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# Toward biodegradable nanogel star polymers *via* organocatalytic ROP†

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**Organocatalytic ring opening polymerization (OROP) is used to effect the rapid, scalable, room temperature formation of size-controlled, highly uniform, polyvalent, nanogel star polymer nanoparticles of biodegradable composition.**

Nanogel star polymers (unimolecular, globular, nanoscale architectures comprised of a high local density of polymeric arms emanating from a nanogel core[1a]) are currently under widespread development as an organic nanoparticle platform.[1,2] Driving this development is the advancement and application of living polymerization methodologies that can generate these complex structures with improved control over size, uniformity, chemical structure and synthetic scale. Nanogel star polymers of biocompatible compositions, in particular, are beginning to emerge and are now being auditioned for a growing range of biomedical applications.[3]

Among the most attractive methods for affording polymers of biocompatible composition are the ring opening polymerizations (ROP) of cyclic esters, cyclic carbonates and epoxides.[4] The Sn(II) catalyzed ROP of cyclic esters, in particular, is among the most widely used, traditional, method for accessing polyesters.[5] Sn(II) is, however, notoriously difficult to remove post-polymerization owing to its oxophilic nature, with residual tin levels for linear polyesters often exceeding 1000 ppm.[6] However, owing to its high toxicity, the United States Food and Drug Administration (FDA) has set the limit for Sn(II) in commercially used biomedical polymer materials at 20 ppm.[7]

As an alternative to metal catalysts, organocatalyic ROP (OROP), *i.e.* effecting ROP using organic molecules, is a rapidly maturing field applicable to a wide variety of cyclic monomers.[8] This approach to living polymerizations has been recently applied to a range of polymer architectures and compositions of biomedical relevance but has yet to be applied to the creation of nanogel star polymers. Consequently, we report herein the development of OROP as a highly efficacious approach to uniform nanogel star polymers of biodgradable composition[9] and polyvalent functionality.

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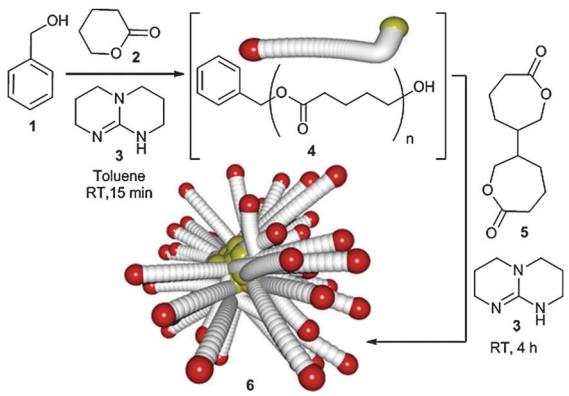


**Scheme 1** The use of organocatalyst TBD **3** to effect the rapid, room temperature, one pot/two step OROP synthesis of polyester nanogel star polymer **6** with addressable core and peripheral functionalities.

In this work, we chose to use the arm first approach[1a] for nanogel star polymer formation (Scheme 1). δ-Valerolactone **2** was chosen as the monomer for arm formation due to its demonstrated rapid and controlled room temperature OROP with organic catalysts including 1,5,7-triaza-bicyclo[4.4.0]dec-5-ene **3** (TBD).[10] Benzyl alcohol **1** was used as the initiator owing to the potential for further peripheral synthetic transformations after star polymer formation. 5–5′-Bis(oxepanyl-2-one) **5** (BOP) was used as the crosslinking agent based on its demonstrated utility in previous methodologies.[11]

In our initial approach, "living" poly(δ-valerolactone) arms **4** of mass (Mn) = 3 kDa (degree of polymerization ~30) and polydispersity index (PDI) = 1.06 were first synthesized in anhydrous toluene at room temperature over 15 min using a relative molar ratio (**1**:**2**:**3**) equal to 0.03 : 1 : 0.005. After this time, BOP **5** and a second quantity of TBD **3** were added to the solution of living macroinitiator **4** in the ratio of 5 : 0.15 : 1 respectively. Analysis by gel permeation chromatography (GPC) of the crude product formed after 4 h showed the formation of a single, high molecular weight species with PDI = 1.28 (Fig. 1) and little trace of any residual arms. After quenching with benzoic acid, the crude product was isolated by precipitation from methanol and purified by a *single* solvent fractionation process. The viscous oil isolated was re-precipitated into methanol to afford polyester nanogel star polymer **6a** with a high molecular weight and low PDI = 1.24 (Fig. 1) as a white, amorphous, free flowing powder in 50% yield on a 10 g scale.

