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Cyclodextrin-Containing Polymers. 1. Preparation of Polymers

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ABSTRACT: The synthesis of polymers containing cyclodextrin residues on the side chain is described. Four monofunctional monomers, acryloyl-α-cyclodextrin (α-CD-A), acryloyl-β-cyclodextrin (β-CD-A), *N*-acrylyl-6-aminocaproyl-α-cyclodextrin (α-CD-NAC), and *N*-acrylyl-6-aminocaproyl-β-cyclodextrin (β-CD-NAC), were prepared by the reaction of *m*-nitrophenyl acrylate or its derivative and cyclodextrin. Acryloyl and *N*-acrylyl-6-aminocaproyl groups were found to be attached at one of the secondary hydroxyl groups of cyclodextrin. These monomers were polymerized in high yields except α-CD-A by a radical initiator to give water soluble polymers, which were purified by gel chromatography or dialysis. These monomers were also copolymerized with other water soluble monomers to give water soluble copolymers.

Cyclodextrins (cycloamyloses which are cyclic α-1,4-linked D-glucose oligomers[1]) display various characteristic chemical and physical properties[2] due to their cyclic nature when compared to the flexible open-chain analogues. The most specific property is their ability to form inclusion complexes in aqueous solution[3] as well as in the crystalline state.[4] The inclusion properties of cyclodextrins have been studied extensively to clarify the nature of the cavity, i.e., the driving force[5] for binding and the binding specificity. Cyclodextrins have also been studied as an enzyme model,[6] the results having disclosed the substrate specificities in the binding step as well as in the catalytic step based on the size of their hydrophobic cavities.

In order to obtain polymers equipped with substrate specificity caused by inclusion, it seems advantageous to study the behavior of cyclodextrins when incorporated into a polymer as a definite structural unit. In this paper we wish to report the preparation of cyclodextrin-containing polymers. To obtain linear polymers, it is necessary to prepare monovinyl derivatives of cyclodextrin. Since cyclodextrin has many primary and secondary hydroxyl groups, we used Bender's acylation technique,[6f] in which the reaction proceeds by way of inclusion and the acylation occurs selectively at one of the secondary hydroxyl groups under mild conditions.

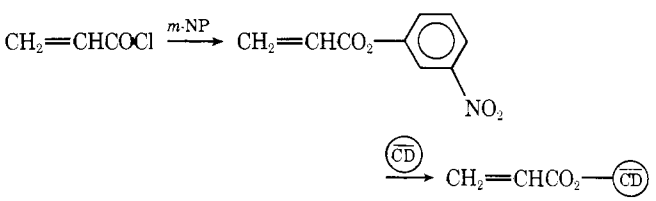
Results and Discussion

Preparation of Monomers. Cyclodextrin-containing monomers were newly synthesized by the reactions shown in Scheme I. The main feature of this synthesis is the reaction of *m*-nitrophenyl esters and cyclodextrins. This procedure, first found by Bender et al.,[6f] was used because this reaction proceeds by way of inclusion, which would permit selective transesterification of cyclodextrin at one of the secondary hydroxyl groups under mild conditions, minimize multifunctional products, and suppress thermal polymerization.

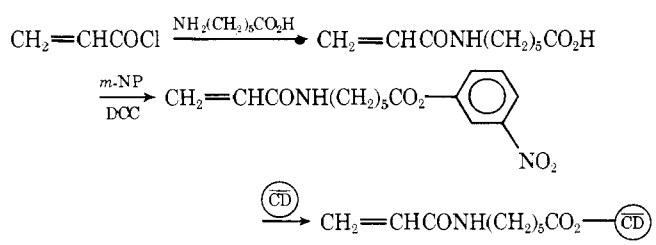
In a typical synthesis, cyclodextrin was allowed to react with an equimolecular amount of *m*-nitrophenyl ester in carbonate buffer, pH 11, at room temperature for 5 min. The product was purified by gel chromatography on a Sephadex G-15 column[7] and, if necessary, was subjected to ultrafiltration using an Amicon UM-05 UF-membrane to remove sodium chloride. In the case of β-cyclodextrin monomers, final purification was carried out by a Sephadex G-15 column (2.5 × 200 cm). Elution diagrams were obtained by following cyclodextrin and monomer concentrations as shown in Figure 1. Small amounts of multifunctional products with higher extinction coefficients were eluted at the beginning of the main fraction. The extent of the reaction was limited by solubilities of the reactants to about 40% and the yield of the pure monomer was about 20%. All monomers except α-CD-A were chromatographically pure, giving satisfactory results in the elemental analysis as monofunctional products. α-CD-A was found to contain a small

