



Proceeding

Synthesis of degradable polyMMA via copolymerization with cyclic ketene acetals

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Abstract: Copolymerization of the cyclic ketene acetal 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) with methyl methacrylate (MMA) is studied with respect to its copolymerization parameters and the suitability to control BMDO/MMA copolymerizations via the reversible addition-fragmentation chain transfer (RAFT) technique to obtain linear and 4-arm star polymers. BMDO shows disparate copolymerization behavior with MMA and $r_1 = 0.33 \pm 0.06$ and $r_2 = 6.0 \pm 0.8$ have been determined for polymerization at 110 °C in anisole from fitting copolymer composition vs. comonomer feed data to the Lewis-Mayo equation. Copolymerization of the two monomers is successful in RAFT polymerization employing both a linear and a tetra-functional control agent. As desired, polymers contain only little amount of polyester units stemming from BMDO units and preliminary degradation experiment show that the polymer degrades slowly but steadily in aqueous 1 M NaOH dispersion. Within ten days, the polymers are broken down to low molecular weight segments from an initial molecular weight of $M_n = 6000 \text{ g}\cdot\text{mol}^{-1}$.

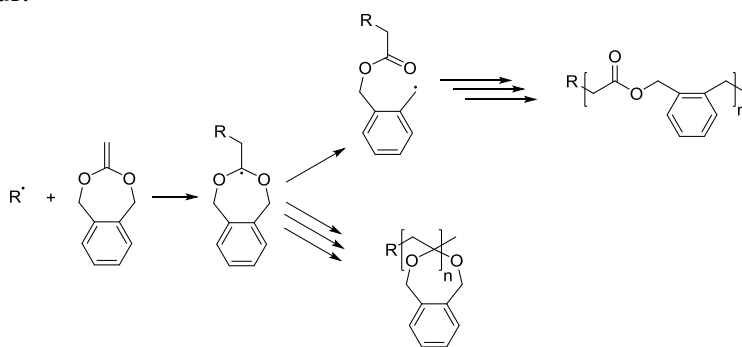
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1. Introduction

The introduction of the conventional polycondensation reaction between diols and dicarboxylic acids led to a class of polymers (polyesters) with the ability to degrade under ambient conditions. On the other hand, polymers obtained through traditional vinyl addition reaction are often favored due to the superior mechanical properties. The fusion of both techniques has always been an aim for research, which could possibly lead to copolymers with mechanical properties associated to polyvinyls and the ability to degrade. By the discovery of the radical ring-opening polymerization by Bailey *et al.*, this was made possible for the first time [1]. They showed that cyclic ketene acetals (CKAs) will undergo a ring-opening reaction when exposed to peroxides.

Since their introduction, a lot of different CKA structures were screened such as dioxolanes [2,3], dioxanes [4,5], dioxepanes [5,6] and trioxocanes [7]. The screening of different structures lead to some valuable insights in the mechanism of the ring-opening reaction. It was shown that rings containing more carbon- and oxygen-atoms, will result in more ester formation with respect to vinyl addition. This can be attributed to either the relief in ring strain and formation of more stable C=O ester bond, with respect to the C=C bond [8]. It was shown that the seven-membered rings within dioxepanes are prone to more ring-opening. In particular, the monomer 2-methylene-1,3-dioxepane (MDO, an isomer of ϵ -caprolactone) and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) were shown to lead to almost hundred percent ring-opening [5,6].

Scheme 1: Simplified reaction mechanism for CKA polymerization leading to ring opening polymerization as well as to ring-retaining structures. Note that also a combination of both mechanisms may occur.



After these initial publications, the amount of follow-up papers were limited. However, with recent advances in controlled radical polymerization techniques and the drive to produce more biodegradable materials, renewed interest in CKAs lead to publications focusing in the preparation of copolymers of CKAs with conventional vinyl monomers such as styrene [9], methyl methacrylate [10,11,12] and n-butyl acrylate [13]. In a recent review by S. Agarwal, a lot of these recent developments have been nicely summarized [14]. In this contribution, the preparation of degradable copolymers is discussed, in extension of the research as published in [12].

