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A Novel Synthesis Technology of Ethyl-β-Cyclodextrin

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Abstract: A novel green synthesis process about ethyl-β-Cyclodextrin have been investigated through the reaction between β-cyclodextrin and diethyl carbonate by used anhydrous potassium carbonate as catalyst in DMF. The influence of experimental factors including reaction time, the molar ratio of β-cyclodextrin to diethyl carbonate, reaction temperature and contents of anhydrous potassium carbonate on the average degree of substitution of ethyl-β-cyclodextrin were carried out by a design method of orthogonal experiments. The results shown that the average degree of substitution of ethyl-β-cyclodextrin can be depend on the reaction temperature and the molar ratio of raw material primarily. The optimal maximum average degree of substitution of ethyl-β-cyclodextrin is 6.0 when the molar ratio of β-cyclodextrin to diethyl carbonate, reaction temperature, reaction time and dosage of catalyst are 1:28, 120°C, 24h and 2.0 g, respectively. The structures of ethyl-β-cyclodextrin were characterized by TLC, IR, MS, ^{1}H-NMR and ^{13}C-NMR, and these results are concordant with former ones which synthesized ethyl-β-cyclodextrin by diethyl sulfate or ethyl iodide.

Keywords: β-Cyclodextrin, Orthogonal Experiments, Diethyl Carbonate, Ethylation, NMR

1. Introduction

β-cyclodextrin (CD) is consisted of seven D-(+)-glucopyranose units that has a relatively hydrophobic central cavity and hydrophilic outer surface, each of the units is linked together by α-1,4 bonds. It has hydrophobic internal cavity and hydrophilic external part [1]. This particular structure affords β-CD, the remarkable characteristic including various hydrophobic molecules in their cavity, which leads to changes in the physicochemical properties of the guest molecules. Natural β-CD has 21 hydroxyl groups that can be exploited for the structural modifications of β-CD by introducing various functional groups onto the β-CD molecule. To enlarge the use of the natural β-CD, various kinds of derivatives have been prepared to improve their physicochemical properties and inclusion capacity to enable them to become novel drug carriers. Such structural modifications can optimize the desirable properties of β-CD [2]. 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 drugs [3]. The physicochemical properties of β-CD are markedly modified when ethyl groups are introduced 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 [4]. Ethyl-β-CDs are slightly soluble in water, form complexes with water-soluble pharmaceuticals such as salbutamol or human growth hormone [5, 6]. Ethyl-β-CDs can retard the release of these pharmaceuticals from compressed tablets and have been suggested as useful for drug delivery [7].

The most efficient synthesis of ethyl-β-CDs is prepared from diethyl sulfate and β-CD [4, 8], ethyl-β-CDs can also be synthesized from ethyl iodide and β-CD [9]. All the processes or reactions can be carried out in condition of normal temperature and pressure. However, these methods involve the use of toxic and hazardous materials, and they are incompatible with the concept of green chemistry [10]. So, there has been a drive to develop new method. In this regard,

research is now focused on the need for less hazardous and more effective ethylation regent to replace diethyl sulfate and ethyl iodide. Diethyl carbonate (DEC) has attracted an increased attention as an environmentally friendly chemical raw material [11]. Here, we report on the green preparation and purification of ethyl-β-CDs. Further, their NMR spectra were compared with methyl-β-CD and β-CD.

2. Method

2.1. General Methods

FT-IR spectra of the samples pressed with KBr in the framework region (400–4000 cm^{-1}) were recorded at room temperature with a MAGNA-IR 560 spectrometer. Mass spectra were determined on an LCQ Advantage MAX spectrometer (ESI). NMR spectra (^1H, 500.13 MHz; ^{13}C, 125 MHz) were recorded on a Varian INOVA 500 MHZ instrument. Approximately 30 mg of sample was directly dissolved into the NMR tube in 0.6 mL of solvent. ^1H and ^{13}C NMR spectroscopic data were recorded for solns in DMSO, using a Jeol GSX-500 or Jeol JNM-ECP 500 spectrometer (^1H: 500 MHz, ^{13}C: 125 MHz). Materials were purchased from Kewei Company of Tianjin University, China. β-CD was re-crystallized and dried before use under vacuum at 80 °C, anhydrous potassium carbonate, DEC, DMF, acetone, acetonitrile, ethyl acetate, ammonia water, and ether directly used without further treatment. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; Haiyang, Qingdao, China) and detection by iodine vapor.

