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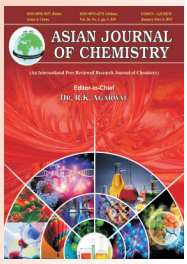

A Novel Preparation and Purification of Penta-Substituted 6-*O*-Propyl-β-cyclodextrin

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A synthetic process about propyl-β-cyclodextrins has been investigated through the reaction between β-cyclodextrin and dipropyl carbonate by anhydrous potassium carbonate as catalyst in DMF, penta-substituted 6-*O*-propyl-β-cyclodextrin was purified by silica gel chromatography. The structures of product were characterized by TLC, IR, MS, ^{1}H NMR and ^{13}C NMR. Mass spectra and ^{1}H NMR proved the average degree of substitution of propyl-β-cyclodextrin is 5. ^{13}C NMR proved the position of propyl at 6-position.

Keywords: β-Cyclodextrin, 6-*O*-Propyl-β-cyclodextrin, Dipropyl carbonate, Propylation, NMR.

INTRODUCTION

β-Cyclodextrin (β-CD) is composed of seven cyclic oligosaccharides with truncated cylindrical shapes. It has hydrophobic internal cavity and hydrophilic external part. This particular structure affords β-cyclodextrin, the remarkable characteristic of being able to include various hydrophobic molecules in its cavity, which leads to changes in the physicochemical properties of the guest molecules. The relatively low solubility of native β-cyclodextrin in water as well as in organic solvents, however, is the principal limitation to inclusion complexation processes and reactions. A synthetic challenge is the selective modification of the three different types of hydroxyl group on the hydrophilic surface of the toroidal structure. The more reactive primary hydroxyl (position 6) presents at the smaller opening of the toroid while the less reactive secondary hydroxyls (positions 2 and 3) appear at the larger opening[1]. Such structural modifications can optimize the desirable properties of β-cyclodextrin[2]. Hydrophobic β-cyclodextrin derivatives are useful as sustained-release drug carriers for water-soluble drugs and peptides because they tend to decrease the solubility of the guest molecule[3]. The physicochemical properties of β-cyclodextrin are markedly altered when propyl groups are introduced onto the hydroxyls of β-cyclodextrin. Propyl-β-cyclodextrin has been used in the separation of pharmaceutically interesting compounds[4]. Propyl-β-cyclodextrin can also be used to catalyze hydrolysis of aryl glycosides into glucose and phenol as artificial enzyme[5]. The most efficient synthesis furnished propyl-β-cyclodextrin from propyl bromide and β-cyclodextrin[6]. Another method for the preparation of propyl-β-cyclodextrin was reported in which (i) allyl-β-cyclodextrin was synthesized from allyl bromide and β-cyclodextrin, (ii) allyl-β-cyclodextrin was hydrogenated[7]. Recently, Fernando *et al.*[5] described a multistep synthesis of a certain position propyl-β-cyclodextrin in which needed protection and deprotection steps. All the processes or reactions are carried out in condition of normal temperature and pressure, but propyl bromide or allyl bromide used in these methods are toxic and dangerous chemical. Therefore, there has been a drive to develop alternative methods. Research is now focused on the need for less hazardous and more effective propylation regent to replace propyl bromide or allyl bromide. Dipropyl carbonate (DPC) has recently attracted much attention as a safe solvent[8]. In this paper, we report on the preparation and purification of penta-substituted 6-*O*-propyl-β-cyclodextrin. Further, their NMR spectra were compared with propyl-β-cyclodextrin, ethyl-β-cyclodextrin, methyl-β-cyclodextrin and β-cyclodextrin.

