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Research Article

A Novel Preparation and Purification of Ethyl-β-Cyclodextrins

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Abstract

Ethyl-β-cyclodextrin can be widely used for controlled release of drugs, but its application is greatly limited due to the use of toxic ethylation reagents such as diethyl sulfate, chloroethane, and iodoethane in previous synthesis processes. This article expands the application range of ethyl-β-cyclodextrin by using green ethylation reagent instead of previously toxic ethyl reagents to synthesize ethyl-βcyclodextrin. Ethyl-β-cyclodextrins were studied by reaction with diethyl carbonate and β-cyclodextrin in DMF using anhydrous potassium carbonate as catalyst, During the reaction process, in order to avoid oxidation, the samples were kept in a protective atmosphere of N_2 flow. A new green synthesis process for ethyl-cyclodextrins, using silica gel chromatography to synthesize and purify four substituted 6-O-ethyl-cyclodextrins. Their structures were characterized by IR, MS, ^{1}H-NMR, and ^{13}C-NMR. The final product with a yield of 4% was obtained by chromatographic separation using acetonitrile-concd aq NH_3-H_2O-EtOAc (6:1:3:1) as the eluent. IR data indicate that the obtained product is the expected product. ^{13}C-NMR characterization indicates that the substitution position of the product is at position 6, ^{1}H-NMR, and MS characterization indicate that the degree of substitution of the product is 4. This synthesis method takes full advantage of the spatial selectivity of β-cyclodextrin. The method is green and simple. The target product is synthesized in one step, which is superior to previous reports.

Keywords

Diethyl Carbonate, β-Cyclodextrin, NMR, Ethylation, MS

1. Introduction

β-cyclodextrin (CD) is consisted of seven D-(+)-glucopyranose units, which has a relatively hydrophobic central cavity and hydrophilic outer surface, each of the units is linked together by α-1,4 bonds. This special structure makes β-cyclodextrin have the function of encapsulating hydrophobic substances. [1] This special structure affords β-CD have the function of encapsulating the various hydrophobic molecules in their cavity, which leads to changes in the physicochemical properties of the guest molecules. [2, 3] The 21 hydroxyl groups of natural β-CD can be exploited for the

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structural modifications of β-CD by introducing various functional groups onto the β-CD molecule. To expand the application of the natural β-CD, various kinds derivatives of β-CD have been prepared to improve their physicochemical properties and inclusion capacity to enable them to become novel drug carriers. Such modifications can optimize the desirable properties of β-CD. [4] Hydrophobic β-CD 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. [5, 6] The physicochemical properties of β-CD are markedly improved when ethyl groups are grafted onto the hydroxyls of β-CD, and ethylated β-CDs are promising candidates for release control carriers for water-soluble drugs because of the formation of a less-soluble active, slightly soluble in water, and less hygroscopic than parent β-CD. [7] Ethyl-β-CDs are sparingly soluble in water, form complexes with water-soluble pharmaceuticals such as salbutamol [8] or human growth hormone. [9] Ethyl-β-CDs can retard the release of these pharmaceuticals and have been considered as useful for drug delivery. [10]

The popular method for synthesis ethyl-β-CDs from diethyl sulfate and β-CD, [7, 11], ethyl iodine can also be used as an ethylation reagent. [12] These reactions can be carried out in condition of normal temperature and pressure. However, the reagents used in these synthesis methods are toxic and harmful substances, which is incompatible with the concept of green chemistry. [13] Therefore, it is necessary to find green synthesis methods. The current research focus is to use less dangerous and more effective ethylation reagents to replace diethyl sulfate and ethyl iodide. As a green reagent, diethyl carbonate (DEC) has attracted more and more attention. [14] In this paper, we report a green synthesis and purification method of ethyl-β-CDs.

2. Experimental

2.1. General Methods

At room temperature, FT-IR spectra of the samples pressed with KBr in the framework region (400–4000 cm^{-1}) were recorded with a MAGNA-IR 560 spectrometer. Mass spectra were measured on the LCQ Advantage MAX spectrometer (ESI). NMR spectra (^1H, 500.13MHz; 13C, 125MHz) was measured by the Varian INOVA 500MHZ instrument. 30mg of the sample was dissolved in an NMR tube in 0.6 mL of solvent. Use a Jeol GSX-500 or Jeol JNM-ECP 500 spectrometer (^1H: 500MHz, ^{13}C: 125MHz) to record the ^1H and ^{13}C-NMR spectral data of the sol in DMSO. The materials used in the experiment were purchased from Kewei Company, Tianjin University, China. β- CD was recrystallized twice and dried under vacuum at 80 ℃ before use, anhydrous potassium carbonate, DEC, DMF, acetone, acetonitrile, ethyl acetate, ammonia, and ether were used directly without further treatment. The reaction was monitored by thin layer chromatography (TLC) on a precoated plate of silica gel 60 F254 (layer thickness 0.2mm; Haiyang, Qingdao, China) and detected by iodine vapor detection. Chromatographic separation was performed on silica gel 60 (200/300 mesh, Haiyang, Qingdao, China).

