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Novel Biodegradable Poly(ester−ether)s: Copolymers from 1,4-Dioxan-2-one and D,L-3-Methyl-1,4-dioxan-2-one

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ABSTRACT: Synthesis of random copolymers by the nonsequential polymerization of 1,4-dioxan-2-one with D,L-3-methyl-1,4-dioxan-2-one was first investigated using a range of classical initiators. Experimental conditions such as temperature and initiator concentrations were varied to achieve reasonable monomer conversions and molar masses. In general, copolymers were slightly enriched in 1,4-dioxan-2-one. On the basis of block lengths of the respective (co)monomer sequences, it is proposed that the copolymer consists of longer blocks of dioxanone units and a pseudoperiodic pattern with a random distribution of MeDX units. The thermal properties of the copolymer changed significantly with the percentage of MeDX units incorporated. A copolymer with 8% mole percent of MeDX units exhibits a T_m of 95.5 °C, which is about 15° lower than PDX homopolymer. A range of $(PEG)_m$-*b*-$[(PDX)$-*co*-$(PMeDX)]_n$ block copolymers was also successfully prepared using α-methoxy-ω-hydroxy-PEG as macroinitiator. The amphiphilic character of these copolymers is also here demonstrated with spherical core−shell micelles having an average size of 25−30 nm as determined by TEM. The tunable biodegradability characteristics of the hydrophobic core make these polymers interesting candidates as nanocarriers in controlled drug delivery.

1. Introduction

Copolymerization offers the possibility to achieve a broader spectrum of chemical, mechanical and biological properties suiting various applications in the field of biomaterials and drug delivery. We review here, in particular, the synthesis of copolymers containing poly(ester−ether) units derived from 1,4-dioxan-2-one as listed in Table 1. It is noteworthy that patents[1−5] dealing with such type of copolymers outnumber, by and large, published articles in this area.

A large amount of work covered in patents relates to the random copolymerization of 1,4-dioxanone (DX) with glycolide (GA) or lactide (LA).[2−5] The combination of DX with GA combines the fast absorbing characteristics of PGA with the pliability of PDX while causing a decrease in the crystallinity of the copolymer, thus making it more processable.

Raquez et al.[6] first attempted the random copolymerization of DX and ε-caprolactone (CL) but found that the copolymerization rate was largely in favor of DX incorporation. The resulting copolymer precipitated in toluene due to the insolubility of DX segments. They then successfully prepared PCL−PDX block copolymers via sequential polymerization using $Al(O^iPr)_3$ as initiator.[6] DX polymerization was shown to be living when initiated by ω-Al alkoxide terminated PCL chains at room temperature. The two blocks were immiscible with each other as confirmed by the presence of two T_gs at −65 °C (PCL block) and −10 °C (PDX block).

Hong et al.[7,8] substituted partly CL units by trimethylenecarbonate (TMC) in a block copolymer with a major proportion of DX. The [(PTMC)-*co*-(PCL)]-*b*-(PDX) were prepared using the (PTMC)-*co*-(PCL) unit as macroinitiator in the presence of $Sn(Oct)_2$ as catalyst. CL units provide low stiffness and excellent handling characteristics while TMC segments bring the required elasticity as they exist in the rubbery state at room temperature. The copolymers exhibited a lower T_g compared to PDX. In general, the mechanical properties of [(PTMC)-*co*-(PCL)]-*b*-(PDX) were found to be lower than that of PDX due to a decrease in crystallinity except for the knot pull strength which was higher for the copolymer.

Dihydroxyterminated PEO of various molar masses have been used as macroinitiator in the presence of $Sn(Oct)_2$ to copolymerize DX.[9−12] The content and length of PEO chains did not affect the thermal properties and crystallization behavior of the triblock (PDX)-*b*-(PEO)-*b*-(PDX). The T_g and T_m values of the copolymers varied between −12.7 and −15.2 °C and between 106.6 and 107 °C respectively. Triblock copolymers with PEO central block have also been prepared with outer PDX, PCL or PLA segments.[13−15] All copolymers exhibited a single T_g and T_m showing complete mixing of all segments. Bhattarai et al.[9] showed that random incorporation of PCL units (26−58%) forming a triblock copolymer [(PDX)-*co*-(PCL)]-*b*-(PEO)-*b*-[(PDX)-*co*-(PCL)] lead to a decrease in both T_g (from −23 to −57 °C) and T_m (from 100 to 40 °C).

The lipase-catalyzed copolymerization of ω-pentadecalactone (DL) with DX has been recently described by Jiang et al.[16] in attempt to obtain metal-free copolymers. The resulting copolymer contained nearly random sequences of DL and DX units with a slight tendency toward alternating arrangements. Copolymers with a PDL content exceeding 30% showed enhanced thermal stability compared to PDX homopolymer.

Finally, the hydrolytic[17] and enzymatic degradation[18,19] of multiblock copolymers consisting of PCL and PDX segments have been studied. In general, the hydrolytic degradation rate increased with increasing PDX content whereas the enzymatic degradation rate decreased.

