

NOTES

## Synthesis, Characterization, and Degradation Behaviors of End-Group-Functionalized Poly(trimethylene carbonate)s

Faquan YU<sup>\*,\*\*,\dagger</sup> and Renxi ZHUO<sup>\*\*</sup>

*\*Department of Chemical Engineering, Hubei Key Laboratory of Novel Reactor and Green Chemical Technology, Wuhan Institute of Chemical Technology, Wuhan, 430074 Hubei, China*

*\*\*Department of Chemistry, Wuhan University, Wuhan, 430072 Hubei, China*

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Biodegradable polymers are under investigation for biomedical, pharmaceutical applications, etc. Degradability is one of their important characters. Many factors affect the degradation rate. Besides environmental conditions, such as temperature, the degradation rate is strongly dependent on the film thickness,<sup>1</sup> additives such as monomer,<sup>2</sup> basic compounds,<sup>3</sup> acid drugs<sup>4</sup> or superoxide ion,<sup>5</sup> and catalyst such as SnOct<sub>2</sub> or zinc metal,<sup>6–9</sup> etc. The molecular architecture,<sup>10–13</sup> hydrophilicity,<sup>14–16</sup> reasonable crosslink,<sup>17, 18</sup> and surface modification<sup>19, 20</sup> have vital influence on the degradation properties, too.

End-group effect is demonstrable on the degradation rate.<sup>21</sup> It was shown that poly(lactide-*co*-glycolide) (PLGA) with a free carboxyl group at the polymer terminus (uncapped PLGA) degrades faster than PLGA with a hydrophobic alkyl ester linkage at the polymer terminus (capped PLGA).<sup>22</sup> Lee<sup>21</sup> synthesized various end-group-functionalized, such as OH-, NH<sub>2</sub>-, Cl-, or COOH-terminated polylactides (PLAs) and found that the COOH end group plays a crucial role in the hydrolysis degradation in both alkaline and acidic medium. Protection of OH end group results in a substantial retarded degradation.<sup>23</sup> Polyanhydrides capped with fatty terminals also show a significantly slow degradation and drug release rate.<sup>24</sup>

Linear aliphatic polycarbonates, such as poly(1,3-trimethylene carbonate) (PTMC), have been shown to be potential for use as medical implants and for drug-delivery applications.<sup>25</sup> But they degrade unexpectedly slow.<sup>10</sup> Many efforts have been made to enhance their degradation rate. Copolymers of PTMC were synthesized for adapting to applications requiring different degradation rates and mechanical properties.<sup>10, 26–29</sup> Pendant hydroxyl groups have been introduced to im-

prove the hydrophilicity and hence the degradability.<sup>30</sup>

Since end groups have special effect on degradation rate, end-group functionalized polycarbonates will have different degradation rate. Because the polymers of multiarm architecture have a higher end-group concentration than linear polymers of the same molecular weights, the multiarm structure can strengthen the end group effect. Some researchers have synthesized the OH-terminated PTMC by ring-opening polymerization (ROP), but the degradability has not been involved up to now.<sup>31</sup> In the present study, we synthesize PTMC with different number of arms terminated by hydroxyl group or carboxylic group and study the degradability of such end-group-functionalized PTMCs preliminarily.

