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Understanding cyclic by-products and ether linkage formation pathways in the transesterification synthesis of aliphatic polycarbonates

Qiang He, Qing Zhang, Shurui Liao, Changsheng Zhao, Xingyi Xie*

College of Polymer Science and Engineering, Sichuan University, Chengdu, Sichuan 610065, China

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ABSTRACT

An overall picture of the reaction pathways towards the side products and final polymers during the transesterification synthesis of biodegradable aliphatic carbonates (APCs) were delineated for the first time. Catalysed by sodium ethoxide, the normal reaction between α,ω-diols (carbon number n = 2–6) and diethyl carbonate generates APC oligomers with propagating terminal alkoxide anions. These anions can backbite at the nearest carbonate carbons or the nearest carbonate α-CH_2 carbons in the same APC chains, eliminating corresponding cyclic carbonates or cyclic ethers. Also, each alkoxide anion can randomly attack a carbonate α-CH_2 carbon in another APC chain, generating ether linkages in the final polymers whose percentages are about 100%, 1.35%, 0.08% and 0% for n = 2, 3, 4 and 5, respectively. The content of cyclic carbonates shows a similar decreasing trend; ethylene carbonate (n = 2) even predominates over the final polymer while trimethylene carbonate (n = 3) and 1,4-butylene carbonate (n = 4) are only minor by-products. Moreover, the latter two cyclic carbonates are not stable enough and can further decarboxylate, forming relatively high amount of allyl alcohol and tetrahydrofuran, respectively. However, trimethylene oxide (n = 3) and tetrahydropyran (n = 5) are minor cyclic ethers. The thorough understanding of the chemical process is essential to improve the APC synthesis.

1. Introduction

Aliphatic polycarbonates (APCs) have received increasing attention in biomedical applications since the 1990s [1,2], owing to their good biocompatibility and unique biodegradation patterns. They are considerably resistant to hydrolytic degradation [3,4], but highly sensitive to enzymatic degradation [4–7]. They degrade *in vivo* by surface erosion without changing the remaining bulk [4,8], releasing neutral degradation products with minimal foreign body reactions [8,9]. Consequently, they are promising biodegradable scaffolds to induce tissue regeneration [10–12], and excellent drug delivery carriers [12,13] for proteins and plasmid DNAs that are sensitive to local pH values. Indeed, these biological macromolecules can be denatured by the acidic degradation products from aliphatic polyesters such as polylactide and its copolymers [14,15]. Furthermore, acidic products can catalyse the degradation process on the one hand, especially in the bulk material where they accumulate through degradation [16], while on the other hand they cause aseptic inflammation *in vivo* after being released into the surrounding tissues [17].

Several methods have been explored to synthesise APCs. Copolymerisation of cyclic ethers and CO_2 is suitable for APCs in which the carbonate linkages are separated by two carbon atoms like poly (ethylene carbonate) and poly(1,2-propylene carbonate) [18,19]. Recently, this method has been extended to synthesise poly(trimethylene carbonate) (PTC) from oxetane (i.e. trimethylene oxide, TMO) and CO_2 [20]. Ring-opening polymerisation of cyclic carbonates is very effective for the generation of high molecular weight APCs. However, suitable monomers are largely confined to six-membered trimethylene carbonate (TMC) and its derivatives with functional side groups [2,21–26]. Smaller monomers, ethylene carbonate (EC) and 1,2-propylene carbonate, undergo severe decarboxylation during the polymerisation and form over 50% ether linkages in the final polymers [27,28]. The larger cyclic carbonates are less competitive because of their quite low synthesis yields. Poly(1,4-butylene carbonate) (PBC) has been synthesised from its seven-membered cyclic carbonate monomer. The synthesis yield of this monomer is only 30% [29]. APCs in which the carbonate linkages are connected by five, six and ten methylene groups are available from their corresponding cyclic carbonate dimers whose reported yields are 30% [30], 11% [31] and 9.3% [32], respectively.

Unlike the aforementioned methods, transesterification synthesis from dialkyl carbonates and aliphatic diols is almost suitable for all types of APCs. The most used carbonyl source is dimethyl or diethyl carbonate that can be synthesised from CO_2 and corresponding alcohol [33,34]. This is a green process that consumes CO_2 to relieve global

* Corresponding author.
E-mail addresses: xiexingyi@263.net, xiexingyi@scu.edu.cn (X. Xie).

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warming. Moreover, the cyclic carbonates for ring-opening polymerisations are mainly obtained by the thermal degradation of polycarbonate oligomers that are synthesised by transesterification as well [29–32]. For these reasons, the transesterification synthesis is fundamentally important. Early investigations using this method resulted in low molecular weight APCs [35–37], the most successful application of which is to serve as soft segments in polyurethanes showing excellent hydrolytic and oxidative stability [37–39]. The recent advances in the art and catalyst optimisation have achieved high molecular weight APCs with good mechanical properties [6,40,41]. For example, poly (hexamethylene carbonate) (PHC) with M_w of 166,000 g/mol was synthesised via transesterification using a TiO_2/SiO_2-based catalyst [6]. The tensile strength (40.0 MPa) and elongation at break (over 500%) were comparable to those of polypropylene, a widely used plastic.

Despite the remarkable advances in the transesterification synthesis of APCs, the chemical process is not crystal clear. For example, tetrahydrofuran (THF) has been detected during the synthesis of PBC by several researchers [6,7,42,43]. However, no clear mechanism regarding its formation has been available until now. With this in mind, we systematically investigated the transesterification between diethyl carbonate and aliphatic diols with carbon numbers from 2 to 6, focusing on any by-products formed during the polycarbonate polymerisation. Two new by-products, allyl alcohol (AAl) and 1,4-butylene carbonate (BC), were identified. An overall picture of the reaction pathways towards the side products and final polymers was delineated for the first time. We believe this deep understanding of the transesterification synthesis of APCs to be essential to improve the synthesis and to control the quality of the final polymers.

