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A novel synthesis of ethyl carbonate derivatives of β-cyclodextrin

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ABSTRACT

The carbonate ester derivatives of β-cyclodextrin play a very important role in several fields, such as catalytic reaction and enantiomer separation. In this work, a novel synthesis process of the β-cyclodextrin carbonate ester has been investigated through the reaction between β-cyclodextrin and diethyl carbonate with anhydrous potassium carbonate as catalyst. The compounds were separated by semi-preparative chromatography and characterized by FT-IR, MS, ^{1}H NMR, and ^{13}C NMR spectroscopy. The position of the substituent was confirmed by ^{13}C NMR and this conclusion coincides with the analyses of MS and ^{1}H NMR in the main. The yield of the mono-6-O-ethoxycarbonyl β-CD is 65.8%.

1. Introduction

With cyclodextrins (CDs) discovered as degradation products of starch, first reported in 1891 by Villiers, many kinds of CDs were prepared and isolated.[1] Typical CDs called α-CD, β-CD, and γ-CD are composed of six, seven, and eight α-D-(1,4) glucopyranoside moieties, respectively. More than 95% of research on CDs is about β-CD.[2] The β-CD is a truncated cone-shaped macrocyclic molecule with a hollow, tapered cavity with an inside diameter of 6.0–6.5 Å and height of 7.9 ± 0.1 Å.[1] The interior of the cavity is composed of hydrogen atoms of C-3, C-5 and oxygen atoms of the glycosidic linkage, which make the intracavity hydrophobic while the exterior of the cavity is hydrophilic due to the assembly of alcoholic hydroxyl groups. Compared with β-CD, numerous chemical modifications of β-CD have more satisfactory water solubility, physicochemical properties, inclusion capability, and enantioresolution properties.[3] The functional groups used in the modifications of β-CD included alkyl-, hydroxyalkyl-, alkylcarboxy-, amino-, glucosyl-, etc.[4] Two primary factors need to be considered in the chemistry of β-CD for their modification. Firstly, the nucleophilicity of the different hydroxyl groups and, secondly, the ability of β-CD to complex with the reagent used. Of the three types of hydroxyl groups, those at the C-6 position are the most reactive in kinetic conditions (and often the most nucleophilic), those at the C-2 position are the most acidic, and those at the C-3 position are the most hindered. These differences in reactivity can easily explain the possibility of access to β-CD with modification at the C-6 position. In particular, a large proportion of derivatives of β-CD is the ester derivatives of β-CD. They are of great theoretical and practical significance for the improvement of the β-CD solubilization, the inclusion performance, the enantioresolution properties, and the catalytic properties. Zerbinati[5] investigated that the ethyl carbonate derivative of β-CD showed the best enantiomer resolution properties, compared with both native and derivatized β-CD commercially available. Gordano's[6] research revealed that the β-CD acyclic carbonate ester derivative showed an effective catalytic action when incorporated in PEEK-WC membranes, by showing an enzyme-like behavior. Natoli[7] researched the performance of catalytic β-CD carbonate membrane reactor in PNPA hydrolysis.

In the previous, carbonate derivatives of β-CD are obtained via a synthetic procedure based on the use of α,ω-diols activated with carbonyldiimidazole.[8] The synthesis of carbonate derivatives of β-CD included a series of protection and deprotection steps, and the toxic materials of aromatic disulfonyl chlorides were used in the past. The aim of our work is to report a novel synthesis of ethyl carbonate derivatives of β-CD. In this work, we successfully investigated a novel synthetic process through the reaction between β-CD and diethyl carbonate (DEC) with anhydrous potassium carbonate (K_2CO_3) as catalyst in *N*,*N*-dimethylformamide (DMF).[9] The synthesis is achieved in one step without protection or deprotection steps in this paper. The process is simple, convenient, and innoxious for the use of environmentally friendly ethoxycarbonylating reagent diethyl carbonate (DEC). These derivatives were separated by semi-preparative chromatography and characterized by FT-IR, MS, ^{1}H NMR, and ^{13}C NMR spectroscopy. The position of the substituent is at the C-6 position confirmed by ^{13}C NMR and the conclusion coincides with the analyses of ^{1}H NMR in the main. We obtained the pure ethyl carbonate derivatives of β-CD and the yield of mono-6-O-ethoxycarbonyl β-CD is 65.8%.