EXPERIMENTAL

FT-IR spectra of the samples pressed with KBr in the framework region (4000-400 cm^{-1}) were recorded at room temperature with a MAGNA-IR 560 spectrometer. TGA was recorded with a differential scanning calorimeter (SEIKO EXSTRA6000) (under N_2 at 5 °C/min). Mass spectra were determined on an LCQ Advantage MAX spectrometer (ESI). NMR spectra (^{1}H, 500.13 MHz; ^{13}C, 125 MHz) were recorded on a Varian INOVA 500 MHZ instrument. Approximately 30 mg samples were directly dissolved into the NMR tube in 0.6 mL DMSO solvent. Materials were purchased from Kewei Company of Tianjin University (China). β-Cyclodextrin was re-crystallized and dried before use under vacuum at 80 °C, anhydrous potassium carbonate, dipropyl carbonate, DMF,

acetonitrile, ethyl acetate and ammonia water directly used without further treatment. Reactions were monitored by thin-layer chromatography on a precoated plate of silica gel 60 F254 (layer thickness 0.2 mm; Haiyang company, Qingdao, China) and detected by iodine vapor. Flash column chromatography was performed on Silica Gel 60F254 (200/300 mesh, Haiyang company, Qingdao, China).

General procedure 6-*O*-propyl-β-cyclodextrins: Anhydrous β-cyclodextrin (4 g, 3.52 mmol) was added to DMF (120 mL) in a 250 mL three-necked flask equipped with a dropping funnel and a condenser. When the solution was stirred to clear, 1 g K_2CO_3 was added, then 8 mL (7.52 g, 51.5 mmol) dipropyl carbonate was added dropwise and reaction temperature was controlled at 125 °C by oil bath under N_2 atmosphere. The mixture was stirred for 24 h. The course of reaction was monitored by TLC (6:1:3:1 acetonitrile-EtOAc-H_2O-conc. aq NH_3). After reaction, catalyst was separated by means of centrifugation, solvent and surplus dipropyl carbonate was removed in high vacuum at 60-95 °C. When the residue was concentrated till dry, 3.5 g white powdered product was obtained. In a typical experiment, 3 g 6-*O*-propyl-β-cyclodextrins were dissolved in water (180 mL) and 30 g of silica gel were added[9]. The suspension was evaporated to dryness (weight 33 g). The powdered solid thus obtained was added to the top of a silica gel (300 g) column (i.d. 10 cm), which was poured using the eluent mixture acetonitrile-EtOAc-water-concd aq ammonia (6:3:1:1). The column was eluted with 3 L of eluent mixture, using pressurized air (70 kPa) at the rate of 10 mL/min; 25 mL fractions were collected. Separation was followed by TLC of fractions. The fractions containing the product were combined and evaporated to dryness at 40-90 °C *in vacuo*. The final product, penta-substituted 6-*O*-propyl-β-cyclodextrin (140 mg 3.45 %), was characterized by IR, MS, ^{1}H NMR and ^{13}C NMR.

Penta-substituted 6-*O*-propyl-β-cyclodextrin (1): As a white powder: m.p. 341 °C; ^{1}H NMR (500 MHz, DMSO): δ 6.52-5.83 (m 16H, OH), 4.83-4.72 (m 7H, H-1), 4.10-4 (m 10H, H-CH_2 (a)), 3.64-3.56 (m 28H, H-3, 5, 6), 3.43-3.31 (m 14H, H-2, 4), 1.64-1.52 (m 10H, H-CH_2 (b)), 0.89-0.76 (m 15H, H-CH_3); ^{13}C NMR (125 MHz, DMSO): δ 102.8 (7 × C-1), 82 (7 × C-4), 73.8 (7 × C-2), 73.6 (7 × C-3), 72.7 (7 × C-5), 69.6 (7 × C-6), 60.4 (5 × C-CH_2 (a)), 21.9 (5 × C-CH_2(b)), 10.4 (5 × C-CH_3); MS (%) = 1351 (100) *m/z*.

RESULTS AND DISCUSSION

A green synthesis of 6-*O*-propyl-β-cyclodextrins is described *via* dipropyl carbonate and β-cyclodextrin. The strategy is shown in **Scheme-I**.

