ELSEVIER

Polymer 43 (2002) 2161–2167

polymer

www.elsevier.com/locate/polymer

Synthesis of novel bis- and tris-(cyclic carbonate)s and their use in preparation of polymer networks

Talal F. Al-Azemi, Kirpal S. Bisht*

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, Tampa, FL 33620, USA

Received 25 July 2001; received in revised form 13 November 2001; accepted 7 December 2001

Abstract

Novel six-membered bis- and tris-(cyclic carbonate)s that are useful as cross-linking agents in the synthesis of structurally stable yet biodegradable polycarbonates and polyesters have been synthesized in good to moderate yield (85–45%). Cross-linked aliphatic polycarbonates, and polyesters were prepared by copolymerization of the bis-cyclic carbonate (**3f**) with trimethylene carbonate, and ε-caprolactone. The polymers swelled in a wide variety of organic solvents, including $CHCl_3$, CH_2Cl_2, ethyl acetate, acetone, DMSO, and DMF but not in protic polar solvents, such as methanol, ethanol, and water. Swelling ratios of trimethylene carbonate/**3f** and ε-caprolactone/**3f** networks at different feed ratios were investigated in dichloromethane. The glass transition temperature of the TMC/**3f** networks increased with increasing cross-link density.

Keywords: Cyclic carbonate monomers; Copolymerization; Polymer networks

1. Introduction

Aliphatic polyesters and polycarbonates are materials that have attracted much attention lately [1–7]. Unlike their aromatic counterparts, these are biodegradable and hence, in recent years, interest in their potential application as polymeric carriers in the design of drug delivery systems and as a bioresorbable material has grown exponentially [8–10]. One such aliphatic polycarbonate that has attracted much attention is poly(trimethylenecarbonate) (PTMC) [7]. For example, PTMC films implanted subdermally in rats showed a weight loss of 21% and a decrease in the molecular weight of 50% over 30 weeks [7]. The biodegradability of PTMC makes it a good candidate for use in biomedical applications as a bioresorbable material. Similar observations have also been made with aliphatic polyesters, which have been evaluated extensively for their biodegradability [11–14]. Poly(ε-caprolactone), an aliphatic polyester derived from the ring opening of ε-caprolactone, has been used in the manufacture of thin-walled tree seeding containers [12] and implantable drug delivery devices, e.g. Capronol [13]. The use of degradable plastics in these applications avoids removal of the polymer, in the latter case by a surgical procedure, when it is no longer needed. Several other ε-caprolactone and TMC-containing copolymers have also been subjects of detailed investigations for biodegradable applications [15,16].

Although biodegradable, aliphatic polycarbonates and polyesters generally lack structural stability, which precludes or limits their utility in many applications such as in the manufacture of polymer scaffolds in tissue engineering [17], and orthopedic implants [18]. Enhanced branching or cross-linking of aliphatic polymer chains has been suggested to enhance their mechanical properties [19–21]. The cross-linking is achieved by incorporating suitable reactive chemical groups in the polymer chain at its time of manufacture, as an additive to the resin after manufacture, or both [19–24]. However, these reactive groups, i.e. acrylate [19], epoxy [22,23], isocyanate [20] and alkenes [24], etc. and the reactions they undergo are generally dissimilar from that characteristic of the polycarbonates/polyesters themselves and are therefore prone to have detrimental side effects on the physical and/or chemical properties of the polymers.

The development of new reaction methodologies for economical and efficient synthesis of degradable functional polymers continues to be an active area of research in our laboratories [25,26]. We have recently described the synthesis of a novel carbonate monomer, 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (MBC) and its enzymatic polymerizations to a polycarbonate, containing pendant carboxyl groups on the polymer backbone [25]. Copolymerization of MBC with trimethylene carbonate

* Corresponding author. Tel.: +1-813-974-0350; fax: +1-813-974-3203.
E-mail address: kbisht@chuma1.cas.usf.edu (K.S. Bisht).

0032-3861/02/$ - see front matter
PII: S0032-3861(02)00010-1

(TMC) was also investigated and it was possible to control the pendant carboxyl content of the copolymers by adjusting the monomer feed ratio [26]. The objectives of this research were to design carbonate monomers for the synthesis of aliphatic polycarbonates, and polyester/carbonates with improved structural stability. While five-membered bis(cyclic carbonate)s from carbondioxide and diglycidyl terephthalate have been reported, they do not react with alcohols, carboxylic acids, and diethylcarbonate and hence are not useful as cross-linking agents in polycarbonate synthesis [27,28].

In this report, we describe the synthesis of novel six-membered bis- and tris-(cyclic carbonate)s (Fig. 1) which were then used as cross-linking agents for network formation during polymerization of TMC and ε-CL. These carbonate monomers, to the best of our knowledge, are being reported for the first time. The advantage of using the bis- and tris-(cyclic carbonate)s as cross-linking agents is that they have similar structures and reactivity to that of the polycarbonate backbone. The cross-linked polymers swell in methylene chloride, a solvent in which the linear polymers are freely soluble. In subsequent communications, we will report the thermal and mechanical properties of this exciting new family of materials.

2. Experimental section

2.1. Materials

Isopropylidene-2,2-bis(hydroxymethyl) propionic acid [29], compounds **2e** [29] and **2f** [29], 4-(dimethylamino)-pyridinium *p*-toluenesulfonate (DPTS) [30], and trimethylene carbonate [26] were prepared according to the literature procedures previously reported. The catalyst $Sn(Oct)_2$ was purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received. All other chemicals were of analytical grades and used without any further purification, unless otherwise specified. Toluene was dried over sodium metal and distilled under atmospheric pressure.