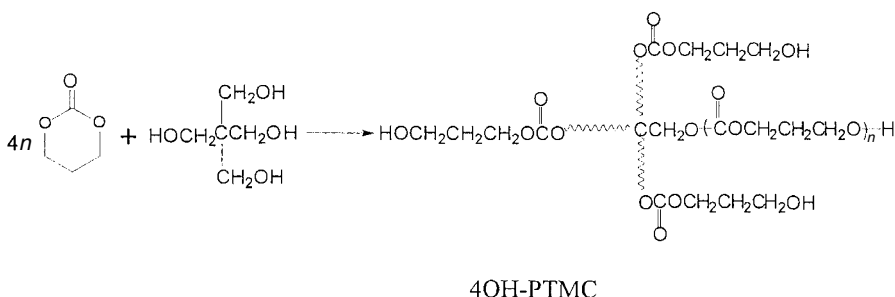
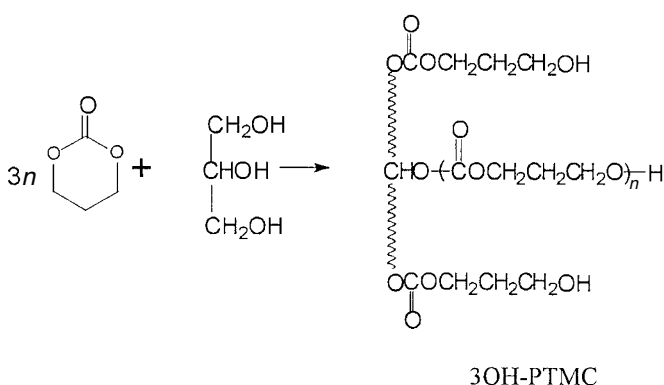
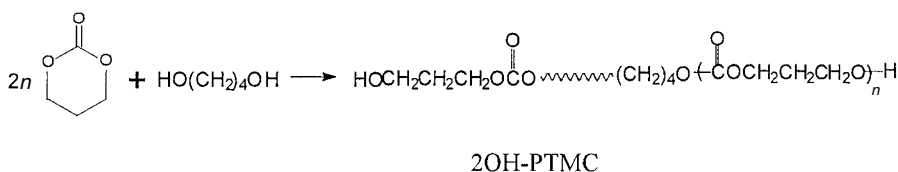
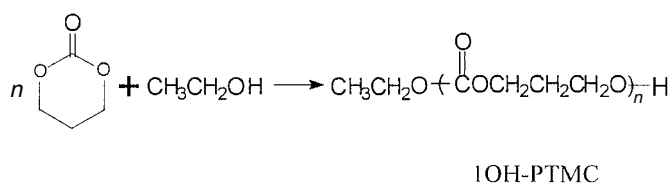
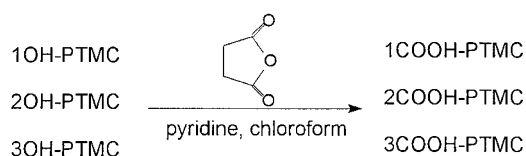
### EXPERIMENTAL

1,3-Trimethylene carbonate (TMC) was synthesized according to the reported method.<sup>32</sup> All other reagents were treated just before use.

#### *Synthesis of OH-Terminated PTMC (OH-PTMC)*

The ring-opening polymerizations (ROP) of TMC initiated by alcohols are illustrated in Scheme 1. These polymerization reactions were carried out in the melt bulk. All reaction reagents were used just after treated. A known amount of TMC was charged into a previously flamed and nitrogen-purged glass polymerization tube, containing a Teflon-coated magnetic stirring bar. Then an exhausting-refilling process was repeated three times with a 15 s nitrogen sweeping every 10 min exhausting at 60 °C. After the tube was cooled at room temperature, alcohol (ethanol, 1,4-butanediol, glycerol, or pentaerythritol) and TFA were added through a dried syringe under N<sub>2</sub> atmosphere. The tube was degassed

<sup>\dagger</sup>To whom correspondence should be addressed (Tel: +86-27-87195671, Fax: +86-27-87194465, E-mail: fqyu@public.wh.hb.cn).

**Scheme 1.** Synthesis of multiarm OH-terminated PTMCs.**Scheme 2.** Synthesis of multiarm COOH-terminated PTMCs.

again and sealed under vacuum within 60 s and immersed in a thermostated oil bath at 120°C for 48 h with stirring. After the reaction, the tube was broken and the product was dissolved in chloroform, followed by microfiltering through a 0.45 μm pore membranes filter. The polymer was precipitated by the polymer solution being poured into an excess of cold diethyl ether, filtered, and dried under vacuum until constant weight.

