SYNTHESIS OF NUCLEIC ACID BASE FUNCTIONALIZED β-CYCLODEXTRINS: THE NUCLEOSIDE ANALOGUE

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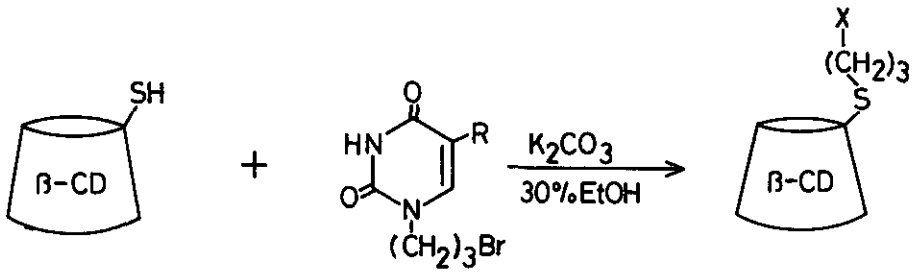
Abstract - The β-cyclodextrins functionalized with the nitrogen-bases of nucleic acid such as thymine, uracil, cytosine, and adenine by a flexible polymethylene bridge have been synthesized and their structures were determined on the basis of the spectroscopic data.

Cyclodextrins (CDs) are known to show in many reactions the enzyme-like activities such as the reaction rate enhancement, stereoselection, regioselection, and enantioselection.[1] These are due to their characteristic ability of formation of inclusion complexes with various compounds. However, it is still needed to synthesize the more effective enzyme models by chemical modifications of the CDs. Their catalytic activities are sometimes remarkably improved by modifying the hydroxyl groups of CDs with the suitable functional groups.[2,3] Since the method of a selective tosylation of the different hydroxyl groups of CDs had been developed,[4-7] a variety of enzyme models have been synthesized from the appropriate CD-tosylates.

Considering the enormous biological importance of nucleosides, it seems to be interesting to prepare and investigate the properties of the CDs which are functionalized with the nitrogen-bases of nucleic acid, a good model of nucleoside. To the best of our knowledge, however, there have been no reports on the chemical modifications of CDs with such nitrogen-bases. We now report the preparation of the β-CD derivatives attached to the nitrogen-bases by a flexible polymethylene bridge. The synthesis is based on the nucleophilic substitution reaction of the halogenoalkylated nitrogen-bases and β-CD monothiol as shown in Scheme I. The 1-bromopropyl-2-pyrimidinones, IIa,b and III, were prepared from the corresponding pyrimidine bases (thymine, uracil, and cytosine) in 20-60% yields via silylation with

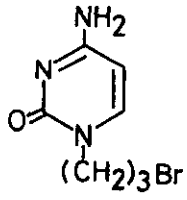
Scheme I



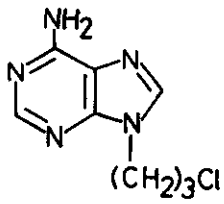
Ia

IIa. R=CH3
b. R=H

Va. X=Thy
b. X=Ur
c. X=Cyt
d. X=Ad



III



IV

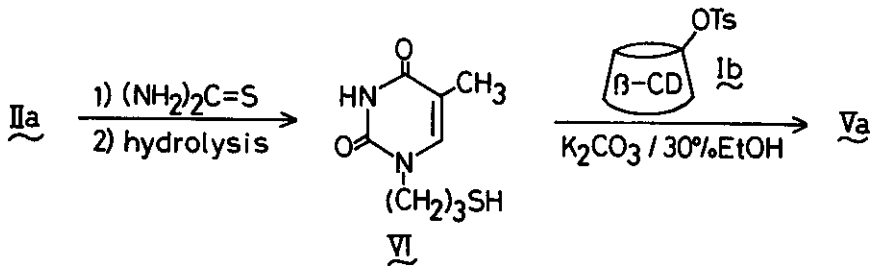
Me_3SiCl/Et_3N and alkylation with 1,3-dibromopropane.[8] 6-Amino-9-chloropropylpurine (IV) was prepared by the reaction of sodium adenide and 1-bromo-3-chloropropane in 70% yield.[9] A solution of 100 mg of IIa and 260 mg of 6-deoxy-6-mercapto-β-CD (Ia)[10] in aqueous 30% EtOH in the presence of K_2CO_3 was stirred at room temperature under nitrogen for 7 days. After removal of the solvent the residue was dissolved in water and reprecipitated by addition of trichloroethylene. Recrystallization of the precipitate from H_2O-MeOH gave 60 mg (23%) of Va as a colorless powder, mp 282-288 °C (decomp); Anal. Calcd for $C_{50}H_{80}N_2O_{36}S \cdot 9H_2O$, C,40.60; H, 6.61; N, 1.89. Found: C, 40.64; H, 6.68; N, 1.61. Silica gel tlc eluted with water-propanol-ethyl acetate-aq NH_4OH (3:5:1:1) shows a single round spot at R_f 0.38. The IR and ^1H NMR spectra (Table 1) show the presence of both β-CD and thymine moieties. The UV spectrum of Va exhibits very similar absorptions to those of IIa and β-CD-IIa inclusion complexes (1:1). Similar reactions of IIb, III, and IV with the CD-thiol Ia afforded Vb (38%), Vc (20%), and Vd (27%), respectively. Spectral characteristics of these β-CD derivatives are listed in Table 1. As an alternative way for the preparation of Va, the bromide IIa was first treated