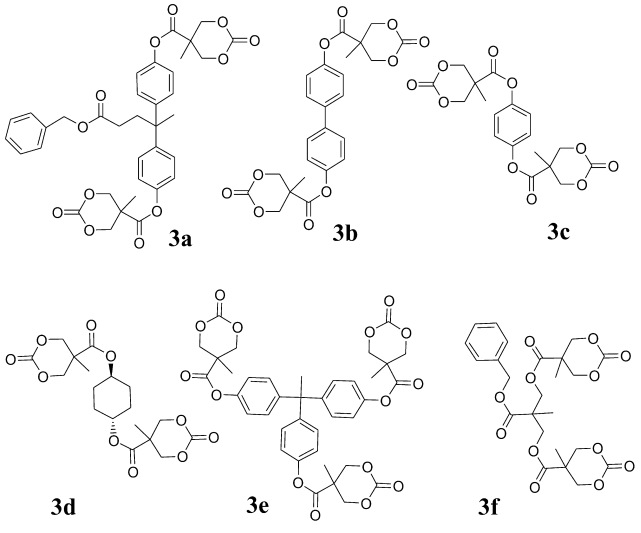


Fig. 1. Chemical structures of bis- and tris-(cyclic carbonate)s.

2.2. NMR spectroscopy

^{1}H- and ^{13}C NMR spectra were recorded on a Bruker ARX-360 spectrometer at 360 and 90 MHz, respectively. ^{1}H NMR chemical shifts (ppm) are reported downfield from 0.00 ppm using tetramethylsilane (TMS) as an internal standard. The concentrations used were ~4% w/v in chloroform-*d* ($CDCl_3$) or DMSO-d_6. ^{13}C NMR chemical shifts in ppm are referenced relative to the DMSO-d_6 or chloroform-*d* at 39.5 and 77.00 ppm, respectively. The chemical shift differences ($\Delta\nu$) were estimated using the equation, $\Delta\nu = \sqrt{(P_1 - P_4)(P_2 - P_3)}$, in which the peak positions (P_1, P_2, P_3, and P_4 from the left to right) are given in hertz from TMS.

2.3. Monomers synthesis

2.3.1. Synthesis of benzyl-4,4-bis(4-hydroxyphenyl) valerate

4,4-Bis(4-hydroxyphenyl) valeric acid 3.00 g (10.50 mmol), and 2.15 g (10.50 mmol) of KOH were dissolved in 30 ml of DMF. The potassium salt was allowed to form at 100 °C for 1 h, then 2.20 g (12.5 mmol) of benzyl bromide was added drop-wise. After 15 h of stirring at 100 °C, the DMF was removed under reduced pressure. The residue was dissolved in 150 ml of ethyl acetate and extracted three times with 15 ml of water. The organic phase was then dried over Na_2SO_4 and the solvent was removed. The crude product was purified by column chromatography on silica gel, eluting with 30:70 ethyl acetate/hexanes to give benzyl-4,4-bis(4-hydroxyphenyl) valerate as a colorless, viscous oil, yield 2.76 g (70%). ^{1}H NMR ($CDCl_3$): 1.45 (s, 3H, $-CH_3$), 2.11 (t, $J = 7.56$, 2H, $-CH_2-$), 2.32 (t, $J = 7.56$, 2H, $-CH_2C{=}O$), 5.00 (s, 2H, $-CH_2Ar$), 6.63 (d, $J = 8.28$, 4H, *Ar*), 6.92 (d, $J = 8.28$, 4H, *Ar*), and 7.25 (m, 5H, *Ar*) ppm. ^{13}C NMR ($CDCl_3$): 23.68 (CH_3), 27.62 (CH_2), 36.41 ($CH_2C{=}O$), 44.36 (*C*), 66.62 ($ArCH_2O-$), 128.33, 128.55, 128.79, 135.54, 140.92, 153.56 (Ar*C*), and 174.74 ($OC{=}O$).

2.3.2. Synthesis of ***1a*** and a general procedure for esterification

Isopropylidene-2,2-bis(methoxy)propionic acid (1.73 g, 9.92 mmol), benzyl 4,4-bis(4-hydroxyphenyl) valerate (1.87 g, 4.96 mol), and 0.485 g (1.62 mmol) of DPTS were suspended in 30 ml of CH_2Cl_2. After the reaction flask was flushed with nitrogen, 2.05 g (9.92 mmol) DCC in 15 ml CH_2Cl_2 was added drop-wise. The reaction mixture was stirred under nitrogen atmosphere for 24 h, after which the dicyclohexylurea was filtered off. The filtrate was collected and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the DPTS catalyst (insoluble in this solvent) was filtered off. The compound was further purified by column chromatography on

silica gel, eluting with 30:70 ethyl acetate/hexanes to give 3.23 g of **1a** as colorless viscous oil (91%). ^{1}H NMR ($CDCl_3$): 1.24 (s, 3H, –CH_3), 1.30 (s, 3H, –CH_3), 1.31 (s, 3H, –CH_3), 1.52 (s, 3H, –CH_3), 2.05 (t, $J = 7.92$, 2H, –CH_2–), 2.36 (t, $J = 7.92$, 2H, –CH_2C=O–), 3.65 (d, $J = 11.88$, 2H, –CH_2O–), 4.21 (d, $J = 11.88$, 2H, –CH_2O–), 5.11 (s, 2H, –CH_2Ar), 6.91 (d, $J = 8.64$, 4H, *Ar*), 7.09 (d, $J = 8.64$, 4H, *Ar*), and 7.23 (m, 5H, *Ar*) ppm. ^{13}C NMR ($CDCl_3$): 18.39 (CH_3), 22.29 (CH_3), 24.56 (CH_3), 26.03 (CH_3), 27.65 (CH_2), 32.37 (*C*H_2C=O), 42.15 (*C*CH_3), 45.17 (*C*(Ar)$_2$), 65.91 (–*C*H_2O–), 66.22 (Ar*C*H_2O–), 98.09 (O–*C*$(CH_3)_2$–O), 120.91, 128.16, 128.42, 128.67, 135.72, 145.83, 148.67 (Ar*C*), 172.78 (O*C*=O), and 173.29 (O*C*=O).

