Exploring the versatility of hydrogels derived from living organocatalytic ring-opening polymerization†

Fredrik Nederberg,[ab] Vivian Trang,[c] Russell C. Pratt,[a] Sung-Ho Kim,[a] John Colson,[d] Alshakim Nelson,[a] Curtis W. Frank,[e] James L. Hedrick,[a] Philippe Dubois[f] and Laetitia Mespouille*[aef]

Received 28th September 2009, Accepted 9th February 2010
First published as an Advance Article on the web 9th March 2010
DOI: 10.1039/b920216a

In this work we have bridged the use of mild and living organocatalytic ring-opening polymerization to facilitate the synthesis of cross-linked networks with an emphasis on hydrogels. Amidine-catalyzed ring-opening polymerization of bis-carbonate macromonomers in the presence of an alcohol provides the onset for the reaction and various building blocks issued from the initiator, macromonomer and comonomer can be used in different proportions to tailor the swelling behavior and mechanical integrity of final networks. Easy modifications of the building blocks additionally allow for finely tuning the hydrogel functionality and/or promoting responsiveness in the final structure.

Introduction

Recent advances in organic catalysis have allowed living ring-opening polymerization (ROP) to expand into new areas. In the last few years our group has developed catalysts for a variety of monomeric building blocks to provide novel high performance materials with tunable properties.[1] This development was initially fueled from the need for a metal free catalyst alternative to meet the demanding needs for microelectronic materials and more recently for biomaterials in biomedical applications.[2–4] Successful organocatalysts for living ROP of cyclic esters and carbonates include N-heterocyclic carbenes,[5–10] bifunctional thiourea-amines,[11,12] amidine and guanidine[13,14] based-catalysts such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), N-methyl-TBD (MTBD), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). Living ROP has traditionally found application in the production of (co)polymers of various topologies (block, graft, star-shape, comb-like, *etc.*) presenting targeted molecular weights and narrow molecular weight distributions.[1,15,16] These features have now been bridged towards hydrogels, an important category of materials finding a lot of applications in the field. Hydrogels are a unique class of aqueous swollen networks that have found a multitude of use both *in vitro* and *in vivo* including separation membranes, soft contact lens, cornea replacement, bioadhesives, tissue engineering scaffolds, and drug delivery applications.[17,18] Several synthetic routes to hydrogels are available today and ultimately hydrogel characteristics such as swelling, tensile strength, and biocompatibility in combination with the application determine which system to use.[18–21] Recently we described an organocatalytic ROP approach to network and subsequent hydrogel formation using bis-carbonate functional poly(ethylene glycol) (PEG) oligomers[3] initiated from alcoholic initiators in the presence of an amidine-based organic catalyst. From our initial report a key model reaction identified the critical monomer concentration dependent reaction regime and enhanced kinetic control was demonstrated by the introduction of trimethylene carbonate (TMC) as a comonomer. The addition of the comonomer allowed for near quantitative conversion of monomer to polymer, once initiated from an alcoholic initiator, providing an efficient route to hydrogel formation. The addition of the comonomer is not only crucial for enhanced kinetic control, but also suggests a possible means to introduce functionality together with the judicious choice of the initiator. Here we report the impact of the initial feed composition as the initial monomer to initiator ratio (*i.e.* the degree of polymerization DP), concentration of comonomer relative to macromonomer as well as the introduction of functional macroinitiator or comonomers over final hydrogel properties (such as swelling, and mechanical behavior). This was otherwise made possible by our recent ability to produce functional carbonate monomers from a synthetic strategy derived from 2,2-bis(methylol)propionic acid (bis-MPA) (MTC-COOH), a common building block for the construction of biocompatible dendrimers.[22] Our pursuit of versatility stems from the potential to tag an arbitrary alcohol or amine onto the free acid of MTC-COOH to generate new ROP monomers having a wider range of functional groups and to introduce new properties to the hydrogel.[23] In the frame of this work, a particular interest was devoted to an urea-based carbonate monomer susceptible to strengthen the resulting network by formation of H-bonds with the PEO cross-linker. A second option to introduce functionalities and therefore interesting properties is the use

[a]*IBM Almaden Research Center, 650 Harry Road, San Jose, 95120 CA, USA. E-mail: hedrick@almaden.ibm.com*
[b]*Department of Chemistry, Stanford University, Stanford, 94305 CA, USA*
[c]*Department of Chemistry, University of California, Berkeley, CA 94720, USA*
[d]*Department of Chemistry and Biochemistry, University of Oklahoma, Norman, 73069 OK, USA*
[e]*Department of Chemical Engineering, Stanford University, Stanford, CA 94305, USA*
[f]*Center of Innovation and Research in Materials and Polymers, Laboratory of Polymeric and Composite Materials, 20, Place du Parc, 7000 Mons, Belgium. E-mail: laetitia.mespouille@umons.ac.be; Fax: +003265373484; Tel: +003265373482*

† Electronic Supplementary Information (ESI) available: Provided in the supporting information are stress-strain curves of hydrogels, hydrogel pictures, and differential scanning calorimetry thermograms. See DOI: 10.1039/b920216a/

