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One-pot synthesis of cyclodextrins, modified with poly(ethylene oxide)

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SUMMARY

A new series of bouquet-like molecules based on cyclodextrins (CD) is described. They result from the polymerization of ethylene oxide initiated by hydroxyl groups of cyclodextrins, that constitutes the organizing core. Analysis of the structure and composition of the conjugates based on α-, β- and γ-CDs was done using ^{13}C-NMR and data of molecular mass of conjugates. Glass transition behavior of conjugates shows that they are amorphous compounds.

INTRODUCTION

Cyclodextrins and their derivatives has been extensively studied as drug solubilizers (1). Inclusion complexes of drugs with natural, crystalline CD, which are also crystalline, have been used for pharmaceutical purposes, but the solubilization procedures are not straightforward, and physico-chemical studies must be performed prior to use. In the study of solubilizers suitable for biomedical use amorphous CD derivatives characterized by high solubility in water were developed and tested (2).

Keeping this purpose in mind we elaborated a new simple method of synthesis of poly(ethylene oxide)-containing conjugates of CDs. Their structure is close to the bouquet-shaped molecules based on CD and oligomers of ethylene oxide (3). In these structures short polyoxyethylene chains are coupled to glucopyranose units on both sides of truncated cone of CD forming a microcapsule. These molecules are incorporated in vesicle membranes and display transmembrane transport of alkaline metals (4,5). It was shown that these compounds are not soluble in water; hence they can not be used as solubilizers. One can assume that a statistical mixture of substituted PEO- derivatives of CD would be much more soluble than pure compounds because of their poorer tendency to crystallize. Really until now only statistically substituted derivatives have been used industrially. We proposed that these type of PEO-CD derivatives may be obtained using polymerization of ethylene oxide, initiated by hydroxyl groups of CDs.

EXPERIMENTAL

Materials

α- and β-cyclodextrins were purchased from "Cyclolab" (Hungary). Ethylene oxide was purified by distillation.

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Typical synthetic procedure

A solution of β-CD (3.5 g, 0.003 mole) in 50 ml of 0.9% solution of NaCl (pH 11.2) was poured in the reaction vessel from stainless steel equipped with stirrer, thermometer and input of a gas. Ethylene oxide (EO) is added at 80°C under pressure 0.145-0.196 MPa. After stirring for 4-10 hours the reaction mixture was cooled up to 40°C and unloaded. The solution was dialyzed against water using Seamless tubing (Sigma). The end of dialysis was controlled with thin layer chromatography on Silufol plates in $CHCl_3$:C_2H_5OH:H_2O (36:12:1). The spots were revealed by iodine. The solution was filtered through a glass fiber filter (Sigma) and lyophilized. A repeated drying of conjugates was performed by heating in vacuum in the presence of phosphorous pentoxide at 95-100°C during an hour. The water content in a series of conjugates was estimated as 10 - 13%. Anal. Calc. for the conjugate based on β-CD with maximal degree of polymerization: C 45.7%; H 8.7%; found C 45.8%; H 8.5%.

Measurements

Number average molecular masses of conjugates was determined by means of vapour pressure osmometry using Vescan osmometer (USA) with ethanol as a solvent. Measurements was conducted at 30°C. All measurements was repeated 3-5 times.

^{1}H-NMR spectra were recorded on CXP-200 Bruker spectrometer. ^{13}C-NMR spectra were recorded on AM-300 Bruker spectrometer. Chemical shifts are given in ppm with sodium (4,4'-dimethyl-4-) silapentane sulfonate and dimethylsulphoxide as internal references.

Glass-transition temperatures were recorded with a Mettler TA 400 thermoanalyzer using a DSK-30 unit. Temperature variation rate was 20 K/min.

RESULTS AND DISCUSSION

PEO-CD conjugates were synthesized in one-pot manner by initiating the polymerization by hydroxyl groups of multifunctional core of CD. This reaction was developed for the synthesis of graft copolymers of ethylene oxide on starch (6). As the polymerization was conducted in the excess of ethylene oxide the formation of statistically substituted derivatives was the most favorable. In analogy with the data on the determination of the patterns of substituents in hydroxyethyl- and hydroxypropyl-CD (7) we proposed that the etherification proceeds favorably at 2- and 6-O-positions of CD. The derivatization at 3-O-position is the least probable especially for bulky polymer substituent. The other source of heterogeneity of conjugates is polydispersity of polymer chains resulting from the mechanism of termination and chain transfer. It would be expected that the polymerization process using CD as polyfunctional initiator may be accompanied by the formation of insoluble network polymer. Really for the system based on PEO-β-CD the content of insoluble product was estimated as ~5%.