In another paper,[20] we reported on the synthesis and homopolymerization of DL-3-methyl-1,4-dioxan-2-one (DL-3-MeDX) monomer using a range of initiators including FDA

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Table 1. PDX Copolymers

copolymer	ref
(PDX)-*co*-(PLA)	2, 3, 5
(PDX)-*co*-(PGA)	4
(PCL)-*b*-(PDX)	6
[(PTMC)-*co*-(PCL)]-*b*-(PDX)	7, 8
(PDX)-*b*-(PEO)-*b*-(PDX)	9−12
[(PDX)-*co*-(PCL)] -*b*-(PEO)-*b*-[(PDX)-*co*-(PCL)]	13
[(PDX)-*co*-(PLA)]-*b*-(PEO)-*b*-[(PDX)-*co*-(PLA)]	14, 15
(PDL)-*co*-(PDX)	16

approved tin(II) octanoate. In this paper, we present for the first time the preparation of a new family of copoly(ester-ether)s derived from DX and DL-3-MeDX by analogy with the glycolide-lactide family. Copolymerization has been tested using various initiator systems such as tin(II) octanoate, tin(II) octanoate/*n*-butyl alcohol, and aluminum tris(isopropoxide). The preparation of copolymers has also been investigated using macroinitiator α-methoxy-ω-hydroxy PEG with the objective of generating amphiphilic block copolymers for encapsulation of hydrophobic drugs.

2. Experimental Section

Materials. Solvents were purchased from Aldrich Chemicals or Fischer and were subjected to purification prior to use in polymerization. 1,4-Dioxan-2-one and D,L-3-methyl-1,4-dioxan-2-one were synthesized according to procedures previously described by us.[20] $Al(O^iPr)_3$ was used as received from Riedel-De-Haën. PEO of molar masses 2000 and 5000 were used as received from International Laboratory, USA.

Measurements. ^1H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker Electrospin spectrometer. Size Exclusion Chromatography analysis of polymer samples was performed using a Polymer Standards Systems apparatus with a refractive index detector. A PSS SDV PC column 1 (8 × 50 mm dimension) and PSS Gram linear column 2 (8 × 300 mm dimension) was used at a flow rate of 1 mL/min, pressure 10 bar, temperature 23 °C and THF as eluent. Calibration was done using polystyrene sandards. Viscometry analysis was performed using a Fisons Scientific viscometer with a Ubbelohde capillary tube type A at 25 °C. Thermal properties were determined using a Mettler Toledo DSC822 controller apparatus in a temperature range between −50 and 160 °C and at a heating rate of 5 K/min. The readings from the second measurement were used. MALDI-TOF spectrometry was performed on a Bruker Ultraflex TOF mass spectrometer using the linear mode and a 337 nm nitrogen laser. The samples were dissolved in chloroform. The matrix was a solution of dithranol (DIT) in chloroform mixed with sodium trifluoroacetic acid (NaTFA) in methanol. The mixing ratio was 5:10:1. As regards microscopy, drops of the sample solutions were allowed to dry onto carbon-coated transmission electron microscopy (TEM) grids. Images of the samples were recorded at room temperature using HITACHI H7650 microscope (TEM) operating at 80 kV.

Copolymerization of DX and DL-3-MeDX using $Sn(Oct)_2$, $Sn(Oct)_2$/*n*-BuOH, and $Al(O^iPr)_3$. A typical copolymerization is here described. DX (0.918 g, 720 μL, 9 mmol) and DL-3-MeDX (0.116 g, 100 μL, 1 mmol) were transferred in a quick-fit tube in a glovebox. The tube was placed in a preheated oil bath at 80 °C and after thermal equilibrium, $Al(O^iPr)_3$ (20.4 mg, 0.1 mmol) dissolved in toluene was injected in the DX/DL-3-MeDX mixture with a syringe via the septum. After the desired polymerization time, the reaction was quenched and the crude sample was characterized by ^1H and ^{13}C NMR. The crude sample was then dissolved in chloroform followed by precipitation in THF. The precipitate was isolated, dried under vacuum and then characterized by ^1H and ^{13}C NMR. ^1H NMR ($CDCl_3$): δ (ppm) = 1.397−1.424 (d, 3H); 3.585−3.688 (m, 2H); 3.757−3.793 (m, 2H); 3.961−4.091 (m, 1H); 4.156 (s, 2H); 4.308−4.343 (m, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 18.8; 63.98; 64.12; 67.93; 68.42; 69.47; 75.21; 170.3; 173.0.

Copolymerization with $Sn(Oct)_2$ was performed at 100 °C in the presence or absence of n-butanol.

Copolymerization of DX and DL-3-MeDX with CH_3O-PEG−OH Macroinitiator. CH_3O-PEG−OH of molar masses 2000 and 5000 were used as macroinitiators in the presence of $Sn(Oct)_2$ at 100 °C in bulk to polymerize DX and DL-3-MeDX. The monomer conversion was determined using ^1H NMR of the crude copolymer. The copolymer was purified by dissolving in $CHCl_3$ and precipitating in diethyl ether. The purified product was characterized by NMR and SEC.

3. Results and Discussion

Copolymerization of DX and DL-3-MeDX. *I. In the Presence of Tin(II) Octanoate/nBuOH or Tin(II) Octanoate Alone.* The cyclic monomers DX and DL-3-MeDX were synthesized in our lab as per methods described previously[20] and fully characterized by NMR (Figures 1A and B). The ^1H NMR spectrum of DL-3-MeDX (Figure 1B) is quite complex. HSQC and COSY experiments have enabled a complete assignment of all signals. Copolymerization of DX and DL-3-MeDX was initially investigated in bulk in presence of $Sn(Oct)_2$/nBuOH. Monomer conversion was determined from the crude samples by ^1H NMR (Figure 1C) using equations below:

$$\%\ \text{conversion DX} = \frac{I_a}{(I_{c'} - I_{f'}) + I_a} \times 100$$

$$\%\ \text{conversion DL-3-MeDX} = \frac{I_g}{I_g - I_{g'}} \times 100$$

A range of copolymers with varying (co)monomer ratios were thus prepared. As shown in Table 2, the conversion of DL-3-MeDX is found to be slightly higher than that obtained during homopolymerization experiments under similar conditions.[20] Copolymers with high DX content were purified by precipitation in THF while those with high 3-MeDX content were precipitated in petroleum ether. Copolymers with 3-MeDX content in the range 0−30% were insoluble in THF and thus their molar masses could not be analyzed by SEC using usual organic eluents. After precipitation, DX, DL-3-MeDX (Figures 1A and B) and possibly oligomers were eliminated as depicted in Figure 1 (D). The molar percentage of (co)monomer units in the copolymer was calculated by comparing the signal intensities of well resolved α-methylene protons of PDX (C(O)-C***H***$_2$OCH$_2$CH$_2$O) and methyl protons of P(3-MeDX) (C(O)CH(C***H***$_3$)OCH$_2$CH$_2$O). The copolymer composition was quite close to the initial monomer feed ratio, with a slight enrichment in DX units. However, the SEC molar masses with respect to polystyrene standards were found to be quite low. The presence of butan-1-ol as co-initiator leads to an increase in polymerization rate but at the same time limits chain growth. It is likely also that depolymerization occurs faster at the higher temperature.

Copolymerization of DX and DL-3-MeDX was further conducted in presence of $Sn(Oct)_2$ (500−1000 ppm) without co-initiator and at temperatures ranging from 60 to 80 °C. As can be seen in Table 3, DX conversion is higher than that of 3-MeDX but both monomer conversions dropped significantly as temperature is lowered. This is even more pronounced at a higher M/I ratio, i.e., at a lower concentration of $Sn(Oct)_2$. In all cases, the copolymer is enriched in DX but an increase in 3-MeDX content is observed at the higher temperature (80 °C). Moreover, molar masses of copolymers

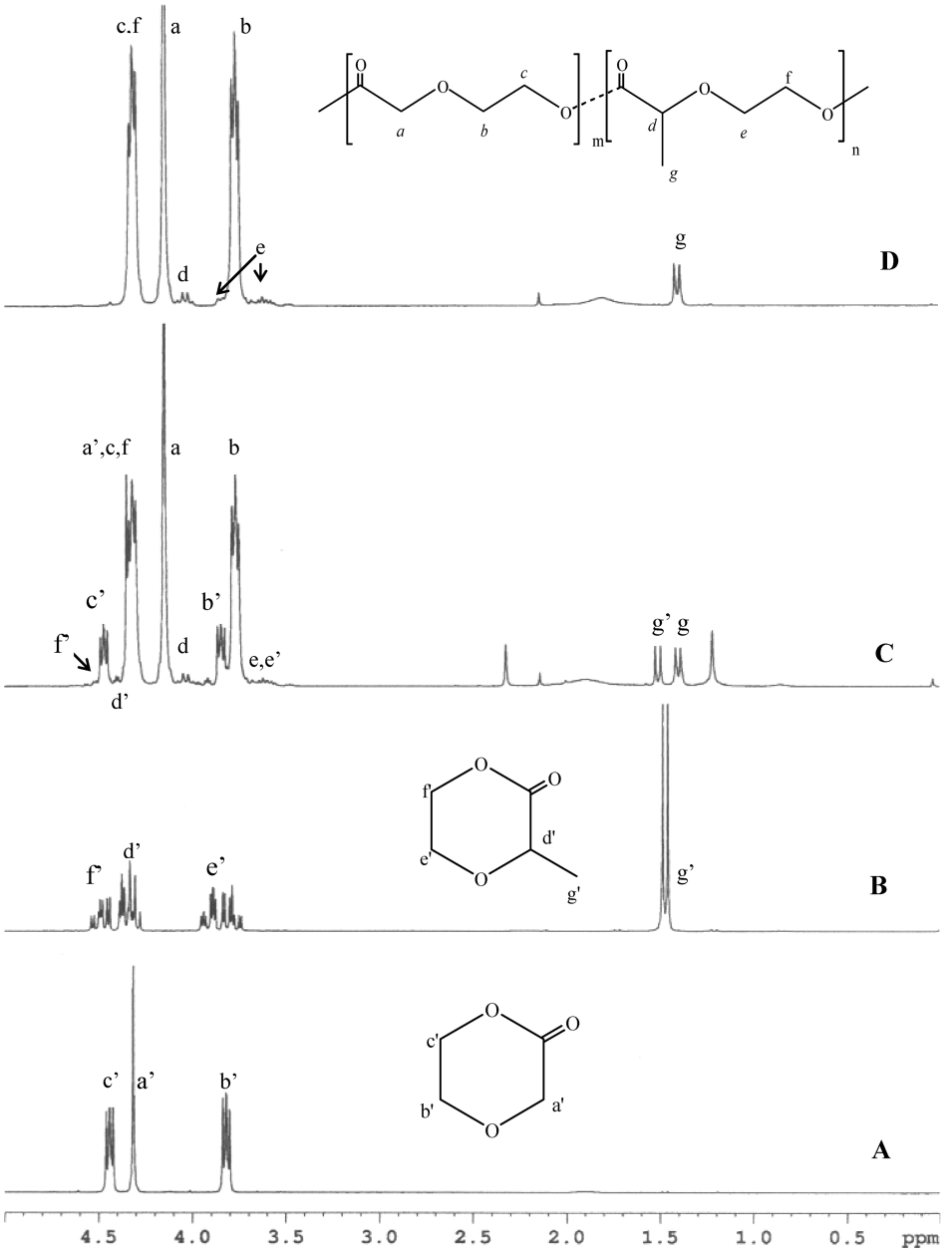


Figure 1. ^{1}H NMR ($CDCl_3$) of (A) DX (B) DL-3-Me-DX (C) crude [(PDX)-*co*-(PMeDX)] (92:8) (D) precipitated [(PDX)-*co*-(PMeDX)] synthesized using $Sn(Oct)_2$.