#### Synthesis of COOH-Terminated PTMC (COOH-PTMC)

OH-PTMC was dissolved in chloroform. Succinic anhydride and pyridine were added and the reaction mixture was kept at 60°C with stirring for 48 h (Scheme 2). The solution was cooled, filtered, and concentrated to dryness under vacuum. The crude product was dissolved in acidic water and extracted with chloroform, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and then the solvents were removed under vacuum.

#### Measurements

Molecular weights ( $\bar{M}_n$  and  $\bar{M}_w$ ) and the distributions ( $\bar{M}_w/\bar{M}_n$ ) were determined by gel permeation chromatography (GPC) on a Waters 2690D unit

**Table I.** The synthetic results of end-group functionalized PTMCs

Run	$[M]/[I]$ (mol/mol)	TMC conversion (%)	$\bar{M}_{n,GPC}$	$\bar{M}_{n,NMR}$	$\bar{M}_w/\bar{M}_n$
1OH	50	92.9	6003	6125	1.82
2OH	56	97.1	6757	6501	1.89
3OH	57	98.1	6248	5936	1.88
4OH	64	80.1	6111	5459	2.09
1COOH	–	–	5865	6254	1.99
2COOH	–	–	6514	6863	2.08
3COOH	–	–	6374	6334	2.07
4COOH	–	–	–	–	–

equipped with Shodex K802.5 & K805 with Shodex K-G guard column, using chloroform as the eluent at a flow rate of 1.0 mL min<sup>-1</sup> at 30 °C. Calibration was carried out with polystyrene standards. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on NMR spectrometer Mercury-300BB “mercury 300” in chloroform-*d* (CDCl<sub>3</sub>) at ambient temperature. Tetramethylsilane (TMS) signal is taken as the zero chemical shift.

#### *In Vitro Degradation*

A round disk of sample was prepared by compression molding (10 mm in diameter and 2 mm in thickness). The *in vitro* degradation was measured by immersion of polymer disks in phosphate-buffered saline (PBS, pH 7.4) at 37 °C. Each 24 h, the samples were transferred into fresh buffer solution. Samples were recovered at various intervals of time, water washed, and vacuum dried, while weight loss was determined gravimetrically.

## RESULTS AND DISCUSSION

#### *Synthesis of OH-Terminated PTMC (OH-PTMC)*

Polycarbonate degrades slowly although it has many advantages as biomaterials. Incorporation of end group may be a route to enhance its degradation rate in terms of the fact that end-group functionalized polylactide degraded faster.

We first synthesized OH-terminated PTMCs by ROP of TMC initiated by various kinds of alcohols. All polymerizations were conducted in melt bulk with vigorous stirring. The results of polymerization are compiled in Table I. Under these conditions, high conversions of TMC were achieved after the predetermined polymerization time.

The content of end-group is higher for the multiarm-structure polymers of the same molecular weight. Ethanol, 1,4-butanediol, glycerol, and pentaerythritol were used as a respective initiator for the synthesis of

OH-terminated poly(trimethylene carbonate) with different arms (Scheme 1). Figures 1, 2, and 3 show the <sup>1</sup>H NMR of 1OH-PTMC, 2OH-PTMC, and 3OH-PTMC, respectively, with the peak assignments of these products. The peaks of the fragments of alcohols as initiators were observed in NMR spectra. The existence of these fragments in the polymers and the peaks of the proton of CH<sub>2</sub> attached to OH group at the chain end at 3.73 ppm testified that alcohol was the real initiator (Figures 1 and 2). The CH<sub>2</sub> (a) and CH (b) proton resonance from glyceryl group occurred at 4.24 ppm in Figure 3, overlapped with the –COOCH<sub>2</sub> proton (c). The proton (f) of CH<sub>2</sub> attached to OH group at the chain end was observed at 3.73 ppm. If the peak (f) was attributed to CH<sub>2</sub> (G-CH<sub>2</sub>-OH) and CH (G-CH-OH) proton attached to the OH groups which might not participated in the ROP, occurring at 3.73 ppm also, the appearance of peak (e) at 1.90–1.93 ppm similarly demonstrated the ring-opening polymerization shown in Scheme 1. The following equation was suggested for the determination of the average degree of polymerization (*DP*) of each arm:

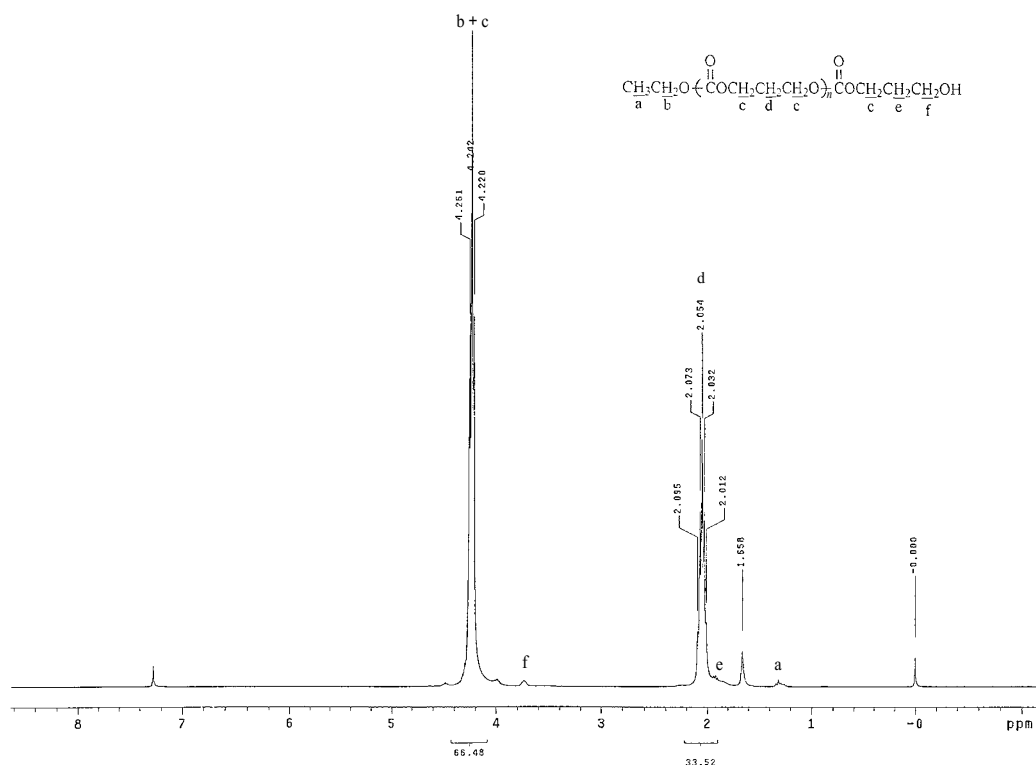
$$DP = \frac{x}{\frac{1}{2}(y+z)} + 1 \quad (1)$$

where *x*, *y*, and *z* are equal to the integration intensities of peaks d, f, and e, respectively. For the sample of run 3OH in Table I, the calculated average degree of polymerization was 19.4. This value is very near to the theoretical average degree of polymerization for each OH group because the feed molar ratio of TMC over glycerol was 57. The result implied that all the three OH groups of glycerol initiated the ROP of TMC and the obtained polymer has three arms, each arm terminated by OH group. Other results, including molecular weights, are listed in Table I.