2.2. General Procedure Ethyl-β-CDs

Anhydrous β-CD (4.00 g, 3.52 mmol) was added to DMF (150 mL) in a 250 mL three-necked flask equipped with a dropping funnel and a condenser. When the solution was stirred to clear, 1.0 g K_2CO_3 was added, 20 mL (10.7 g, 98 mmol) diethyl carbonate was added dropwise in 5 minutes, reaction temperature was controlled at 120 °C by oil bath under CO_2 atmosphere. The course of reaction was monitored by TLC (6:1:3:1 acetonitrile-EtOAc-H_2O-concd aq NH_3). Catalyst was separated by means of centrifugation after reaction. Then solvent and surplus DEC was removed in high vacuum at 60-95 °C. When the residue was concentrated till syrupy, 100 mL acetone was added. Product was scattered in acetone by quickly stirring, then acetone was removed by filtration, and powdered product was obtained. The product was marinated by anhydrous ether 2-3 times, white powdered product was obtained after filtration.

Ethyl-β-CD: As a white powder. Mp 353 °C; ^1H-NMR (500 MHz, DMSO): δ 4.85-5.10 (m 22H, 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 102.6 (7×C-1), 83.0 (7×C-4), 74.0 (7×C-3), 73.0 (7×C-2), 69.5 (7×C-5), 67.0-67.4 (7×C-6), 64.2-64.4 (6×C-CH_2), 14.3-14.8 (6×C-CH_3); MS (%) =1331 (100) m/z.

3. Results

A green synthesis of ethyl-β-CDs is described via DEC and β-CD. The strategy is shown in Figure 1.

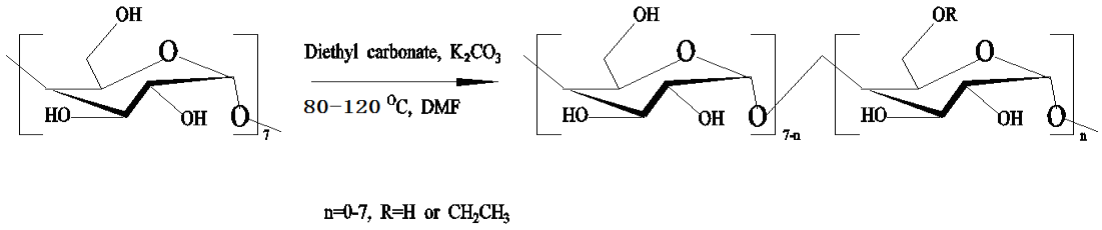

Figure 1. *Synthetic scheme for ethyl-β-CDs.*

N, N-Dimethylformamide (DMF) was found to be the appropriate medium in which the reaction of β-CD with DEC could be carried out well with anhydrous potassium carbonate as catalyst. During the whole process, the samples were held under a protective atmosphere of CO_2 flow in order to avoid oxidation. The products have physical properties in complete agreement with previous report [4, 8, 9]. A convenient, selective, novel and green synthesis of ethyl-β-CDs is reported in this paper. Ethylation is more difficult than methylation because of steric hindrance. Therefore, ethylation needs higher temperature than methylation [12].

Degree of substitution (DS) is the average number of substituted hydroxyls per glucopyranose unit of CD ring. Since the number of reactive hydroxyls per mole of glucopyranose unit is 3, the maximum numbers of substituents possible for α-, β-, and γ-CDs are 18, 21, and 24, respectively [13]. DS plays an important role in balancing the CD water solubility and its complexing ability. It was reported that increasing the degree of substitution up to an optimum level improves the CD aqueous solubility, but beyond that, the steric hindrances of the host molecule impair CD complexing capacity. The DS of ethyl-β-CD has a very significant effect on its solubility and drug solubilization, and it is an important character of ethyl-β-CD [13].

So the DS of ethyl-β-CD was studied in the paper. It was found that the reaction temperature, the molar ratio of β-cyclodextrin to diethyl carbonate, reaction time and contents of anhydrous potassium carbonate had infuence on the DS of ethyl-β-cyclodextrin.