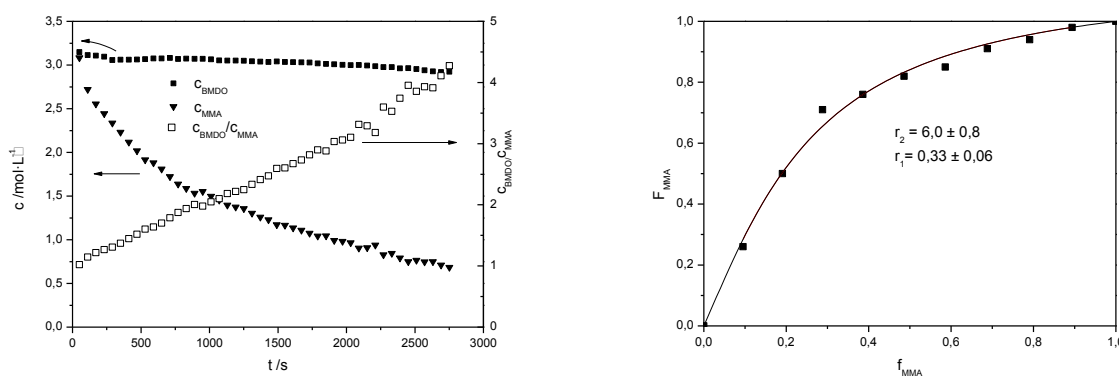
2. Results and Discussion

2.1. Copolymerization of BMDO and MMA

The required CKA monomer, 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), was synthesized according to a slightly altered procedure from Wickel *et al.* [11]. In early research by Bailey *et al.* [6], it was shown that the polymerization of BMDO is rather slow (43% conversion after 15 hours at $T=120^\circ$). However, there was a beneficial effect for the ring-opening reaction (100% of ring-opening at $T=120^\circ\text{C}$). Choosing a proper comonomer, can also improve the reactivity of BMDO. In this contribution, MMA was chosen. This system has already been studied by Wickel *et al.* in 2003 [9]. Their work consisted of creating copolymers with different compositions using ATRP. They also incorporated an 2D NMR study to determine the reactivity ratios.

For our research it is important to understand the copolymerization behavior in high detail. This was done by following the reaction with in-situ IR and analyzing the formed polymers by $^1\text{H-NMR}$. The IR is especially useful in keeping the conversion low to avoid composition drift, which can lead to erroneous values for the reactivity ratios. To calculate the conversion, a peak fitting analysis is performed using the IR chromatogram by taking the change in the peak area. An exemplary result for a 50/50 mixture BMDO/MMA is shown in Figure 1a.

Figure 1: (a) Monomer concentration versus time plot for both BMDO (squares) and MMA (triangles) as obtained from integration of the IR bands. The change in the ratio of BMDO over MMA concentration is additionally indicated. (b) Polymer composition as a function of comonomer feed composition for copolymerizations of BMDO and MMA. The monomer feed concentration ratio is given by f (with respect to MMA) and the copolymer composition ratio is given by F (with respect to MMA). The curve displays the best fit of the data to the Mayo-Lewis equation (Eq. 1). (both taken from [12])



$$F_{\text{MMA}} = \frac{r_2 f_{\text{MMA}}^2 + f_{\text{MMA}} f_{\text{BMDO}}}{r_2 f_{\text{MMA}}^2 + 2 f_{\text{MMA}} f_{\text{BMDO}} + r_1 f_{\text{BMDO}}^2} \quad (1)$$

This figure shows the decrease in concentration for BMDO and MMA with equal starting concentration. The consumption of MMA is shown to be much faster than BMDO. This gives a preliminary indication that the expected reactivity ratio for BMDO is possible lower than the one for MMA, since more MMA is built in in the early stages of copolymerization.

