Polycarbonates from Sugars: Ring-Opening Polymerization of 1,2-*O*-Isopropylidene-D-Xylofuranose-3,5-Cyclic Carbonate (IPXTC)

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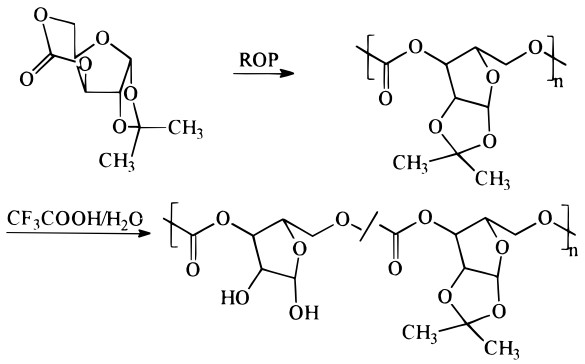
A number of applications in biomedical materials will greatly benefit by further research in bioresorbable polymers that have various side group attributes. By careful design, these functional groups can be used to regulate hydrophilicity/hydrophobicity, permeability, bioresorption and mechanical properties.[1−3] The pendant functional groups provide active sites for cross-linking and grafting as well as the opportunity to attach bioactive substances to modulate cellular responses for tissue engineering applications.[4−8] Aliphatic polycarbonates represent one family of bioresorbable materials that are being engineered for biomedical applications.[9−12] Various aliphatic polycarbonates, such as poly(trimethylene carbonate) (PTMC)[13] and poly(2,2-dimethyl trimethylene carbonate) (PDTC)[14] have been synthesized by ring-opening polymerization. Polycarbonates with hydroxyl pendant groups have been used to regulate bioresorption kinetics. For example, the in vitro degradation of PTMC in pH 7.4 buffer solution for 30 weeks at 37 °C resulted in only a 9% weight loss and a 7% decrease in molecular weight.[13] In contrast, water-soluble poly(hydroxyalkylene carbonates) undergo rapid degradation even in neutral water.[15] Specifically, the intrinsic viscosity of poly[[(oxycarbonyl)oxyl]-1,4-threityl] decreased to ca. one-third of its original value within 14 days in phosphate-buffered saline at 37 °C.

Recently, we prepared the cyclic carbonate monomer 1,2-*O*-isopropylidene-D-xylofuranose-3,5-cyclic carbonate (IPXTC) from a natural sugar. This monomer was successfully copolymerized with lactide and also trimethylene carbonate. The result was the formation of copolymers that have ketal-protected hydroxyl side groups.[16,17] The ketal groups were hydrolyzed to give hydroxyl pendant groups.[16,17] The homopolymer of IPXTC and its deprotected product (Scheme 1) would give a carbohydrate-based polymer with carbonate main-chain linkages. Due to the steric constraints around the carbonate of IPXTC, this monomer has thus far proved to be difficult to homopolymerize. Previously, it was only possible to obtain low molecular weight P(IPXTC) oligomers in poor yield by $Sn(Oct)_2$ catalyzed IPXTC homopolymerization.[16] In this paper, we report the successful use of anionic and rare-earth isopropoxide catalysts for IPXTC homopolymerizaton. Structural, thermal, and X-ray analyses of P(IPXTC) are described.

IPXTC was synthesized by the method similar to that reported by Ariga *et al.*,[18] exactly as was described elsewhere.[16,17] The general polymerization protocol and polymer characterization methods were also previously published.[16,17]

Scheme 1. Synthesis of Polycarbonate with Pendant Hydroxyl Groups



Organometallic catalysts that contain aluminum, zinc and rare-earth metals as well as ^{t}BuOK were evaluated for their abilities to homopolymerize IPXTC. The results of this work are summarized in Tables 1 and 2. The catalysts MAO, $AlEt_3-H_2O$, $ZnEt_2-H_2O$, and Et_2AlOEt are known as coordination-catalysts that are highly active for lactones, lactide, and TMC polymerizations.[1,19−22] However, the use of these catalysts for IPXTC homopolymerization gave low molecular weight chains. For example, by MAO catalysis at 70 °C for 48-hours gave only ca. 67% polymer yield with M_n of 5400. These results likely reflect the steric constraints imposed by the ketal-protected vicinal diol groups of IPXTC. This might negatively shift the equilibrium toward a decrease in the coordination of IPXTC with metal ions (M^+).[23]