2.2. General Procedure Ethyl-β-Cyclodextrins

Anhydrousβ- CD (8.00 g, 7.04 mmol) was added to DMF (150 mL) in a 500 mL three necked flask containing a drip funnel and condenser. When the solution was stirred to clear, 2.0 g K_2CO_3 was added, 40 mL (39.0 g, 330 mmol) diethyl carbonate was added dropwise in 10 minutes, reaction temperature was controlled at 120 ℃ by oil bath under CO_2 atmosphere. The entire reaction process was monitored by TLC (6:1:3:1 acetonitrile-concd aq NH_3 -H_2O-EtOAc). After the reaction, the catalyst was separated by centrifugation. Then removed the solvent and unreacted DEC in high vacuum at 60-95 ℃. When the residue was concentrated to a syrup, added 200 mL of acetone. The product was dispersed in acetone through rapid stirring, and then removed by filtration to obtain a powdered product. The product was added 100mL of anhydrous ether, stirred, sealed, soaked for 2-3 times, and filtered to obtain a white powdery product. In the separation experiment, 3.9g of the product was dissolved in water (200mL) and 30g of silica gel was added. [15] The suspension was evaporated to dryness (weight 33.4 g). Add the powdered solid obtained from this to the top of the silica gel (300g) column (i.d.10cm) and pour it using an eluent mixture Use pressurized air (80kPa) to elute the column with a 3L eluent mixture, 20 mL fractions were collected. Each separated portion was monitored by TCL. Four substituted 6-O-ethyl-β-CD was obtained after silica gel chromatography.

Four substituted 6-O-ethyl-β-CD. Yield 160 mg (4.0%), as a white. powder. Mp 341°C; ^1H-NMR (500 MHz, DMSO): δ 4.83-4.94 (m 24H, H-1, OH), 3.46-3.72 (m 28H, H-3, 5, 6), 3.25-3.46 (m 14H, H-2, 4), 1.11-1.28 (m 12H, H-CH_3); ^{13}C-NMR (125 MHz, DMSO): δ 102.5 (7×C-1), 82.7 (7×C-4), 73.4 (7×C-3), 72.5 (7×C-2), 69.4 (7×C-5), 67.0 (7×C-6), 63.8-64.2 (4×C-CH_2), 14.0-14.6 (4×C-CH_3); MS (%) =1251 (100) m/z (Figure 1).

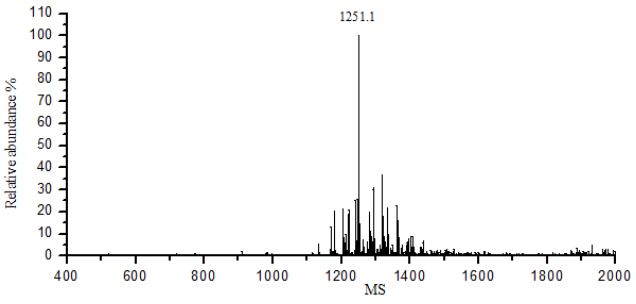

Figure 1. *MS spectrum of four substituted 6-O-ethyl-β-C.*

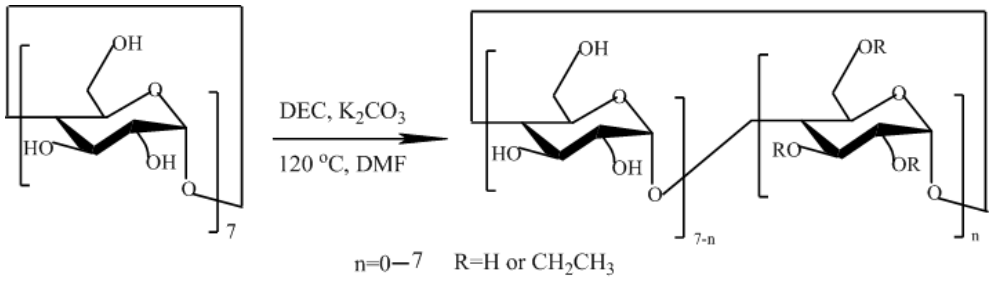

Figure 2. *Synthetic scheme for ethyl-β-CDs.*

3. Results and Discussion

3.1. Synthesis

A green synthesis of ethyl-β-CD is described using DEC and β-CD as raw materials is described. The synthesis method is shown in Figure 2.