Hydroxyl groups present at the 2-, 3- and 6-positions compete for the reagent and make selective modification extremely difficult. Khan *et al.*[10] described the 'longest' method consisting in a series of protection and deprotection steps to obtain a certain substituted position β-cyclodextrin derivatives. In previous reports, a certain substituted position propyl-β-cyclodextrin, (2,6-di-*O*-propyl)-β-cyclodextrin, mono-2-*O*-propyl-β-cyclodextrin, were synthesized[5-7]. A convenient, selective, novel and green synthesis of 6-*O*-propyl-β-cyclodextrins is reported in our paper. DMF was found to be the appropriate medium in which the reaction of β-cyclodextrin with DPC could be carried out well with anhydrous potassium carbonate as catalyst. Propylation is more difficult than methylation because of steric hindrance. Therefore, propylation needs higher temperature than methylation[11]. During the whole process, the samples were held under a protective atmosphere of CO_2 flow in order to avoid oxidation. The final purification of 6-*O*-propyl-β-cyclodextrins was achieved through a regular silica gel column chromatography.

FTIR analysis: Fig. 1 shows IR spectra in the 3500-400 cm^{-1} region of 6-*O*-propyl-β-cyclodextrins. IR spectroscopy was used to confirm the structure of the product, which exhibits the absorption peaks at 3322, 2966, 2930, 1655, 1438, 1381,1412, 1156, 1080, 1030, 854,757, 580 cm^{-1}. We noted that samples after propylation had relatively stronger peaks of CH_3 groups than those samples before propylation, judging by the characteristic C-H asymmetric stretch (2966 cm^{-1}) and symmetric deformation (1381 cm^{-1}) in the methyl groups. The peaks at 1448, 854 cm^{-1} are characteristic of methyl and methene. The others are mainly consistent with the data of β-cyclodextrin. These data were in agreement with the proposed structure[6].

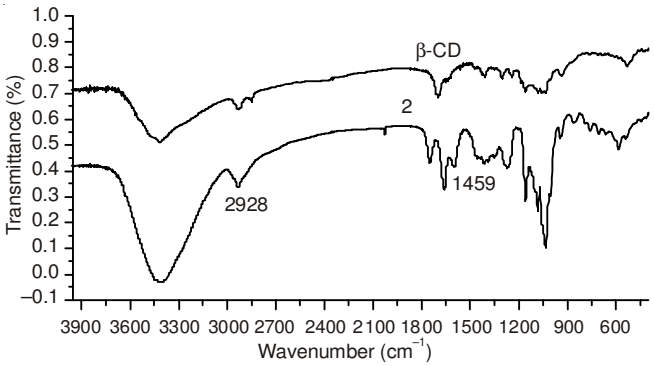
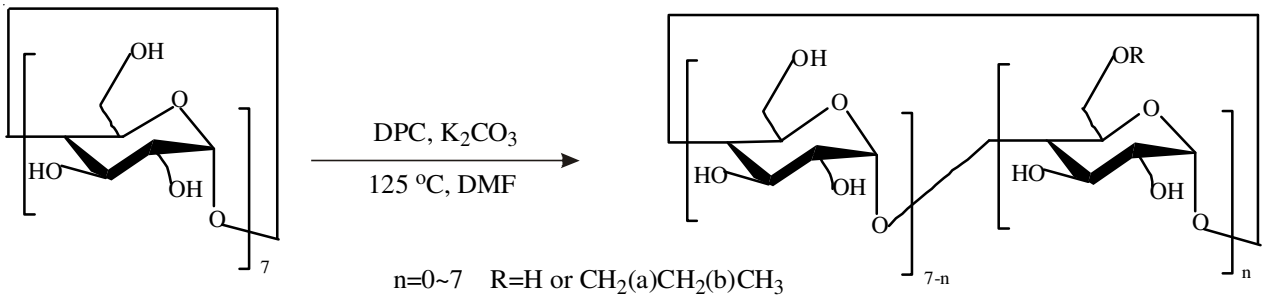


Fig.1. IR spectrum of β-cyclodextrin and 6-*O*-propyl-β-cyclodextrins (**2**)