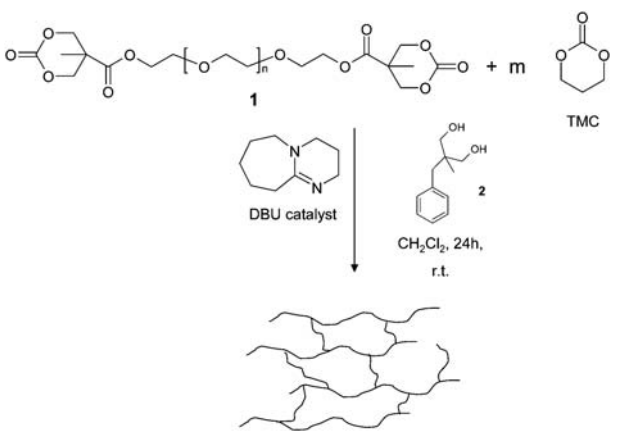
of functional initiator, which can range from a simple alcohol to a biologically important nucleophile, or an environmentally responsive hydroxyl functional macroinitiator to create compartmental hydrogels or gels responsive to pH, pressure, temperature or other factors.[24] Not only does this approach allow for tunable properties, but also for post modifications or selective incorporation of functionality and/or to conjugate drugs, proteins, *etc.* Moreover it provides a simple alternative to existing condensation or radical approaches.[18–21]

Result and discussion

The synthetic strategy envisioned as a new route for producing amphiphilic polycarbonate networks consists in the ring-opening copolymerization of a bis-carbonate functional poly(ethylene glycol) (PEG) (**1**) (macromonomer) with trimethylene carbonate (TMC) initiated from the 2-benzyl-2-methylpropane-1,3-diol and catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, $pK_a = 24.3$, Scheme 1) in CH_2Cl_2 at r.t. The choice of DBU as catalyst relies on its ability to activate both the initiating and propagating alcohol; facilitating ROP under mild reaction conditions while the TMC comonomer has proved to enhance the kinetic control to obtain near quantitative conversion of monomer to polymer, providing an efficient route to network formation.[3]

In the frame of this work, a series of hydrogels P(TMC-*g*-PEO) were prepared in which the individual constituents as the initial monomer-to-initiator and cross-linker-to-monomer ratios were varied. The effect of the composition of the feed was evaluated in terms of tensile strength properties and swelling behavior.

Table 1 summarizes the results including mechanical properties and swelling measurements obtained by varying either the initiator concentration or the comonomer composition for the reaction of bis-carbonate PEG (M_n~8000 g mol^{-1}, PDI 1.03) in the presence of DBU. In a general procedure, a 1.0 g macromonomer scale was used and the reaction was performed in anhydrous methylene chloride at a 25 wt% concentration of all constituents. Initially the comonomer concentration was held constant at 5 equivalents to macro-monomer and the monomer-to-initiator concentration was varied to give targeted degrees of polymerization (DP)'s of 10, 50, and 100. For the lower DP



Scheme 1 General cross-linking procedure employing bis-carbonate PEG macromonomer (**1**) as cross-linker in the presence of an alcohol initiator DBU catalyst.

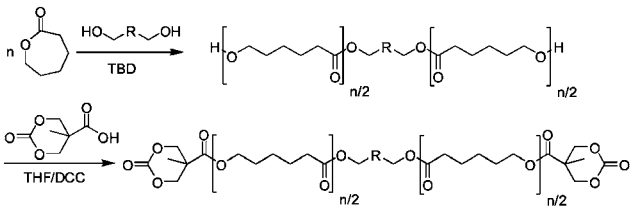
Table 1 Hydrogel properties and the effect from initiator and comonomer (TMC) concentration[a]

Cross-linker[b,c]	TMC[c] (eq. to cross-linker)	DP[d]	E (kPa)[e]	Strain at break (%)[e]	Degree of swelling (%)[f]
PEG-8k	5	10	50	156	1 160
PEG-8k	5	50	366	65	430
PEG-8k	5	100	450	61	420
PEG-8k	5	100	450	60	450
PEG-8k	10	100	580	81	420
PEG-8k	50	100	1 170	137	170

[a] All hydrogels were obtained using 5 eq. of DBU catalyst relative to cross-linker. [b] Cross-linking performed on a 1.0 g cross-linker scale. [c] For the cross-linking reaction the concentration of cross-linker + TMC was held at 25 wt% in methylene chloride. [d] Degree of polymerization DP = $(n_{cross\text{-}linker} + n_{TMC})/n_{initiator}$. [e] From tensile testing in water at 37 °C, each sample measured three times and average is given. [f] S = (mass swollen gel−mass polymer precursor)/(mass polymer precursor)*100, average from three samples given.