2.3.3. Synthesis of *1b*

With the procedure described earlier, the compound **1b** was isolated by column chromatography (eluent 30:70 ethyl acetate/hexanes) as a white solid (72%, mp 116–8 °C). ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H, –CH_3), 1.46 (s, 6H, –CH_3), 1.49 (s, 6H, –CH_3), 3.77 (d, $J = 11.81$, 4H, –CH_2O–), 4.33 (d, $J = 11.81$, 4H, –CH_2O–), 7.15 (d, $J = 8.53$, 4H, *Ar*), and 7.55 (d, $J = 8.64$, 4H, *Ar*) ppm. ^{13}C NMR ($CDCl_3$): 18.53 (CH_3), 22.36 (CH_3), 24.99 (CH_3), 42.31 (*C*CH_3), 66.04 (–*C*H_2O–), 98.25 (O–*C*$(CH_3)_2$–O), 121.78, 128.12, 138.16, 150.13 (Ar*C*), and 172.94 (O*C*=O) ppm.

2.3.4. Synthesis of *1c*

Following the general procedure for esterification, **1c** was isolated by column chromatography (eluent 30:70 ethyl acetate/hexanes) as white solid (86%, mp 131–3 °C). ^{1}H NMR ($CDCl_3$): 1.33 (s, 6H, –CH_3), 1.44 (s, 6H, –CH_3), 1.47 (s, 6H, –CH_3), 3.74 (d, $J = 11.63$, 4H, –CH_2O–), 4.30 (d, $J = 11.63$, 4H, –CH_2O–), and 7.11 (s, 4H, *Ar*) ppm. ^{13}C NMR ($CDCl_3$): 18.37 (CH_3), 22.07 (CH_3), 25.13 (CH_3), 42.25 (*C*CH_3), 65.95 (–*C*H_2O–), 98.16 (O–*C*$(CH_3)_2$–O), 127.26, 148.05 (Ar*C*), and 172.69 (O*C*=O) ppm.

2.3.5. Synthesis of *1d*

Following the general procedure for esterification, the *trans*- and *cis*-isomers of compound **1d** were separated by column chromatography, eluted with 10:90 ethyl acetate/hexanes increased gradually to 30:70 ethyl acetate/hexanes. *Trans*-**1d** (white solid, 40% yield, mp 105–8 °C). ^{1}H NMR ($CDCl_3$): 1.19 (s, 6H, –CH_3), 1.38 (s, 6H, –CH_3), 1.44 (s, 6H, –CH_3), 1.77 (m, 4H, –CH_2–), 1.81 (m, 4H, –CH_2–), 3.64 (d, $J = 11.59$, 4H, –CH_2O–), 4.17 (d, $J = 11.59$, 4H, –CH_2O–), and 4.93 (m, 2H, –C*H*–) ppm. ^{13}C NMR ($CDCl_3$): 18.63 (CH_3), 22.57 (CH_3), 24.64 (CH_3), 27.25 (CH_2), 41.81 (*C*CH_3), 66.45 (–*C*H_2O–), 70.27 (–*C*H–O), 97.98 (O–*C*$(CH_3)_2$–O), and 173.75 (O*C*=O) ppm. *Cis*-**1d** (38%): ^{1}H NMR ($CDCl_3$): 1.16 (s, 6H, –CH_3), 1.37 (s, 6H, –CH_3), 1.43 (s, 6H, –CH_3), 1.65 (m, 4H, –CH_2–), 1.95 (m, 4H, –CH_2–), 3.62 (d, $J = 11.52$, 4H, –CH_2O–), 4.17 (d, $J = 11.52$, 4H, –CH_2O–), and 5.17 (m, 2H, –C*H*–) ppm. ^{13}C NMR ($CDCl_3$): 18.53 (CH_3), 22.22 (CH_3), 24.99 (CH_3), 26.71 (CH_2), 41.91 (*C*CH_3), 66.07 (–*C*H_2O–), 70.64 (–*C*H–O), 97.98 (O–*C*$(CH_3)_2$–O), and 173.64 (O*C*=O).

2.3.6. Synthesis of *1e*

Compound **1e** was synthesized according to Ref. [29]. Yield (80%). ^{1}H NMR was in complete agreement with the one reported previously.

2.3.7. Synthesis of *1f*

Compound **1f** was synthesized according to Ref. [29]. Yield (88%). ^{1}H NMR was in complete agreement with the one reported previously.

2.3.8. Synthesis of *2a* and a general procedure for the removal of acetonide protecting groups

Compound **1a** (3.23 g, 4.48 mmol) was dissolved in 30 ml of methanol. 3.00 g of Dowex-H^+ resin was added and the solution was stirred for 24 h. The Dowex-H^+ was filtered off, and the solvent was evaporated to obtain a crude product, which was purified by column chromatography over silica gel (eluent 5:95 methanol/dichloromethane) to give pure **2a** as viscous oil (2.50 g, 80%). ^{1}H NMR ($CDCl_3$): 1.26 (s, 3H, –CH_3), 1.59 (s, 3H, –CH_3), 2.13 (t, $J = 7.34$, 2H, –CH_2–), 2.43 (t, $J = 7.34$, 2H, –CH_2C=O), 3.78 (d, $J = 11.41$, 4H, –CH_2OH), 3.99 (d, $J = 11.41$, 4H, –CH_2OH), 5.05 (s, 2H, –CH_2Ar), 6.99 (d, $J = 8.53$, 4H, *Ar*), 7.17 (d, $J = 8.53$, 4H, *Ar*), and 7.33 (m, 5H, *Ar*) ppm. ^{13}C NMR ($CDCl_3$): 17.03 (CH_3), 27.64 (CH_3), 30.07 (CH_2), 36.22 (*C*H_2C=O), 45.25 (*C*CH_3), 49.55 (Ar*C*), 66.36 (Ar*C*H_2O–), 68.01 (–*C*H_2OH), 121.07, 128.30, 128.51, 135.73, 146.09, 148.58 (Ar*C*), 173.46 (O*C*=O), and 174.69 (O*C*=O) ppm.