^{t}BuOK is an effective anionic catalyst for the polymerization of ϵ-caprolactone and other cyclic esters.[23,24] Relative to these systems, the polymerization of IPXTC occurs at a slower rate. For example, the ^{t}BuOK-catalyzed polymerization of ϵ-caprolactone at room temperature was complete within several minutes.[24] In contrast, the polymerization of IPXTC gave only 10 and 44% monomer conversion after 25 min and 3 h, respectively (Table 1). As above, this relatively slower polymerization of IPXTC may be associated with steric constraints imposed by the ketal-protected vicinal diol. The yield, molecular weight, and polydispersity of P(IPXTC) increased with prolonging the polymerization from 25 min to 3 h (Table 1, entries 21−23). Between 3 and 11 h, M_n decreased from 9800 to 6500 while the P(IPXTC) yield and polydispersity increased slowly. Such results can be explained by the occurrence of intra- and interchain exchange reactions between carbonate groups.[23,24] It is relevant that IPXTC oligomers were observed by GPC after only a 1 h reaction.

It has been reported that the rare-earth-metal alcoholates are very effective catalysts for the ring-opening polymerization of ϵ-caprolactone, lactide and cyclic carbonates.[25−29] Also, relative to alkaline-metal alcoholates, they decelerate transesterification reactions. Hence, yttrium isopropoxide was evaluated as a potential catalyst for IPXTC homopolymerization (see Table 2). At room temperature in THF, the $Y(O^iPr)_3$-catalyzed IPXTC polymerization was slow. For example, after 8 h, only 12% IPXTC was converted to P(IPXTC). Further

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Table 1. Homopolymerization of IPXTC with Coordinative and Anionic Catalysts[a]

entry	catalyst[b]	IPXTC/catal	temp (°C)	time (h)	yield (%)	M_n	M_w/M_n	$[\alpha]_{589}^{25}$
1	MAO	25	70	48	67	5400	1.21	−17.0
2	MAO	25	70	96	44	1000	1.20	−4.2
3	MAO	100	70	24	<2			
4	IBAO	25	70	48	61	800	1.30	−3.86
5	IBAO	25	70	96	53	1000	1.16	−12.7
6	$AlEt_3-0.5H_2O$	25	70	48	52	1800	1.26	−2.63
7	$ZnEt_2-0.5H_2O$	25	70	48	73	2500	1.23	−14.6
8	$ZnEt_2-0.5H_2O$	25	70	96	69	1700	1.43	−12.1
9	$ZnEt_2-0.5H_2O$	50	70	48	80	2100	1.36	−12.1
10	$ZnEt_2-0.5H_2O$	100	70	24	50	3800	1.88	−26.0
11	Et_2AlOEt	100	70	24	14			
21	^{t}BuOK	100	25	0.42	10	2500	1.22	−19.0
22	^{t}BuOK	100	25	1	34	6800	1.52	−21.2
23	^{t}BuOK	100	25	3	44	9800	1.72	−21.0
24	^{t}BuOK	100	25	11	56	6500	1.97	−21.0

[a] 1,4-dioxane (DOX) as solvent, [IPXTC]= 4.63 mol/L. [b] MAO, methyl aluminoxane; IBAO, isobutyl aluminoxane.

Table 2. Homopolymerization of IPXTC Catalyzed by Yttrium Isopropoxide[a]

entry	IPXTC/Y	solvent	temp (°C)	time (h)	yield (%)	M_n	M_w/M_n	$[\alpha]_{589}^{25}$
1	100	THF	25	8	12			
2	100	THF	25	24	4			
3	100	DOX	25	3	10	2500	1.22	−9.0
4	100	DOX	25	8	34	4600	1.25	−21.1
5	100	DOX	25	24	24	4300	1.29	−21.1
6	50	CH_2Cl_2	70	24	35	2100	1.42	−19.7
7	100	toluene	70	24	45	2600	1.88	−19.7
8	100	DOX	70	1	15	4300	1.47	−19.2
9	100	DOX	70	3	58	13200	1.69	−19.7
10	100	DOX	70	6	62	12800	1.71	−21.4
11	100	DOX	70	16	69	11300	1.83	−21.4
12	100	DOX	70	24	75	9200	1.75	−21.8
13	100	DOX	70	48	64	4300	1.76	−21.4
14	200	DOX	70	36	44	8200	1.92	−24.5