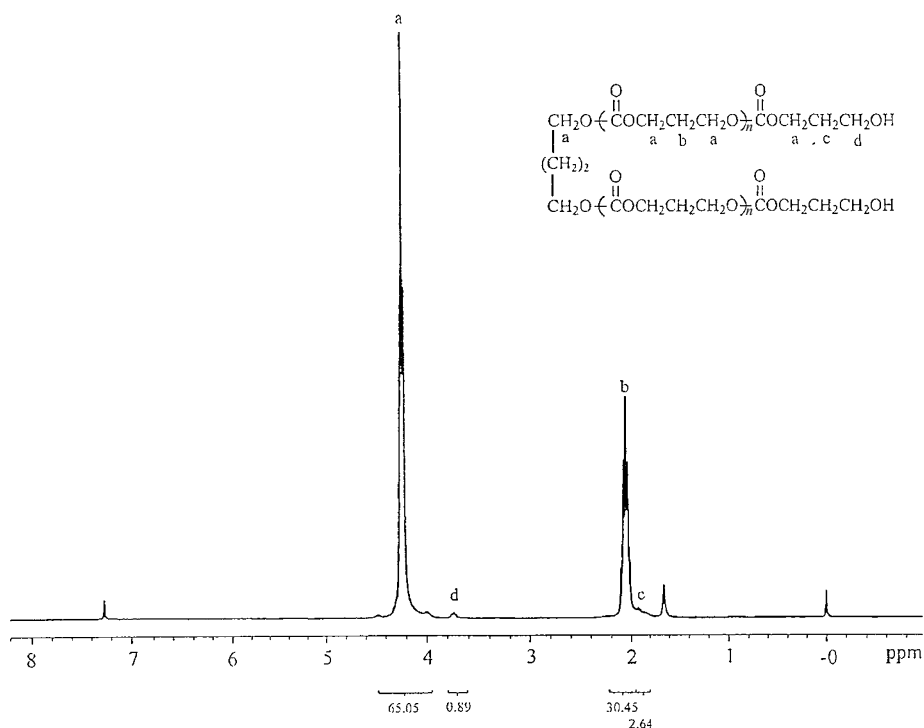
When pentaerythritol was used as the initiator for the synthesis of four-armed structure, a gel was observed. Part of the product did not solve in chloroform and the conversion of TMC was relatively lower. So the structure and properties of the expected four-armed structure were not successfully studied.

#### *Synthesis of COOH-Terminated PTMC (COOH-PTMC)*

If introducing COOH end group into polycarbonate, the end group of COOH may catalyze the degradation by virtue of the hydrolytic degradation mechanism of polycarbonate catalyzed by both acid and base. COOH-terminated PTMC was synthesized through the ring-opening reaction of the OH-PTMC end group with succinic anhydride (Scheme 2). When pyridine and chloroform were used as the catalyst and sol-