Table 2. Bulk Copolymerization of DX and DL-3-MeDX at 100 °C Using $Sn(Oct)_2$/nBuOH [$Sn(Oct)_2$, (1.02 μg, 2.52 μmol), nBuOH (15.5 μL, 166.7 μmol), [M]/[I] = 30, t = 24 h]

	monomer feed (%)		conversion (%)[a]		incorporation (%)[b]			
ref	DX_o	3-$MeDX_o$	DX	3-MeDX	DX	3-MeDX	M_n^{SEC}/g mol^{-1} [c]	I
1	90	10	73	56	92	8	d	d
2	78	22	74	58	85	15	d	d
3	50	50	72	53	56	44	540	2.27
4	22	78	71	50	25	75	700	2.48
5	10	90	76	48	13	87	710	2.24

[a] Determined by ^{1}H NMR. [b] Mole percentage of comonomer units in purified copolymer, determined by ^{1}H NMR. [c] M_n^{SEC} determined using THF as eluent. [d] Not determined.

were quite higher in the absence of co-initiator. The molar mass of the copolymer obtained at M/I = 4000 was found to increase upon prolonged reaction time (36 h), as confirmed by a higher reduced viscosity. Upon halving the $Sn(OR)_2$ concentration, a significant increase in molar mass is observed. On the basis of preliminary studies, higher molar mass copolymers were prepared with incorporation of MeDX up to 20% (Table 4).

II. In the Presence of Al(O^{i}Pr)$_3$. A range of copolymers with varying ratios of DX to DL-3-MeDX has also been synthesized using $Al(O^iPr)_3$ as initiator at 80 °C. As depicted in Table 4, higher conversions of both (co)monomers

were achieved as compared to the previous initiator systems due to the lower polymerization temperature used. The general trend observed is a slight enrichment of DX units in the copolymer as observed previously. CP5, with 86% Me-DX units, was the only one soluble in THF and had a molar mass M_n = 3450 and I = 1.65. The other copolymers were analyzed by viscometry but reduced viscosity values listed in Table 5 cannot be used to compare copolymers with different proportions of (co)monomers. In general, a decrease in reduced viscosity is noted as the % of 3-MeDX units increases. The same trend is obtained with the thermal transitions, T_g and T_m. This is in accordance with a decrease in crystalline character of the copolymer as the percentage of DL-3-MeDX units increases. P(3-MeDX) homopolymer is totally amorphous. It is interesting that an incorporation of 8 mol % of 3-MeDX into the copolymer brings about a 15 °C drop in T_m, as compared to the melting temperature of PDX homopolymer.

According to results in Table 6, only a minor variation in percentage conversion of monomers and their incorporation in the copolymer are noted with temperature in the range 40 to 80 °C. However, reduced viscosity values go through a maximum such that the highest viscosity was achieved at 60 °C which appears as the optimal copolymerization temperature. This is also confirmed by the highest M_n value as calculated by NMR and the highest T_m value. Analysis of copolymers by MALDI−TOF MS (Figure 2) shows that the presence of a small amount of macro-cycles cannot be ruled out (M_n^{peak} = 5170).

Calculation of Block Lengths of Copolymers. The ^{13}C NMR spectrum (Figure 3) of a purified copolymer synthesized using Al(O^{i}Pr)$_3$ at 80 °C with an initial monomer feed ratio of 90 mol % of DX and 10 mol % of 3-MeDX depicts signals due to all primary and carbonyl carbon atoms as well as that of the methyl group of poly(3-MeDX). A close analysis of the spectrum shows that the methine signals of poly(DL-3-MeDX) units are here not splitted as was the case for the homopolymer.[20] This implies the absence of tacticity effects, suggesting that DL-3-MeDX may have a preference for copolymerization over homopolymerization. To get a better insight into the fine structure of the copolymer, block lengths of the two comonomer units were calculated using signal intensities of the carbonyl group. On the basis of previous NMR interpretation for poly(lactide-*co*-caprolactone),[21] poly(caprolactone-*co*-butyrolactone),[22] and poly(pentadecalactone-*co*-dioxanone),[16] the five carbonyl signals have been assigned to triads MeDX−MeDX−MeDX + DX−MeDX−MeDX (173.0 ppm), MeDX−MeDX−DX + DX−MeDX−DX (172.9 ppm), MeDX−DX−MeDX (171.1 ppm), DX−DX−MeDX + MeDX−DX−DX (170.8 ppm) and DX−DX−DX (170.3 ppm). This assignment takes into account the central unit of the triad.

Equations 1a and 1b, were used to compute block lengths of P(3-MeDX) (L_1) and PDX (L_2). For instance, the block lengths for a copolymer containing 92% DX units and 8% MeDX units were found to be $\overline{L}_1$ = 1.25 and $\overline{L}_2$ = 5.4, indicating the presence of longer DX segments and a pseudo periodic pattern with a random distribution of 3-MeDX units in the copolymer.

Table 3. Bulk Copolymerization of DX (90%) and DL-3-MeDX (10%) Using Sn(Oct)$_2$ [500 and 1000 ppm]; t = 24 h

			conversion (%)[a]		incorporation (%)[b]		
ref	M/I	temp. (°C)	DX	3-MeDX	DX	3-MeDX	η_{red}[c] (dL·g^{-1})
1	4000	80	80	58	92	8	0.33
2		60	60	25	94	6	0.33
3		60[d]	85	54	94	6	0.46
4	8000	60	45	24	96	4	e
5		80	75	43	94	6	0.91

[a] Determined by ^1H NMR. [b] Mole percentage of comonomer units in the copolymer after precipitation in THF, as determined by ^1H NMR. [c] Reduced viscosity in $CHCl_3$ at 25 °C (c = 0.2 g·dL^{-1}). [d] Time = 36 h. [e] Not determined.