Orthogonal experiment with three factors and four levels was designed on the base of the preliminary exploratory experiment. L9 (34) orthogonal experiment was adopted, and orthogonal experiment factors are in table 1.

Table 1. *Factors and levels of orthogonal test method.*

Level	A/ React temp.	B/ molar ratio of β-CD to DEC	C/ time	D/dosage
1	80°C	1:7	2h	1.0 g
2	100°C	1:14	16h	2.0 g
3	120°C	1:28	24h	3.0 g

CD: cyclodextrin; DEC: diethyl carbonate

The anlysis of orthogonal experiment result

The orthogonal experiment result was in the table 2. The intensity sequence of factors on DS are A, B, D, C form extreme differece anlysis. The optimum condition is $A_3B_3C_3D_1$.

The factor A, reaction temperature influenced the DS of ethyl-β-CD obviously, the DS of ethyl-β-CD is enhanced with the increasing reaction temperature. The factor B, molar ratio influenced the DS of ethyl-β-CD, the DS of ethyl-β-CD is enhanced with the increasing molar ratio. The DS of ethyl-β-CD was not changed obviously while the reaction time was prolonged. The factor D, the dosage of cat. influenced the DS of ethyl-β-CD obviously, neither.

Table 2. *Results of orthogonal experiments.*

Number	A	B	C	D	DS	yield
1	1	1	1	1	0.32	67.9%
2	1	2	2	2	0.40	62.4%
3	1	3	3	3	0.96	71.5%
4	2	1	2	3	2.67	58.3%
5	2	2	3	1	2.92	48.3%
6	2	3	1	2	3.29	64.2%
7	3	1	3	2	4.82	58.8%
8	3	2	1	3	5.69	62.9%
9	3	3	2	1	5.93	51.1%
K_1	1.68	7.81	9.30	8.27		
K_2	8.88	9.01	9.00	9.51		
K_3	16.44	10.18	8.70	9.32		
R	14.76	2.37	0.60	1.24		

DS: The average degree of substitution of ethyl-β-CD

4. Discussion

4.1. FTIR Analysis

Figure 2 shows IR spectra in the 3500-400 cm^{-1} region of ethyl-β-CD. IR spectroscopy was used to confirm the structure of the product, which exhibits the absorption peaks at 3322, 2926, 1661, 1448, 1370, 1412, 1156, 1080, 1030, 854，757, 581 cm^{-1}. We noted that samples after ethylation had relatively stronger peaks of CH_3 groups than those samples before ethylation, judging by the characteristic C-H asymmetric stretch (2926 cm^{-1}) and symmetric deformation (1370 cm^{-1}) in the methyl groups. The peaks at 1412, 854 cm^{-1} are characteristic of methyl and methene. The others are mainly consistent with the data of β-CD. These data were in agreement with the proposed structure [7].

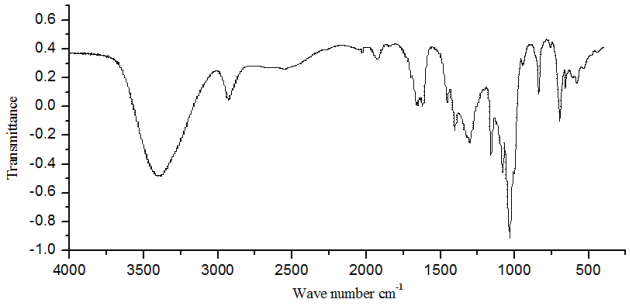

Figure 2. *IR Ethy-β-CD.*

4.2. MS Analysis

There are 1134, 1221, 1275, 1331, 1551, 1469 MS spectrum of the product in the MS spectrum. The DS of the product could be calculated according to the MS spectra [14]. The MS spectrum of 1331 is the 6 degree of substituted ethyl-β-CD, and other MS spectra are respectively the 0, 3, 5, 7, 9, 12 DS ethyl-β-CD.

Figure 3 shows the MS spectrum of ethyl-β-CD.

