Macromolecules

Volume 40, Number 10 May 15, 2007

Communications to the Editor

End-Group-Catalyzed Ring-Opening Polymerization of Trimethylene Carbonate

Jonas Mindemark, Jöns Hilborn, and Tim Bowden*

Department of Materials Chemistry, Polymer Chemistry, Uppsala University, Box 538, SE-751 21 Uppsala, Sweden

Received December 19, 2006
Revised Manuscript Received March 28, 2007

Resorbable and biodegradable polyesters are of great interest for various biomedical as well as ecological applications, including drug-delivery systems and tissue engineering.[1] Such materials can be synthesized with a high level of control through ring-opening polymerization (ROP) of cyclic esters, most often accomplished using organometallic catalysts. This has however raised concerns over metallic residues in the final polymer material with release upon degradation. Organocatalysts are thus attractive alternatives to the predominant organometallics, as there is no concern of contamination, waste, and the removal of metals.[2] Over the past couple of years we have seen great progress in the development of organocatalysts for the controlled ROP of cyclic esters, first reported by Nederberg et al. on poly(lactide) synthesis catalyzed by strongly basic amines.[3] This work has been followed by a variety of nucleophilic ROP catalysts, including phosphines[4] and N-heterocyclic carbenes,[5] the latter having proved to be a most versatile catalyst platform, capable of polymerizing a wide range of monomers such as ϵ-caprolactone, β-butyrolactone, and δ-valerolactone. Just recently, thiourea−amine catalyst systems[6] as well as triazabicyclodecene[7] were presented as useful strategies for organocatalytic polymerization of lactide and other cyclic esters.

These developments have however until just recently only concerned the ROP of lactides and lactones. Another cyclic ester monomer of biomedical interest is trimethylene carbonate, TMC, a cyclic carbonate ester that can be ring-opened to yield poly(trimethylene carbonate), PTMC, first reported in 1930 by Carothers and Natta.[8] PTMC is biodegradable in vivo through a probable enzymatic mechanism while at the same time being significantly more resistant to in vitro hydrolysis than, e.g., poly(ϵ-caprolactone).[9]

PTMC has so far been synthesized using several initiator/catalyst systems[10] including tin-, bismuth-, and zinc-containing species.[11] A recent development toward more benign catalyst systems has been achieved using metal salen complexes based on the low-toxicity metals zinc, magnesium, and calcium.[12]

There have also been reports of syntheses that have employed lipase enzymes as catalysts for the preparation of TMC homo- and copolymers,[13] but they have all suffered from lack of molecular weight control as well as broad molecular weight distributions at high monomer conversions, especially for TMC homopolymers.

Given the recent developments in the field of organocatalytic ROP of lactides and lactones, such simple, all-organic catalysts could be an alternative strategy for the ROP of cyclic carbonates. Indeed, Nederberg et al. recently reported on the successful ROP of TMC using several organocatalysts, including nucleophilic species.[14]

Here we present the novel concept of a controlled self-catalyzed polymerization reaction, yielding well-defined α,ω-heterotelechelic polymer chains and at the same time eliminating low molecular weight catalyst residues in the final polymer product. This has been accomplished by utilizing the tertiary amine 2-(dimethylamino)ethanol (DMAE) as an efficient catalyst for the ROP of TMC. The catalytic behavior of DMAE was investigated in bulk polymerizations of TMC at temperatures down to slightly above the monomer melting point (46−48 °C), well below the temperatures at which spontaneous polymerization of TMC is known to occur.[15] The results of these experiments are summarized in Table 1. The molecular weights were kept relatively low to facilitate easy end-group analysis by ^{1}H NMR spectroscopy. Figure 1 illustrates the linear correlation between the degree of polymerization and monomer conversion found in the experiments, consistent with a controlled polymerization. Further support for this notion is given by the narrow molecular weight distributions and the high level of molecular weight control. It was in fact found that it was

* Corresponding author. E-mail: tim.bowden@polymer.uu.se.