(DP 10), resulting hydrogels swelled significantly in water (~1160%) and with an elastic modulus of about 50 kPa. Conversely, for the highest targeted DP's (50 and 100), hydrogels with considerably higher elastic modulus (366 and 450 kPa respectively) and significantly lower swelling degree were formed (450–400%). We rationalize these data through the number of cross-links generated per chain. That is, for the low DP, chains form with fewer cross-links producing a low cross-linking density, resulting in an increased swelling capability and a lower modulus. Alternatively by increasing the DP, the cross-linking density increases with the expected increase in modulus and decrease in swelling.[12]

In a second set of experiments, the amount of comonomer (TMC) relative to the macromonomer (from 5 to 50 equivalents) was varied, while the initiator concentration was held constant to give a targeted DP of 100. The swelling is largely reduced with increasing TMC concentration and the modulus increases to exceed 1 MPa for the highest concentration. In addition, noticeable hydrogel turbidity is observed as the concentration of TMC increases. Poly (trimethylene carbonate) (PTMC) homopolymer is hydrophobic, and with a contact angle (water–polymer) exceeding 70°. Thus, when increasing the concentration of TMC it likely produces PTMC domains or regions that decrease the overall water–hydrogel interaction. In line with previous results[25] the modulus of the hydrogels increases with TMC concentration (from 450 kPa [5eq] to 1170 kPa [50eq]), additionally strain at break values increases (from ~60% [5eq] to >130% [50eq]). Improvement of mechanical properties by introduction of hydrophobic segments with low T_g was already observed with other systems. For example, Dubois *et al.*[26] demonstrated that incorporation of poly(ε-caprolactone) (PCL) cross-linkers in poly(*N*,*N*-dimethylamino-2-ethyl methacrylate) PDMAEMA network led to an increase of the Young modulus from 0.69 ± 0.09 MPa to 2.72 ± 0.12 MPa and an increase of the strain at break from 12 to 215%. Thermal micro-structure analysis of dried samples using differential scanning calorimetry (DSC) indicated a phase separated morphology in which the melting transition of PEG and the glass transition temperature (T_g) of PTMC are observed (Fig. S1, ESI†). This observation supports both the mechanical behavior and visual observation as



Scheme 2 Polymerization of CL and end-group derivatization with carbonate groups.

phase separated hydrophobic PTMC domains are expected to form when increasing the concentration of TMC, leading to mechanical strength enhancement.

To further explore the use of hydrophobicity to toughen hydrogels, carbonate functional PCL, (M_n~8000 g mol^{-1}, PDI 1.40), polymerized from 2-benzyl-2-methylpropane-1,3-diol (DP of 70) in the presence of triazabicyclo-[4.4.0]dec-5-ene [TBD] (pK_a = 26.0), was surveyed as a co-cross-linker (Scheme 2).[25] PCL, as PTMC, is non-soluble in water and with a contact angle (water–polymer) exceeding 90°.[27]

The bis-carbonate PCL cross-linker was used in different concentrations to bis-carbonate functional PEG, with a target DP of 100 and with 5eq of TMC relative to the total concentration of PCL and PEG. The addition of PCL had a significant effect on the mechanical properties of the hydrogels explained through the formation of phase separated hydrophobic domains similar to the behavior previously observed with PTMC (Fig. 1). This led to a significant decrease of the degree of swelling. Visual inspection revealed an increased turbidity of the hydrogel with increasing PCL content, in addition the modulus increases and swelling decreases with increasing PCL concentration. For example, a 1 : 1 (PEG:PCL) weight ratio generates a hydrogel with a modulus of ~4.5MPa and with a degree of swelling of about 100% (Table 2). This material was particularly tough as it exhibited the highest tensile strength of all materials made and was shown to possess high strain values, in fact strain exceeded 200% when the material slipped through the grips without breaking (Fig. S2, ESI†). DSC analysis supports phase separation of PEG and PCL as both melting transitions of PEG and PCL were observed after drying the samples (Fig. S3, ESI†). These data demonstrates that this general synthetic route can be bridged to other families of polymers and that such combinations may be used to tailor hydrogel properties.

To further demonstrate the versatility of the synthetic approach, the initiating alcohol was replaced with a macro-initiator. For this purpose, a bifunctional initiator able to promote

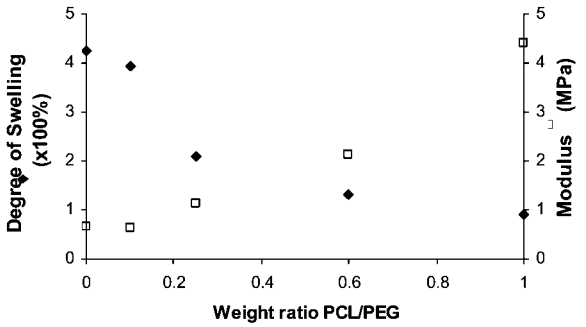


Fig. 1 Degree of swelling (◆) and modulus (□) as function of PCL/PEG macromonomer ratio.

both controlled radical polymerization (CRP) and ROP was employed (Scheme 3). More precisely, N-isopropylacrylamide (NiPAAm) was polymerized by nitroxide mediated polymerization (NMP) (M_n~5800 g mol^{-1}, PDI 1.12) using an alkoxyamine initiator bearing a hydroxyl group. The post NMP preservation of the PNiPAAm hydroxyl group was confirmed in a chain extension experiment. Indeed, PNiPAAm was chain-extended by polymerization of L-lactide using a thiourea/sparteine catalyst/co-catalyst system. As attested by ^{1}H NMR analysis by the presence of PLA signals, and gel permeation chromatography by a shift of the SEC trace toward lower retention volume, (GPC, M_n~8900 g mol^{-1}, PDI = 1.11), PNiPAAm was cleanly chain extended by PLA.

