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Nanosponge formation from organocatalytically-synthesized poly(carbonate) copoplymers

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Abstract

Advanced organocatalytic synthesis methods were employed to prepare linear poly(carbonate)s with control over functional group incorporation and molecular weight. Pendant allyl or epoxide groups served as reaction partners in thiol-ene click or epoxide–amine reactions with ethylene oxide-containing crosslinking groups to form a panel of six novel poly(carbonate) nanosponges with crosslinking densities ranging from 5%, 10% and 20% *via* an intermolecular chain-crosslinking approach.

Keywords

Polycarbonate nanosponges; drug delivery; organocatalytic ring-opening polymerization; functional poly(carbonate)s

Value-driven engineering and the synthesis of biomaterials for applications in tissue engineering, wound healing and drug delivery are the driving forces in the development of defined and functionalized materials. While the preparation of poly(ester)-and poly(carbonate)-based particles has been mainly driven by precipitation processes,[1–3] chemically-driven nanoparticle formation has given the opportunity to control sizes and the architectural nature of the particles. Intramolecular[4,5] and interchain crosslinking processes[6,7] have been developed into suitable methods to form versatile supramolecular structures. In particular, intermolecular chain cross-linking of side-chainfunctional poly(ester)s derived by ring opening polymerization (ROP) of substituted δ-valerolactone monomers[8–11] affords controlled nanoparticle sizes that can be varied *via* the percentiles of side-chain functionalities into the linear poly(ester) precursor. Furthermore, the morphology and size can be controlled with the amount of difunctionalized cross-linking units, which react with the side-chain functionality of the polymer. With this, functionalized particles that are further post-modified with targeting units and, upon drug encapsulation, can be tested for their biological response as drug delivery systems[11,12]

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ASSOCIATED CONTENT

Supporting Information. Synthesis of polymers, nanoparticles as well as characterization methods are described. (http://pubs.acs.org/page/jacsat/submission/authors.html).

Author Contributions

The project was conceptualized and planned by A.P.D. and E.H. The manuscript was written through contributions of all authors. S.T. and D.M.S. synthesized the linear polymers. The linear polymers were oxidized and the particles were prepared and characterized by D.M.S. at Vanderbilt University. All authors have given approval to the final version of the manuscript.

A range of degradable polymers have been investigated for *in vivo* applications.[13–16] Poly(ester)s are most commonly studied, however, the introduction of side-chain functional groups is typically challenging and can limit their applicability in advanced applications.[16,17] Poly(carbonate)s prepared by the ROP of 6-membered cyclic monomers have been widely explored for these applications, and organocatalysis has provided efficient routes to realize a range of functionalized polymer structures.[18–20] Recently, a range of functional monomers and polymers have been explored from simple precursors giving access to unprecedented levels of functional group incorporation.[21–23] Importantly, poly(carbonate) materials display slower degradation profiles with less toxic byproducts than poly(ester)s, thus making them ideal candidates as one of the building blocks for advanced nanomaterials.[17] Herein we demonstrate that for the first time, the organocatalytic copolymerization of an allyl-functional cyclic carbonate monomer with a cyclic carbonate monomer with a functional group that cannot undergo post-polymerization modification yields aliphatic copoly(carbonate)s that can be employed in the intermolecular chain crosslinking process for the synthesis of poly(carbonate) nanosponges. (Figure 1).

Extension of the organocatalytic methods for ROP of 5-methyl- 5-allyloxycarbonyl-1,3-dioxane-2-one (MAC) to prepare a series of novel copolymers with 5-methyl-5-ethyloxycarbonyl-1,3- dioxane-2-one (MTC-Et) to provide a series of three copolymers (Table 1) initiated from benzyl alcohol using the (−)– sparteine/thiourea catalyst system (Scheme 1) with controlled functional group densities was undertaken.[24,25] The observed copolymers showed a good control in molecular weight but slightly broad dispersities that are a consequence of high molecular weight tailing of the polymer distributions at high conversions (Figure 2).