10.1021/ma0629081 CCC: $37.00
Published on Web 04/18/2007

Table 1. Bulk Polymerizations of TMC Using DMAE and DMAEB as Catalysts

entry	catalyst−initiator system[a]	T (°C)	t (h)	[M]/[I][b]	conversion (%)[c]	DP[c]	PDI[d]
1	DMAE[e]	50	4	30	94	31	1.27
2	DMAE[e]	50	6	40	96	45	1.29
3	DMAE[e]	50	89	40	>99	43	1.83
4	DMAE[e]	50	9	60	90	54	1.24
5	DMAE[e]	50	13	80	90	72	1.43
6	DMAE[e]	60	3.5	40	98	44	1.47
7	DMAE[e]	80	2	40	>99	44	1.72
8	DMAEB (1 equiv)−$PhCH_2OH$	50	7.5	40	84	31	1.26
9	DMAEB (0.5 equiv)−$PhCH_2OH$	50	7.5	40	97	39	1.24
10	DMAEB (0.2 equiv)−$PhCH_2OH$	50	14.5	40	99	38	1.30
11	DMAEB (0.1 equiv)−$PhCH_2OH$	50	17	40	97	38	1.22
12	DMAEB (0.05 equiv)−$PhCH_2OH$	50	29	40	89	32	1.21
13	DMAEB (0.2 equiv)−$PhCH_2OH$	50	16.5	60	95	55	1.29
14	DMAEB (0.4 equiv)−$HO(CH_2)_4OH$	50	4	30	>99	31	1.26
15	DMAEB (0.4 equiv)−$HO(CH_2)_4OH$	50	5.5	40	>99	40	1.33
16	DMAEB (0.4 equiv)−$HO(CH_2)_4OH$	50	8	60	97	58	1.37

[a] Equivalents of DMAEB catalyst relative to initiating alcohol are given in parentheses. [b] Monomer-to-initiator ratio (DMAEB catalysis) or monomer-to-catalyst ratio (DMAE catalysis). [c] Determined by ^{1}H NMR. [d] Determined by GPC. [e] Bifunctional initiation by DMAE catalyst.

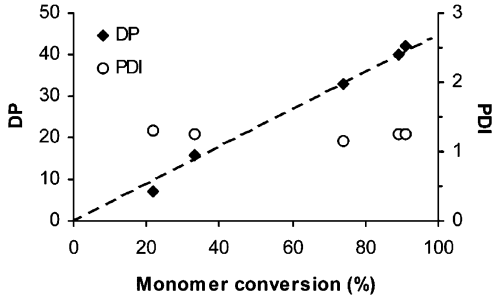
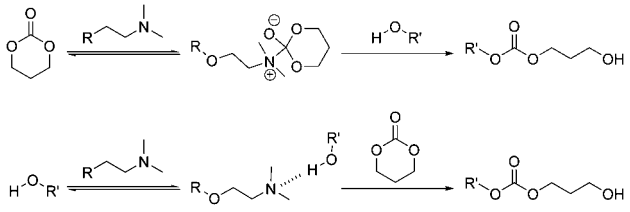


Figure 1. Bulk ring-opening polymerizations of TMC bifunctionally catalyzed and initiated by DMAE. The targeted degree of polymerization was 40.

Scheme 1. Proposed Mechanisms for the ROP of TMC Catalyzed by DMAE and DMAEB: Monomer-Activating Mechanism (Top) and Alcohol-Activating Mechanism (Bottom)



possible to achieve molecular weight distributions that were significantly narrower than those typically reported for PTMC synthesized using conventional catalysts.[11] The polydispersities remained low even at high monomer conversions, but prolonged reaction times after full conversion led to a broadening of the molecular weight distribution (entry 3), not unlike what can be seen when using organometallic catalysts.[16] The same was true for increased reaction temperatures (entries 6 and 7).

The catalytic mechanism is believed to be analogous to previously reported nucleophilic ROPs of cyclic ester monomers,[3−5,14] requiring an alcohol as the initiating species, thus enabling molecular weight control by means of the monomer/initiator ratio. By carrying a tertiary amine as well as an alcohol functionality, in the initiating step DMAE is bifunctional, acting as both the catalyst and the initiator. There are two likely pathways for the initiation step: one monomer-activating and one alcohol-end-group-activating mechanism (Scheme 1). By ^{1}H NMR spectroscopy (Figure 2) we have confirmed that the DMAE catalyst is attached to the growing polymer chain, revealed by a downfield shift from 2.44 to 2.56 ppm of the triplet from the methylene protons adjacent to the DMAE dimethylamino group as well as the disappearance of the triplet from the DMAE methylene protons adjacent to the hydroxyl group at 3.58 ppm, consistent with the formation of a carbonate ester linkage.

Just as for the initiation, there are several plausible mechanisms for the propagation of the polymerization reaction, the most likely being monomer-activating and chain end-activating mechanisms similar to the proposed initiation mechanisms (Scheme 1). In the case of DMAE catalysis/initiation, however, the propagation is actually catalyzed by the growing polymer chain α-end functionality, making the propagation step a uniquely self-catalyzed reaction. Furthermore, as the catalyst species is incorporated into the polymer chain, the polymerization does not lead to any products other than the desired polymer, thus effectively eliminating the need for removal of the catalyst or any other potentially detrimental species from the final product.