As mentioned earlier, an in-depth study was performed by Wickel *et al.* on the copolymerization behavior of BMDO and MMA. They determined the copolymerization parameters of $r_1 = 0.53$ and $r_2 = 1.96$ whereby:

$$r_1 = \frac{k_{p,\text{BMDO-BMDO}}}{k_{p,\text{BMDO-MMA}}} \quad \text{and} \quad r_2 = \frac{k_{p,\text{MMA-MMA}}}{k_{p,\text{MMA-BMDO}}}$$

and $k_{p,\text{BMDO-BMDO}}$ and $k_{p,\text{MMA-MMA}}$ denote the respective homopropagation rate coefficients and $k_{p,\text{BMDO-MMA}}$ and $k_{p,\text{MMA-BMDO}}$ denote the crosspropagation rate coefficients. However, as mentioned earlier, composition drift can have a big influence on the reactivity ratios. Unfortunately, no conversion data was reported in the aforementioned study.

Herein, the reactivity ratios are determined at an average conversion of 10%. This is done by investigating the $^1\text{H-NMR}$ and calculating the copolymer composition as described in [12]. By plotting the composition in the feed (f , with respect to MMA) and the copolymer composition (F , with respect to MMA) and fitting the Mayo-Lewis equation (1), the reactivity ratios can be determined (Figure 1b). The calculated reactivity ratios are $r_{\text{MMA}} = 6,0 \pm 0,8$ and $r_{\text{BMDO}} = 0,33 \pm 0,06$. These differ from the values as determined by Wickel *et al.*, probably due to the difference in conversion.

2.2. Synthesis of linear and 4-arm star copolymers by RAFT

Taking into account the known copolymerization parameters, we opted for the introduction of RAFT as a technique to control the molecular weight of the copolymers. The combination of the BMDO/MMA system with RAFT polymerization has not yet been described and it opens new possibilities for end-group modification and tuning copolymers for specific applications. The procedure for the RAFT copolymerization was adopted from the free-radical copolymerization by the simple addition of a RAFT-agent. In this research, the used RAFT-agent, methyl-2-(((octylthio)carbonothioyl)thio)propanoate (RA-1), was synthesized according to [12]. To visualize the control over the copolymerization, a kinetic evaluation was performed by taking samples at given time intervals and analyzing them with SEC in THF. The result is shown in figure 2a.

Figure 2: (a) Evolution of molecular weight distributions with time for a RAFT copolymerization of BMDO and MMA (conditions: [DCP]:[RA-1]:[BMDO]:[MMA] 0.1:1:50:50 at $T=110^\circ\text{C}$). Samples were taken after given time intervals and the molecular weight was determined by SEC in THF using pMMA Mark-Houwink parameters. (b) Evolution of molecular weight distributions for the degradation of the BMDO/MMA copolymer prepared from RAFT polymerization. (both taken from [12])

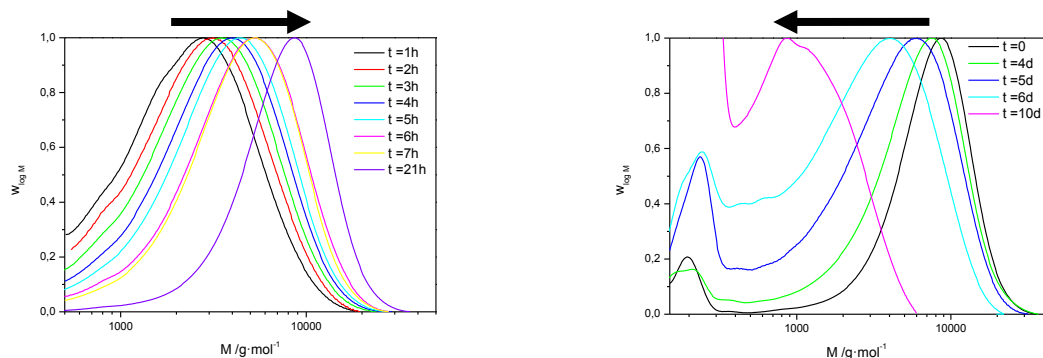
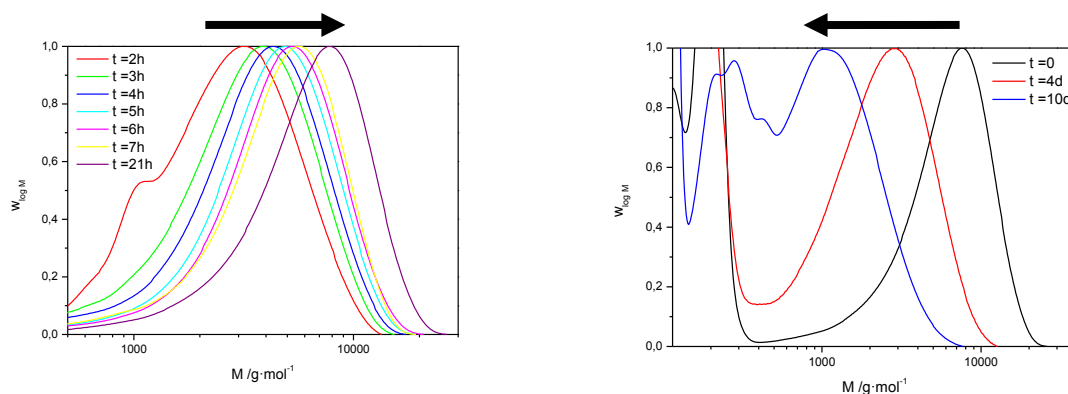