Table 4. Characteristics of Copolymers (DX-*co*-DL-3-MeDX) Obtained Using Sn(Oct)$_2$ (500 ppm, t = 24 h, 80 °C)

	incorporation (%)[a]		
ref	DX	DL-3-MeDX	η_{red}[b] [dL·g^{-1}]
6	94	6	0.93
7	91	9	0.88
8	88	12	0.82
9[c]	80	20	0.95

[a] Mole percentage of comonomeric units in the purified copolymer as determined by ^1H NMR. [b] Reduced viscosity in $CHCl_3$ at 25 °C (c = 0.2 g·dL^{-1}). [c] Time = 40 h.

Table 5. Bulk Copolymerization of DX with DL-3-MeDX at 80 °C Using Al(O^{i}Pr)$_3$ ([M]/[I] = 100, t = 24 h)

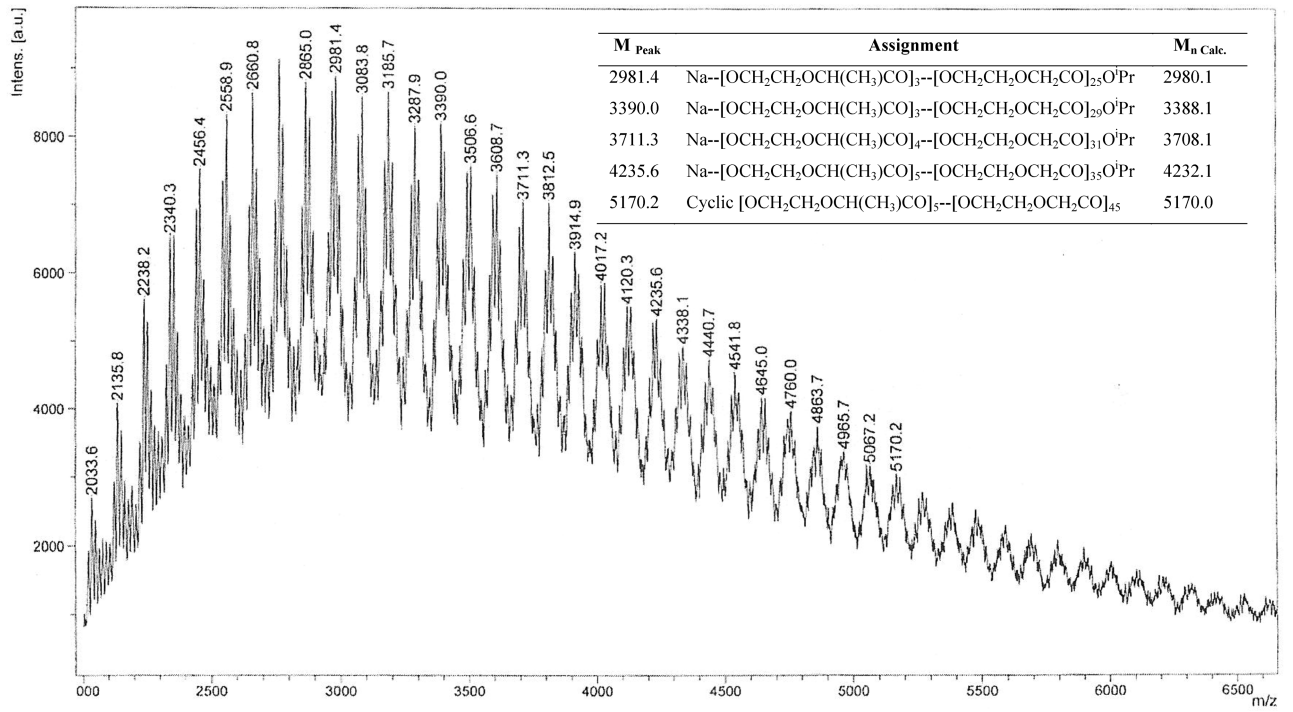
	monomer feed (%)		conversion (%)[a]		incorporation (%)[b]				
ref	DX	3-MeDX	DX	3-MeDX	DX	3-MeDX	η_{red}[c](dL·g^{-1})	T_g (°C)	T_m (°C)
CP1	90	10	82	58	92	8	0.62	−19.2	95.5
CP2	85	15	77	63	87	13	0.46	−18.7	84.4
CP3	80	20	79	60	85	15	0.33	−17.6	83.1
CP4	50	50	*d*	62	57	43	*d*	*d*	*d*
CP5	15	85	*d*	56	14	86	*d*	*d*	*d*

[a] Determined by ^1H NMR. [b] Mole percentage of comonomer units in the purified copolymer, determined by ^1H NMR. [c] Reduced viscosity in $CHCl_3$ at 25 °C (c = 0.2 g.dL^{-1}). [d] Not determined.

Table 6. Influence of Temperature on Bulk Copolymerization of DX (90%) and DL-3-MeDX (10%) Using Al(O^{i}Pr)$_3$. ([M]/[I] = 100, Time = 24 h)

		conversion (%)[a]		incorporation (%)[b]					
ref	temp (°C)	DX	3-MeDX	DX	3-MeDX	η_{red}[c] (dL·g^{-1})	M_n ^1H NMR (g mol^{-1})	T_g (°C)	T_m (°C)
CP6	40	94	73	94	6	0.79	3800	−20.5	97.1
CP7	60	93	76	93	7	1.10	3900	−18.6	98.6
CP8	80	92	78	91	9	0.69	2600	−20.9	91.1

[a] Determined by ^1H NMR. [b] Mole percentage of comonomer units in purified copolymer, determined by ^1H NMR. [c] Reduced viscosity in $CHCl_3$ at 25 °C (c = 0.2 g.dL^{-1}).



