of the absorptions of all protons α to S and N.

was separated through Sephadex column. Eluent containing practically pure IIf was condensed to 1 ml and precipitated by the addition of trichlorethylene. Spectral characteristics of these disubstituted β-cyclodextrins are listed in Table 1.

In literature, only a few disubstituted cyclodextrins[3] are reported, the structure, of which are not clearly described, although a plenty of well-defined monosubstituted cyclodextrins[1a,3,4] are known. The present procedure of the bifunctionalization of cyclodextrins would afford a very ready and general procedure to prepare any specifically disubstituted cyclodextrin.

References

1) For examples; (a) N.Hennrich and F.Cramer, J.Amer.Chem.Soc., 87, 1121(1965); (b) R.L.Van Etten, J.F.Sebastian, G.A.Clowes, and M.L.Bender, ibid., 89, 3242(1967); (c) R.Breslow and P.Campbell, ibid., 91, 3085(1969); (d) W.J.James and D.French, Proc.Iowa Acad.Sci., 59, 197(1952), H.von Dietrich and F.Cramer, Chem.Ber., 87, 806(1954)

2) I.Tabushi, K.Shimokawa, N.Shimizu, H.Shirakata, and K.Fujita, J.Amer.Chem.Soc., 98, 7855(1976)

3) (a) F.Cramer and G.Mackensen, Angew.Chem., 78, 641(1966) and Chem.Ber., 103, 2138(1970); (b) J.F.Kennedy and H.Cho.Tun, Carbohyd.Res., 26, 401(1973)

4) (a) F.Cramer and G.Mackensen, Chem.Ber., 103, 2138(1970); (b) L.D.Melton and K.N.Slessor, Carbohyd.Res., 18, 29(1971); (c) R.Breslow and L.Overman, J.Amer.Chem.Soc., 92, 1075(1970); (d) A.R.Gibson, L.D.Melton, and K.N.Slesson, Can.J.Chem., 52, 3905(1974)