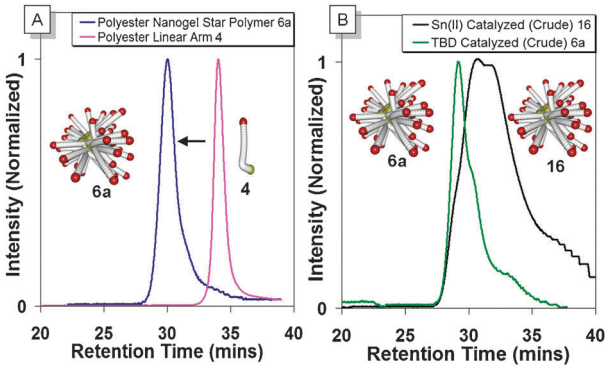


**Fig. 1** GPC traces of (**A**) linear poly(δ-valerolactone) **4** and the corresponding polyester nanogel star polymer **6a** as highly uniform polymers of increasing molecular weight (**B**) crude polyester nanogel star polymers **6a** and **16**, formed from TBD **3** and Sn(II) catalysts respectively, showing the increased product uniformity afforded by **3**.

Dynamic Light Scattering (DLS) analysis of nanogel star polymer **6a** indicated a hydrodynamic radius ($R_h$) = 5.0 nm (THF) with a PDI = 1.21 and $M_n$ = 333 kDa. $^1$H-NMR (400 MHz, $CDCl_3$) analysis of the linear arm **4** and the nanogel star polymer **6a** showed the integration of the individual signals of the ester moieties (~4.1, 2.8, and 1.7 ppm) increased from 60, 60 and 120 to approx. 88, 88, and 198, respectively (Fig. 2). This is attributed to the inclusion of an average of 7 BOP **5** units into the nanogel core for every linear arm **4** incorporated into the structure of **6a**. This implies that the molecular weight of star polymer **6a** is comprised of *ca.* 35% BOP- **5** based core and 65% linear polyester arms. This corresponds to **6a** having approx. 72 arms per macromolecule. Differential scanning calorimetry (DSC) indicated a melting temperature ($T_m$) of 47 °C and a glass transition temperature ($T_g$) of −34 °C, for **6a**, both lower than for the constituent linear arms **4** (50 °C and −24 °C, respectively).