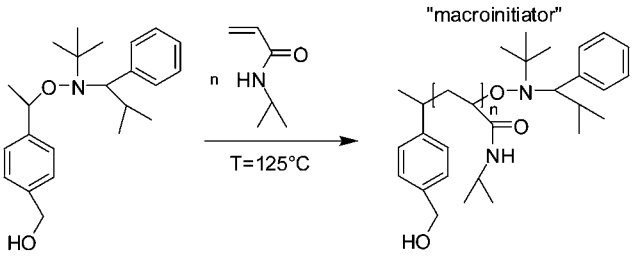
Hydrogel formation was accomplished as described before, using the hydroxy functional PNiPAAm as the initiator for a targeted DP of 100 and 5eq of TMC to PEO cross-linker. Interestingly, when the dry gel is immersed in water at ambient temperature a clear gel formed with a degree of swelling of about 700%, however increasing the temperature to 37 °C (physiological conditions) the hydrogel became opaque (white) due to the lower critical solubility temperature (LCST) transition of PNiPAAm around 32–35 °C (Fig. S4, ESI†). This phase separation confirms the successful incorporation of the macro-initiator into the hydrogel and demonstrates how a thermally induced response may be provided to the final hydrogel. The tensile strength increased above the LCST transition due to the collapse of the PNiPAAm block and the modulus was measured to 0.47 MPa at 37 °C and with a strain at break value of ~150%. The same material at room temperature (21 °C) possessed a modulus of 0.31 MPa and a strain at break value of ~50% (Table 2).

The use of functional carbonates as comonomer provides another route to influence the hydrogel properties or to introduce

Table 2 Mechanical properties of functional polycarbonate-based networks[a]

Initiator[b]	Cross-linker	Comonomer	E (kPa)[d]	Strain at break (%)[d]	Degree of swelling (%)[f]
2	PEO + PCL	TMC	4500Pa	>200	100
PNiPAAm-OH	PEO	TMC	310[e]	50[e]	700
PNiPAAM-OH	PEO	TMC	470	120	—
2[c]	PEO	TMC/sIPN	100	150	376

[a] All hydrogels were obtained using 5eq. of DBU catalyst relative to macromonomer. [b] Cross-linking performed on a 1.0 g PEO scale. For the cross-linking reaction the concentration of cross-linker + TMC was held at 25 wt% in methylene chloride. [c] P(TMC-*g*-PEO) primary network semi-interpenetrated by PUC. [d] From tensile testing in water at 37 °C, each sample measured three times and average is given. [e] From tensile testing in water at 25 °C, each sample measured three times and average is given. [f] S = (mass swollen gel-mass dry gel)/(mass dry gel)*100, average from three samples given at r.t.



Scheme 3 Synthesis of hydroxyl terminated poly(NiPAAm) macroinitiator.

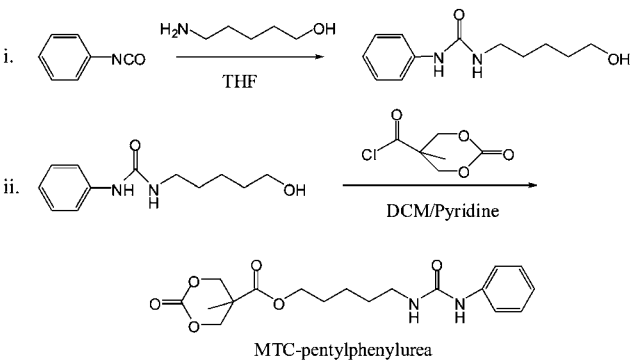
selective functional groups. We have recently demonstrated how 1,3-diols may be used as universal building blocks for functional carbonates, and their controlled ROP using our organocatalytic platform. More precisely, bis-MPA is the starting building block that after simple COOH derivatization and ring-closure provides a functional cyclic carbonate tag for further hydrogel functionalization.[23] In this work we targeted a different MTC monomer carrying an urea group and its synthesis is shown in Scheme 4. Initially, 5-amino-1-pentanol was reacted with phenyl isothiocyanate to provide a phenylurea containing pentanol. This intermediate was subsequently used to acylate MTC-COCl yielding the MTC-pentylphenylurea monomer, which was obtained in high purity and yield. The choice of MTC-pentylphenylurea as comonomer was motivated by its ability to form H-bonds with itself or with PEO. Bulk characterization of the homopolymer has revealed a T_g of ~15 °C for poly(MTC-pentylphenylurea) which is significantly higher than that of PTMC (~−20 °C).

In the present work, various strategies to incorporate the urea containing polymer were attempted demonstrating both the strength and synthetic limitations dictated by the functional group.