Varying the concentration of EO in a reaction system we synthesized a series of conjugates with PEO-arms with different degrees of polymerization. PEO-CD conjugates were studied using ^{1}H-and ^{13}C-NMR spectra. In ^{1}H-NMR spectra the signals of protons of glucose rings were hidden by the strong signal of PEO-chains protons(Fig. 1a). In ^{13}C-NMR spectra we can observe distinct signals corresponding to carbon atoms of polymer chains, characterized with the following chemical shifts: 62.173 ppm, 71.315 ppm and 73.477ppm. Additionally, there are broad signals of carbon atoms belonging to CD moiety (the range 62 ppm, 71-75 ppm, 80-84 ppm and 100-103 ppm) (Fig. 1b). Our efforts to achieve better resolution of lines in the spectra by heating of the sample up to 90°C did not result in the sufficient change of the quality of spectra. This is, probably, due to the statistical character of substitution at different position of hydroxyl groups and crowding effect of PEO-substituents.

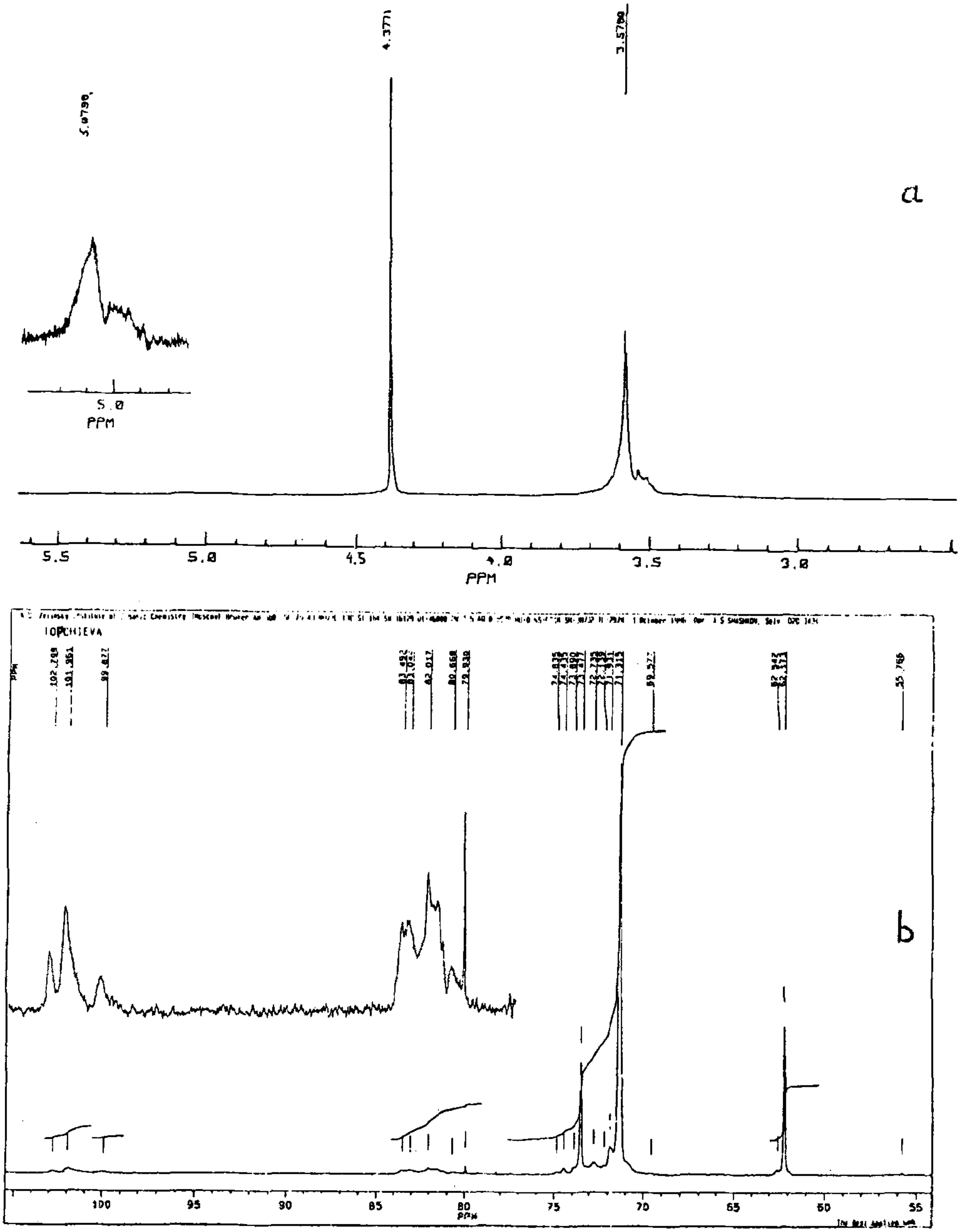


Figure 1. ¹H-NMR (a) and ¹³C-NMR (b) spectra of conjugate

The composition of conjugates was characterized by molecular masses determined by vapour osmometry method (Table 1). Based on the values of number average molecular masses of conjugates we calculated the total degree of polymerization. These data are presented in Table 1.