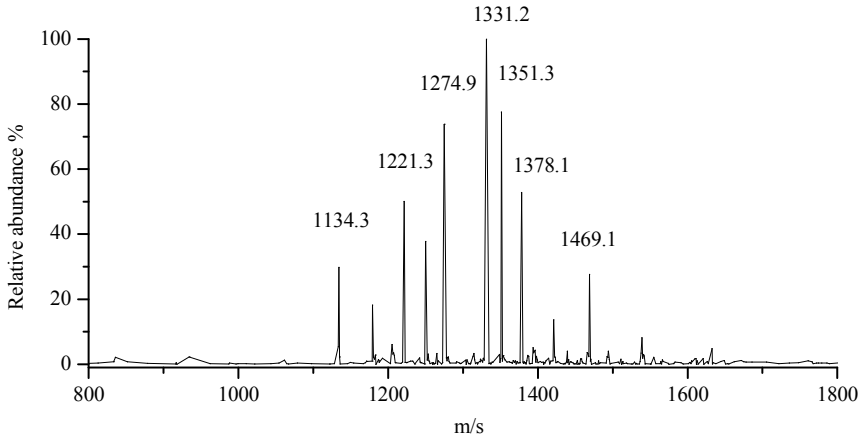

Figure 3. *MS spectrum of ethyl-β-CD.*

4.3. ^{1}H NMR Analysis

The ^{1}H-NMR spectrum was used for the structural analysis of the ethyl-β-CDs. The characteristic peaks of grafted ethyl at 4.10-4.30, 1.07-1.29 ppm for $–CH_2$ and $–CH_3$ protons, respectively, were detected by ^{1}H-NMR. DS could be calculated from the signals in nuclear magnetic resonance spectra. The region at 4.78-5.10 ppm is the protons of C-1 and OH groups of parental β-CD, 4.10-4.30 ppm is the protons of CH_2-groups of grafted ethyl, and 1.07-1.29 ppm is the protons of CH_3-groups of grafted ethyl. The integration ratio between the peak at δ= 4.10-4.30 ppm and the peak at δ = 1.04-1.29 ppm is close to 0.67, which indicates that they belong to the same ethyl group. The region at 4.78-5.10 ppm was compared to the region at 1.07-1.29 ppm, there are 28 protons at 4.78-5.10 ppm region for the protons of parental β-CD. The region at 4.78-5.10 ppm was compared to the region at 1.04-1.29 ppm, so the protons of CH_3-groups of grafted ethyl and the DS of product could be calculated. The conclusion coincides with the analyses of MS in the main.

4.4. ^{13}C-NMR Analysis

Table 3 summarizes ^{13}C-NMR chemical shifts of ethyl-β-CDs in DMSO-d_6 in comparison with β-CD and methyl-β-CD. The reaction position was shown to be the C-6 hydroxyl of β-CD in view of the clear shift of C-6 from 59.9 to 67.0-67.4 ppm in the ^{13}C-NMR spectrum, with no clear shift for C-2 and C-3 when compared with the original ^{13}C-NMR spectrum of β-CD. Hydroxyl position (OH-6) of the β-CD substituted lead to the shift of C-2 from 72.4 to 79.0-82.0 ppm in the ^{13}C-NMR spectrum in references 12, 15 and 4. Preferential ethylation at the primary hydroxyl position (OH-6) of the β-CD 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 3. *^{13}C-NMR of ethyl-β-CD, methyl-β-CD and β-CD.*

δ	β-CD [4]	methyl-β-CD [12, 15]	ethyl-β-CD [4]	ethyl-β-CD This paper
C-1	101.9	99.1-102.6	100.7	102.6
C-2	72.4	79.0-82.0	80.0	73.0
C-3	73.0	81.3-82.5	72.9	74.0
C-4	81.5	82.2-83.5	82.9	83.0
C-5	72.0	72.6-72.9	69.9	69.5
C-6	59.9	60.7-61.0	68.7	67.0-67.4
$-CH_2-$			67.2-65.5	64.2-64.4
$-CH_3$		58.8-61.4	15.0-15.1	14.3-14. 8

a All samples are in the solvent of DMSO.

5. Conclusion

Thus, a convenient, simple, efficient, novel and green synthesis of ethyl-β-CD is developed. In the present paper the green ethyl-β-CDs were synthesized through the reaction between green ethylation reagent DEC and β-CD by using anhydrous potassium as catalyst. This method is more environmentally friendly than the reported.

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