Our initial strategy envisioned to introduce the MTC-pentylphenylurea monomer into the polymer network upon the macroinitiator method, following the same strategy as with the PNiPAAm-OH. Practically, MTC-urea was initiated in CH_2Cl_2 at r.t. using benzyl alcohol as initiator and (−)-sparteine with N-(3,5-trifluoromethyl)benzyl-*N*′-cyclohexylthiourea (TU) as catalyst and cocatalyst, respectively. The initial $[MTC\text{-}urea]_0/[I]_0/[(-)\text{-sparteine}]_0/[TU]_0$ ratio was fixed at 32/1/5/5 and the initial monomer concentration was fixed to 1.5 mol L^{-1} (M_n NMR = 10 500 g mol^{-1} and $M_w/M_n = 1.14$). After 2 h of polymerization, the reactive medium was poured in to a Petri dish already charged with TMC and PEG cross-linker dissolved in DCM. The targeted DP was fixed at 100 and the composition in TMC at 5 equivalents to PEO cross-linker. Surprisingly, after 48 h of reaction, the solution remained viscous and no gel was formed. This unsuccessful observation cannot be ascribed to the less active (−)-sparteine catalyst since preliminary tests aiming at synthesizing P(TMC-*co*-PEG) hydrogels or P(MTC-pentylphenylurea) homopolymers (conv. = 90%, $M_w/M_n = 1.14$) were conducted successfully (data not shown). Therefore, it was assumed that H-bonding interactions were taking place in the polymerization medium, inhibiting the propagating site due to the resulting steric hindrance. This assumption was verified by DSC of the P(MTC-pentylphenylurea) (M_n = 10 500 g mol^{-1} and $M_w/M_n = 1.14$) and PEG (M_n = 3.4 kg mol^{-1}) precursors but also of P(MTC-pentylphenylurea)/PEG blends of various compositions. As illustrated by Fig. 2 only one glass transition temperature (T_g) comprised between the individual T_g's of the two respective polymers was observed and corresponded in each composition to the value predicted by the Fox equation.

The miscibility between the two polymer chains was further evidenced by the absence of the melting point related to the PEG cross-linker. The miscibility observed between P(MTC-pentylphenylurea) and PEG gives evidence for the secondary interactions present between the two polymer counterparts and may explain the absence of gelation. To lower the impact of H-bonding over the gel formation, the MTC-pentylphenylurea was directly copolymerized with TMC and the PEG cross-linker. The homogeneous dispersion of MTC-pentylphenylurea into the matrix is expected to suppress the cooperative effect observed in the polymer and reduce the steric hindrance of the self-assembled domains. Various compositions of 14.5, 21.5 and 26.6 mol% were targeted by varying the $[MTC\text{-}pentylphenylurea]_0/[TMC]_0$ initial ratio while the experimental conditions were kept unchanged. Interestingly, only the hydrogel containing the lowest amount of MTC-pentylphenylurea was obtained successfully with a gel fraction of 80%. Increasing the composition in MTC-urea to 21.5 and 26.6 mol% led only to viscous solutions corresponding to polymer chains with high molecular weight as observed by SEC (Mn_{app} = 28 600 and 26 700 g mol^{-1}, respectively, multimodal signals). Again, it seems that urea-urea and urea-PEG H-bonding have a strong inhibiting effect over the cross-linking process.

In order to introduce H-bonding within the network and overcome the synthetic limitations observed above, semi-interpenetrating



Scheme 4 Synthesis and structure of urea-functional MTC monomer (MTC-pentylphenylurea).

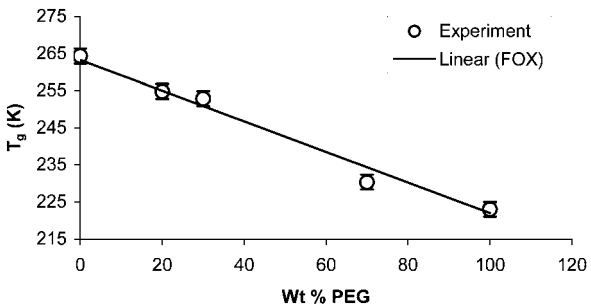


Fig. 2 Experimental T_g's obtained by DSC (5 °C min^{-1}, 2nd scan) for PEG (PEO) (3.4 k), P(MTC-pentylphenylurea) (M_n = 10 500 g mol-1, $M_w/M_n = 1.14$), and PEG/P(MTC-pentylphenylurea).

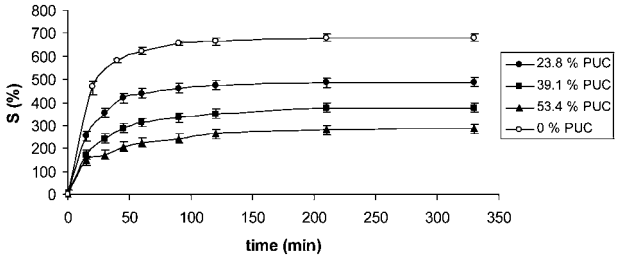


Fig. 3 Swelling profiles for semi-interpenetrating networks (sIPNS) containing various amounts of P(MTC-pentylphenylurea) (PUC).

network (SIPN) were envisioned as the more feasible route to incorporate the urea groups. In the present case, the P(TMC-*g*-PEO) primary network was made by standard methods and subsequently swollen in a solution containing P(MTC-pentylphenylurea) allowing the latter to penetrate the initial network during the course of 24 h. In detail, P(TMC-*g*-PEO) hydrogels slabs (m $\sim$ 16 mg, diameter = 0.25 inch) were pre-swollen in 50 mg of THF in order to dissolve the PEG crystalline micro domains and to open the pores. P(MTC-pentylphenylurea) (M_n NMR = 10 500 g mol^{-1} and M_w/M_n = 1.14), previously dissolved in 0.1 mL of THF was added to the pre-swollen slabs to reach a composition of 25, 50 or 75 wt% of P(MTC-pentylphenylurea) in the network. Excess polymer on the surface was washed out with water and the slabs dried overnight under vacuum. After this treatment, SIPNs containing 23.8, 39.1 and 53.4 wt% of P(MTC-pentylphenylurea), respectively, were successfully obtained. Swell tests of the SIPNs in deionized water revealed that increasing amount of urea in the polymer network decreased the swelling behavior of the primary network (Fig. 3). Tensile testing on a 39.1 wt% P(MTC-pentylphenylurea) SIPN revealed very high strain at break values ($\sim$150%) and an elastic modulus of about 0.1 MPa (Fig. S5, ESI†) (Table 2).