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2. Results and discussion

2.1. Synthesis of ethyl carbonate derivatives of β-CD

DEC, like dimethyl carbonate (DMC), is of great concern in recent years as new green chemical raw materials. Tundo[10] undertook a lot of research on DMC and got the conclusion that in the presence of a nucleophile (Y^-) DMC can react either as a methoxycarbonylating or as a methylating agent on the basis of the experimental conditions. Higher homologs of dialkyl carbonates exhibit alkylating/carboxyalkylating reactivity and selectivity similar to that of DMC. The main difference concerns the reaction rates, which undergo a neat decrease according to the steric expectations for nucleophilic displacements as the alkyl chain of the carbonate increase. According to his conclusion, we can infer the reaction of β-CD (Y^-) and DEC. So a green synthesis of ethyl carbonate derivatives of β-CD is described and the strategy is shown in Scheme 1.

The synthesis of ethyl carbonate derivatives of β-CD is a typical transesterification process. Transesterification, or ester alcoholysis reaction, is such a reaction in which esters and alcohols interact to generate a new ester and a new alcohol catalyzed by acid or alkaline. Transesterification is based on the reversibility of the esterification. There are always a small amount of free alcohol and acid in the solution of the ester. When a new kind of alcohol is added to the ester solution, esterification is supposed to occur between the new alcohol and the free acid. New ester is produced constantly along with the old one breaking down into corresponding alcohol (free alcohol) and acid (free acid). Due to the reversibility of the esterification, the transesterification could not occur unless the stability of the newly generated ester is stronger than that of the old one or the new alcohol is continuously steamed during the reaction. The β-CD is a kind of alcohol containing multiple hydroxyl groups and DEC is a carbonic ester. Ethyl carbonate derivatives of β-CD and ethanol are expected to emerge via the reaction between them catalyzed by anhydrous potassium carbonate. The new ethanol was continuously steamed in the reaction and ethyl carbonate derivatives of β-CD are stable and less volatile, so the reaction occurred smoothly and ethyl carbonate derivatives of β-CD were successfully synthesized.

2.2. FT-IR analysis

To confirm the structure of the product, FT-IR spectra of the β-CD and the pure product which was obtained by semi-preparation chromatography were evaluated and presented in Figure 1. Figure 1 shows the IR spectra of the β-CD before and after being modified by DEC. We noted that samples after synthesis had relatively stronger peaks of CH_3 groups than those samples before synthesis, judging by the characteristic C–H asymmetric stretch (2960 cm^{-1}) and symmetric deformation (1380 cm^{-1}) in the methyl groups. This observation suggested that the samples after synthesis increase the number of methyl groups. At the same time, the existence of methylene was also supported by the fact that the IR band at 2920.41 cm^{-1} belonging to the ethyl-carbonate groups, judging