Scheme-1: Synthetic scheme for 6-*O*-propyl-β-cyclodextrins

Mass spectra analysis: By using negative ion fast-atom bombardment, well defined and clearly separated signals were obtained in the mass spectra of 6-*O*-propyl-β-cyclodextrins. Each peak corresponds to monoanions formed by loss of one proton from the 6-O-propyl-β-cyclodextrins. There are 1179.8, 1265.1, 1352.1, 1437.1 MS spectrum of the product in the MS spectrum (Fig. 2 (2)). The MS spectrum of 1352.1 is the molecular ion (M-) of 5 degree of substituted 6-*O*-propyl-β-cyclodextrin and other MS spectra are respectively the 1, 3, 7 degree of substituted 6-*O*-propyl-β-cyclodextrin. The average degree of substitution of the product could be calculated according to the MS spectra[12]. Because there is no major peak in the mass spectra which corresponds to the structure of one β-cyclodextrin with more than 7 propyl substituent, it is possible that no more than 7 substitutions occurred on the same β-cyclodextrin. This is not surprising because the average degree of substitution is relatively low for each derivative and steric factors favor a low substitution degree. Fig. 2 (1) shows the MS spectrum of penta-substituted 6-*O*-propyl-β-cyclodextrin.

^{1}H NMR analysis: The ^{1}H NMR spectrum was used for the structural analysis of the 6-*O*-propyl-β-cyclodextrins. The characteristic peaks of grafted propyl at 4-4.10, 1.52-1.64 and 0.76-0.89 ppm for -CH_2 (a), -CH_2 (b) and -CH_3 protons, respectively, were detected by ^{1}H NMR. The integration ratio of the peak at 4-4.10, 1.52-1.64 and 0.76-0.89 is close to 2:2:3, which indicates that they belong to the same propyl groups. The degree of substitution of the product could be calculated from the signals in nuclear magnetic resonance spectra. The region at 4.72-4.83 ppm is correlated to the 7 protons of C-1 of parental β-cyclodextrin and the protons of CH2 (a) of grafted propyl appear in the region δ = 4-4.10 ppm. The integration ratio between the peak at 4.72-4.83 ppm and the peak at 4-4.10 ppm is close to 7:10. So there are 10 protons at CH_2 (a)-groups of grafted propyl and the average degree of substitution of the product could be calculated. The result is fairly close to the calculated from the MS data.

^{13}C NMR analysis: The substitution at different positions usually increases the chemical shift of the substituted carbon signal[13]. The C-6 of 6-O-propyl-β-cyclodextrins and 5-substituted 6-*O*-propyl-β-cyclodextrin has a chemical shift of 70 ppm, which increase the chemical shift about 10 ppm relative to the one in the native β-cyclodextrin[3,14]. And it coincides with the C-6 of (2,6-di-*O*-propyl)-β-cyclodextrin (DP-β-CD), (2,6-di-*O*-ethyl)-β-cyclodextrin (DE-β-CD) and (2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD)[3,6]. But the C-2 of 6-*O*-propyl-β-cyclodextrins and 5-substituted 6-*O*-propyl-β-cyclodextrin has a chemical shift of 73 ppm, which decrease the chemical shift about 7 ppm relative to the one in DP-β-CD, DE-β-CD and DM-β-CD. And it coincides with the C-2 of the native β-cyclodextrin. The chemical shift of C-3 of 6-*O*-propyl-β-cyclodextrins (a) and 5-substituted 6-*O*-propyl-β-cyclodextrin coincides with the C-3 of the native β-cyclodextrin, DP-β-CD, DE-β-CD and DM-β-CD. All the data coincides with previous report[5]. According to the elegant explanation from Ueno and Breslow[5], the substituent position of the product could be clearly indicated on the 6-OH of β-cyclodextrin. Preferential propylation at the primary hydroxyl position (OH-6) of the β-cyclodextrin is probably due to the fact that the primary hydroxyl groups are sterically less hindered when compared with the secondary ones (OH-2 and OH-3) (Table-1).