Figure 2a nicely shows a linear increase in molecular weight, indicating decent control over the polymerization. Another interesting observation to note is that, to achieve decent control, BMDO always has to be present, as the RAFT-agent by itself is not optimal for MMA homo polymerization. To check whether this would apply to other CKAs as well, some tests were performed with 2-methylene-1,3-dioxepane (MDO) under the same conditions. However, this CKA proved to be incompatible with RAFT.

In order to verify the copolymer structure, a degradation experiment was performed under influence of 1M NaOH. The result is shown Figure 2b. This figure shows a significant decrease after 10 days, going from roughly $10000 \text{ g}\cdot\text{mol}^{-1}$ to $1000 \text{ g}\cdot\text{mol}^{-1}$. This confirms that the copolymer consists of MMA parts alternated by ester units. This system was expanded to the use of a tetra-functional analogue of RA-1. The idea is to create 4-arm star degradable polymers that can be potentially used in biomedical applications.

The tetra-functional RAFT-agent (RA-4) was synthesized according a procedure by Bosschmann *et al.* [15]. As with the linear counterpart, a kinetic study was performed to evaluate the control over the polymerization. The result is shown in Figure 3a.

Figure 3: (a) Evolution of molecular weight distributions with time for the RAFT star-copolymerization of BMDO and MMA (conditions:[DCP]:[RA-4]:[BMDO]:[MMA] 0.25:1:50:50 at $T=100^\circ\text{C}$). Samples were taken after given time intervals and the molecular weight was determined by SEC in THF based on pMMA Mark-Houwink parameters. (b) Molecular weight distributions for the degradation of the RAFT-star copolymers of BMDO and MMA in 1 molar aqueous NaOH. (taken from [12])



A nice and gradual increase in molecular weight is observed, which indicates decent control over the polymerization. To confirm the copolymer structure, a degradation test performed in a similar manner as the linear analogue. The result is shown in Figure 3b. It shows a nice shift to lower molecular weight after 10 days, as was also observed in the linear counterpart.

3. Experimental section

5,6-benzo-2-methylene-1,3-dioxepane (BMDO) was synthesized according to Wickel *et al.* [11] with some minor adaptations. The tetra-functional RAFT agent was prepared using a method as

published by Boschmann *et al.* [15]. 2-methylene-1,3-dioxepane (MDO) was synthesized according to method B as published in [5]. All other synthetic procedures can be found in [12].

4. Conclusion

In this contribution, we were successful in creating biodegradable copolymers. The copolymerization behavior was evaluated and the reactivity ratios at low conversion were determined to be $r_{\text{MMA}}=6,0 \pm 0,8$ and $r_{\text{BMDO}}=0,33 \pm 0,06$. In addition, it was also possible to control the polymerization by employing RAFT. This was shown for linear polymers as well as 4-arm star polymers. While the results looked promising, the strong sensitivity to water limits the use BMDO. An alternative was possibly found in MDO and BA, which do not show this sensitivity and possibly exhibit similar behavior.

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Conflict of interest

The author declares no conflict of interest

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