Table 1

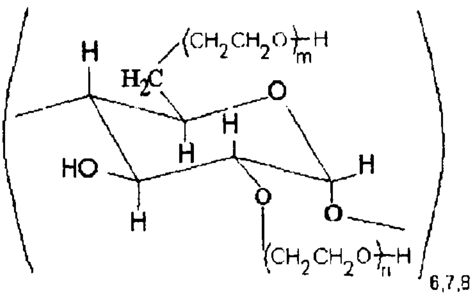
Characteristics of conjugates based on cyclodextrins and poly(ethylene oxide).

N°	CD	Ratio of EO, mole/mole of CD	Number average molecular mass	Number of monomer units per one mole of CD	T_g, °C
1	α	159.0	3100	48	-62.6
2	β	63.6	3000	42	-74.4
3	β	159.0	4200	70	-73.3
4	β	318.0	4800	84	-72.7
5	γ	522.2	3500	48	-54.5

On the basis of the data on molecular mass, chemical analysis and the estimation of water content the brutto formula for PEO-β-CD conjugate with maximal degree of polymerization (preparation N°4) $C_{210}H_{406}O_{119} \cdot 38\ H_2O$ was calculated.

The comparison between the amount of added EO per a molecule of β-CD in preparations 2-4 and the degree of polymerization shows that the increase of the ratio EO/CD in 7.5 times results in no more than twofold increase of the degree of polymerization of PEO-blocks in conjugates. At the same time a reaction media contains a great amount of free oligo(oxyethylene). Taking these facts into account it is possible to expect that the oxyethylation process is accompanied by chain transfer reaction to water (8).

Thus the formula of conjugates may be presented as



m+n=6-12

Additional information on the physical state of conjugates can be obtained from the study of glass transition behavior and evaluation of glass transition temperatures, T_g (Fig.2 and Table 1). For comparison in Fig. 2 the thermogram of PEG 300 was presented. It should be noted that the parent β-CD is a crystalline compound with a melting point equal to 300°C. It is seen that the value of T_g of PEG 300 is close to T_g for conjugates 2 and 3. At the same time the temperature interval of transition relating with the degree of cooperativity is significantly wider for bound polymer chains, compared to the initial polymer. It is seen from Fig.2 that in contrast to the behavior of PEG 300 characterized with both picks of crystallization and melting, the corresponding thermograms of conjugates contain only the region of glass transition. Comparing the values of T_g for conjugates based on β-CD, characterized by the different total degree of polymerization one can see that they increase in parallel with the increase of the degree of polymerization.

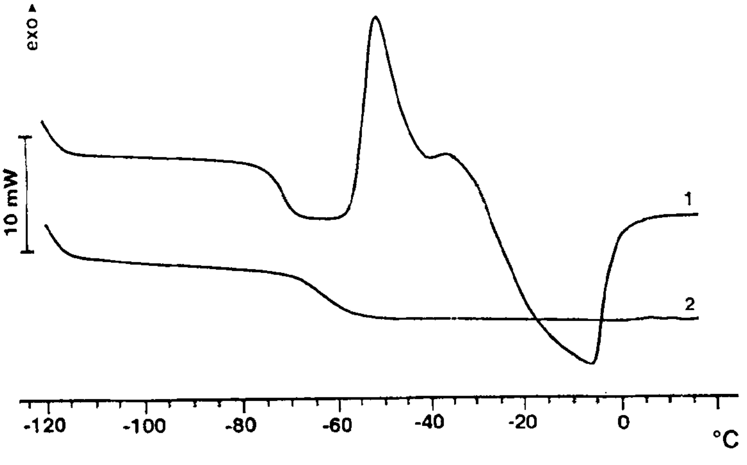


Figure 2 Curves of DSC of glass transition of PEG 300 (1) and PEO-β-CD (preparation N°4) (2). The rate of heating is 10°C/min.

The characteristic property of conjugates is their unlimited solubility in water.

Thus the structure of the conjugates obtained using the polymerization of EO in the presence of NaCl presents a bouquet-like structures in that a bundle of polymer chains are grafted onto primary and secondary hydroxyl groups of cyclic core of CD. They are amorphous and water-soluble compounds. Preliminary study of complexation properties of these conjugates shows that they are able to form inclusion complexes with organic "guests". The detailed study of complexation process with these conjugates is under investigation.

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