M_{Peak}	Assignment	$M_{n\ Calc.}$
2981.4	Na--$[OCH_2CH_2OCH(CH_3)CO]_3$--$[OCH_2CH_2OCH_2CO]_{25}O^iPr$	2980.1
3390.0	Na--$[OCH_2CH_2OCH(CH_3)CO]_3$--$[OCH_2CH_2OCH_2CO]_{29}O^iPr$	3388.1
3711.3	Na--$[OCH_2CH_2OCH(CH_3)CO]_4$--$[OCH_2CH_2OCH_2CO]_{31}O^iPr$	3708.1
4235.6	Na--$[OCH_2CH_2OCH(CH_3)CO]_5$--$[OCH_2CH_2OCH_2CO]_{35}O^iPr$	4232.1
5170.2	Cyclic $[OCH_2CH_2OCH(CH_3)CO]_5$--$[OCH_2CH_2OCH_2CO]_{45}$	5170.0

Figure 2. MALDI−TOF MS of CP3 [PDX/PMeDX: 85/15] synthesized using $Al(O^iPr)_3$ showing both linear chains and macrocycles.

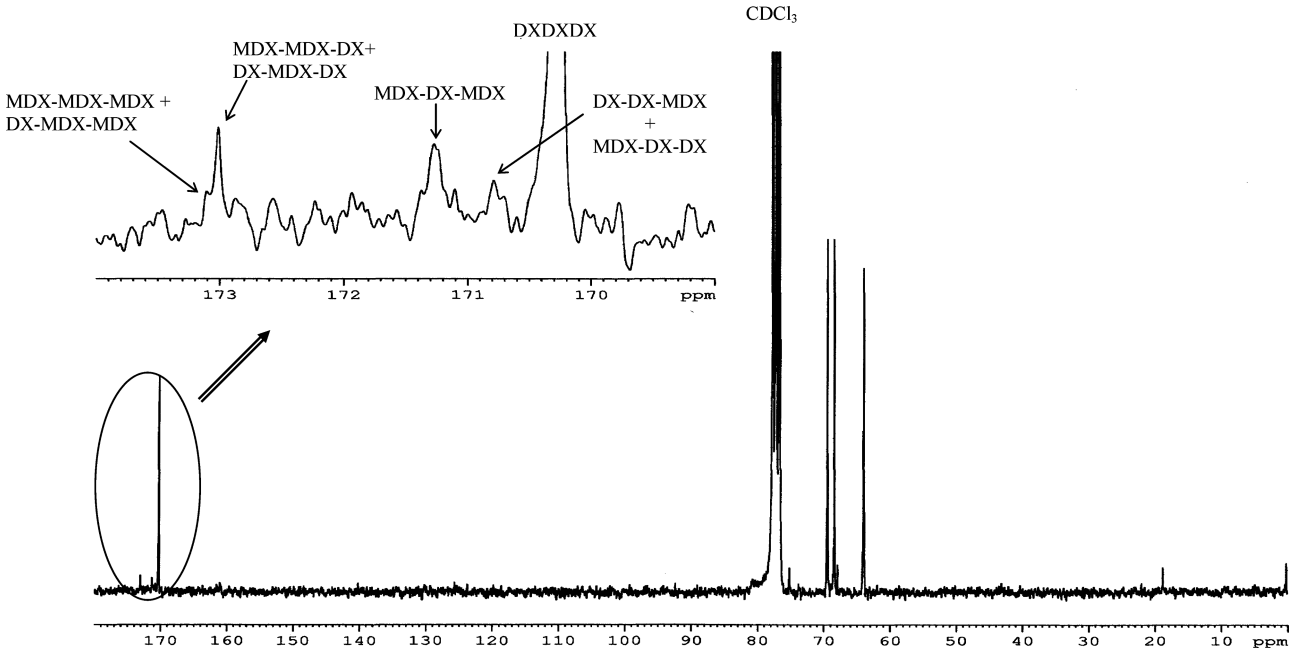


Figure 3. ^{13}C NMR ($CDCl_3$) of the precipitated copolymer [(PDX)-*co*-(PMeDX)] (92:8) (synthesized using $Al(O^iPr)_3$ at 80 °C).

$$\overline{L_1} = \left[\frac{(I_{111} + I_{211})}{(I_{112} + I_{212})}\right] + 1 \qquad (1a)$$

$$\overline{L_2} = \left[\left(\frac{(I_{222}(I_{221} + I_{122})/2)}{(I_{221} + I_{122})/2 + I_{121}}\right) + 1\right]\frac{1}{2} \qquad (1b)$$

III. Copolymerization Using $CH_3O-PEG-OH$ as Macroinitiator. The bulk copolymerization of DX and DL-3-MeDX was conducted using α-methoxy-ω-hydroxy poly(ethylene glycol) (M_n = 2000, 5000) as macroinitiator in the presence of $Sn(Oct)_2$. The objective here is to obtain amphiphilic block copolymers consisting of a hydrophilic PEG and adjustable hydrophobic (PDX)-*co*-(PMeDX). A range of copolymers were synthesized of varying compositions of DX and 3-MeDX (0−60%). As can be seen in Table 7, both monomer conversions are lower compared to previous initiator systems and this is even more pronounced with a higher molar mass of PEG as initiator. The overall enrichment in DX units of copolymers is also more significant with the PEG−OH/ $Sn(Oct)_2$ system.