Scheme I

Acryloyl cyclodextrin (CD-A)



N-Acrylyl-6-aminocaproylcyclodextrin (CD-NAC)



m-NP = *m*-nitrophenol;

(CD) = α- or β-cyclodextrin (mol wt 973 or 1135)

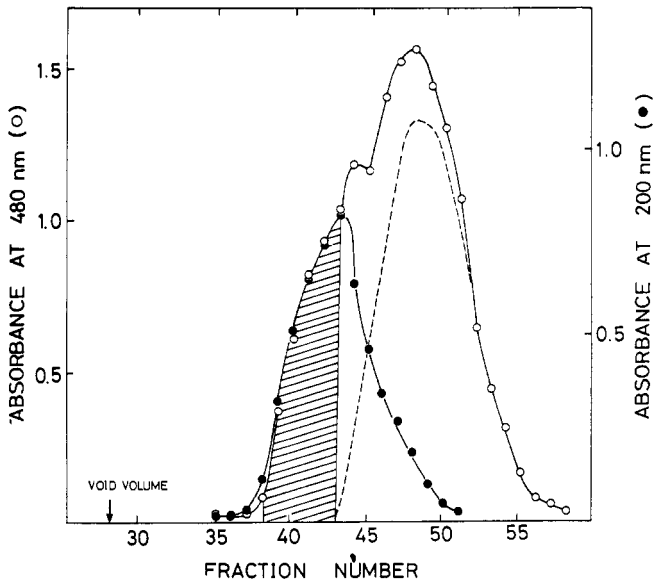


Figure 1. Purification of α-CD-NAC by gel chromatography on Sephadex G-15 column (2.5 × 90 cm). Fractions of 5 ml of effluent were collected: (●) absorbance at 200 nm, which indicates the α-CD-NAC concentration; (○) absorbance at 480 nm in the phenol–sulfuric acid method, which indicates total sugar content. The broken line shows the difference of two curves, which corresponds to the unreacted α-CD concentration. The fractions indicated by the shaded area, which corresponds to pure α-CD-NAC, were collected.

amount of α-CD as detected by paper chromatography and iodine test. Results of the monomer characterization are summarized in Table I.

The acyl substitution was reported to occur at secondary hydroxyl groups by the study of the reactivity of partially protected cyclodextrins.[6f] However, there was no direct evidence for the substitution position. ^{13}C NMR[8] was studied and the spectra in Figure 2 clearly show that the acylation had occurred at C-2 and C-3 positions at almost the same ratio in the cases of β-CD-A and β-CD-NAC, at the C-3 position selectively in the case of α-CD-A, and at mostly C-3 but in part C-2 for α-CD-NAC. The changes of the chemical shift due to the acyl substitution on a glucose ring were reasonable;[8b] in the case of β-CD monomer two peaks for the acrylyl carbons attached at C-2 and C-3 positions were clearly observed. The difference of the substitution positions between α-CD and β-CD might relfect tightness of inclusion[6a] of *m*-nitrophenyl esters, i.e., α-CD might bind the substrate more tightly than β-CD, thereby "freezing" the esters in favorable positions for the selective acylation at the C-3 hydroxyl group.

Polymerization. The monomers were polymerized in aqueous methanol solutions using 2,2′-azobis(isobutyronitrile) as an initiator at 60 °C for 20–43 h. All the polymerization in H_2O–MeOH (1:1) proceeded in homogeneous solution and gave water soluble polymers in 59–82% yields except α-CD-A, which gave a poor conversion of 8%. The low conversion of α-CD-A might be due to the position of the acryloyl group, which was attached at the C-3 hydroxyl group. In 95% MeOH the polymers were precipitated as the polymerization proceeded. α-CD-A and β-CD-A were copolymerized with other water soluble monomers, such as acrylamide, acrylic acid, and vinyl pyrrolidone, to give water soluble polymers in high yields. The results of the polymerization are shown in Tables II and III.

The polymers were purified by gel chromatography on Sephadex G-15. The polymers were eluted at the void volume and were completely separated from unreacted monomer and initiator as shown in Figure 3. Purification by dialysis was also effective. The polymers obtained were characterized by the infrared spectra, ultraviolet spectra, and elemental analysis. The ir and uv spectra clearly indicated the disappearance of vinyl groups.

To estimate the molecular size of the poly-β-CD-A, a GPC study of the polymer solution was carried out on Sephadex G-50 (fractionation range of dextran, 500–10 000), G-100 (1 000–100 000), and Biogel P-2 (200–2 600), P-10 (5 000–17 000). In the case of Sephadex G-50 and Biogel P-2, the polymer was completely excluded from these gel phases. In the case of Biogel P-10 most of the polymer was also eluted at the void volume but some tailing was observed. The polymer showed a wide distribution curve in the case of Sephadex G-100. From these results the molecular weight of poly-β-CD-A was estimated to be 10^4–10^5. The molecular weight was also estimated by a vapor pressure osmometer to be 10^4.

