Communications

New Ground for Organic Catalysis: A Ring-Opening Polymerization Approach to Hydrogels

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Herein, we describe an organocatalytic living polymerization approach to network and subsequent hydrogel formation. Cyclic carbonate-functionalized macromolecules were ring-opened using an alcoholic initiator in the presence of an organic catalyst, amidine 1,8-diazabicyclo[5.4.0]undec-7-ene. A model reaction for the cross-linking identified monomer concentration-dependent reaction regimes, and enhanced kinetic control was demonstrated by introducing a comonomer, trimethylene carbonate. The addition of the comonomer facilitated near-quantitative conversion of monomer to polymer (>96%). Resulting poly(ethylene glycol) networks swell significantly in water, and an open co-continuous (water−gel) porous structure was observed by scanning electron microscopy. The organocatalytic ring-opening polymerization of cyclic carbonate functional macromonomers using alcoholic initiators provides a simple, efficient, and versatile approach to hydrogel networks.

Natural and synthetic hydrogels comprise an important class of biomaterials that have distinctive properties including water compatibility/uptake, making them ideal candidates for certain biological applications. In drug and protein delivery, hydrogels have been used as temporary carriers designed to release an active substance according to different pathways, including simple network degradation, thermal response, pH change, or hydrophilic stimuli response.[1−7] In the emerging field of regenerative medicine, hydrogels in vitro act as essential and temporary scaffolds into which extracellular matrix (ECM) proteins and cells are integrated.[8] The coexisting presence of scaffold, matrix, and cells forms the foundation for proliferation, and, over time, the initial scaffold is degraded and replaced with ECM and cells produced in vivo. However, the fragility of most synthetic hydrogels poses a formidable obstacle to their application as substitutes for natural tissues, which have exceptional mechanical properties despite high water content (>75%).

Hydrogel cross-linking chemistries have been predominantly based on free-radical[9−10] or condensation[11−12] methods. Synthetic limitations of these methods often result in nonideal network structures that stem from incomplete reactions and/or broad molecular weight distributions between cross-linking junctions.[10] New synthetic strategies are needed to address some of the important chemical requirements for hydrogel synthesis: functional group tolerance, mild conditions, and an efficient, high-yielding reaction. Ideally, robust and flexible cross-linking chemistries generating well-defined and functional network structures could enhance its viscoelastic response and network toughness. To this end, Hubbell et al. have designed hydrogels made selectively from the Michael-type addition between a vinyl sulfone poly(ethylene glycol) (PEG) chain and a cysteine-containing peptide,[11] and Malkoch et al. have demonstrated the generation of well-defined networks by Cu(I)-catalyzed cycloadditions between azide- and acetylene-terminated PEG chains.[12] These condensation reactions have both high selectivity and tolerance toward functional groups as well as high efficiencies. Ossipov et al. demonstrated the gel formation of poly(vinyl alcohols) in a similar fashion.[13] Alternatively, the readily available naturally occurring polysaccharides such as hyaluron or chitosan have excellent in vivo performance.[14] Herein, we describe an alternative approach to hydrogel networks based on the organocatalytic ring-opening polymerization (ROP) of cyclic carbonate-terminated PEG macromonomers. Our expectation was that the control provided by the living ROP would give rise to connectivities by kinetic pathways distinct from the free-radical or condensation approaches, while maintaining an operational simplicity suitable for variation of the network properties or inclusion of interesting functional groups.

The general strategy of our approach is outlined in Scheme 1, with the key building block being a six-membered cyclic carbonate bearing a free carboxylic acid (**1**).[15−16] Reactive oligomers (**5**) were synthesized by acylation of commercial PEG-diols with **1** in the presence of dicyclohexylcarbodiimide (DCC). The incorporation of the carbonate end-groups to the macromonomer was characterized by ^{1}H NMR (Figure 1). The carbonate functional PEG macromonomers were then used to