Table 1

Compound	m.p.	IR(cm^{-1})	^{1}H-NMR(ppm[a], D_2O)	UV $\lambda_{max}^{H_2O}$ nm (ε)
Va	282-288°C (decomp.)	3400 1690 (C=O) 1670 (C=O) 1640 1160	1.83(5H, Thy-CH_3, -CH_2-), 2.52(2H, -SCH_2-), 2.90(2H, CD-CH_2S-), 3.20-4.10(42H, CD C_2-C_6H, -NCH_2-), 4.96(7H, CD C_1H), 7.27(1H, Thy-C_6H)	273(2.4×10^3)
Vb[c]	240-249°C (decomp.)	3400 1690 (C=O) 1675 (C=O) 1640 1160	1.84(2H, -CH_2-), 2.49(2H, -SCH_2-), 2.91(2H, CD-CH_2S-), 3.20-4.00(42H, CD C_2-C_6H, -NCH_2-), 4.93(7H, CD C_1H), 5.71(d, 1H, Ur-C_5H, J=7.7 Hz), 7.45(d, 1H, Ur-C_6H, J=7.7 Hz)	266(2.18×10^3)
Vc[d]	231-239°C (decomp.)	3400 1665 (C=O) 1640 1160	[b] 2.08(2H, -CH_2-), 2.60(2H, -SCH_2-), 2.96(2H, CD-CH_2S-), 3.10-4.05(42H, CD C_2-C_6H, -NCH_2-), 4.80(7H, CD C_1H), 5.50(d, 1H, Cyt-C_5H, J=7.5 Hz), 7.40(d, 1H, Cyt-C_6H, J=7.5 Hz)	276(2.53×10^3)
Vd[e]	270-278°C (decomp.)	3400 1640 1160	2.22(4H, -CH_2-, -SCH_2-), 2.85(2H, CD-CH_2S-), 3.05-4.02(42H, CD C_2-C_6H, -NCH_2-), 4.90(7H, CD C_1H), 7.96, 8.15 (2s, 2H, Ade-C_2H, C_8H)	263(4.47×10^3)

a) The center of the broad absorption. b) in DMSO-d_6+D_2O c) Anal. Calcd for $C_{49}H_{78}N_2O_{36}S\cdot10H_2O$, C, 39.68; H, 6.68; N, 1.89. Found: C, 39.66; H, 6.68; N,1.69. d) Anal. Calcd for $C_{49}H_{79}N_3O_{35}S\cdot4H_2O$, C, 42.80; H, 6.45; N, 3.06. Found: C, 42.61; H, 6.58; N, 3.41. e) Anal. Calcd for $C_{50}H_{79}N_5O_{34}S\cdot8H_2O$, C, 41.10; H, 6.43 N, 4.71. Found: C, 41.04; H, 6.37, N, 4.75.

Scheme II



with thiourea to give the corresponding thiol VI in 77% yield, which was easily purified by a silica gel chromatography (Scheme II). This thiol was allowed to react with 6-O-tosyl-β-CD (Ib)[6] in aqueous 30% EtOH in the presence of K_2CO_3 at room temperature. The similar work-up afforded the practically pure product without recrystallization, which was identical with the above-mentioned Va in all aspects. This route turned out to be much advantageous over the former one due to the high yield of product, easy purification, and the potential applicability to the multi-functionalization of CDs.

Further studies on the chemical reactivity of these water-soluble products as well as the double-functionalization of CDs using the ion-pairing of the nitrogen-bases are currently under way.

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