^1H NMR analysis of the purified copolymers is quite interesting as it not only enables determination of the length

of the respective sequences but it also provides information on the amphiphilic character of the copolymers. ^{1}H NMR was recorded both in D_2O and $CDCl_3$. The methylene protons of PEG appear as a singlet at 3.75 ppm in D_2O and 3.6 ppm in $CDCl_3$. The signals due to hydrophobic Me-DX and DX repeat units were well resolved in $CDCl_3$ compared to D_2O, an indication of the micellar organization of the copolymer. The $-OCH_3$ end group of PEG was detected at 3.35 ppm. From the ratio of intensities of signals due to $-(OCH_2CH_2)_m$ and combined intensities of $(PDX-PMeDX)_n$, the composition of the copolymer can be determined. Interestingly, the ratio of PEG:PDX/PMeDX was found to be 1:0.78 in $CDCl_3$ while it was 1:0.5 in D_2O (Figure 4) confirming that a fraction of the hydrophobic part is masked in the latter solvent. The SEC trace of a $(PEG)_{50}$-*b*-$[(PDX)_{35}$-$(PMeDX)_4]$ copolymer in THF as eluent shows a shift to higher molar mass compared to the PEG macroinitiator (M_n = 1900, I = 1.26, Figure 5A), thus confirming the formation of a block copolymer. M_n (2750) was lower than expected (M_n^{th} = 6000) probably due to the core−shell structure of the copolymer and the use of polystyrene as standard. In water, the copolymer exhibited a narrow particle size distribution (Figure 5B) with micelles having an average size of about 60 nm. The spherical shape of the micelles was confirmed by TEM (Figure 6) where a

Table 7. Characteristics of Copolymers Obtained with PEG−OH as Macroinitiator ([M]/[I] = 50, t = 24 h, 100°C)

	monomer feed (%)		conversion (%)[a]		incorporation (%)[a]	
M_n PEG	DX	3-MeDX	DX	3-MeDX	DX	3-MeDX
2000	90	10	64	34	95	5
	80	20	63	32	90	10
	50	50	52	25	69	31
5000	80	20	33	15	90	10
	50	50	30	14	68	32

[a] Determined by ^{1}H NMR.

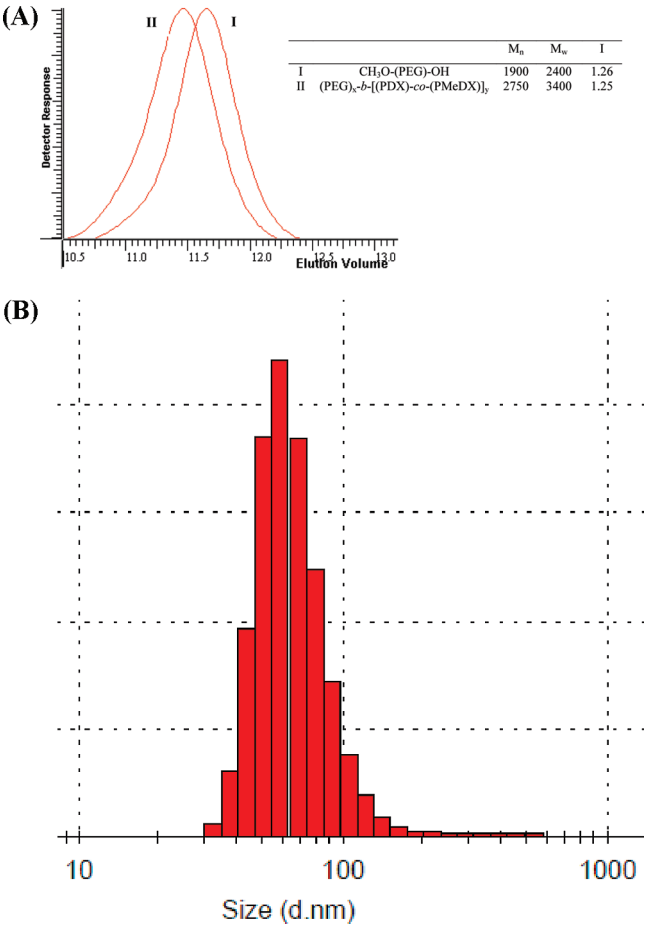


Figure 5. (A) SEC traces of CH_3O-(PEG)−OH and $(PEG)_x$-*b*-[(PDX)-*co*-$(PMeDX)]_y$ (1:0.78) (THF as eluent). (B) DLS particle size distribution of $(PEG)_{50}$-*b*-$[(PDX)_{35}$-*co*-$(PMeDX)_4]$ block copolymer in distilled water (c = 0.1 mg/mL).