It was decided that these polymers were suitable to test the ability and performance in nanoparticle formation since the incorporation of the MAC monomer, which contains the allyl functionality, was consistent with the monomer feed ratios as confirmed by ^{1}H NMR spectroscopy (Supporting Information). The ability of the copolymers (Figure 2) to form nanoparticles was investigated initially *via* the previously-developed thiolene “click” chemistry.

To investigate poly(carbonate)-based nanosponge formation, a panel of 3 copolymers containing 5%, 10% and 20% of MAC was planned to react with the dithiolethyleneoxide cross-linker in a thiolene reaction. We sought to keep the equivalencies of the difunctionalized cross-linker constant to investigate the control of size dimensions with a variation of the cross-linking density in the linear precursor; therefore, all reactions were completed using 4 equivalents of respective difuctionalized cross-linker (8 equivalents thiol/allyl). Transmission electron microscopy (TEM) and dynamic light scattering (DLS) analysis demonstrated that poly(carbonate)-based nanosponges could be prepared employing intermolecular crosslinking reactions. The increasing amount of allyl functionality in the polymer backbone led to larger particles for the series as displayed by the number-average hydrodynamic diameters, D_h of =220 nm for the 20% cross-linker-containing particles, in contrast to smaller particle sizes of D_h = 150 nm for the particles prepared with 5% MAC comonomer incorporated. The DLS data shown in Figure 3 in logarithmic scale underlined the chemically-driven nanoparticle formation *via* the intermolecular chain collapse process using the cross-linking density to control the nanoparticle formation. In comparison to thiolene-“click” reactions with analogous poly(ester) linear polymers[10], the poly(carbonate)-derived particles are smaller than expected, attributed to a lower degree of polymerization of the poly(carbonate) copolymers (DP = 20) than those reported from the poly(ester) polymers and its analogs (DP = 50).[8]

As an alternative methodology, particle formation using epoxide- amine cross-linking chemistry, analogous to the functionalized poly(ester) particles, was employed. As previously demonstrated by Storey and co-workers,[25] the oxidation of allylfunctional poly(carbonate)s with *m*-CPBA results in the formation of the epoxide-functional polymers to provide an alternative group that has been proven to be very valuable to the synthesis of nanoparticles and functionalization reactions in surface labeling. The MAC-containing copolymers were fully epoxidized by treatment with 1.2 eq. *m*CPBA in CH_2Cl_2 to form the suitable linear precursor. The disappearance of the characteristic vinyl resonances in the range $\delta = 5.9 – 5.3$ ppm was observed with the appearance of resonances that are clearly attributable to the formation of epoxide-functional polymers at $\delta = 3.19$, 2.82 and 2.63 ppm (Supporting Information). Other resonances in the ^{1}H NMR spectrum of the polymers did not change and the same chain length was determined by end group analysis.

Reaction of the panel of functionalized copolymers containing 5%, 10% and 20% epoxide pendant functional groups with 4eq. diaminoethyleneoxide (8 eq. amine/epoxide) was performed to crosslink the polymers (Supporting Information). Analysis of the resultant nanosponges, again by TEM and DLS, demonstrated that particles slightly increased sizes of $D_h = 230$ nm for the particles with 20% cross-linking in contrast to $D_h = 160$ nm for particles prepared from the lowest cross-linking density available in the study (Figure 2). In comparison to analogous poly(ester) materials, the particle sizes are again smaller, attributed to the lower degree of polymerization in contrast to the previously investigated poly(ester) materials. Notably however, the different preparation methods have resulted in comparably sized particles, demonstrating the versatile synthesis of these nanomaterials.