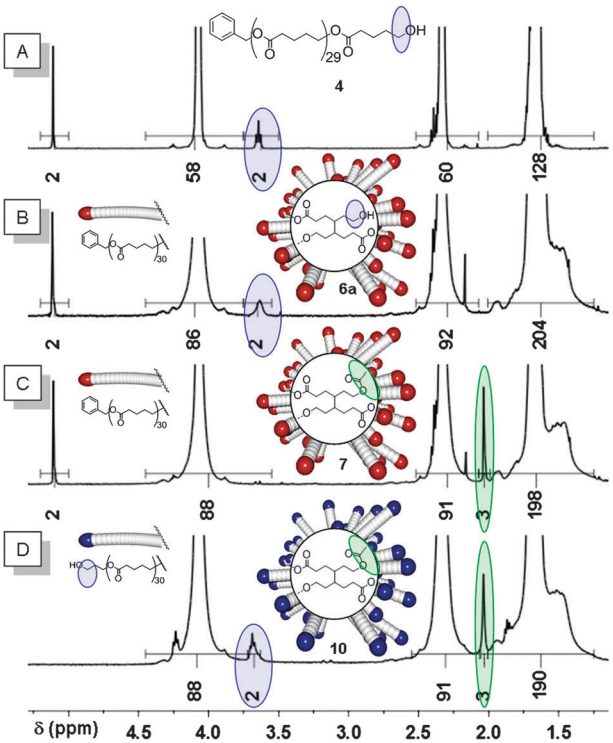


**Fig. 2** Partial $^1$H NMR (400 MHz, $CDCl_3$) spectra of (**A**) linear poly(δ-valerolactone) **4** (**B**) polyester nanogel star polymer **6** formed from **4** showing the increased integral values of the ester signals arising from the incorporation of the core-forming BOP **5** units and the methylene signal adjacent to the hydroxyl terminus from the nanogel core region (**C**) the quantative acetylation of the core hydroxyl groups of **6** to form core functionalized nanogel star polymer **7** and (**D**) the core (acetylated) and peripherally (alcohol) functionalized polyester nanogel star polymer **10**.

The $^1$H-NMR analysis of nanogel star polymer **6a** also showed that the signal from the methylene adjacent to the hydroxyl terminus of the linear arm **4** is retained in the spectrum of the star polymer **6a**, although broadened (Fig. 2). This is attributed to the residual alcohol groups from the "living" polymerization being now located within the core of the star polymer structure, with approx. one hydroxyl existing for every arm incorporated into the star polymer structure. These core hydroxyl groups of **6a** could be quantiatively acetylated using the TBD **3** catalyzed reaction with acetic anhydride[10] as confirmed by $^1$H-NMR analysis (Fig. 2) of the resulting product **7** without noticeable change to the $R_h$, $M_n$ or PDI of **7** as compared to **6a**. The synthetic accessibility of the core hydroxyl groups of **6a** was also confirmed by quantitative tosylation to the corresponding core-tosylated nanogel star polymer **8**. The ability of the tosylate groups of **8** to undergo nucleophilic displacement reactions to form higher core-functional systems is now under evaluation.

The introduction of peripheral functionality to the polyester nanogel star polymer structure was then studied. The removal of the benzyl groups of nanogel star polymer **6a** was not readily achieved in a quantitative fashion. Consequently, 1-*tert*-butyldimethylsiloxy-propan-3-ol was used as an initiator to produce star polymer **9** with size, arm number and BOP **5** incorporation similar to nanogel star polymer **6a.** After acetylation of the core hydroxyl groups (to preclude overlapping hydroxyl signals) the peripheral protecting groups of nanogel star polymer **9** were removed with TBAF to produce the peripherally hydroxy-functional nanogel star polymer **10** (Fig. 2) which was then transformed into the peripherally tosylated form **11**. This ability to manipulate both core and peripheral functionality orthogonally now provides a viable route to the formation of biodegradable nanogel star polymer systems with tandem "dual-mode" functionality.[1a]

In the course of this work, it was found that catalyst purity was critical in promoting a controlled polymerization to nanogel star polymer systems (Table 1). The initial use of

**Table 1** The effect of varying catalyst **3** purity, reaction temperature and reaction time in OROP polyester nanogel star polymer formation

| Entry | Catalyst | Reaction time (h) | Reaction temp. (°C) | Mn[a] (kDa) | Crude[a] PDI | Sn(II) content |
|---|---|---|---|---|---|---|
| 1 (**6a**) | TBC[c] | 4 | RT[e] | 340 | 1.21 | < 2 ppm |
| 2 (**6b**) | TBD[b] | 16 | RT[e] | 333 | 1.31 | — |
| 3 (**6c**) | TBD[c] | 16 | RT[e] | 1126 | 1.84 | — |
| 4 (**6d**) | TBD[c] | 4 | 40 | 1200 | 1.51 | — |
| 5 (**6e**) | TBD[c] | 16 | 40 | 1804 | 2.20 | — |
| 6 (**16**) | Sn(II)[d] | 48 | 110 | 290 | — | 1800 ppm |

[a] Determined by DLS. [b] Used as received. [c] Purified by sublimation. [d] Tin(II) 2-ethylhexanoate. [e] Temperature of glove box *ca.* 30 °C.

