

STUDIES ON THE POLYMERIZATION OF β -CYCLODEXTRIN WITH EPICHLOROHYDRIN *

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ABSTRACT

Different proportions of β -cyclodextrin and epichlorohydrin were used to prepare a group of β -cyclodextrin polymers. The relationship between the reaction extent and the molar ratios of reactants was discussed according to the results of ^1H -NMR, ^{13}C -NMR spectra and elemental analysis. Especially, high resolution ^1H -NMR spectra were used for studying the reaction active sites and the extent of reaction. The solubility of oil soluble drugs in water was largely improved in the presence of water-soluble β -cyclodextrin polymer.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligomers of α -(1, 4)-linked D(+)-glucopyranose. The three simplest oligomers are: α -CD, β -CD, γ -CD which contain 6, 7, 8 D(+)-glucopyranose units respectively. They have shape of trunklike cones with the primary hydroxyls of C(6) on their narrow sides and the secondary hydroxyls of C(2) and C(3) on the wide sides. Because of the different size and hydrophobicity of the cavity, CDs are able to form inclusion complexes with a variety of organic molecules and ions in solid or liquid state. Thus, CDs have been widely utilized for stabilization, solubilization, and formulation of drugs, pesticides, flavoring substances and also for enzyme modeling and catalysts, etc. ^[1, 2, 3] Among the three CDs, β -CD is easily obtained, but owing to its relatively low solubility (1.84g/100 ml water, at room temp.), its applications are limited.

A series of water-soluble and cross linked β -CD polymers have been prepared by the reaction of β -CD with epichlorohydrin in an alkaline medium under different reaction conditions. the water-soluble β -CD polymers can be used for dissolving water-insoluble dyes in the photochemical industry ^[4], to enhance the bioavailability of orally administered drugs ^[5] and to reduce the lipophilicity of components in reversed-phase thin-layer chromatography (RPTLC) ^[6] etc. The crosslinked β -CD polymers can be used for chiral stationary phase in HPLC, GLC and LC to separate structural, geometric and optical isomers.

A series of β -CD polymers were synthesized by changing the molar ratios of β -CD to epichlorohydrin. The reaction sites in β -CD and the reaction extent of β -CD with epichlorohydrin were studied by NMR spectra and elemental analysis.

EXPERIMENTAL

Materials

(1) β -CD (>95%) used was recrystallized in water and filtrated, washed 3 times with acetone and then dried in vacuum for 6 h. at 100 °C .

(2) NaBH₄, NaOH, acetone and epichlorohydrin were of analytical grade. Epichlorohydrin was redistilled prior to use. Paraffin oil was of CP grade.

(3) Preparation of water-soluble β -CD polymers

The molar ratios of β -CD with epichlorohydrin were : 1:1, 1:2, 1:3 respectively. The reactions were carried out in NaOH aqueous solution containing small amount of NaBH₄ at 50 °C for 3 h. The products were neutralized with hydrochloric acid to PH=7 and purified by membrane separation process (only molecules with average-molecular-weight less than 3000 can pass through the membrane used). The reaction mixture was precipitated, extracted with acetone for 10 h, and then dried in vacuum at 96 °C for 4 h. The water-soluble β -CD polymer were obtained.

(4) Preparation of crosslinked β -CD polymers

The crosslinked β -CD polymers were prepared by the reactions of β -CD with epichlorohydrin with reactant molar ratios 1:5, 1:8, 1:10, 1:12, 1:15 according to the modified procedure of Hoffman^[7]. After prepolymerization of β -CD with epichlorohydrin (molar ratio 1:2) in NaOH aqueous solution containing small amount of NaBH₄ for 15 min. at 50 °C, a definite amount of paraffin oil was added to the reaction mixture to form a dispersion solution. The rest epichlorohydrin was continuously dropped into the reaction system with vigorous stirring and the reaction was kept in paraffin oil with stirring for 2.5 hrs. at 50 °C. The products were extracted with acetone and dried in vacuum. The crosslinked β -CD polymers were colourless bead-form resins.

(5) Improvement of water solubility for oil soluble Ftorafurum

A kind of water-soluble β -CD polymer was chosen as solubilizing agent to observe its effects on the solubility of the anticancer drug, Ftorafurum, in water. The results are excellent.

RESULTS AND DISCUSSION

1. Polymerization of β -CD with epichlorohydrin in different reactant molar ratios

One mole β -CD contains twenty-one hydroxyls which could partly react with epichlorohydrin. The new hydroxyls produced during the reaction could further react with epichlorohydrin. Therefore, the more epichlorohydrin presents in the reactants, the more active groups in the reaction system would be involved within a certain ratios. A variety of β -CD polymers from water-soluble to crosslinked forms could be prepared by using suitable molar ratios of β -CD and epichlorohydrin and at the same time by controlling the reaction degree. The different polymers are listed in Table 1.