[a] [IPXTC] = 4.63 mol/L.

increase in the reaction time was nonbeneficial (see entries 1 and 2, Table 2). The activity of $Y(O^iPr)_3$ for IPXTC polymerization increased in dioxane. P(IPXTC) yield and molecular weight increased steadily from 3 to 8 h reaction periods reaching 34% and 4600, respectively. Once again, an increase in the reaction time from 8 to 24 h did not improve the P(IPXTC) yield or M_n. At room temperature, the molecular weight distribution of P(IPXTC) was narrow (about 1.2) but showed a tendency to broaden (∼1.3) during prolonged reaction times. When the reaction temperature was increased to 70 °C, substantial increases in P(IPXTC) yield and molecular weight were achieved. For example, the yield and molecular weight of P(IPXTC) were greater than 70% and 1.0×10^4, respectively. However, P(IPXTC) yield and molecular weight did not reach their maximum points simultaneously. The molecular weight (M_n) of P(IPXTC) reached 1.32×10^4 at 3 h (58% yield). Further increases in the reaction time to 6, 16, and 24 h gave gradually increased yields and decreases in M_n (see entries 9−12, Table 2). The molecular weight distribution of P(IPXTC) was narrow early in the polymerization and increased slowly at extended polymerization time. The decrease in yield and molecular weight along with broadened molecular weight distribution as the polymerization proceeded is likely a result of backbiting-type reactions.

The structure of P(IPXTC) was analyzed by NMR. Figure 1 shows the ^1H and ^{13}C NMR spectra of P(IPXTC). The $^1H-^1H$ NMR (COSY) spectrum of P(IPXTC) showed that there were cross-peaks between 5.96/4.63, 5.11/4.50, and 4.50/4.35 ppm. Also, the $^1H-^{13}C$ NMR (HETCOR) showed cross-peaks between 5.96/104.97, 5.11/80.27,80.04, 4.63/83.24,83.13, 4.50/77.36, 4.35/65.05,64.67, 1.51/26.85, and 1.31/26.38 ppm. On the basis of the above, the signals in the ^1H and ^{13}C NMR spectra of P(IPXTC) were assigned (see Figures 1a and 1b as well as ref 30). The cross-peaks between H3 and

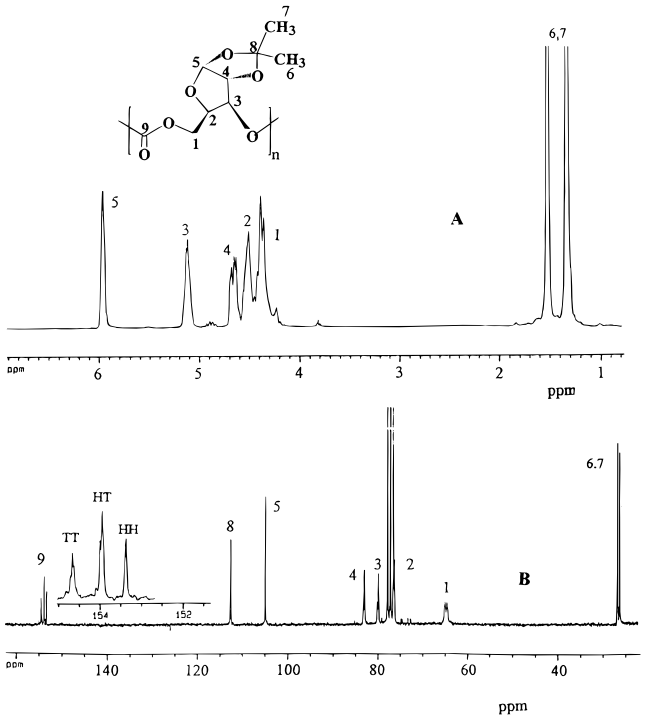
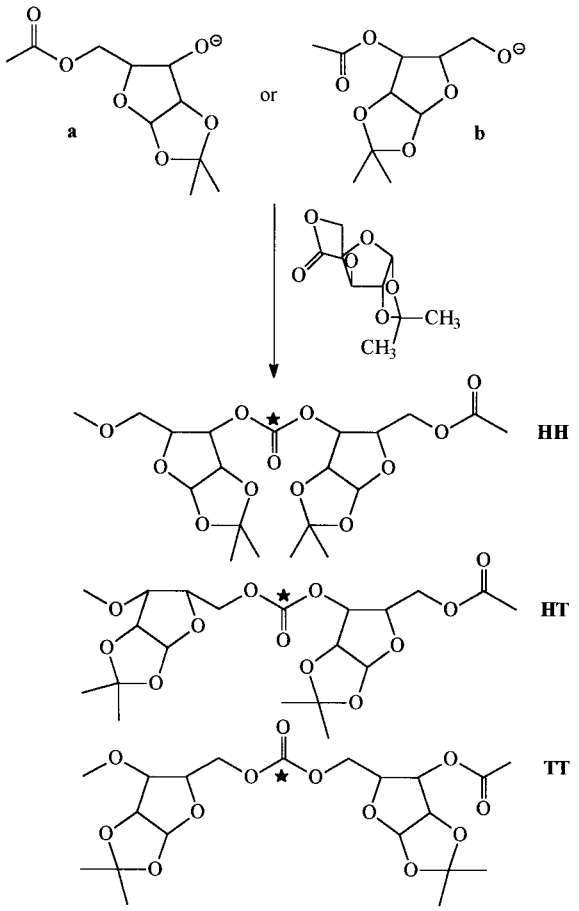