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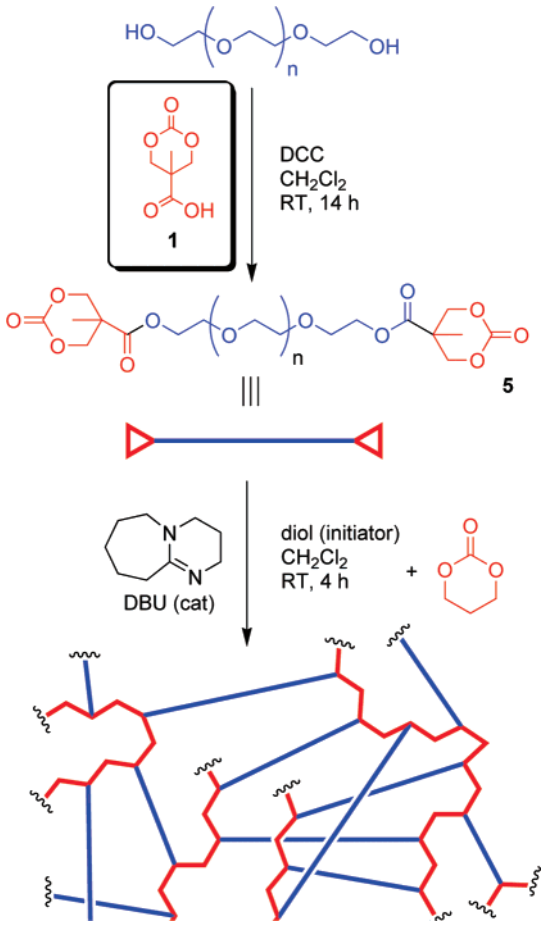
Scheme 1. Synthesis of Biscarbonate PEG Macromonomers (**5**) from PEG-diols and **1** and the Formation of Poly(carbonate)-Linked PEG



generate polymeric networks through organocatalytic ROP in CH_2Cl_2 using an alcoholic initiator (i.e., benzyl-2,2-bis(methylol)propionate) in the presence of amidine 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) ($pK_a = 24.3$), conditions previously developed for organocatalytic polycarbonate formation.[17] Gels were obtained within 4 h.

One concern with this approach is the reported ring−chain equilibrium observed in the polymerization of functional cyclic carbonates.[18−21] This equilibrium provides a challenging limitation to the ROP of carbonates and has been shown to be dependent on both the degree and type of monomer substitution and the monomer concentration.[18−22] As hydrogels are difficult to characterize in situ, a model mono(cyclic carbonate)−monomethylether PEG ($PEG_{1.9k}$−C) was prepared (Figure 2) using **1** and commercial monomethylether PEG (M_n = 1 900 g/mol, polydispersity index (PDI) = 1.02) in the presence of DCC. Subsequently, poly(carbonate-*graft*-PEG) brush formation using $PEG_{1.9k}$−C in CH_2Cl_2 solution catalyzed by DBU and initiated from benzyl alcohol was monitored using both ^{1}H NMR and gel permeation chromatography (GPC). At 55% $PEG_{1.9k}$−C conversion,[23] the M_n of the resulting brush polymer reaches a maximum; upon further conversion, M_n is diminished as a result of the increased formation of low-molecular-weight fractions, as judged by GPC (Figure S1, Supporting Information). Ultimately, the conversion of $PEG_{1.9k}$−C peaks at ~80%. In this case, the limited, low concentration of cyclic carbonate (0.2 M) dictated by the attachment of a large PEG substituent causes the ring−chain equilibrium to dominate so that a stable high-molecular-weight population cannot form. As a means of increasing the concentration of cyclic carbonate present, 2 equiv of trimethylene carbonate (TMC) comonomer was added per $PEG_{1.9k}$−C, effectively tripling the total carbonate monomer concentration to about 0.6 M. Under these conditions, and in contrast to the first experiment, GPC analysis demonstrated the formation of chain-extended polymers, no noticeable regression in molecular weight, and near-quantitative conversions (Figure S2, Supporting Information). These data, consistent with previous studies[18] of carbonate ROP, clearly indicate that comonomer addition is critical to the formation of stable poly(carbonate)-linked hydrogels.

Three biscarbonate PEG macromonomers (**5**) were now synthesized from commercial PEG-diols having molecular weights of 3400, 8000, and 18 500 g/mol (PDI = 1.03 in all cases). Gels were prepared on a 1.0 g scale of **5** and TMC (1.35 mmol combined) in CH_2Cl_2 at a total monomer concentration of 0.6 M using catalytic DBU (2 mol equiv to PEG) and benzyl-2,2-bis(methylol)propionate as the initiator with a targeted degree of polymerization (DP) of 6.[24] Gels were formed within 4 h, after which the films were soaked with benzoic acid (1.2 equiv to DBU in CH_2Cl_2), rinsed with methylene chloride, and dried. Thermal gravimetric analysis (TGA) of washed and dried gels supported the incorporation of TMC as two separate degradation temperatures were observed matching those of poly(trimethylene carbonate) (PTMC) (T = 230 °C) and PEG (T = 400 °C) homopolymers. Moreover, the respective weight loss correlated to the initial feed ratio. ^{1}H NMR analysis of dried gels showed resonances of both PEG and PTMC, and infrared spectroscopy (IR) showed a carbonyl stretch at 1746 cm^{-1} originating from the carbonate unit in the gel structure.