When these polymers were hydrolyzed in aqueous alkali, cyclodextrins were detected by GPC on Sephadex G-15[9] and TLC.[10] We did not prove the polyvinyl structure but it was reasonably supposed from the following evidence: the monomers copolymerize with acrylic acid and with acrylamide with nearly comparable relative reactivities and *N*-methacryloyl-D-glucosamine was similarly known to undergo vinyl polymerization.[11]

Experimental Section

Cyclodextrins were obtained from Hayashibara Biochemical Laboratory Inc. β-Cyclodextrin was recrystallized from water and dried in vacuo at 80 °C for 24 h. α-Cyclodextrin was recrystallized first from 50% 1-propanol–water and then from water and was dried in vacuo. Their purities were checked by elemental analysis, optical rotation and TLC.[10]

***m*-Nitrophenyl acrylate**[12] was prepared by adding 10 g of acrylyl chloride dropwise to a solution of 5 g of potassium hydroxide and 7 g of *m*-nitrophenol in 500 ml of water at 0 °C. It was recrystallized from ether, mp 34 °C (yield 70%).

Acryloyl-β-cyclodextrin (β-CD-A). β-Cyclodextrin (2.0 g, 1.75

Table I
Cyclodextrin-Containing Monomers

Monomer	R_f value[a]	$[\alpha]^{25}D$,[b] deg	Spectral data: Ir (KBr) $\nu_{C=C}$, cm^{-1}	Ir (KBr) $\nu_{C=O}$, cm^{-1}	Uv (H_2O) λ_{max}, nm	ϵ
α-CD-A	0.35	+145	1635	1725	197	9 350
α-CD-NAC	0.56	+131	1625	1660, 1725	200	13 000
β-CD-A	0.36	+159	1635	1725	198	12 000
β-CD-NAC	0.48	+149	1620	1660, 1725	200	13 000

[a] Descending paper chromatography. Solvent, *n*-BuOH–DMF–H_2O in 2:1:1 (v/v/v). R_f for α-CD = 0.26, R_f for β-CD = 0.20. [b] *c* = 1 g/dl in water, $[\alpha]^{25}D$ for α-CD = +150°, $[\alpha]^{25}D$ for β-CD = +162°.

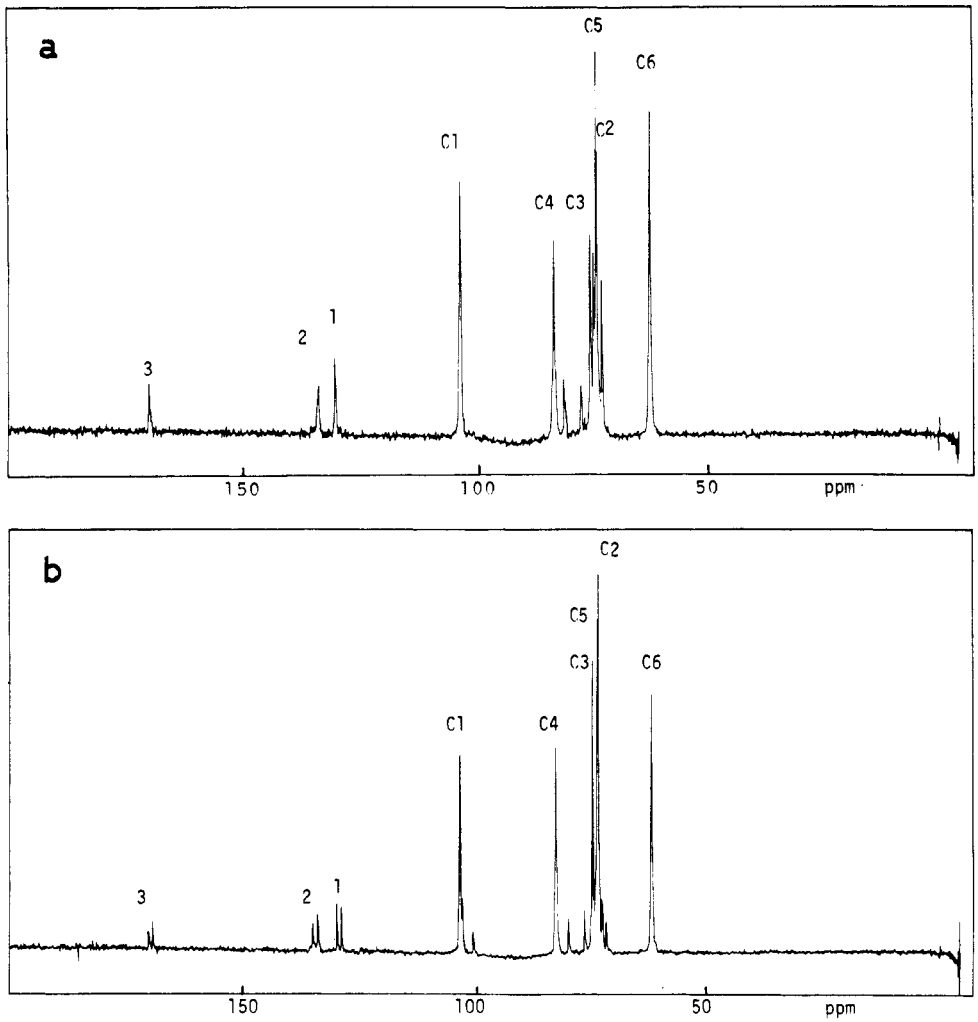
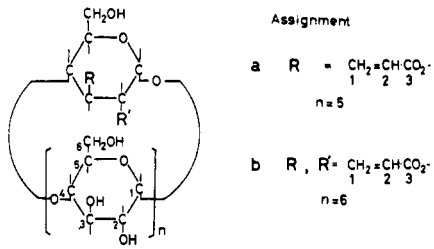