2.3.9. Synthesis of *2b*

The compound **2b** was isolated after column chromatography (eluent 5:95 methanol/dichloromethane) as a white solid (96%, mp 256–8 °C). ^{1}H NMR (DMSO-d_6): 1.22 (s, 6H, –CH_3), 3.53 (d, $J = 10.08$, 4H, –CH_2OH), 3.80 (d, $J = 10.08$, 4H, –CH_2OH), 7.15 (d, $J = 8.64$, 4H, *Ar*), and 7.69 (d, $J = 8.64$, 4H, *Ar*) ppm. ^{13}C NMR (DMSO-d_6): 16.90 (CH_3), 50.93 (*C*CH_3), 64.01 (–*C*H_2OH), 122.37, 127.60, 136.74, 150.41 (Ar*C*), and 173.71 (O*C*=O) ppm.

2.3.10. Synthesis of *2c*

The compound **2c** was isolated after column chromatography (eluent 5:95 methanol/dichloromethane) as a white solid (97%, mp 266–8 °C). ^{1}H NMR (DMSO-d_6): 1.25 (s, 6H, –CH_3), 3.56 (d, $J = 10.44$, 4H, –CH_2OH), 3.71 (d, $J = 10.44$, 4H, –CH_2OH), and 7.16 (s, 4H, *Ar*) ppm. ^{13}C NMR (DMSO-d_6): 16.90 (CH_3), 50.92 (*C*CH_3), 64.01 (–*C*H_2OH), 122.74, 148.08 (Ar*C*), and 173.75 (O*C*=O) ppm.

2.3.11. Synthesis of *2d*

The compound **2d** was isolated after column chromatography (eluent 5:95 methanol/dichloromethane) as a white

solid (92%, *trans*-isomer, mp 115–7 °C). ^{1}H NMR (DMSO-d_6): 1.05 (s, 6H, –CH_3), 1.69 (m, 8H, –CH_2–), 3.44 (d, $J = 4.43$, 2H, –CH_2OH), 3.50 (d, $J = 4.43$, 2H, –CH_2OH), and 4.58 (m, 4H, –CH–O–) ppm. ^{13}C NMR (DMSO-d_6): 16.92 (*C*H$_3$), 26.83 (*C*H$_2$), 50.14 (*C*CH$_3$), 63.79 (–*C*H$_2$OH), 68.63 (–*C*HO–), and 174.05 (O*C*=O) ppm.

2.3.12. Synthesis of **2e**

Compound **2e** was synthesized according to Ref. [29]. Yield (98%). ^{1}H NMR was in complete agreement with the one reported previously.

2.3.13. Synthesis of **2f**

Compound **2f** was synthesized according to Ref. [29]. Yield (98%). ^{1}H NMR was in complete agreement with the one reported previously.

2.3.14. Synthesis of **3a** and the general procedure for carbonate ring formation

Triethylamine (1.00 g, 9.87 mmol) was added drop-wise to a solution of **2a** (0.500 g, 0.822 mmol) and ethyl chloroformate (1.07 g, 9.87 mmol) in THF(100 ml) at 0 °C over a period of 30 min. The reaction mixture was then stirred at room temperature for 2 h. The precipitated triethylamine hydrochloride was filtrated off, and the filtrate was concentrated under reduced pressure. Bis(cyclic carbonate) **3a** was isolated by flash column chromatography (eluent 30:70 ethyl acetate/hexanes) as viscous oil (343 mg, 63%). ^{1}H NMR (CDCl3): 1.48 (s, 6H, –CH_3), 1.61 (s, 3H, –CH_3), 2.13 (t, $J = 7.59$, 2H, –CH_2–), 2.45 (t, $J = 7.59$, 2H, –CH_2C=O–), 4.36 (d, $J = 10.69$, 4H, –CH_2O–), 4.81 (d, $J = 10.69$, 4H, –CH_2O–), 5.06 (s, 2H, –CH$_2$Ar), 7.00 (d, $J = 8.60$, 4H, *Ar*), 7.19 (d, $J = 8.60$, 4H, *Ar*), and 7.33 (m, 5H, *Ar*) ppm. ^{13}C NMR (CDCl$_3$): 17.38 (CH$_3$), 22.06 (CH$_3$), 29.97 (CH$_2$), 36.12 (*C*H$_2$C=O), 40.58 (*C*CH$_3$), 45.25 (Ar*C*), 67.32 (Ar*C*H$_2$O–), 68.96 (–*C*H$_2$O–), 120.66, 128.17, 128.37, 128.45, 135.67, 146.47 (Ar*C*), 147.29 (O*C*–OO), 169.80 (O*C*=O), and 173.16 (O*C*=O).

2.3.15. Synthesis of **3b**

The compound **3b** was crystallized from ethyl acetate/hexanes as a white solid (81%, mp 182–4 °C). ^{1}H NMR (DMSO-d_6): 1.29 (s, 6H, –CH_3), 4.48 (d, $J = 10.33$, 4H, –CH_2O–), 4.72 (d, $J = 10.33$, 4H, –CH_2O–), 7.24 (d, $J = 8.56$, 4H, *Ar*), and 7.76 (d, $J = 8.56$, 4H, *Ar*) ppm. ^{13}C NMR (DMSO-d_6): 16.22 (CH$_3$), 40.12 (*C*CH$_3$), 72.39 (–*C*H$_2$O–), 121.97, 128.00, 137.30, 149.64 (Ar*C*), 147.21 (O*C*=OO), and172.83 (O*C*=O) ppm.