Conclusions

In summary, our report has explored various routes to hydrogels from an organocatalytic ring-opening polymerization approach. The various constituents used for the cross-linking, *i.e.* initiator, comonomer, and (co) cross-linker, may be used in different proportions in order to affect swelling behavior and tensile strength of the final network. In addition, selective functional groups and responsiveness may be added to the material by the use of functional macro initiators or comonomers. Not only is our approach simple and versatile, it also provides a simple alternative to the existing condensation or radical methods to provide hydrogels.

Experimental part

Materials and instrumentation

For the synthesis of bis-carbonate PEG, and monomeric carbonate building block see previous work.[13] For the synthesis of PCL see previous work.[28] 2,2,5-Trimethyl-3-(4′-p-hydroxymethyl-phenylethoxy)-4-phenyl-3-azahexan was prepared according to literature procedures.[1] Solvents were dried using activated alumina columns from Innovative Systems. N-Isopropylacrylamide, phenyl isothiocyanate, 5-amino-1-pentanol (all Aldrich) were used as received. Poly(ethylene glycol) (PEG): 8000g mol^{-1} (PDI: 1.03) [Fluka], trimethylene carbonate (TMC) and L-lactide (Bohringer-Ingelheim) were all azeotropically dried from toluene prior of use. ε-Caprolactone (Aldrich) was distilled from calcium hydride prior of use. 1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU) (Aldrich) was distilled twice prior of use. ^{1}H NMR was performed on a Bruker Avance 400 MHz instrument. Gel permeation chromatography (GPC) was performed in THF using a waters column chromatograph with refractive index detection and compared with known polystyrene standards. Differential scanning calorimetry (DSC) 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 Watlow thermostat, error range are approximately of about 10%. Swelling studies were performed in distilled water and an average from three parallel measurements was given. Degree of swelling (%) = (mass swollen gel−mass polymer precursor)/(mass polymer precursor)*100.

Polymerization of N-isopropylacrylamide

N-Isopropylacrylamide, 2,2,5-trimethyl-3-(4¢-p-hydroxymethyl-phenylethoxy)-4-phenyl-3-azahexan (concentration determined by the desired degree of polymerization), and DMF (1 mL g^{-1} monomer) were charged in a Schlenk tube and degassed by three pump/freeze/thaw cycles. The mixture was heated under stirring at 125 °C and typically stopped when the conversion was $\sim$80–90%. The reaction mixture was diluted with dichloromethane and precipitated in diethyl ether. The formed white powder was filtrated, dried until constant weight under vacuo, and further analyzed with ^{1}H NMR ($CDCl_3$), and GPC (THF).

General procedure for synthesis of bis-carbonate PCL

PCL and MTC-COOH (3eq to PEG) was charged in a 50 mL round bottom flask equipped with a stir bar and dry THF was added to dissolve the compounds. DCC (4eq to PEG) dissolved in THF was added the flask and the formed DCC-urea derivative started to precipitate after about 5 min. The solution was left under stirring for an additional 2 h for the reaction to complete. Following the reaction the DCC-urea was filtrated off and the polymer precipitated in cold methanol. The formed precipitate was collected and dried until constant weight, yield typical >85%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, 4H, 2 × CH_2OCOO), 4.38 (m, 4H, 2 × PCL-$(CH_2)_4CH_2$-OCO), 4.22 (d, 4H, 2 × CH_2OCOO), 4.06 (m, PCL-backbone), 2.30 (m, PCL-backbone), 1.65−1.33 (PCL-backbone).

Polymerization of L-lactide from a PNiPAAm macroinitiator

Hydroxy terminated PNiPAAm macro initiator was azeotropically distilled from toluene, dried under vacuum, and brought inside a glove-box. The PNiPAAm, thiourea catalyst (1eq to PNiPAAm), and sparteine (1eq to PNiPAAm) were dissolved in dry methylene chloride (3 g methylene chloride/0.5 g polymer) and left under stirring for 10 min. L-Lactide monomer was added (ratio dependent on the targeted molecular weight) and the polymerization left under stirring for 14 h. Benzoic acid (2eq to PNiPAAm) was added to quench the catalyst and the formed

diblock copolymer was precipitated in cold methanol. The white precipitate was collected by filtration, rinsed with additional methanol and dried under vacuum until a constant weight was reached. ^{1}H-NMR ($CDCl_3$): 6.47 (bs, 1H, PNiPAAm-NH), 5.20 (q, 1H, PLA-CH), 4.0 (bs, 1H, PNIPAAm-CH), 2.20–1.20 (m, 3H, PNIPAAm-CH_2CH), 1.60 (d, 3H, PLA-CH_3) 1.13 (s, 6H, PNiPAAm-$(CH_3)_2$). GPC: typical PDI~1.10–1.15.