Table 1 summarizes the characteristics of PEG/PTMC hydrogels for the different PEG molecular weights. Swelling experiments were performed on 6 mm diameter disks immobilized in water, and the equilibrium swelling was reached after an immersion time of 6 h, yielding clear hydrogels (Figure S3, Supporting Information). Gel fractions were obtained on lyophilized samples following swelling. These results demonstrate, as expected, that the cross-linking density is inversely proportional to the degree of swelling[25]. The degree of swelling increased with higher molecular weight and was shown to exceed 1100% for the 18.5kg/mol PEG sample (low cross-linking density) and was around 700% for the lower molecular weight samples (high cross-linking density). The elastic modulus was directly proportional to the cross-linking density and was shown to increase with decreasing molecular weight, about 510 kPa for the 3400 g/mol PEG sample and about 200 kPa for the 18.5 kg/mol PEG, in good agreement with other conventional PEG-based hydrogels.[12] Strain at break values were comparable to those of conventional PEG gels but were lower than click PEG hydrogels previously reported.[12] In general, the stress−strain curves showed elastic deformation for the low-molecular-weight samples and strain hardening for the higher molecular weight samples (Figure S4, Supporting Information).

Figure 3 shows a scanning electron micrograph (SEM) of hydrogels made from PEG precursors with molecular weights of 18 500 g/mol and 3400 g/mol that were swollen in water, freeze-dried, and cut to display cross-sections leaving soft and elastic materials. Both samples show a co-continuous (PEG/water) open porous structure, and the pore size shows a strong correlation with the PEG molecular weight.

In summary, we describe an organocatalytic approach to network formation from reactive carbonate functional PEG oligomers. Studies of the growth of polycarbonate−PEG graft copolymers were important in establishing the carbonate concentration required to generate kinetically stable polycar-

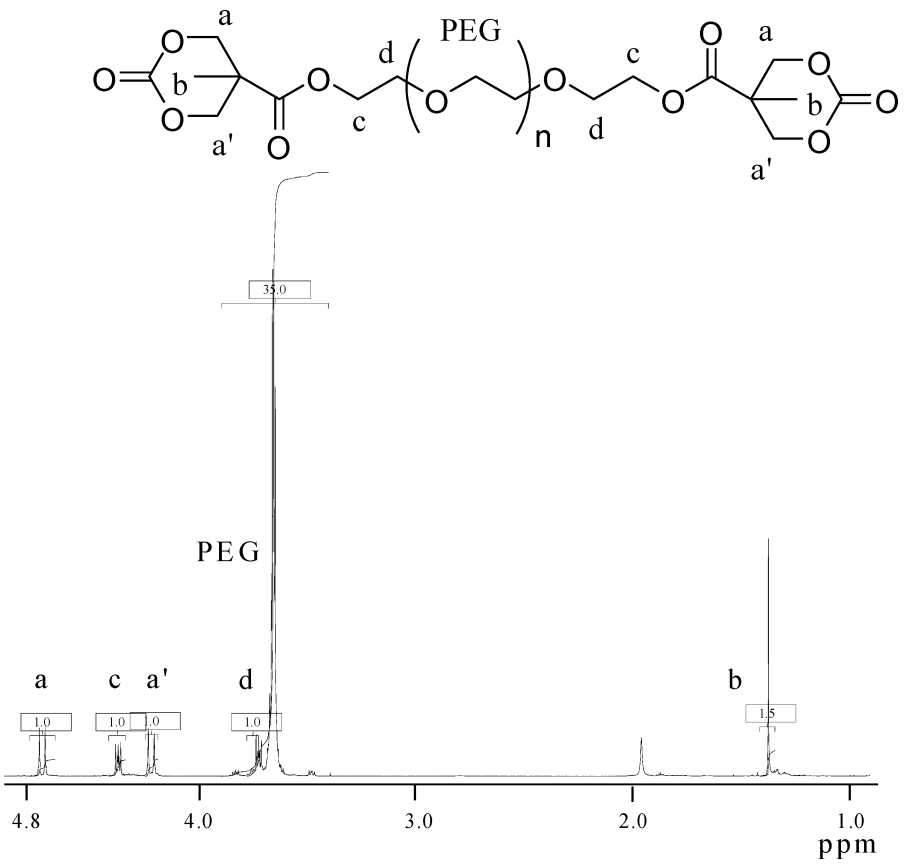


Figure 1. ^{1}H NMR ($CDCl_3$) spectrum of biscarbonate PEG (**5**).