2.3.16. Synthesis of **3c**

The compound **3c** was crystallized from ethyl acetate/hexanes as a white solid (61%, mp 192–4 °C). ^{1}H NMR (DMSO-d_6): 1.37 (s, 6H, –CH_3), 4.48 (d, $J = 10.33$, 4H, –CH_2O–), 4.73 (d, $J = 10.33$, 4H, –CH_2O–), and 7.24 (s, 4H, *Ar*) ppm. ^{13}C NMR (DMSO-d_6): 16.22 (*C*H$_3$), 40.20 (*C*CH$_3$), 72.36 (–*C*H$_2$O–), 122.79, 147.22 (Ar*C*), 147.76 (O*C*=OO), and 170.71 (O*C*=O) ppm.

2.3.17. Synthesis of *trans*-**3d**

The compound **3d** was crystallized from ethyl acetate/hexanes as a white solid (60%, *trans*-isomer mp 96–8 °C). ^{1}H NMR (DMSO-d_6): 1.19 (s, 6H, –CH_3), 1.72 (m, 8H, –CH_2–), 4.36 (d, $J = 10.33$, 4H, –CH_2O–), 4.55 (d, $J = 10.33$, 4H, –CH_2O–), and 4.73 (m, 2H, –CH–O) ppm. ^{13}C NMR (DMSO-d_6): 16.28 (*C*H$_3$), 26.61 (–*C*H$_2$–), 50.14 (*C*CH$_3$), 72.50 (–*C*H$_2$O–), 71.05 (–*C*H–O), 147.23 (O*C*=OO), and 171.02 (O*C*=O) ppm.

2.3.18. Synthesis of **3e**

Compound **3e** was crystallized from ethyl acetate/hexanes as a white solid (41%, mp 176–8 °C). ^{1}H NMR CDCl$_3$): 1.49 (s, 9H, –CH_3), 2.16 (s, 3H, –CH_3), 4.30 (d, $J = 10.80$, 6H, –CH_2O–), 4.82 (d, $J = 10.80$, 6H, –CH_2O–), 7.00 (d, $J = 7.20$, 6H, *Ar*), and 7.11 (d, $J = 7.20$, 6H, *Ar*) ppm. ^{13}C NMR (CDCl$_3$): 17.53 (CH$_3$), 30.78 (CH$_3$), 40.12 (*C*CH$_3$), 51.66 (*C*(Ar)$_3$) 72.85 (–*C*H$_2$O–), 120.52, 129.79, 146.72, 148.30 (Ar*C*), 147.29 (O*C*=OO), and 174.74 (O*C*=O) ppm.

2.3.19. Synthesis of **3f**

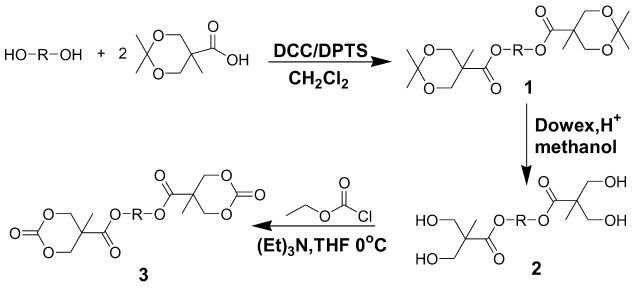
Compound **3f** was crystallized from ethyl acetate/hexanes as a white solid (85%, mp 106–8 °C). ^{1}H NMR (CDCl$_3$): 1.22 (s, 6H, –CH_3), 1.30 (s, 3H, –CH_3), 4.09 (d, $J = 11.30$, 4H, –CH_2O–), 4.30 (d, $J = 11.33$, 4H, –CH_2O–), 4.41 (d, $J = 11.33$, 4H, –CH_2O–), 4.51 (d, $J = 11.30$, 4H, –CH_2O–), 5.19 (s, 2H, –CH_2Ar), and 7.37 (m, 6H, *Ar*) ppm. ^{13}C NMR (CDCl$_3$): 17.06 (CH$_3$), 17.74 (CH$_3$), 40.18 (*C*CH$_3$), 46.37 (*C*CH$_3$), 65.94 (–*C*H$_2$O–), 67.23 (–*C*H$_2$Ar), 72.77 (–*C*H$_2$O–), 128.62, 135.23 (Ar*C*), 147.17 (O*C*=OO), 170.48 (O*C*=O), and 171.67 (O*C*=O) ppm.

2.4. General procedure for cross-linked polymer synthesis

Solution (1 mol/l) of the catalyst, Sn(Oct)$_2$ was prepared in toluene. The polymerization vials (6 ml) were treated with trimethylsilyl chloride, washed with methanol, dried at 100 °C in an oven, and flamed-dried while being purged under dry nitrogen. The monomers and the catalyst were added to the polymerization vials under nitrogen atmosphere. Toluene added with the catalyst was removed under vacuum, and the vials were filled with nitrogen. Finally, the vials were sealed under nitrogen atmosphere, and placed in an oil bath at 140 °C for 6 h. The polymer was purified by repeated extraction with chloroform, and the soluble portion was analyzed by ^{1}H NMR.

2.5. Swelling ratio

The swelling ratios were measured at room temperature in dichloromethane. The dried gels were immersed in CH_2Cl_2 for three days. The swollen samples were then removed from the solvent and weighed. The excess solvent



Scheme 1. R = benzyl-4,4-bis(phenyl)valerate (a), phenyl (b), biphenyl (c), cyclohexane (d), 1,1,1-triphenyl ethane (e) and benzyl-2,2-bis(hydroxymethyl)proponiate.

on the surface was removed by gently tapping the swollen samples with a tissue paper. Then the gels were dried under vacuum (40 °C/0 mmHg; 15 h). The swelling ratios were calculated using the following equation [31].

$(W_s + W_p)/W_p$,

where W_s and W_p are the weight of the adsorbed solvent and the dry sample, respectively.