Synthesis of phenylureapentanol

In a dry 100 mL round bottom flask equipped with a stir bar was charged amino pentanol (5.0 g, 48.5 mmol, 1eq). Dry THF (30 mL) was added and the resulting solution cooled to 0 °C using an ice bath. A dropping funnel was attached in which phenylisocyanate (5.19 g, 4.74 mL, 43.6 mmol, 0.9eq) and 30 mL of dry THF was charged. The resulting solution was added drop wise during a period of 30 min. The resulting solution was allowed to warm to ambient temperature and then left under stirring for an additional 16 h. THF was removed through rotational evaporation the following morning. The crude product was recrystallized from ethyl acetate and then stirred rigorously for an additional 4 h. The solids thus formed were removed by filtration, washed with further ethyl acetate and dried until a constant weight was reached, yield 7.0 g (~80%). ^{1}H-NMR (DMSO-d6) δ: 8.19 (s, 1H, NH), 7.39 (d, 2H, ArH), 7.21 (t, 2H, ArH), 6.88 (s, 1H, ArH), 6.10 (t, 1H, NH), 4.40 (t, 1H, OH), 3.40 (q, 2H, CH_2), 3.05 (q, 2H, CH_2), 2.43 (m, 4H, CH_2), 2.32 (m, 2H, CH_2).

Synthesis of MTC-pentylphenylurea

MTC-COOH (4.3 g, 26.8 mmol) was initially converted to MTC-Cl using standard procedures with oxalylchloride. The formed intermediate was dissolved in 50 mL of dry methylene chloride and charged in an addition funnel. In a dry 500 mL round bottom flask equipped with a stir bar was charged phenylureapentanol (5.55 g, 25 mmol), pyridine (1.97 g, 2.02 mL, 25 mmol) and dry methylene chloride (150 mL). The addition funnel was attached under nitrogen and the flask cooled to 0 °C using an ice bath. The MTC-Cl solution was added drop wise during a period of 30 min and the solution allowed an additional 30 min under stirring. The ice bath was removed and the solution allowed to gently heat to ambient temperature and left under stirring for an additional 16 h. The crude product was purified by column chromatography the following morning using silica gel. Methylene chloride was initially used as eluent before gently increasing the polarity finishing with a final concentration of 5 vol% methanol. The product fractions were collected and the solvent removed through rotational evaporation. The isolated product was dried under vacuum until a constant weight was used yielding 8.0 g (~80%) of an off-white oil which crystallized upon standing. ^{1}H NMR (DMSO-d^6) δ: 8.39 (s, 1H, NH), 7.40 (d, 2H, ArH), 7.20 (t, 2H, ArH), 6.88 (t, 1H, ArH), 6.10 (t, 1H, NH), 4.57 (d, 2H, CH_2), 4.39 (d, 2H, CH_2), 4.16, t, 2H, CH_2), 3.10 (q, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 1.18 (s, 3H, CH_3).

General procedure for gel formation. Bis-carbonate PEG (1.0g) and TMC were charged in a Petri-dish and dissolved in methylene chloride to give a final concentration of 25 wt% (both monomers combined). DBU catalyst (2eq. to cross-linker) and benzyl-2,2-bis(methylol)propionate initiator (for a degree of polymerization (DP) relative to both monomers) were added and the dish was sealed and left for a total of 14 h. Following the reaction benzoic acid (1.2eq 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, typical gel fraction ~85–90%.

Preparation of semi-interpenetrated network. The primary PEG-network was produced following the general procedure described here above. TMC (5 equivalents to PEG cross-linker) and benzyl-2,2-bis(methylol)propionate were used as comonomer and initiator, respectively and a degree of polymerization of 100 was targeted. DBU (2 equivalents to PEG cross-linker) and TU (10 equivalents to initiator) were used as catalyst and co-catalyst respectively. Gel fraction of 91.7% was calculated after extraction of unreactive monomer by swelling in CH_2Cl_2. In parallel, P(MTC-pentylphenylurea) was produced in CH_2Cl_2 for a targeted DP of 32. The polymerization was initiated by benzyl alcohol and catalyzed by (−)-sparteine (5 equivalents to initiator) in presence of TU cocatalyst (5 equivalents to initiator). Polymerization was carried out at r.t. for 2 h before to be stopped by addition of benzoic acid. (M_n NMR = 10 500 g mol^{-1}, M_w/M_n = 1.19). Semi-interpenetration was performed in THF by swelling the primary network in a minimal amount of THF to open the pores. The solution of P(MTC-pentylphenylurea), previously dissolved in THF was then added over the pre-swollen sample and the network was allowed to absorb the polymer solution overnight at 40 °C. Then the network was dried under vacuum and the surface of the gel washed by deionized water.