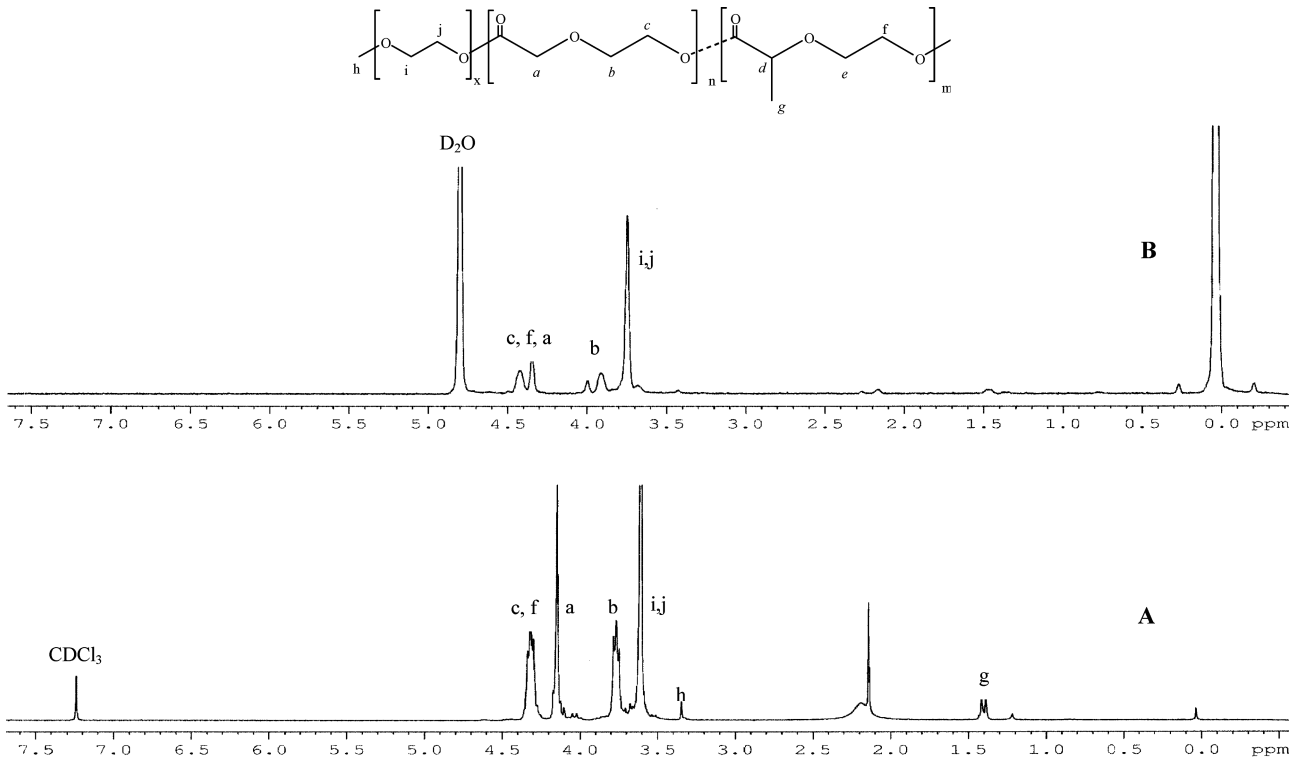


Figure 4. ^{1}H NMR of $(PEG)_x$-*b*-$[(PDX)$-*co*-$(PMeDX)]_y$ copolymer in (A) $CDCl_3$ (1:0.78) and (B) D_2O (1:0.5).

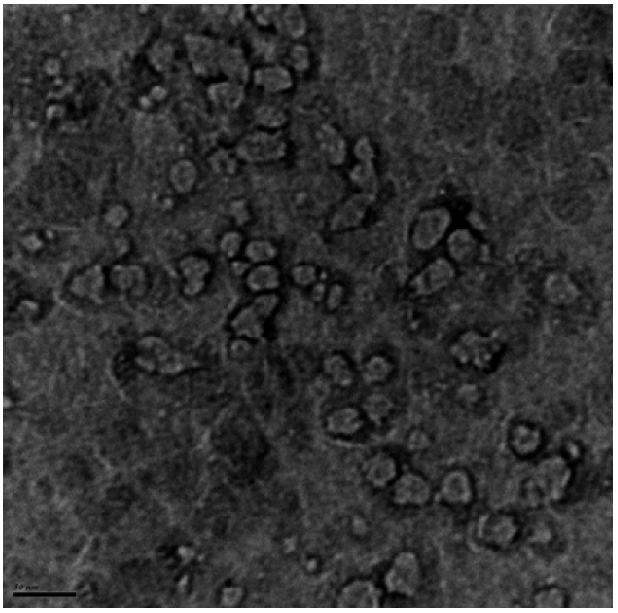


Figure 6. TEM of $(PEG)_{50}$-*b*-[$(PDX)_{35}$-*co*-$(PMeDX)_4$] micelles (c = 5 mg/mL, size range = 25−30 nm).

smaller average size of 25−30 nm was obtained due probably to the dry state of the TEM measurement.

A range of copolymers have thus been synthesized with MeDX incorporation varying from 0 to 60%.

4. Conclusions

The successful preparation of a range of copolymers of DX and DL-3-MeDX of varying composition and molar masses using $Sn(Oct)_2$ or $Al(O^iPr)_3$ or PEG−OH/$Sn(Oct)_2$ initiator systems is here described for the first time. Experimental conditions to achieve highest conversions of (co)monomers and highest molar masses have been identified. On the basis of calculation of block lengths, it can be inferred that copolymers consist of long blocks of PDX with random units of MeDX. Thermal properties of the copolymers and, in particular T_m, decrease with increasing 3-MeDX units. A copolymer with a molar ratio of DX:3-MeDX/92:8 has a T_m 15 °C lower than PDX. The stiffness of PDX can thus be reduced by introducing small amounts of 3-MeDX. Electrospinning of copolymers rich in DX units is currently under study. PEG−PDX-*co*-PMeDX block copolymers were shown to self-assemble into micelles in aqueous solution. Interestingly in such systems, the biodegradability characteristics of the hydrophobic core can be tailored to meet the requirements of specific applications and could be a potential advantage over other known systems based on PEG−PLA or PEG−PCL. This new class of poly(ester-ether)s thus opens up new perspectives for applications in the biomedical sector in general. In a forthcoming paper, we shall report on the applications of such amphiphilic polymers in drug encapsulation.

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