commercial grade TBD **3** resulted in the reaction stalling within 16 h, at which time a nanogel star polymer **6b** had formed (Entry 2). Using purified catalyst under the same conditions produced nanogel star polymer **6c** (Entry 3), larger than **6b** but with increased PDI. Reducing the reaction time to 4 h enabled the formation of the previously described **6a** (Entry 1). Increasing the reaction temperature to 40 °C formed nanogel star polymer **6d** in 4 h with a similar mass to **6c** but with lower PDI (Entry 4) and extending the reaction time to 16 h at 40 °C produced a very large nanogel star polymer **6e** (Entry 5) but again with increased PDI. The crude products **6b–e** could be purified (as for **6a**), with varying efficiency, to produce uniform polyester nanogel star polymers of different sizes and structural parameters.

We next performed a comparative study of TBD **3** *versus* Sn(II) catalysis for polyester nanogel star polymer formation. In our hands, the Sn(II) catalysed reaction,[11d] after 48 h in refluxing toluene, produced a crude nanogel star polymer **16** of similar arm length and molecular weight to **6a** (*i.e.* that formed by TBD **3** in four hours at room temperature), although with a much higher PDI (Fig. 1b, Table 1). ICP-MS analysis showed **16** had a Sn(II) content much higher than it's constituent linear polymer arm (1800 *vs.* 610 ppm respectively). The residual tin content of **6a** produced by TBD **3** catalysed OROP was $<2$ ppm, below both detection limits and the current FDA limits of 20 ppm.[7] One of the advantages of nanogel star polymer architectures lies in the high local density of polyvalent function. In the context of residual tin(II) catalyst sequestration however, this problem is exacerbated for these systems when created through Sn(II) catalysis and stands to hinder current Sn(II) removal techniques (which typically rely on bi-dentate competitive ligation agents).[7b,12] The ability of OROP to rapidly produce tin-free polyester nanogel star polymers is expected to help accelerate their biomedical application.

Finally, two other key features of the OROP formation of nanogel star polymers were noted. First, the sequential addition of monomer **1** and cross-linker **5** is unnecessary owing to the relatively low solubility of **5** and the rapid polymerization of the **1**. Consequently, the reaction could be readily performed as a one step, one pot reaction in which all reagents can be combined from the outset, increasing the practicality of the reaction (Fig. 3). More importantly, it was also determined that OROP nanogel star polymer synthesis could also be accomplished using preformed hydroxyl-terminated poly(δ-valerolactone) arms using BOP **5** and TBD **3** directly (Fig. 3). This suggests a potential verstaility of this reaction platform for the formation of nanogel star polymers of varying compositions by other alcohol terminated polymers relevant to biomedical application such as poly(alkylene oxides), polylactides and polyoxazolines.

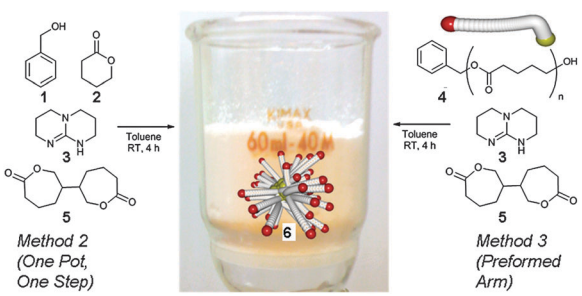


**Fig. 3** The OROP formation of polyester nanogel star polymers as either a one pot process (left) or a process using preformed alcohol-terminated linear polymers **4** (right) and a photograph (middle) of the result from a single large scale synthesis of **6**.

In summary, we have described the first use of OROP as a means for producing nanogel star polymers comprised of biodegradable compositions. This process results in the rapid, room temperature controlled formation of highly uniform, size controlled nanoparticles which can be effectively functionalized, either internally or peripherally in an orthogonal fashion. The further development of OROP for nanogel star polymer formation as a general platform using other polymers and block co-polymers of biomedically relevant compositions is ongoing and will be described in due course.

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