Table 1 The different polymers prepared

Sample	P-1	P-2	P-3	P-4	P-5	P-6
Molar ratios *	1:1	1:2	1:3	1:5	1:8	1:10

* β -CD /epichlorohydrin

The results of elemental analysis of water-soluble polymer P-1, P-2, P-3 are given in Table 2.

Table 2 The results of elemental analysis of polymers P-1, P-2, P-3

No.	P-1		P-2		P-3	
	C(%)	H(%)	C(%)	H(%)	C(%)	H(%)
Calc. **	45.38	6.26	46.22	6.30	47.00	6.34
Found	44.89	6.60	45.80	6.67	46.23	6.85

** Calculated on the basis of the polymer structure unit formed by complete polymerization of β -CD with epichlorohydrin

These data indicated that epichlorohydrin reacted almost completely with β -CD in accordance to the original reactant ratios. The molecular weights were measured by VPO method. The range of molecular weight for P-1, P-2, P-3 was 4000—5000.

2. ^1H -NMR and ^{13}C -NMR spectra of β -CD and polymers P-1, P-2, P-3

^1H -NMR spectra of β -CD and β -CD polymers P-1, P-2, P-3 are shown in Fig. 1. The reaction extent and the active sites of β -CD can be determined according to the changes of the peaks of different hydroxyls-protons on the sugar skeleton. There are four kinds of protons corresponding to the four groups of proton-peaks

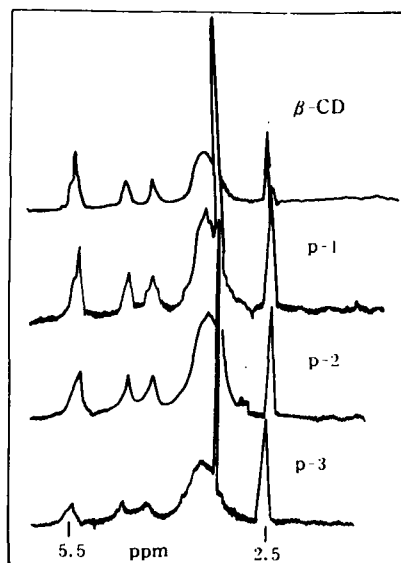


Fig. 1 ^1H -NMR spectra of β -CD and P-1, P-2, P-3 (EM-360L, 60MHz, NMR spectrometer, ref. TMS)

in ^1H -NMR spectrum of β -CD. The peaks at 5.5 ppm and 4.4 ppm disappeared when D_2O was added, so the peaks at 5.5 ppm are the resonance of hydroxyl-proton of C(2), C(3) on sugar skeleton due to the hydrogen bond between $\text{HO}-\text{C}(2)$ and $\text{HO}-\text{C}(3)$ and the peaks at 4.4 are the resonance of hydroxyl-proton of C(6)

on sugar skeleton. The chemical shifts of different protons of β -CD are given in Table 3.

Table 3 The chemical shifts of protons for β -CD

Chemical environment	C (2,3) - OH ^a	C (1) - H ^b	C (6) - OH ^c	C (2,3,4,5,6,6) - H ^d
No. of protons	14	7	7	42
Chemical shifts	5.5ppm	4.7ppm	4.4ppm	3.3—3.4ppm

By comparison of ^1H -NMR spectra of β -CD with that of polymers P-1, P-2, P-3, we found that the integral heights of H^c remained almost the same to H^b and that of H^a gradually decreased relatively to H^b with the increase of epichlorohydrin proportion in the reaction mixture. These results also indicated that the extent of reaction increased continuously with the increase of epichlorohydrin added into the reaction system. The reaction sites in β -CD under alkaline condition were on the secondary C (2) and C (3) hydroxyls.

The chemical shifts of different carbons on sugar skeleton in ^{13}C -NMR spectra of β -CD and β -CD polymer P-3 (in D_2O) are listed in Table 4.

Table 4 The chemical shifts of carbons for β -CD and polymer P-3

Compound	Solvent	C (1)	C (2)	C (3)	C (4)	C (5)	C (6)
β -CD	D_2O	102.73	72.79	74.03	81.90	72.79	60.96
P-3	D_2O	102.72	71.35	73.96	81.86	72.82	60.95

From the above results, the HO - C (6) was not involved in the reaction because of the same chemical shift of C (6) of ^{13}C -NMR spectra of β -CD and polymer P-3.

3. High resolution ^1H -NMR spectra of polymers P-4, P-5, P-6

^1H -NMR and ^{13}C -NMR spectra of β -CD and its derivatives have been reported. We further studied the characteristics of the reactions by the high resolution ^1H -NMR spectra. Figs. 2 and 3 show the high resolution ^1H -NMR spectra of β -CD, polymers P-1, P-3 and ^1H -NMR spectra of polymers P-4, P-5, P-6, performed on the same apparatus respectively.