Figure 1. ^1H NMR (a) and ^{13}C NMR (b) spectra of poly(IPXTC) prepared by $Y(O^iPr)_3$ at 70 °C (entry 9, Table 2).

Scheme 2. Three Different Linkages of IPXTC Repeat Units in Its Polymer



H4 in the COSY were not seen. The weak coupling between H3 and H4 may be explained when the conformational properties of this new polymer are understood.

Expanding the ^{13}C NMR carbonyl carbon region for P(IPXTC) synthesized by $Y(O^iPr)_3$ (Table 2, entry 9) shows that there are three well-resolved signals. This signal pattern was also observed for other P(IPXTC) products synthesized as part of this work (Tables 1 and 2). The ring-opening polymerization mechanism for six-membered cyclic carbonates catalyzed by metal alcholates is said to involve an "oxygen-anion-attacked acyl-oxygen bond cleavage" process.[31] For IPXTC, acyl-oxygen bond cleavage at the different sides of the carbonyl (C═O) leads to two possible metal-chelated alkoxides (see Scheme 2, structures a and b). The successive addition of IPXTC monomers at one of the two types of chain terminal metal chelated alkoxides can lead to three different linkage types: head−head (HH), head−tail (HT), and tail−tail (TT) (see Scheme 2). If the acyl−oxygen bond cleavage of IPXTC occurs randomly at either side of the carbonate carbonyl, the probability ratio of HH:HT:TT should be 1:2:1 (Scheme 2). The integration ratio of the three signals in Figure 1b was 1.08:2.0:1.02, which is in excellent agreement with a random propagation mechanism. A calculation by ACD/CNMR software (Version 1.0 for Microsoft Windows, Bruker Inc.) indicated that the relative chemical shift positions of the carbonyl carbons for the three diad linkage orientations was TT > HT > HH. Therefore, the carbonyl (C9) ^{13}C NMR signals at 154.43, 153.96, and 153.43 ppm were assigned to the diads TT, HT, and HH, respectively. Additional shoulders associated with these signals may be due to long-range sequence effects. Other carbons in the ^{13}C NMR spectrum that also appear sensitive to repeat unit sequence are C-1 and C-3. For both of these carbons, baseline resolution of three distinct signals corresponding to HH, TT, and HT diads was not achieved. The two partially resolved signals corresponding to C-1 are at 64.67 and 65.05 ppm, while those for C-3 are at 80.27 and 80.04 ppm.