2. Materials and methods

2.1. Materials

Diethyl carbonate (DEC, from Aladdin Chemistry Co., Shanghai, China) and various α,ω-diols (referred as C_n diol, n = 2–6 representing the carbon number) were used as starting materials. Ethylene glycol (C_2 diol) and 1,4-butanediol (C_4 diol) were from Kelong Chemical Reagent Plant (Chengdu, Sichuan, China) while 1,3-propanediol (C_3 diol) was from Nanjing Arima Trade Co., Ltd. (Nanjing, Jiangsu, China). The other diols 1,5-pentadiol (C_5 diol) and 1,6-hexanediol (C_6 diol) were purchased from Aladdin Chemistry Co. (Shanghai, China). Sodium ethoxide, also from Aladdin Chemistry, served as a transesterification catalyst.

2.2. Synthesis of polycarbonate oligomers

As shown in Scheme 1, a three-stage method was adopted to synthesise APCs. In stage I, weighed C_n diol (n = 2, 3, 4, 5 or 6, e.g. C_4 diol 34.70 g), DEC (0.35 mol or 41.35 g) and sodium ethoxide (0.176 g or 2.6 mmol) were charged into a 100-mL three-necked round-bottomed flask which was equipped with a mechanical stirrer, a nitrogen inlet, a Liebig condenser and a thermometer. Note that the molar ratio of each C_n diol to DEC was set as 1.1:1 (C_n diols were overdosed to synthesise APC diols as polyurethane soft segments). The temperature was raised to 90–100 °C within 20 min, and the whole mixture was refluxed at this temperature for 2 h. Ethanol was released into the reaction system with the advance of the transesterification reaction. In stage II, the Liebig condenser was quickly replaced by a 20-cm-long Vigreux fractionating column. The reaction temperature was then gradually increased to 150 °C in 3 h and then maintained for 1 h to remove the ethanol by distillation. The distillate was kept for further characterisation. In stage III, the fractionating column was replaced by a short-path still head, and a vacuum was applied to the whole system to further remove ethanol and other possible by-products. A final reaction pressure of about 90 kPa was achieved in about 2 h. For C_2/DEC system, the final mixture was distilled out under this low pressure, and then characterised without further purification. For the other systems, all of the viscous final products remained in the flasks. Each product was cooled, dissolved in methylene chloride, washed with water, precipitated with *n*-heptane, and finally dried in vacuum at 80 °C for 3 h. All of the intermediate solutions and final products were characterised to identify their compositions and structures.

2.3. Control reactions

To understand the by-product formation pathway during the transesterification, ethyl butyrate was used to replace DEC to react with equimolar C_3, C_4 and C_5 diols (0.28 mol) respectively, in the presence of sodium ethoxide (2.1 mmol) as well. The molar ratio of catalyst to diol was the same as that in the APC synthesis. Since ethyl butyrate and DEC possess similar boiling points (121.3 °C vs. 125.8 °C), the reaction process was almost the same as that described above for APC synthesis, but without vacuum reaction stage. The reaction products were carefully characterised as well.

2.4. Characterisations

^1H and ^{13}C NMR spectroscopy were used to characterise the chemical structures of all the intermediate solutions and final products. The distillates from both APC and control syntheses were qualitatively characterised by gas chromatography-mass spectrometry (GC-MS). The identified minor components, i.e·THF and tetrahydropyran (THP), were quantified using corresponding external standards (A.R. grade, both from Aladdin Chemistry Co., Shanghai, China). The reaction mixtures in Stage I and II were characterised by electrospray ionisation mass spectrometry (ESI-MS). Selected final products (PTC and PBC oligomers) were characterised by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS). The details about these characterisations can be found in the Supporting Information (SI).

3. Results

3.1. Identifying the intermediate products during the APC synthesis

To understand the APC polymerisation process, all of the intermediate solutions (the refluxed and bottom mixtures, and the top distillates, Scheme 1) were characterised thoroughly by both NMR and mass spectrometry (ESI- or GC-MS). These methods confirmed the formation of both linear APC oligomers (with ether linkages in some cases) and cyclic by-products due to the reaction between C_n diols and DEC. The chemical structures of these oligomers and by-products are shown in Scheme 2. The detailed NMR and MS data of the by-products are summarised in Table S1. The 400 MHz ^1H NMR spectrum of THP is not available from the literature and is therefore shown in Fig. S1. It is worth noting that all of the raw materials contained none of the detected by-products, as revealed by GC-MS (Fig. S2).

The ^1H NMR spectra of the C_2/DEC system (Fig. 1) reveal the presence of a large amount of EC in both the refluxed and bottom mixtures. The generated polymer mainly contained ether linkages (peak e, Fig. 1). Both cyclic carbonate by-product (TMC) and ether linkages can be found in C_3/DEC system as well (Fig. 2), but not so prominent. The presence of EC and TMC was further proved by ^{13}C NMR spectroscopy (Fig. 3A). Additional by-products in the C_3/DEC system, allyl alcohol (AAl) and TMO, were confirmed by means of both ^1H NMR (Fig. 2) and GC-MS (Fig. 4A).

The C_4/DEC and C_5/DEC systems produced THF and THP, respectively, as revealed by the ^1H NMR spectra of the top distillates (Fig. 3B). Also, their structures were confirmed by GC-MS (Fig. 4B and C). No by-product was found in the C_6/DEC system.

For the completeness of data, the detailed NMR spectra from C_2 to C_6/DEC systems are displayed in Figs. S3–S7. No more by-product formation can be found in these supporting spectra, except that the