The peaks at 4.8ppm are the peaks of solvent (D_2O) and the data indicated in the spectra are the areas of each group peaks. Obviously, the resonance of H - C (1) appears at 5.06ppm, while the signal for H - C (2,4) appears at 3.5 - 3.7 ppm, and the signal for H - C (3,5,6,6) at 3.75 - 4.05 ppm. The H - C peaks from -OCH₂ - produced by the reaction of β -CD with epichlorohydrin were

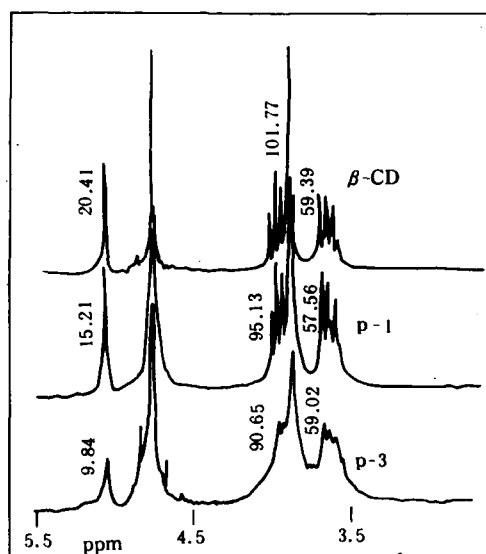


Fig. 2 ^1H -NMR spectra of β -CD and polymers P-1, P-3 (MSL-300, 300MHz, NMR spectrometer, ref. DSS)

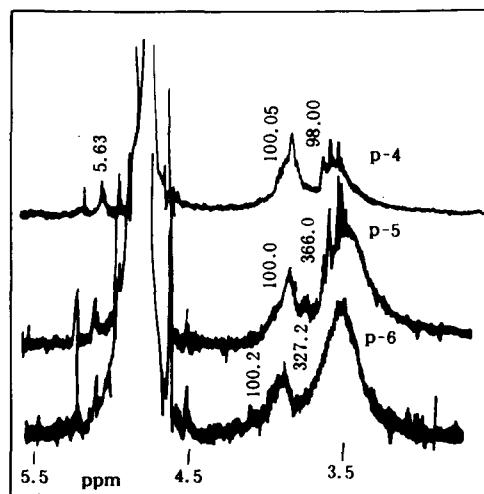


Fig. 3 High resolution ^1H -NMR spectra of polymers P-4, P-5, P-6

overlapped with H-C (2, 4) peaks at 3.5 – 3.7ppm. With increasing amounts of epichlorohydrin, the ratios of peak area at 3.5 – 3.7ppm to that at 3.75 – 4.05ppm were increased. The peak area ratios of the peaks at 3.5 – 3.7 ppm and at 3.75 – 4.05 ppm are shown in Table 5.

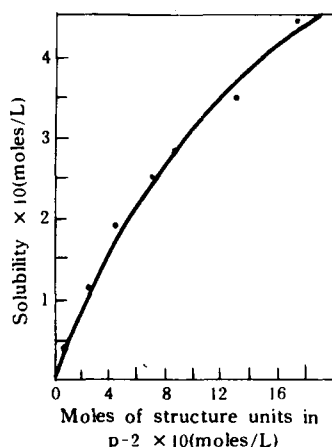
Table 5 The peak area ratios of the peaks at 3.5 – 3.7ppm and 3.75 – 4.05ppm

Compound	β -CD	P-1	P-3	P-4	P-5	P-6
Area ratios	0.58	0.61	0.65	0.98	3.66	3.27

The results of the high resolution ^1H -NMR spectra exhibited that the reaction extent of β -CD with epichlorohydrin raised with the increase of epichlorohydrin in the reactants. When the molar ratio (β -CD/epichlorohydrin) was 1 : 8 , the reaction extent reached approximately the maximum.

4. Improvement of water- solubility for oil soluble drugs

The water- soluble β - CD polymer P- 2 was chosen for solubilization agent for Ftorafurum. Ftorafurum was put into water solution containing different amounts of β - CD polymer P- 2 and the mixture was shaken vigorously for 5 min. And then let stand for different times (such as 0.5 h . and 48 h.) to reach the maximum solubility of Ftorafurum in water, judging from the results determined by UV absorbance . Fig .4. shows the solubility curve for Ftorafurum.

**Fig .4** The solubility curve for Ftorafurum

A series of β - CD polymers with different properties and usages can be prepared by changing the reactant molar ratios. The water- soluble β - CD polymers have low- molecular- weight and consist of two- five β - CD moieties linked with glyceryl bridges, but the structure of crosslinked β - CD polymers are relatively complicate.

In our experiment only HO - C (2) and HO - C (3) on sugar skeleton react with epichlorohydrin. The reaction extent has a regular relationship with the proportions of reactants.

Keywords :

β - Cyclodextrin; Epichlorohydrin; Water- soluble polymers β - CD.

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