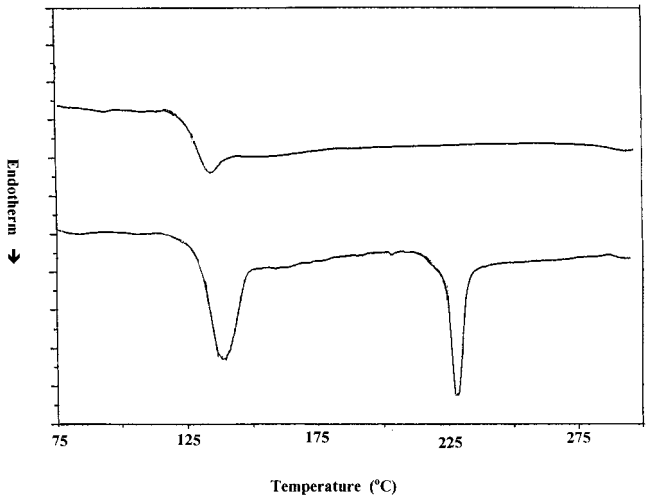


Figure 2. DSC scans recorded during the first heating scan a) and second scan (b) of P(IPXTC) prepared by $Y(O^iPr)_3$ at 70 °C (entry 9, Table 2).

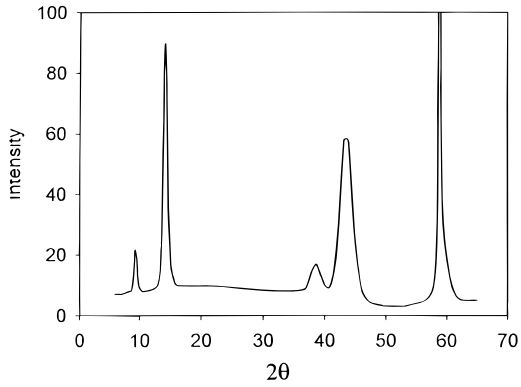


Figure 3. WAXS patterns of P(IPXTC) (entry 9, Table 2).

DSC thermograms of P(IPXTC) are displayed in Figure 2. In the first heating scan, P(IPXTC) showed two endothermic peaks at 138 and 228 °C, respectively. The second heating DSC scan, after rapid quenching from the melt, showed that P(IPXTC) has a T_g transition at 128 °C. The X-ray diffraction results, shown in Figure 3, indicate that P(IPXTC) is semicrystalline. The major diffraction peaks were at 2θ = 9.33, 14.07, 38.6, 43.5, and 58.8°, corresponding to *d* spacings of 9.46, 6.28, 2.33, 2.07, and 1.56 Å, respectively. The endothermic transition with a peak at 228 °C is believed to be due to the melting of crystalline domains. The endothermic transition and peak at ∼136 °C that was observed during both the first and second heating scans is attributed to physical aging caused by densification of the amorphous phase. The glass transition temperature of P(IPXTC) was much higher than those of other aliphatic polycarbonates which have substituents attached to the 1,3-dioxane-2-one ring. Relevant examples of polycarbonates with disubstituted 1,3-dioxane-2-one derived repeat

units are as follows: poly(5-(allylxyo)methyl-5-ethyl)-1,3-dioxan-2-one) ($T_g = -29$ °C), poly(5,5-dimethyl-1,3-dioxan-2-one) ($T_g = 27$ °C), poly[5,5-bicyclo[2,2,1]hept-2-en-5,5-ylidene)-1,3-dioxan-2-one] ($T_g = 60$ °C).[31] The high T_g of P(IPXTC) is ascribed to chain rigidity caused by substitution at two different main chain carbons as well as restricted rotation imposed by the sugar ring side groups.

The pendant ketal groups along P(LA-*co*-IPXTC) chains were transformed to vicinal diol groups by using CF_3COOH/H_2O.[16,17] Similar attempts to reach high extents of ketal deprotection for P(IPXTC) were carried out. P(IPXTC) that was soluble in $CHCl_3$, CH_2Cl_2, and THF became insoluble in these solvents after the deprotection experiments. However, solubilization of these products was possible in DMF. Product solubility suggests that if chain cross-linking occurred, the extent of cross-linking must be low. Detailed studies are in progress to determine the influence of pendant hydroxyl groups on the crystallization, physicomechanical properties, and biodegradability. We are hopeful that these new carbohydrate-based polymers will find applications in hydrogel formation, protein stabilization, and other biomedical applications.

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