3. Results and discussion

3.1. Monomers synthesis

Compounds **3a**–**f** were synthesized in three steps starting from the diols and the isopropylidene-2,2-bis(hydroxymethyl) propionic acid [29] (IPA) as shown in Scheme 1. The coupling reactions, of the diol and propionic acid, were performed in dry dichloromethane using *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) as catalysts. The acetonide protecting groups were removed at room temperature by stirring the methanol solutions of **1a**–**f** with Dowex 50W-X2 acidic resin. The product was isolated quantitatively after removal of the ion-exchange resin by filtration.

The benzyl 4,4-bis(hydroxyphenyl) valerate (**1a**) was synthesized from benzyl 4,4-bis(hydroxyphenyl) valeric acid. The acid was heated to 100 °C in DMF with potassium hydroxide for 30 min to form the potassium salt, which was treated with benzyl bromide to give the benzyl ester exclusively.

Trans- and *cis*-isomers of the compound, **1d** were separated by column chromatography by eluting with an ethyl acetate/hexanes gradient mixture in which the percentage of ethyl acetate was gradually increased from 10 to 30% (Fig. 2). The isomers were isolated in 1:1 ratio. The *trans*-isomer was isolated first followed by the *cis*-isomer. The ^{1}H NMR spectra of the *cis*- and *trans*-isomers were superimposable except for the methylene protons resonances in the cyclohexane ring. Both the isomers showed two sets of multiplets (~1.9 ppm) each for four protons but with different chemical shift difference ($\Delta\nu$). In the *cis*-isomer the two multiplets were further apart (108 Hz or 0.30 ppm) than in the *trans*-isomer (14 Hz or 0.04 ppm). In *trans*-isomer, the small difference in the chemical shift of the two sets of protons was expected because of its symmetry about the plane of the cyclohexane ring. In contrast, in the *cis*-isomer the asymmetry about the ring plane results in two distinct groups of protons, which are in very different chemical shift environments, i.e. proximity to the two-acyl groups.

The formation of the carbonate ring was accomplished by reaction of the tetrahydroxy, **2a**–**e** or the hexahydroxy, **2f** with ethyl chloroformate in THF at 0 °C [25]. To minimize intermolecular coupling, a dilute solution of **2** and low reaction temperature were used (Scheme 2). The product was isolated and purified by column chromatography and repetitive crystallization from THF. The structures of the bis- and tris-(cyclic carbonate)s were determined from detailed spectral analysis. A new resonance around 147 ppm (O(*C*=O)O) in the ^{13}C NMR indicated the formation of the cyclic carbonate product.

3.2. NMR characterization

The carbonate monomers were analyzed using the ^{1}H-, ^{13}C NMR spectral data. Important correlations and connectivities were established using 2D ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-HETCOR experiments. The ^{1}H NMR spectra of the bis- and tris-(cyclic carbonate)s (**3a**–**f**) contained resonances that accounted for all protons and corresponded well with the expected chemical shift positions and multiplicities.

One of the interesting features of the ^{1}H NMR spectra was a double doublet at ~4.2 ppm due to the methylene protons in the carbonate rings. The double doublet was observed in compounds, (**1**–**3**)**a**–**f** having a similar diastereotopic system. In Fig. 3, the rigid carbonate ring system showing the axial (Ha) and equatorial (Hb) protons is presented. The axial (Ha) and equatorial (Hb) protons on two different carbons are chemically equivalent but the two protons on each carbon are not, i.e. protons Ha and Hb are

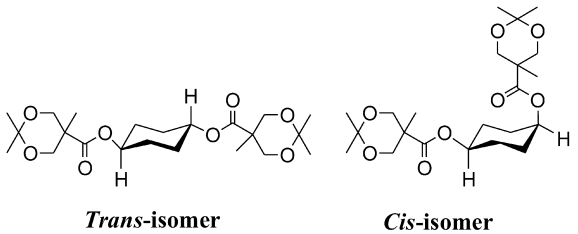
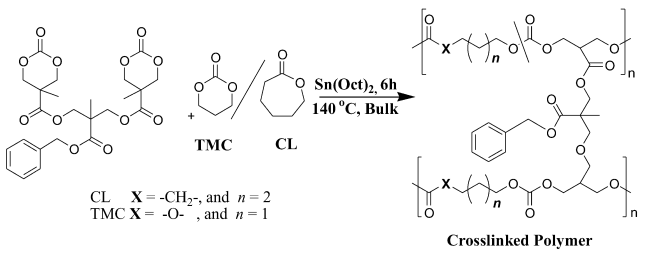


Fig. 2. Structures of *trans*- and *cis*-isomer of compound **1d**.



Scheme 2.

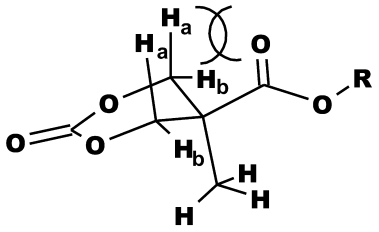


Fig. 3. An illustration of the six-membered carbonate ring system with the axial (Ha) and equatorial (Hb) hydrogens is shown.

diastereotopic. The two protons in axial positions (Ha) were determined to have lower chemical shift than those in the equatorial position (Hb) because they lie in the shielding zone of the carbonyl group of the ester functionality (Fig. 3). The magnitude of the chemical shift difference ($\Delta\nu$) between the resonance position of the Ha and Hb protons was dependent on the rigidity of the diastereotopic system and the NMR solvent. In compounds, **2a**–**f**, in which free rotation about the carbon–carbon bond is possible, the diastereotopic methylene protons were resolved as a double-doublet but with much smaller $\Delta\nu$. For example, in compound **2b** the chemical shift difference ($\Delta\nu$) is 42.8 Hz compared to 77.5 Hz in the compound **3b**. In general, $\Delta\nu$ was higher in $CDCl_3$ (93.4 Hz in **3f**) than in DMSO-d_6 (23.2 Hz in **3f**). Compound **3f** has diastereotopic protons in the carbonate ring (limited flexibility) and protons that are not part of the ring (higher flexibility). The carbonate ring methylene protons with limited flexibility appear at 4.09, and 4.51 ppm, as a double-doublet with $\Delta\nu = 93.4$ Hz and $J = 11.30$ Hz, whereas double-doublet of the more flexible non-ring methylene protons appeared more like a distorted quartet at ~4.30 ppm with $\Delta\nu$ of 9.68 Hz and $J = 11.33$ Hz.