**Figure 1.** <sup>1</sup>H NMR spectrum of the product of 1OH-PTMC.



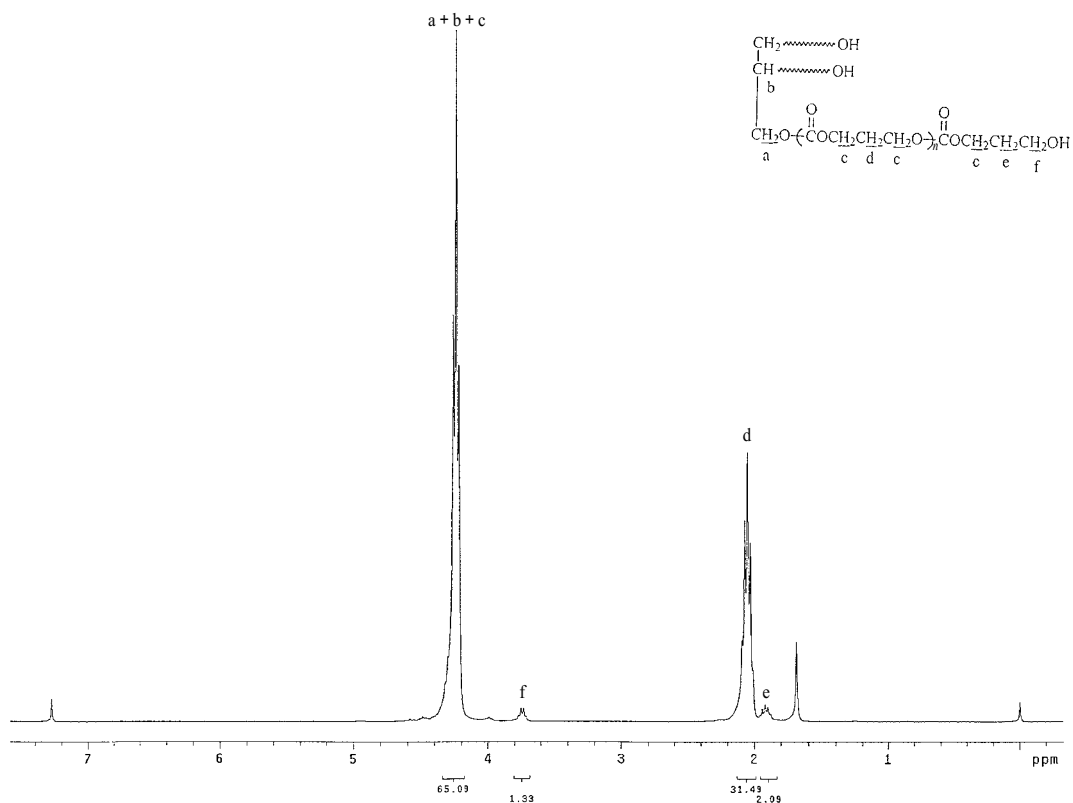
**Figure 2.** <sup>1</sup>H NMR spectrum of the product of 2OH-PTMC.

vent, respectively, the ring-opening reaction proceeded efficiently. Figure 4 shows the <sup>1</sup>H NMR spectrum of COOH-terminated three-arm poly(trimethylene carbonate). The methylene proton at 3.73 ppm (Figure 3, f) attached to OH group at the chain terminus disappeared, and the methylene proton formed by the ring-opening reaction of succinic anhydride was observed at

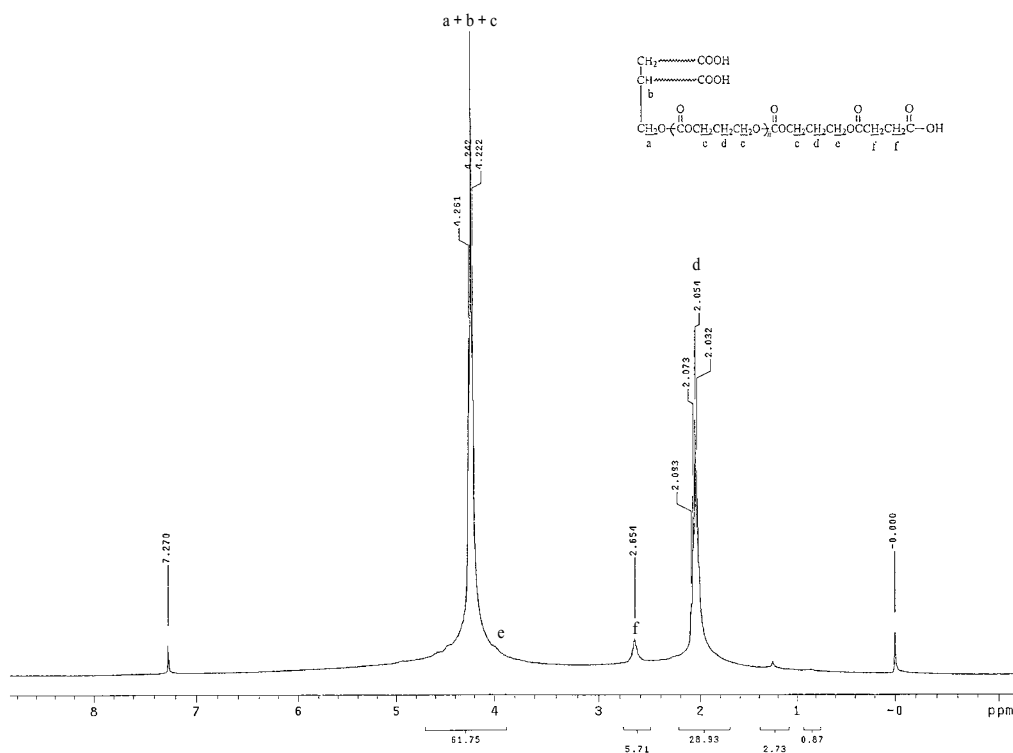
2.65 ppm. These observations confirmed the expected reaction shown in the Scheme 2 and that all the OH termini were consumed to form COOH termini.