The suitable solvent for the reaction between between CD and DEC is N, N-Dimethylformamide (DMF) with anhydrous potassium carbonate as catalyst. During the reaction process, in order to avoid oxidation, the samples were kept in a protective atmosphere of N_2 flow. Ethyl-β-CDs were purified by conventional silica gel column chromatography. The characterization of the obtained product is consistent with what has been reported. [1, 7, 8]

3.2. FTIR Analysis

The structure of the product was characterized by infrared spectroscopy, which exhibited absorption peaks at 3322, 2929, 1661, 1448, 1370, 1412, 1156, 1080, 1030, 854, 757, 581cm^{-1}. 1370, 1448, and 854cm^{-1} are typical absorption peaks for methyl and methyl groups. 2929cm^{-1} is significantly enhanced, which is another typical absorption peak of methyl group. The others absorption peaks are mainly consistent with the data of β-CD. These data indicate that the obtained product is the expected product. Figure 3 shows IR spectra of the product.

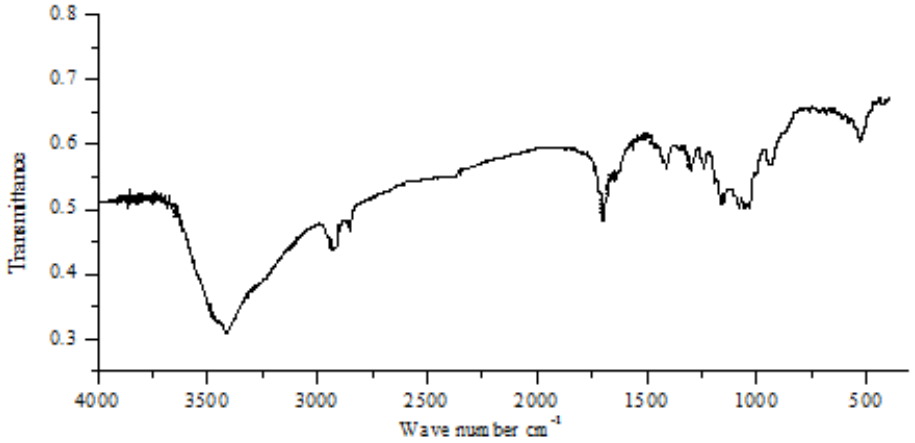

Figure 3. *IR spectrum of ethyl-β-CDs*

3.3. MS Analysis

There are are peaks of 1205, 1251, 1323, 1395, 1467 in the MS analysis of the product. The degree of substitution (DS) of the product could be calculated according to the MS spectra. MS spectroscopy can calculate the degree of substitution (DS) of the product. The MS spectrum of 1323 is the 6 DS ethyl-β-CD, and other MS spectra are respectively the 2, 4, 6, 8, 12 DS ethyl-β-CD.

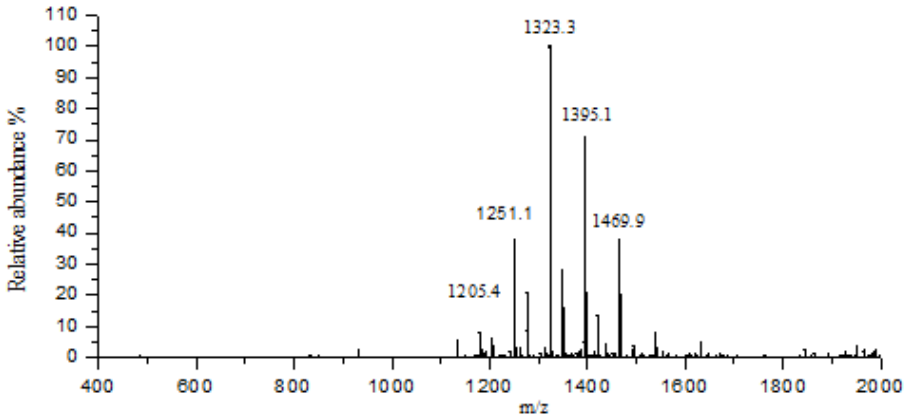

Figure 4. *MS spectrum of ethyl-β-CDs.*

3.4. ^{1}H-NMR Analysis

The ^{1}H-NMR spectrum was used for the structural analysis of the products. The ^{1}H-NMR spectrum at 4.10-4.30, 1.07-1.29 ppm is $-CH_2$ and $-CH_3$ protons of the characteristic peaks of grafted ethyl. The peaks at 4.10-4.30 and 1.07-1.29 ppm are the characteristic peaks of the ethyl – CH_2 and – CH_3 protons grafted on β-CD, respectively. Figure 5 shows the ^{1}H-NMR spectrum of the product.