3.3. Polymer network synthesis

Cross-linked polymers were synthesized by doping the ε-CL and TMC monomer with the bis(cyclic carbonate) **3f**. The **3f** monomer was used as a model system to demonstrate the utility of the bis- and tris-six-membered cyclic carbonates in the synthesis of polymer networks. The polymerization was carried out at 140 °C in bulk for 6 h (see Scheme 2). Four different polymeric samples were prepared with each monomer (TMC and ε-CL) by varying the ratio of the cross-linker, **3f** from 1 to 7% in the monomer feed (Table 1). The polymerizations were catalyzed by $Sn(Oct)_2$ in bulk. The polymers were isolated as transparent solids that swelled in chloroform, an organic solvent in which the homopolymers of TMC and ε-CL are freely soluble. The polymers were thoroughly washed and extracted with chloroform to remove unreacted monomer(s), or the homopolymers, if any. The chloroform extract were evaporated under reduced pressure, and analyzed by ^{1}H NMR. In TMC/**3f** networks, no unreacted TMC or **3f** monomer was detected, although some homopolymer,

Table 1
Swelling ratios of poly(ε-CL), and poly(TMC) based networks at different feed ratio of compound **3f** (co-polymerizations were catalyzed by $Sn(Oct)_2$ in bulk at 140 °C for 6 h; (monomer/catalyst) = 200 (mol/mol))

Entry	Feed ratio ε-CL/(**3f**)	Swelling ratio poly(ε-CL) networks[a]	Feed ratio TMC/(**3f**)	Swelling ratio poly(TMC) networks[a]
1	99:1	8.9	99:1	7.9
2	98:2	7.5	98:2	5.9
3	95:5	6.4	95:5	3.1
4	93:7	5.2	93:7	2.0

[a] Swelling ratio = $(W_s + W_p)/W_p$ [31].

poly(TMC) [3] was recovered (15%) at 1% **3f**. The amount of poly(TMC) decreased with increasing the **3f** to 2%, and no homopolymer was recovered at 5 and 7% of **3f**. In ε-CL/**3f** networks, extraction with chloroform did not indicate (within the NMR detection limit) any unreacted monomer or poly(CL) at any feed ratio. The swelling behavior of the cross-linked polymers was investigated in a number of different organic solvents. While the linear aliphatic polycarbonates and polyesters are highly soluble in solvents such as methylene chloride and tetrahydrofuran [3–5], the polymer samples doped with **3f** were swollen (not dissolved) when placed in these solvents indicating formation of cross-linked materials. The swelling of these polymers was observed in a wide variety of organic solvents, including $CHCl_3$, CH_2Cl_2, ethyl acetate, acetone, DMSO, and DMF but not in protic polar solvents, such as methanol, ethanol, and water, which are not compatible with these polymers.

The swelling ratios [31] were measured at room temperature after the polymers were allowed to equilibrate in dichloromethane, CH_2Cl_2 for three days (72 h, Table 1). The swelling ratio, a measure of the cross-linked density of a material, is defined as the ratio of the total gel weight to the dried gel, i.e. $(W_s + W_p)/W_p$, where W_s is the weight of the absorbed solvent (CH_2Cl_2), and W_p is the weight of the dry polymer sample. In a typical swelling experiment, the dried polymers were immersed in dried and distilled CH_2Cl_2 in closed boiling tubes. After three days, the samples were removed from the solvent and weighed, after excess solvent on its surface was removed by gently tapping the gel with a tissue paper. Increasing the percentage of **3f** in the monomer feed resulted in a lower swelling ratio, which indicated increasing cross-linking density in accordance with higher cross-linker in the monomer feed. For example, at 1% **3f** the swelling ratio for the ε-CL and TMC polymers is 8.9 and 7.9, respectively, which decreases to 5.2 and 2.0 at 7% **3f** for the respective polymers (Fig. 4). In general, the ε-CL/**3f** networks exhibited a higher swelling ratio at all monomer feeds than the corresponding TMC/**3f** networks. This was due to the fact that ε-CL has a seven-membered ring and TMC has a six-membered ring, as a result the space between the cross-links is larger in ε-CL networks for samples having identical cross-linked density.

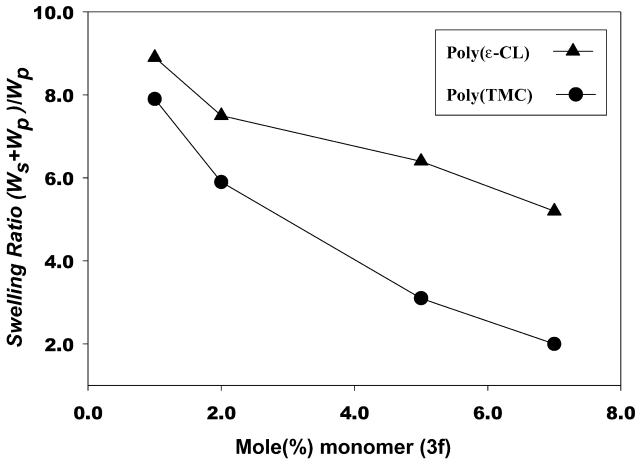


Fig. 4. Swelling ratio vs. mol% of **3f** in poly(ε-caprolactone) and poly(trimethylenecarbonate) based polymer networks.