TABLE-1
^{13}C NMR of β-CD, DM-β-CD, DE-β-CD, DP-β-CD, 6^{A}S,6^{D}S)-6^{A},6^{D}-Di-C-propyl-β-CD (A), 1 and 6-*O*-propyl-β-CDs (2)

	β-CD [Ref. 3,14]	DM-β-CD [Ref. 3]	DE-β-CD [Ref. 3]	DP-β-CD [Ref. 6]	A [Ref. 5]	**1** [This paper]	**2** [This paper]
C-1	101.9-102.6	100.1	100.7	100.8	102.0	102.6	102.4
C-2	72.4-72.7	81.8	80.0	80.4	73.4	73.1	72.9
C-3	73.0-73.9	72.7	72.9	73.5	73.6	73.8	73.6
C-4	81.5-81.9	82.7	82.9	83.5	81.2	82.2	82.0
C-5	72.0-72.9	69.8	69.9	70.4	72.5	72.5	72.5
C-6	59.9-61.2	70.7	68.7	69.1	67.6	69.5	69.6
-CH_2(a)-			65.5	73.0	59.9	60.5	60.4
-CH_2(b)-				22.8	18.7	22.1	22.4
-CH_3		59.6	15.0	10.5	13.3	10.5	10.5

All samples are in the solvent of DMSO except A in D_2O.

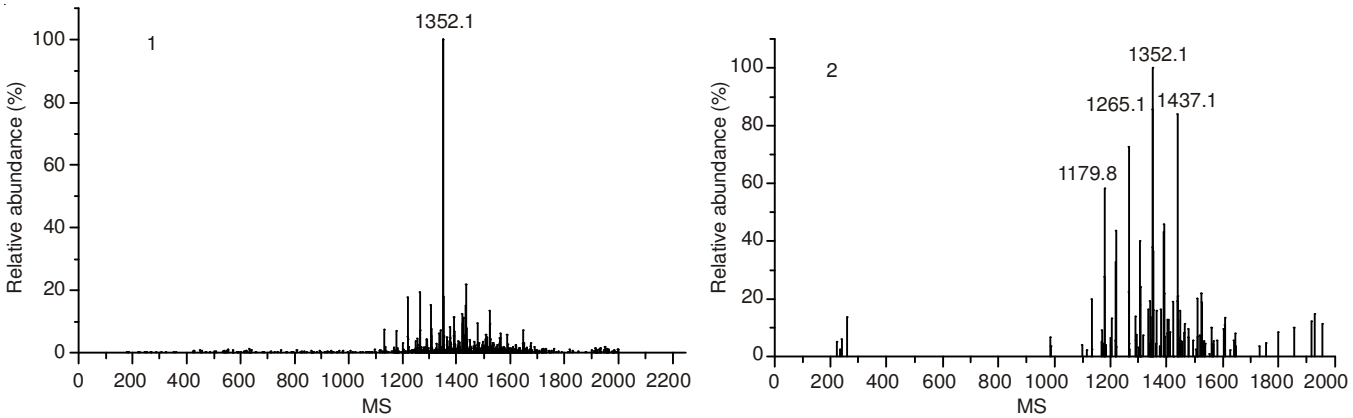


Fig. 2. MS spectrum of penta-substituted 6-*O*-propyl-β-cyclodextrin (1) and 6-*O*-propyl-β-cyclodextrins (2)

Conclusion

Thus, a convenient, simple, efficient, novel and green synthesis of 6-*O*-propyl-β-cyclodextrin is developed. In the present paper, the green 6-*O*-propyl-β-cyclodextrins were firstly synthesized through the reaction between green propylation reagent dipropyl carbonate and β-cyclodextrin by using anhydrous potassium as catalyst. Then the product purification was performed by silica gel chromatography, penta-substituted 6-*O*-propyl-β-cyclodextrin was obtained. This is superior from the point steric selectivity and is more environmentally friendly than the reported methods.

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