Acknowledgements

FN thanks the Swedish Research Council (VR) for financial support. LM was supported by IBM, the Center for Polymeric Interfaces and Molecular Assemblies (CPIMA) under NSF funding, and the Center of Innovation and Research in Materials and Polymers (CIRMAP). CIRMAP is very grateful to "Région Wallonne" and European Union (FEDER, FSE) for general financial support in the frame of Objectif 1-Hainaut: Materia Nova, as well as to the Belgian Federal Government Office of Science Policy (SSTC-PAI 6/27). Further support comes from NSF-GOALI grant (NSF-CHE-0645891). Authors thank Teddie Magbitang, Dolores Miller, and Dave Myung for analytical support, and Debbi Price and Bohringer-Ingelheim for kindly donating the TMC monomer.

References

1 N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer and J. L. Hedrick, *Chem. Rev.*, 2007, **107**, 5813–5840.
2 K. Fukushima, R. C. Pratt, F. Nederberg, J. P. K. Tan, Y. Y. Yang, R. M. Waymouth and J. L. Hedrick, *Biomacromolecules*, 2008, **9**, 3051–3056.
3 F. Nederberg, V. Trang, R. C. Pratt, A. F. Mason, C. W. Frank, R. M. Waymouth and J. L. Hedrick, *Biomacromolecules*, 2007, **8**, 3294–3297.
4 S. H. Kim, J. P. K. Tan, F. Nederberg, K. Fukushima, Y. Y. Yang, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2009, **42**, 25–29.

5 E. F. Connor, G. W. Nyce, M. Myers, A. Mock and J. L. Hedrick, *J. Am. Chem. Soc.*, 2002, **124**, 914–915.
6 G. W. Nyce, T. Glauser, E. F. Connor, A. Mock, R. M. Waymouth and J. L. Hedrick, *J. Am. Chem. Soc.*, 2003, **125**, 3046–3056.
7 O. Coulembier, A. P. Dove, R. C. Pratt, A. C. Sentman, D. A. Culkin, L. Mespouille, P. Dubois, R. M. Waymouth and J. L. Hedrick, *Angew. Chem., Int. Ed.*, 2005, **44**, 4964–4968.
8 O. Coulembier, B. G. G. Lohmeijer, A. P. Dove, R. C. Pratt, L. Mespouille, D. A. Culkin, S. J. Benight, P. Dubois, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 5617–5628.
9 O. Coulembier, L. Mespouille, J. L. Hedrick, R. M. Waymouth and P. Dubois, *Macromolecules*, 2006, **39**, 4001–4008.
10 S. Csihony, D. A. Culkin, A. C. Sentman, A. P. Dove, R. M. Waymouth and J. L. Hedrick, *J. Am. Chem. Soc.*, 2005, **127**, 9079–9084.
11 A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth and J. L. Hedrick, *J. Am. Chem. Soc.*, 2005, **127**, 13798–13799.
12 R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, P. N. P. Lundberg, A. P. Dove, H. B. Li, C. G. Wade, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 7863–7871.
13 B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 8574–8583.
14 R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, R. M. Waymouth and J. L. Hedrick, *J. Am. Chem. Soc.*, 2006, **128**, 4556–4557.
15 C. J. Hawker and K. L. Wooley, *Science*, 2005, **309**, 1200–1205.
16 K. Matyjaszewski and J. H. Xia, *Chem. Rev.*, 2001, **101**, 2921–2990.
17 A. S. H. B. D. Ratner, F. J. Schoen, J. E. Lemons, *Biomaterials Science*, Academic press, 1st edn, 978-0125824613, 1996.
18 S. Lin-Gibson, R. L. Jones, N. R. Washburn and F. Horkay, *Macromolecules*, 2005, **38**, 2897–2902.
19 M. P. Lutolf, G. P. Raeber, A. H. Zisch, N. Tirelli and J. A. Hubbell, *Adv. Mater.*, 2003, **15**, 888.
20 M. Malkoch, R. Vestberg, N. Gupta, L. Mespouille, P. Dubois, A. F. Mason, J. L. Hedrick, Q. Liao, C. W. Frank, K. Kingsbury and C. J. Hawker, *Chem. Commun.*, 2006, 2774–2776.
21 D. A. Ossipov, S. Piskounova and J. Hilborn, *Macromolecules*, 2008, **41**, 3971–3982.
22 M. Malkoch, E. Malmstrom and A. Hult, *Macromolecules*, 2002, **35**, 8307–8314.
23 R. C. Pratt, F. Nederberg, R. M. Waymouth and J. L. Hedrick, *Chem. Commun.*, 2008, 114–116.
24 X. Yin, A. S. Hoffman and P. S. Stayton, *Biomacromolecules*, 2006, **7**, 1381–1385.
25 D. S. Jones, D. W. J. McLaughlin, C. P. McCoy and S. P. Gorman, *Biomaterials*, 2005, **26**, 1761–1770.
26 L. Mespouille, J.-M. Raquez, C. W. Frank and P. Dubois, *Controlled/Living Radical Polymerization: Progress in ATRP*, American Chemical Society, Washington DC, 2009.
27 Z. G. Tang, R. A. Black, J. M. Curran, J. A. Hunt, N. P. Rhodes and D. F. Williams, *Biomaterials*, 2004, **25**, 4741–4748.
28 A. W. Bosman, R. Vestberg, A. Heumann, J. M. J. Frechet and C. J. Hawker, *J. Am. Chem. Soc.*, 2003, **125**, 715–728.