The T_g of the TMC/**3f** networks rose as the fraction of the **3f** was increased from 1 to 7 % as shown in Fig. 5. For example, at 1% **3f** the T_g of the network was −21.8 °C, which increased to −1.90 °C at 7% **3f** in the polymer. Poly(TMC) has a T_g of −29.8 °C, which is 27.9 °C lower than TMC/7% **3f** network polymer. This increase in glass transition temperature is due to the restricted mobility of the polymer chains resulting from increased cross-link density in the polymer network.

4. Conclusion

New six-membered bis- and tris-(cyclic carbonate)s have been synthesized. The utility of the cyclic carbonates has been demonstrated by copolymerization of **3f** with TMC and ε-CL, which led to cross-linked polymers. Cross-linked polymers (CL/**3f** or TMC/**3f**) were prepared at different monomer feed ratios (1, 2, 5, and 7% of **3f**). The swelling behavior of the polymers was investigated in various organic solvents and the swelling ratios were determined. As expected, higher % **3f** in the monomer feed resulted in higher cross-link density and lower swelling ratio. The glass transition temperature of the TMC/**3f** networks increased with increase in the cross-link density. The physical and thermal properties and biodegradability of the cross-linked polymers are being investigated in our laboratories.

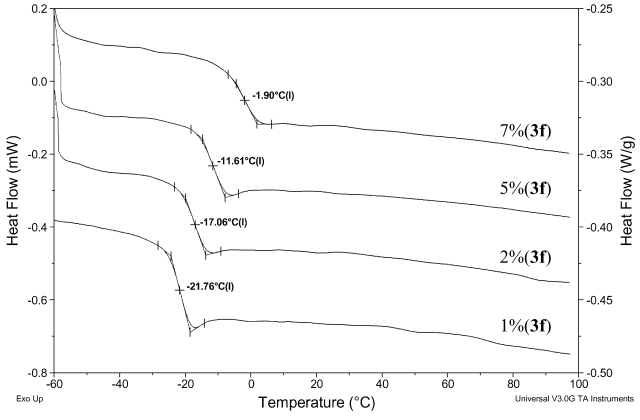


Fig. 5. DSC thermograms of TMC/**3f** networks with different feed ratios of **3f**.

Acknowledgements

Financial support by the Department of Sponsored Research, USF and Moffitt Cancer Institute and Research Center through their Research & Creative Scholarship and ACS-IRG grant programs is greatly appreciated.

References

[1] Mark HF, Bikales NM, Overberger CG, Menges C. Encyclopedia of polymer science and engineering. 2nd ed. New York: Wiley, 1988.
[2] Bisht KS, Deng F, Gross RA, Kaplan DL, Swift G. J Am Chem Soc 1998;120:1363.
[3] Bisht KS, Svirkin YY, Henderson LA, Gross RA, Kaplan DL, Swift G. Macromolecules 1997;30:7735.
[4] Bisht KS, Svirkin YY, Henderson LA, Gross RA, Kaplan DL, Swift G. Macromolecules 1997;30:2705.
[5] Storey RF, Mullen BD, Melchert KM. JMS—Pure Appl Chem 2001;A39(9):897.
[6] Takata T, Matsuoka H, Endo T. Chem Lett 1991:2091.
[7] Zhu KJ, Hendren RW, Jensen K, Pitt CG. Macromolecules 1991;24:1736.
[8] James K, Levene H, Parsons JR, Kohn J. Biomaterials 1999;20:2203.
[9] Edlund U, Albertsson AC. J Appl Polym Sci 1999;72:227.
[10] Ertel SI, Kohn J. J Biomed Mater Res 1994;28:919.
[11] Schnabel W. Polymer degradation: principles and practical applications. New York: Macmillan, 1981 p. 171.
[12] Raghavan D. Polym Plast Technol Engng 1995;34:41.
[13] Engelberg I, Khon J. Biometerials 1991;12:292.
[14] Nagata M, Machida T, Sakai W, Tsutsumi N. Macromolecules 1998;31:6450.
[15] Darwis D, Mitomo H, Enjoji T, Yoshii F, Makuuchi K. Polym Degrad Stab 1998;62:259.
[16] Hirotsu T, Ketelaar A, Nakayama K. Polym Degrad Stab 2000;68:311.
[17] Han DK, Hubbell JA. Macromolecules 1997;30:6077.
[18] Anseth KS, Svaldi DC, Laurencin ST, Langer R. Photopolymerization: fundamentals and applications, ACS Symposium Series. Washington, DC: ACS, 1997. p. 189–202.
[19] Storey RF, Warren SC, Allison CJ, Puckett AD. Polymer 1997;38:6295.
[20] Storey RF, Hickey TP. Polymer 1994;35:830.
[21] Grijpma DW, Kroeze E, Nijenhuis AJ, Pennings AJ. Polymer 1993;34:1496.
[22] Lin ML, Chang KH, Chang FC, Li MS, Ma CM. J Polym Sci, Part B: Polym Phys 1997;35:2183.
[23] Don TM, Bell JP. J Polym Sci, Part A: Polym Chem 1996;34:2103.
[24] Marks MJ, Erskine JS, McCrery DA. Macromolecules 1994;27:4114.
[25] Al-Azemi TF, Bisht KS. Macromolecules 1999;32:6536.
[26] Al-Azemi TF, Harmon JP, Bisht KS. Biomacromolecules 2000;1:493.
[27] Kihara N, Endo T. J Polym Sci, Part A: Polym Chem 1993;31:2765.
[28] Steblyanko A, Choi W, Sanda F, Endo T. J Polym Sci, Part A: Polym Chem 2000;38:2375.
[29] Ihre H, Hult A. Macromolecules 1998;31:4061.
[30] Moore JS, Stupp SI. Macromolecules 1990;23:65.
[31] Makino K, Hiyoshi J, Ohshima H. Colloids Surf, B: Biointerface 2000;19:197.