To further investigate the catalytic activity of DMAE and at the same time creating a more versatile catalyst, 2-(dimethylamino)ethyl benzoate (DMAEB) was synthesized[17] to be used as a model substance. The benzoic acid ester of DMAE was selected because of its straightforward synthesis and easy recognition of the aromatic benzoate group in ^{1}H NMR spectroscopy. By blocking the initiating hydroxyl group of DMAE by esterification, the catalytic behavior of the nucleophilic dimethylamino group could be isolated. The catalyst activity of DMAEB was then investigated in bulk ROP of TMC using primary alcohols (benzyl alcohol and 1,4-butanediol) as initiating species. The results of these experiments can be seen in Table 1. Indeed, the benzoic acid ester of DMAE also proved to be a potent catalyst of the ROP of TMC. The ^{1}H NMR spectra were consistent with

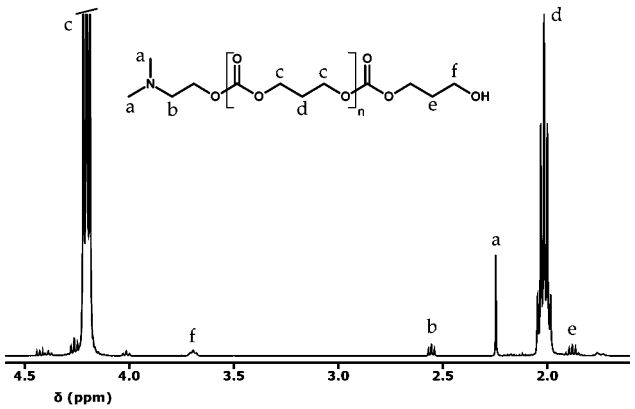


Figure 2. ^{1}H NMR spectrum of DMAE−PTMC.

initiation by the alcohol species, showing the anticipated downfield shift in the peak from the methylene protons adjacent to the initiating hydroxyl group, confirming the polymer chain end incorporation of the initiating alcohol. This was further supported by the high level of molecular weight control. The DMAEB catalyst was seemingly unaffected as judged by ^{1}H NMR and could be efficiently removed by passing the polymer, dissolved in acetonitrile, through a column of cation-exchange resin (H^+ form). After evaporation of the solvent, ^{1}H NMR confirmed the removal of DMAEB as well as the polymer being left unaffected by the treatment.

The ROP of TMC catalyzed and initiated by DMAE does not only yield well-defined polymers of controlled molecular weights and low polydispersities, but the polymer chains are also α,ω-heterotelechelic, bearing the same distinct functional end groups as the DMAE initiator molecule. This provides an outstanding opportunity for creating new functional macromolecular architectures. The results obtained using DMAEB furthermore show that it is possible to use this DMAE derivative as a highly active catalyst for the ROP of TMC. This opens up the possibility for tailoring efficient catalysts for nucleophilic ROP through DMAE derivatization.

Acknowledgment. Uppsala University, Sweden, is acknowledged for financial support. Fibre and Polymer Technology at the Royal Institute of Technology, Sweden, is acknowledged for generously providing access to the GPC instrumentation.

Supporting Information Available: Experimental details and additional NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Benzoyl chloride (3.0 mL, 26 mmol) was dissolved in 100 mL of diethyl ether and cooled in an ice bath. DMAE (2.0 mL, 20 mmol) was slowly added dropwise under stirring, yielding immediate precipitation of 2-(dimethylamino)ethyl benzoate hydrochloride. The ice bath was removed, and another 150 mL of diethyl ether was added. The mixture was left under stirring overnight, after which the white salt was filtered off, washed with diethyl ether, dissolved in 40 mL of 1 M NaOH, and extracted with 80 mL of diethyl ether. The organic phase was separated, dried with $MgSO_4$, and filtered, and the solvent was removed through rotational evaporation, yielding 2.8 g (73%) of 2-(dimethylamino)ethyl benzoate (DMAEB) as a clear liquid. ^{1}H NMR ($CDCl_3$): $\delta = 2.33$ (s, 6H, $-N(CH_3)_2$), 2.70 (t, 2H, $-CH_2-N$), 4.42 (t, 2H, $-CH_2-CO$), 7.38−7.47 (m, 2H, Ar−H), 7.51−7.58 (m, 1H, Ar−H), 8.00−8.09 (m, 2H, Ar−H).

MA0629081