Figure 2. Carbon-13 NMR spectra of cyclodextrin-containing monomer in D_2O. D, external dioxane. (a) α-CD-A (10^{-1} M), 140 000 accumulations (b) β-CD-A (5×10^{-2} M), 131 000 accumulations.



mmol) was dissolved in 120 ml of carbonate buffer, pH 11, and was mixed all at once with 4 ml of acetonitrile solution of *m*-nitrophenyl acrylate (0.338 g, 1.75 mmol). The reaction mixture was shaken vigorously for 5 min, brought to pH 3 with dilute HCl and cooled in an ice bath. The unreacted acrylate crystallized out and was filtered off. The resulting filtrate was subjected to gel chromatography on a Sephadex G-15 column (5 × 100 cm) with water to leave *m*-nitrophenol in the column. The eluate containing monomer, unreacted β-CD, and sodium chloride were subjected to ultrafiltration using an Amicon UM-05 UF-membrane to remove sodium chloride. Then the resulting residue was subjected to gel chromatography on Sephadex G-15 (2.5 × 200 cm) to obtain pure acryloyl-β-cyclodextrin (β-CD-A). Elution was followed by measuring the cyclodextrin concentration using the phenol–sulfuric acid method[13] and the monomer concentration from the absorbance at 200 nm. Small amounts of multifunctional products with higher extinction coefficients were eluted with the beginning of the main fraction. The extent of the reaction was about 40% and the yield of the pure monomer was about 15%. Anal. Calcd for $C_{45}H_{72}O_{36}$: C, 45.46; H, 6.10. Found: C, 45.45; H, 6.10.

Acryloyl-α-cyclodextrin (α-CD-A) was prepared from α-cyclodextrin and *m*-nitrophenyl acrylate by a procedure similar to that described for β-CD-A. α-CD-A was completely separated from *m*-nitrophenol and sodium chloride by gel chromatography on Sephadex G-15. The ultrafiltration process was unnecessary. The conversion was about 40% and the yield was about 20%. Anal. Calcd for $C_{39}H_{62}O_{31}$: C, 45.61; H, 6.09. Found: C, 44.79; H, 6.04.

***N*-Acrylyl-6-aminocaproic acid (NAC)**[14] was prepared by adding dropwise 4.5 g of acrylyl chloride and 10 ml of 20% NaOH aqueous solution simultaneously to a solution of 6.55 g (0.05 mol) of 6-aminocaproic acid and 2 g of NaOH in 20 ml of water at 0 °C and then acidified by 1 N HCl. The precipitate was filtered and recrystallized from acetone–ether: mp 96–98 °C, yield 80%.

***m*-Nitrophenyl *N*-Acrylyl-6-aminocaproate.** *N*-Acrylyl-6-aminocaproic acid (3.7 g, 0.02 mol) and *m*-nitrophenol (3.0 g, 0.022 mol) were dissolved in 100 ml of dry ethyl acetate. The mixture was cooled to 0 °C and dicyclohexylcarbodiimide (DCC)[15] (4.12 g, 0.02 mol) was added. The mixture was kept at 0 °C for 30 min and then at room temperature overnight. Dicyclohexylurea was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized twice from acetone–ether: mp 70–72 °C, yield 72%. Anal. Calcd for $C_{15}H_{18}O_5N_2$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.88; H, 6.13; N, 9.20.