Conclusion

In summary, for the first time, we have demonstrated the formation of a range of novel functionalized poly(carbonate) nanoparticles using two different chemistries with the established intermolecular cross-linking process. We have prepared functionalized poly(carbonate) copolymers of 5-methyl-5-allyloxycarbonyl- 1,3-dioxan-2-one (MAC) and 5-methyl-5- ethyloxycarbonyl-1,3-dioxane-2-one (MTC-Et) *via* organocatalytic synthesis under mild conditions using a thiourea and (−)- sparteine catalyst system. The pendant allyl groups were utilized as cross-linking partners in thiol-ene click reactions forming nanosponges in the sizes of 150– 220nm depending on the cross-linking density of the linear precursor with 5%, 10% and 20% of pendant allyl groups incorporated. The oxidation of the allyl groups in the copolymers to epoxides was successful, and the following cross-linking reaction with diamines enabled the synthesis of the nanosponge particles in size ranges of 160–230 nm using an alternative epoxide-amine chemistry. These studies demonstrate the potential to form a basis for complex degradable nanoparticle syntheses for controlled release applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

NMR	Nuclear Magnetic Resonance Spectroscopy
TEM	Transmission electron microscopy
DLS	Dynamic Light Scattering

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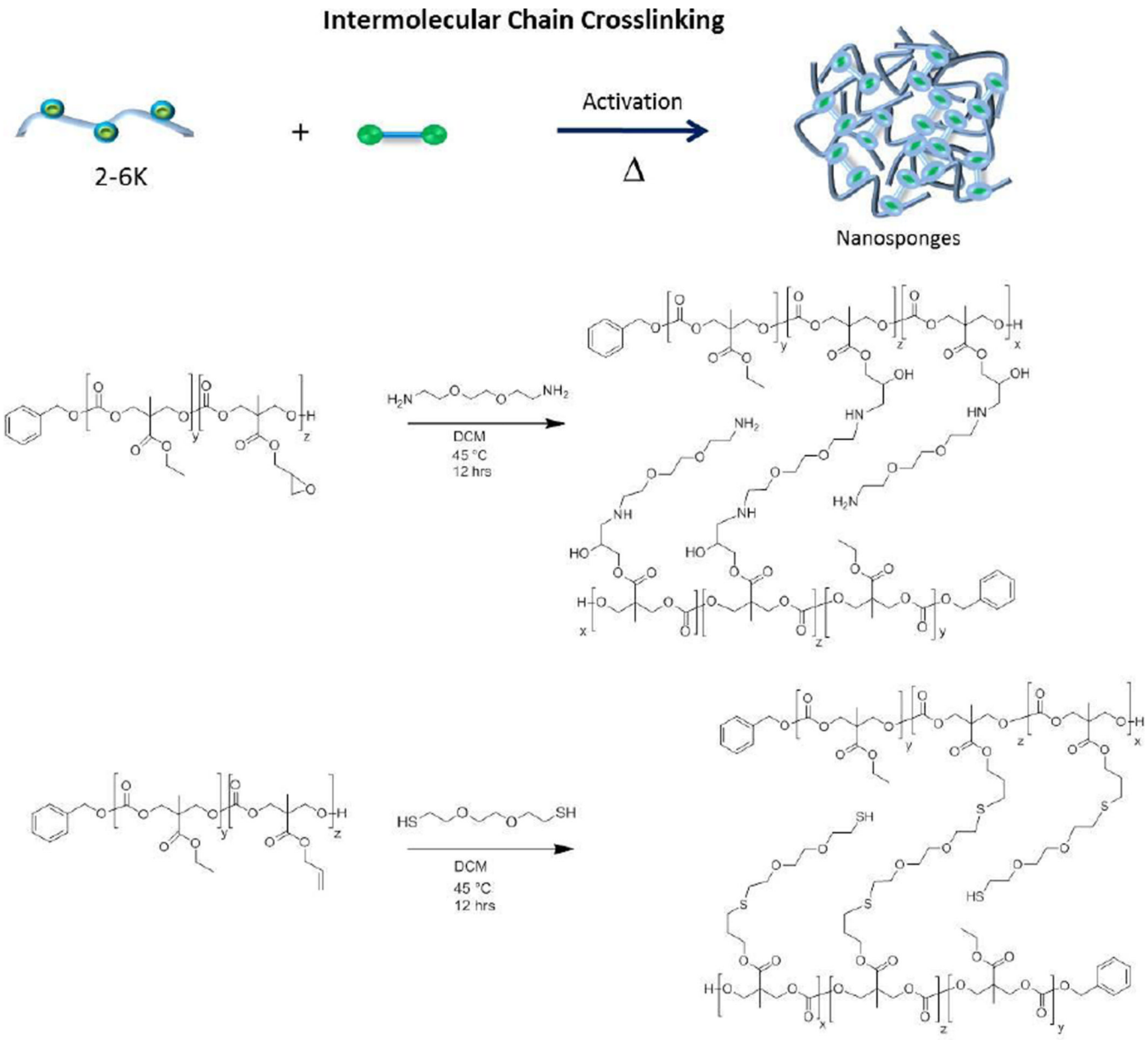
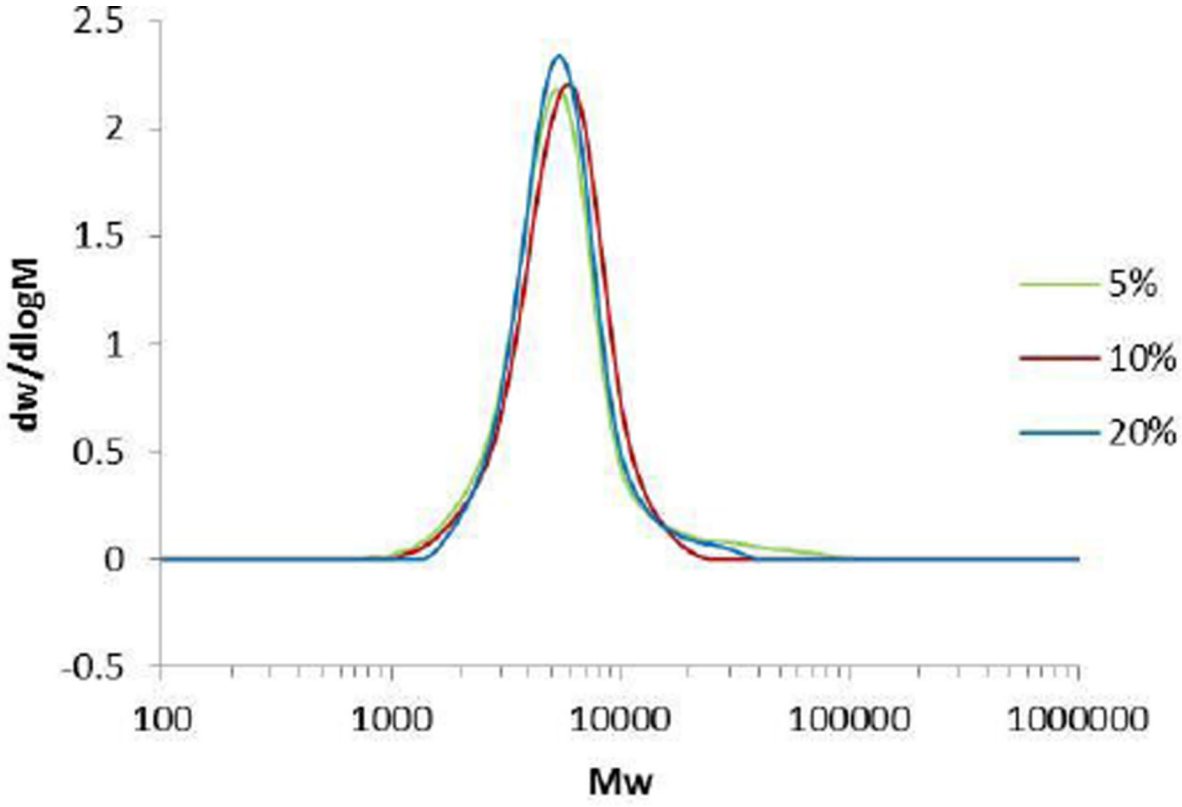


Figure 1.