#### *In Vitro Degradation*

The hydrolysis degradation of such end-functionalized PTMCs was investigated. The factors contribut-



**Figure 3.**  $^1\text{H}$  NMR spectrum of the product of 3OH-PTMC.

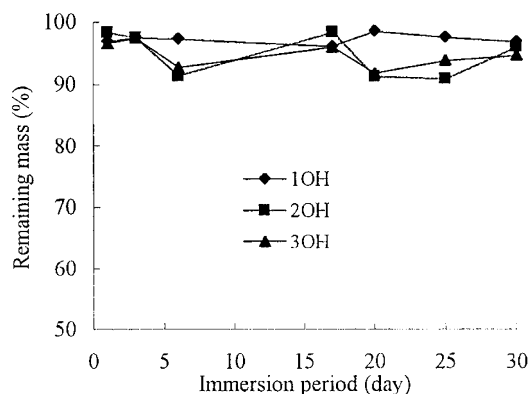


**Figure 4.**  $^1\text{H}$  NMR spectrum of COOH-terminated three-arm PTMC.

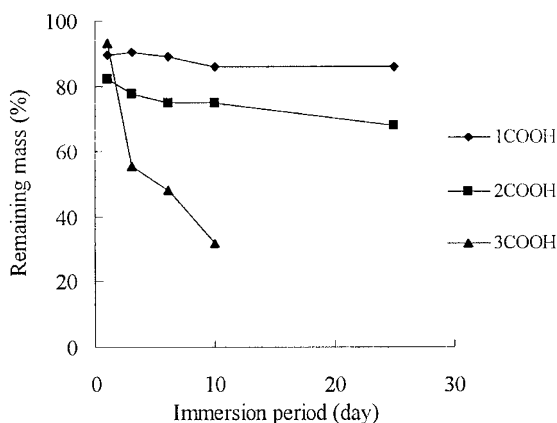
ing to accelerated degradation are the nature and the number of terminal groups.

Figures 5 and 6 illustrate the weight loss behaviors, which occurred by immersion of the samples in a pH 7.4 buffer solution at 37°C. As can be seen, these

characteristics were strongly dependent on the end-group type and number. The OH-end-group seemed no special effect on the increase of degradation rate of PTMC during the observation period no matter what the concentration of terminal groups was. However, it ap-



**Figure 5.** Mass remaining after the hydrolytic degradation of OH-terminated multiarm PTMCs.



**Figure 6.** Mass remaining after the hydrolytic degradation of COOH-terminated multiarm PTMCs.

peared that COOH-PTMCs were hydrolyzed faster than the OH-PTMCs. It is well known that acid plays a role as a degradation catalyst, which accelerates the hydrolysis of ester bonds in the polymer backbone. Generally, hydrolytic degradation increases as acidity increases. The multiarm structure polymers have higher concentration of COOH end group and higher acidity than the linear polymers of the same molecular weight, thus they should degrade faster. This was in line with our observation that the one-, two-, and three-arm structures terminated by COOH degraded increasingly in order.

In summary, although poly(trimethylene carbonate) degrades slowly, the introduction of COOH end-group accelerates its degradation.

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