***N*-Acrylyl-6-aminocaproyl-β-cyclodextrin (β-CD-NAC)** was prepared from β-cyclodextrin and *m*-nitrophenyl *N*-acrylyl-6-aminocaproate by a procedure similar to that described for β-CD-A.[16] The final purification was carried out by gel chromatography on Sephadex

Table II
Polymerization of α-CD-A and α-CD-NAC[a]

No.	Monomer	Comonomer	Mol ratio of α-CD-A:comonomer	Solvent	Time, h	Yield, %	$\bar{M}_n$[b]
1	α-CD-NAC			95% MeOH	24	59	8 000
2	α-CD-NAC			MeOH–H_2O	43	75	10 000
3	α-CD-A			MeOH–H_2O	24	8	
4	α-CD-A	Acrylamide	1:2.5	95% MeOH	24	80	
5	α-CD-A	Acrylic acid	1:9	MeOH–H_2O	24	63	
6	α-CD-A	*N*-Vinyl Pyrrolidone	1:5	MeOH–H_2O	24	11	

[a] AIBN, 60°. [b] VPO method at 37°.

Table III
Polymerization of β-CD-A and β-CD-NAC[a]

No.	Monomer	Comonomer	Mol ratio of β-CD-A:comonomer	Solvent	Time, h	Yield, %	$\bar{M}_n$[b]
1	β-CD-NAC			MeOH	20	77	
2	β-CD-NAC			MeOH–H_2O	24	79	
3	β-CD-A			MeOH–H_2O	24	82	10 000
4	β-CD-A	Acrylamide	1:5.3	MeOH–H_2O	24	90	
5	β-CD-A	Acrylic acid	1:6.7	MeOH–H_2O	20	80	

[a] AIBN, 60°. [b] VPO method at 37°.

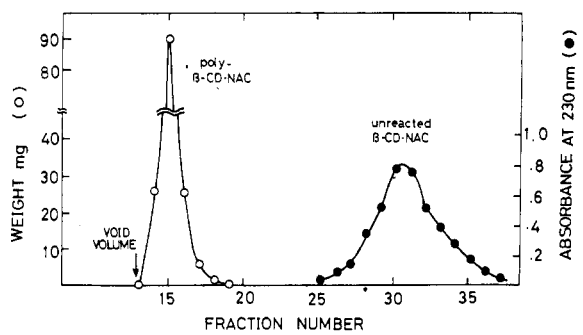


Figure 3. Purification of poly-β-CD-NAC by gel chromatography on Sephadex G-15 (2.5 × 90 cm). Fractions of 10 ml of effluent were collected: (○) weight after freeze drying; (●) absorbance at 230 nm.

G-15 (2.5 × 200 cm). The elution diagram showed two peaks, which corresponded to β-CD-NAC and β-CD. Extent of the reaction was about 40% and the yield of the pure monomer was about 20%. Anal. Calcd for $C_{51}H_{83}O_{37}N$: C, 47.04; H, 6.42; N, 1.08. Found: C, 46.46; H, 6.50; N, 1.02.

***N*-Acrylyl-6-aminocaproyl-α-cyclodextrin (α-CD-NAC)** was prepared by a similar method to that of β-CD-A. Conversion was about 40% and the yield was about 20%. Anal. Calcd for $C_{45}H_{73}O_{32}N$: C, 47.41; H, 6.45. Found: C, 47.41; H, 6.61.

Polymerization. An aqueous methanolic solution of an appropriate amount of monomer and 2,2′-azobis(isobutyronitrile) was thoroughly degassed on vacuum line, and the ampule was sealed off and heated for 24–48 h at 60 °C. After polymerization, the solvent was removed by evaporation and the residue was dissolved in a minimum amount of water and chromatographed on Sephadex G-15. The elution diagrams showed that the polymers were eluted in the void volume and were completely separated from unreacted monomer and initiator. The molecular weights of the polymers were determined using a Mechrolab Model 301 A vapor pressure osmometer with sucrose as a standard in water at 37 °C.

Apparatus. Ultraviolet spectroscopic measurements were made using a Hitachi Spectrophotometer, Model 124. Infrared spectra were measured as KBr disks using a Hitachi, EDI-2 Spectrometer. Optical rotations were measured in a JASCO polarimeter. ^{13}C NMR spectra were recorded in a Varian Associates, Model XL 100, spectrometer operated in the puls-Foulier transform mode.

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