Nanoparticle formation via an intermolecular thiolene-click reaction and the epoxide-amine reaction with either P[(MAC)z-co- (MTC-Et)y] or the oxidized version P[(MTC-Epx)z-co-(MTC-Et)y].



Polymer Composition (MTC-Et:MAC)	Monomer Conversion (%)	M_n (GPC) (Da)	M_n (NMR) (Da)	PDI
95:5	>95	4700	5000	1.56
90:10	>95	5000	5300	1.25
80:20	>95	4900	6400	1.39

Figure 2.

Ring-opening copolymerization of MAC and MTC. All polymerizations were conducted in dichloromethane at 25 °C, [monomer] = 1.6 M, [monomer]/[initiator] = 20 using benzyl alcohol as initiator with 10 mol % TU and 5 mol % (-)-sparteine as catalysts. Molecular weight and dispersity were determined using GPC calibrated with poly(styrene) standards in chloroform. Conversion and molecular weight were determined by NMR. The legend for the GPC traces refers to the percentile of MAC monomer in the copolymer.

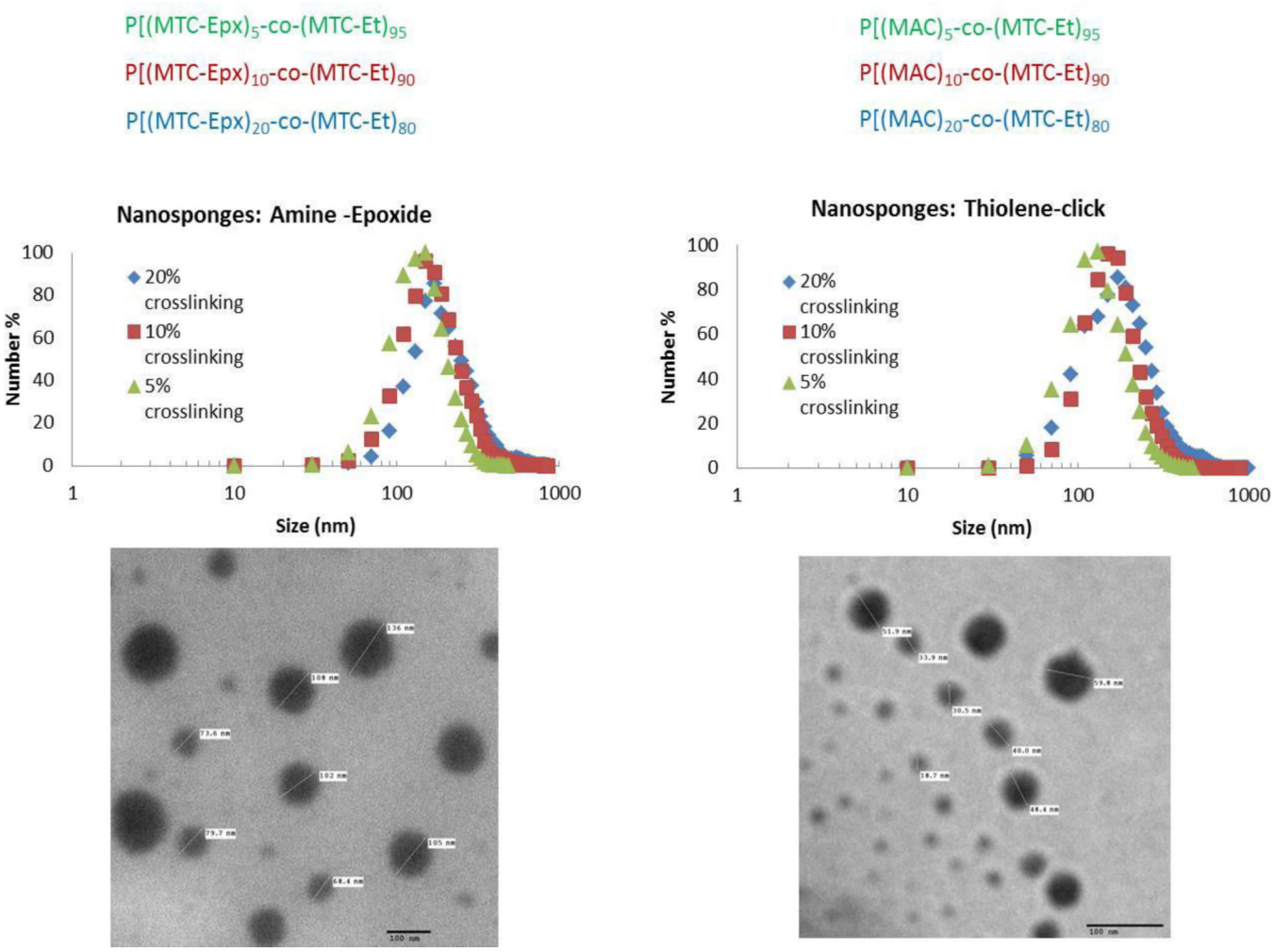
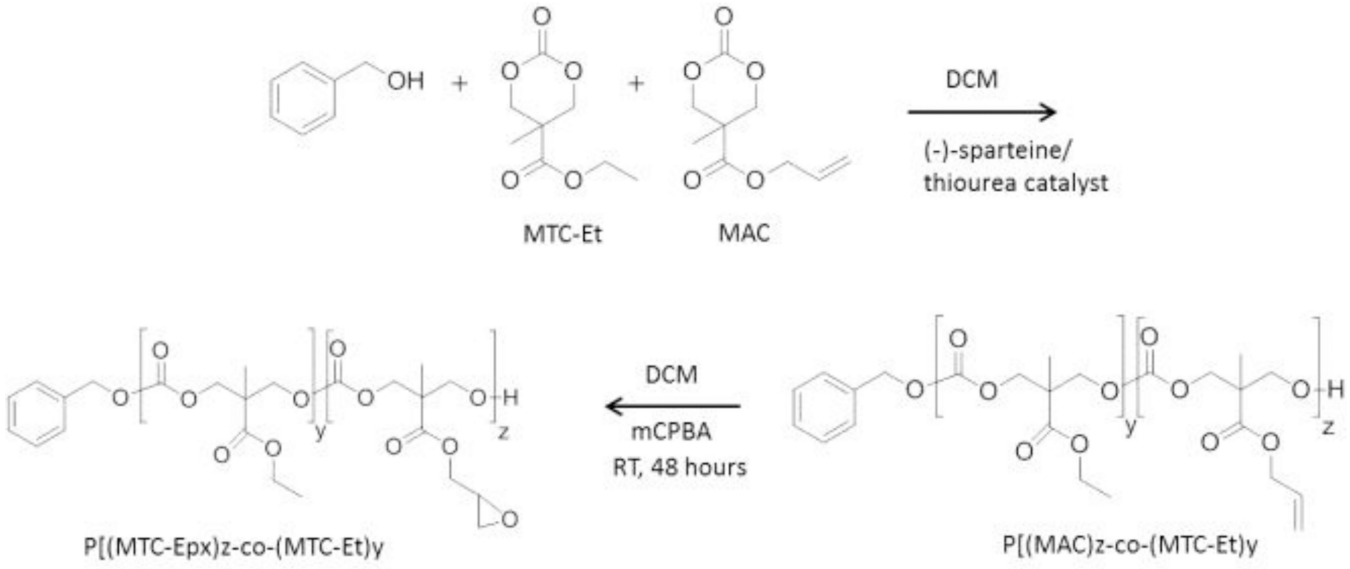


Figure 3.

Top row: DLS analysis data for both particle series derived from the two panels of copolymer precursors with amine-epoxide and the thiolene-click reaction. TEM imagines of two representative poly(carbonate) nanosponges. Left: 5% amine–epoxide. Right: 5% thioleneclick.



Scheme 1.
Synthesis of poly(carbonate) copolymers with 5%, 10% and 20% incorporation of MAC and their subsequent oxidation of the allyl to the pendant epoxide group.