DS can be calculated based on the signals in the ^{1}H-NMR spectrum spectrum. The regional peak of 4.78-5.10ppm is the proton peaks of the C-1 and OH groups in the parental β-CD. The peaks in the range of 4.10-4.30 ppm are the protons of the CH_2 group of the grafted ethyl group, while the peaks in the range of 1.07-1.29 ppm are the protons of the CH_3 group of the grafted ethyl group. The integration ratio between the peak at δ= 4.10-4.30 ppm and the peak at δ = 1.04-1.29 ppm is 0.67, which is just the same as the ratio of hydrogen atoms on the methyl group and on the methine group of ethyl group, indicating that they belong to the same ethyl group. The peak in the region of 4.78-5.10ppm is the peak of 28 protons from the parental β-CD. Therefore, the number of methine group on the grafted ethyl can be calculated by comparing the integral in the region of 4.78-5.10 ppm with the integral in the region of 1.07-1.29 ppm. So the protons of CH_2-groups of grafted ethyl and the DS of product could be calculated. The conclusion of this analysis is consistent with the analysis of MS.

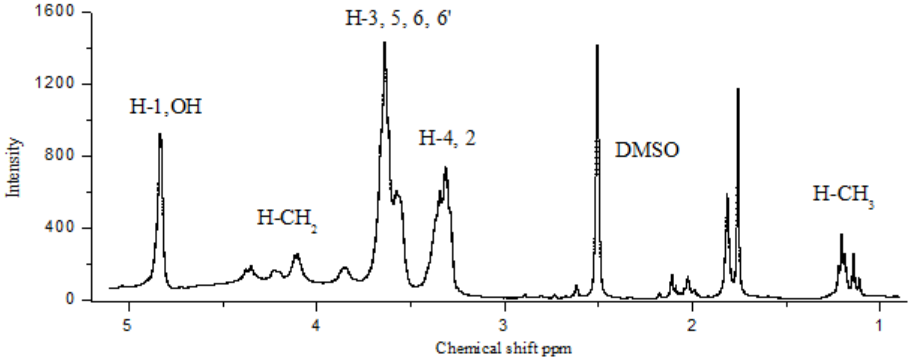

Figure 5. *^{1}H-NMR spectrum ethyl-β-CDs.*

3.5. ^{13}C-NMR Analysis

Figure 6 shows ^{13}C-NMR chemical shifts of ethyl-β-CDs and their separated products in DMSO-d_6 in comparison with β-CD and methyl-β-CD. According to the change of C-6, C-2 and C-3 chemical shift: C-6 has an obvious shift from 59.9 to 67.0-67.4 ppm in the ^{13}C-NMR spectrum, while C-2 and C-3 have no obvious shift, determine where the reaction occurred at C-6 hydroxyl group of β-CD. Ethylation occurs preferentially at the primary hydroxyl position (OH-6) of β-CD is mainly due to the smaller steric hindrance of the primary hydroxyl group compared to the secondary hydroxyl groups (OH-2 and OH-3).

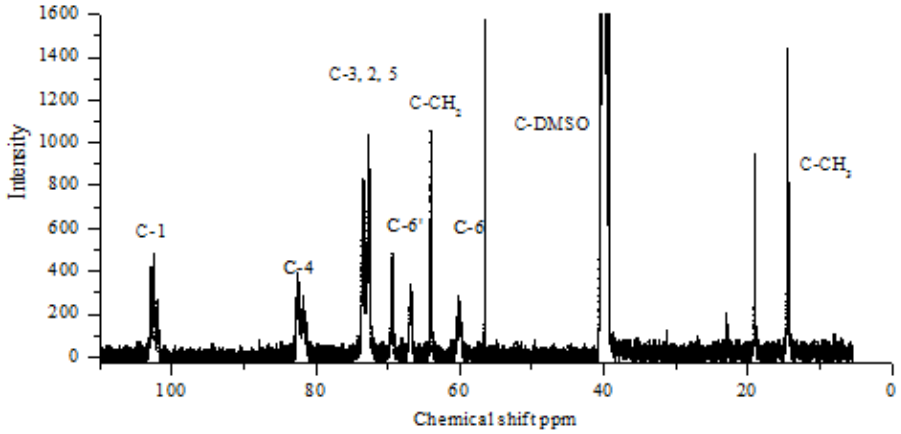

Figure 6. *^{13}C-NMR spectrum of ethyl-β-CDs.*

4. Conclusion

Green ethyl- β- CD was synthesized using green ethylation reagent DEC and β-CD as the raw material, the reaction was catalyzed by anhydrous potassium carbonate, and four substituted 6-O-ethyl-β-CD was separated for the first time using silica gel chromatography. This synthesis method takes full advantage of the spatial selectivity of β-CD. It is green and simple. The target product is synthesized in one step, which is superior to previous reports.

Acknowledgments

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Abbreviations

βCD: β-cyclodextrin, DEC Diethyl Carbonate

Conflicts of Interest

The authors declare no conflicts of interest.

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