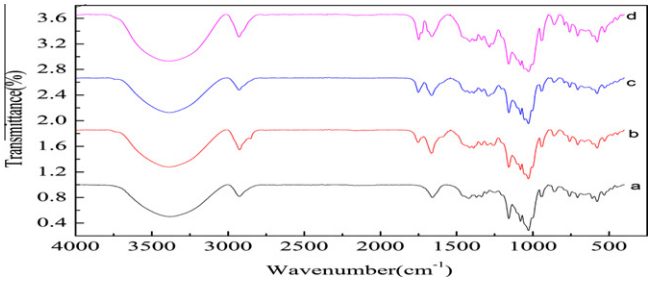


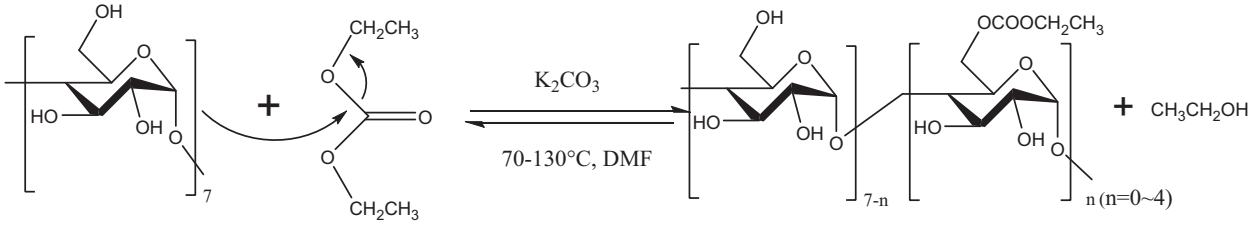
Figure 1. FT-IR spectra of the β-CD (a), the pure mono- (b), di- (c) and tri- (d) substituted 6-O-ethoxycarbonyl β-CD.

by the characteristic C–H vibration bands of CH_2 symmetric (sym, 2850 cm^{-1}) and asymmetric (asym, 2921 cm^{-1}) stretch, could be observed in the specimen after synthesis. The intense band at 1751.62 cm^{-1} observed for only samples after synthesis can be assigned to C=O stretch in ester carbonyl group and another important characteristic band can be at 1157 cm^{-1} due to C–O(–C) stretching vibrations. The much broader absorption peaks in the regions of 3500 cm^{-1} are O–H bonds. The broad peak at 3500 is characteristic peak of hydroxyl groups. In Figure 1, there is a group of absorption peaks at 3384 cm^{-1}, which is due to stretching bands of the OH groups, and the band at 1664 cm^{-1} corresponds to bending bands of the OH groups. A slight reduction can be seen in the intensity of the O–H stretch because a hydrogen atom of the hydroxyl group has been substituted by the ethyl-carbonate groups after synthesis. The others are mainly consistent with the data of β-CD.

2.3. Mass spectrometry

The crude product is obtained when the molar ratio of DEC to β-CD, the reaction temperature, and the reaction time are 28:1, 110 °C, and 16 h, respectively. The molecular ions of the crude products were observed at m/z = 1158.3, 1230.3, 1302.9, 1374.6, and 1446.2 in positive ion mode corresponding respectively to $[M_0+Na^+]$, $[M_1+Na^+]$, $[M_2+Na^+]$, $[M_3+Na^+]$, and $[M_4+Na^+]$.[11] The degree of substitution (DS) of the product could be calculated according to the MS spectra. The MS spectrum of 1230.3 is the 1 degree of substituted ethyl carbonate derivatives of β-CD, and other MS spectra are respectively 2, 3, 4 degrees of substituted ethyl carbonate derivatives of β-CD. The average degree of substitution estimated from the distribution of the mass spectrum peaks is 2.02.

The pure product was obtained by semi-preparative chromatography and the electrospray mass spectra of the pure mono-substituted 6-O-ethoxycarbonyl β-CD are presented in Figure 2. By using negative ion mode electrospray ionization, well defined and clearly separated signals were obtained in the mass spectra of the pure product. Each peak corresponds to mono anions formed by loss of one proton ion from the product and addition of one [$HCOOH^-$] to the product. The molecular ions were observed at m/z = 1179.5, 1251.5, 1323.4, and 1395.2 corresponding to $[M_0+HCOOH^-]$, $[M_1+HCOOH^-]$, $[M_2+HCOOH^-]$, and $[M_3+HCOOH^-]$.



Scheme 1. Synthetic scheme for ethyl carbonate derivatives of β-CD.