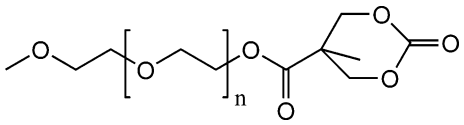


Figure 2. Cross-linking model: cyclic carbonate−monomethylether PEG (PEG1.9k−C).

Table 1. Characteristics of PEG-Based Hydrogels

PEG M_n (g/mol)[a]	degree of swelling (%)[b]	gel fraction[c]	true strain at break (%)[d]	E-modulus (kPa)[d]
3 400	650	0.88	85	510
8 000	700	0.87	90	370
18 500	1170	0.67	100	200

[a] From ^{1}H NMR. [b] (Mass swollen gel − Mass polymer precursor)/(Mass polymer precursor) × 100. [c] Mass dry gel/Mass polymer precursor. [d] From tensile testing in water at 37 °C, neutral pH.

bonates. These data were used to generate defined hydrogel networks. The addition of TMC comonomer not only provides the key for enhanced kinetic reaction control, but also opens new doors for fine-tuning of the functionality of the resulting hydrogel. From our findings, we foresee that our generic networking approach may be bridged to include other families of polymer backbones. Future reports will describe the importance of the individual components necessary for making the gels and their influence on the hydrogel properties, as well as degradation aspects.

Experimental Section

Materials and Instrumentation. Benzyl-2,2-bis(methylol)propionate was made according to a literature procedure.[26] Solvents were dried using activated alumina columns from Innovative Systems. Triphosgene, pyridine, benzyl bromide, DCC, and palladium (10 wt %) on activated carbon (Pd/C) (all Aldrich) were used as received. PEG: 1900 g/mol monomethylether (Polysciences, Inc.), 3400 g/mol (Fluka), 8000 g/mol (Fluka), 18 500 g/mol (Polysciences, Inc.), TMC (Bohringer-Ingelheim) were all azeotropically dried from toluene prior of use. DBU (Aldrich) was distilled twice prior to use. ^{1}H NMR was performed on a Bruker Avance 400 MHz instrument. GPC was performed in THF using a Waters column chromatograph. IR-spectra were measured on a Nexus 670 FT-IR ESP from Thermo-Nicolet using

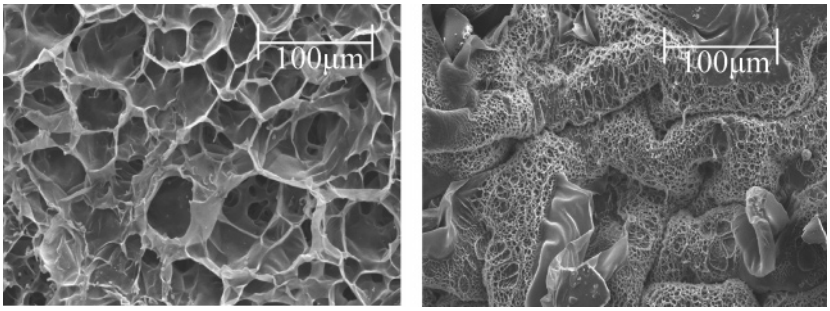


Figure 3. SEM image of swollen hydrogels made from PEG precursor 18 500 g/mol (left) and 3400 g/mol (right).

KBr in transmission mode. TGA was measured on a TA Instruments Hi-Res TGA 2950 thermogravimetric analyzer. Differential scanning calorimetry was measured on a TA Instrument Q1000. Tensile testing was measured on an Instron 5844 using a 10N load cell and a standard video extensometer setup at 37 °C using a Biopuls controlled water bath and a Watlow thermostat. High-resolution mass spectroscopy was performed at the Stanford University Vincent Coates Mass Spectroscopy Laboratory. Swell data were performed in distilled water, and an average from three parallel measurements was given.

General Procedure for Gel Formation. Biscarbonate PEG (1.0 g) and TMC were charged (1.35 mmol combined) in a Petri dish and dissolved in methylene chloride to give a final concentration of 0.6 M (~25% by weight macromonomer + comonomer). DBU catalyst (2 equiv to macro monomer) and benzyl-2,2-bis(methylol)propionate initiator (for a DP of 6 relative to the macromonomer) were added, and the dish was sealed and left for a total of 4 h. Following the reaction, benzoic acid (1.2 equiv relative to DBU) was added to deactivate the catalyst, after which the gel was washed extensively with further methylene chloride and dried until a constant weight was reached.

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Supporting Information Available. Complete synthetic procedures for making carboxylic acid-functional carbonate accompanied by synthetic schemes and ^{1}H NMR and ^{13}C NMR data. Further information is provided regarding GPC, swell profiles, stress−strain curves of hydrogels, hydrogel pictures, and mass spectroscopy.

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