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COMMUNICATION

Cyclodextrin-centred star polymers synthesized *via* a combination of thiol-ene click and ring opening polymerization[†]

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The synthesis of cyclodextrin-centred star polymers *via* thiol-ene addition of per-6-thio- β -cyclodextrin (CD-(SH)₇) with vinyl terminated polymers is described. The obtained thiol-ene product was employed as an initiator for ring opening polymerization (ROP) of ε -caprolactone (ε -CL).

Cyclodextrins (CD) are cyclic oligosaccharides composed of α -1, 4-linked D-glucopyranose units and have been used in drug delivery due to the ability to form inclusion complexes with guest molecules.¹⁻⁴ Modification of CD has offered polymer chemists opportunities to prepare well-defined CD-centred star polymers via core-first approach from different controlled radical polymerization techniques including ATRP,⁵ RAFT⁶ and NMP.⁷ Since the introduction of click chemistry, by Sharpless et al.,8 Cu(I)-catalysed azide-alkyne cyclodextrin (CuAAC) reaction has been employed in modification of CD. Synthesis of seven-arm star-shaped poly(E-CL) was first reported via CuAAC reaction of per-6-azido-B-cyclodextrin with excess low molecular weight acetylene poly(E-CL).9 A similar strategy was then used to prepare well-defined multi-arm CD-centred star polymers¹⁰⁻¹² and stimuli-responsive Janus-type copolymers.¹³ CuAAC has also proved to be highly efficient in the construction of polymers with covalently attached CD for small molecule and drug delivery use.14-17 The thiol-ene reaction has attracted interest due to its facile and versatile process that fulfils the basic requirements of a click reaction.¹⁸ However, the reports on the modification of CD via thiol-ene reaction are limited. B-CD based carbohydrate glycol cluster compounds were prepared by the photoaddition reaction of thiol sugars to allyl ether groups on modified CDs with moderate vields.^{19,20} The sodium salt of CD-(SH)7 was used for the Michael addition reaction with maleimide functionalized dextran to form a crosslinked hydrogel.²¹ Mono thiol-functionalized CD was also used for similar thiol-maleimide conjugation reaction in phosphate buffered saline solution.22

In this current work, we report the modification of β -CD *via* base catalyzed Michael addition using (meth)acrylic monomers and vinyl terminated polymers precursors. These precursors were

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coupled to CD–(SH) $_7$ by thiol-ene click reaction. Furthermore, ROP of ϵ -CL using the thiol-ene product as an initiator was also investigated.

The hydroxyl groups on the primary face of β -CD can be selectively transformed to iodine atoms *via* reaction with PPh₃/I₂ with a subsequent conversion into thiol groups *via* a one pot reaction with thiourea (Scheme 1). The obtained CD–(SH)₇ was then reacted with different (meth)acrylic monomers and vinyl terminated polymers synthesized by catalytic chain transfer polymerization (CCTP), Scheme 2. Reactions were performed in DMSO with either DMPP or HA as catalyst accelerating the rate and increasing the conversion.^{23,24}

Addition of MA with CD–(SH)₇ followed by ¹H NMR showed the disappearance of triplet from the thiol groups at 2.13 ppm and new peaks at 2.5–2.6 ppm (S–CH₂–CH₂), 2.7–2.8 ppm (S–CH₂–CH₂) and 3.6 ppm (O–CH₃), confirming the success of the thiol-ene reaction. ¹³C NMR showed the C–6's shift from 26.0 ppm (CD–(SH)₇) to 34.1 ppm (CD–(S–MA)₇) after reaction and also the appearance of new peaks at 171.8 ppm (C=O), 51.4 ppm (O–CH₃), 33.1 ppm (CH₂–C=O) and 27.7 ppm (S–CH₂) (Fig. S3†). SEC analysis (Fig. 1) showed the molecular weight (MW) increasing after the



Scheme 1 Schematic representation of the synthetic approach to azido and thiol functionalized β -CD.



Scheme 2 Reagents employed in this study; CD–(SH)₇, (meth)acrylic monomers, vinyl terminated polymers and catalysts.

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Fig. 1 DMF eluent SEC traces of CD-(SH)₇, CD-(S-MA)₇ and PCL-CD-(S-MA)₇.



Fig. 2 MALDI-ToF MS spectra obtained for CD–(SH)₇, CD–(S–MA)₇, CD–(S–MMA)₇, CD–(S–DEGMEMA)₇ and CD–(S–diMMA)₇.

reaction and MALDI-ToF MS (Fig. 2) confirmed the complete reaction of all seven thiol groups. Two other methacrylic monomers, MMA and DEGMEMA, were also reacted with CD–(SH)₇ and both reactions also showed complete conversion of thiol groups *via* NMR, SEC and MALDI-ToF MS analysis (Fig. 2).

Moreover, reaction of PEG acrylate ($M_n = 480$, PDI = 1.05) with CD–(SH)₇ ([thiol]:[ene] = 1:1) catalyzed by 5% DMPP in DMSO was carried out. ¹H NMR analysis revealed the disappearance of the vinyl groups after 24 h. ¹H NMR of the isolated product confirmed the disappearance of thiol groups and appearance of PEG moieties whilst ¹³C NMR revealed C–6's shift and existence of CD ring with SEC traces showing the MW increase



Fig. 3 MALDI-ToF MS spectra obtained for (a) CD–(S–PEGMEA480)₇ and (b) CD–(S–PDEGMEMA)₇.

after reaction. Although it tends to be difficult to get a high resolution MALDI-ToF MS spectrum (Fig. 3a) for CD-centred star polymers, polymer peaks which belong to the thiol-ene products at higher MW region than PEGMEA₄₈₀ could be found, which proved the success and efficiency of thiol-ene reaction between CD–(SH)₇ and acrylic polymer.

The thiol-ene reaction is highly efficient in modifying unsaturated CCTP polymers.²⁵ To investigate the possibility of CCTP polymers for the thiol-ene reaction with CD–(SH)₇, a CCTP MMA dimer (diMMA) was first attempted. NMR, SEC and MALDI-ToF MS (Fig. 2) analysis confirmed the formation of desired diMMA modified CD after 24 h.

A linear vinyl terminated PDEGMEMA ($M_n = 900 \text{ g mol}^{-1}$, PDI = 1.40) was investigated using HA catalysis. Purification via dialysis and analysis of the obtained polymer by ¹H and ¹³C NMR (Fig. S11[†]) showed the disappearance of thiol groups and signals for both PDEGMEMA and β-CD. SEC revealed the increase of MW after reaction, although a small tail peak at low MW area was noticed. Further analyses via MALDI-ToF MS (Fig. 3b) confirmed peaks from the thiol-ene product. Relatively small peaks at low MW were also observed and attributed to the side reaction between HA and terminal vinyl groups. The thermoresponsive behaviour of PDEGMEMA before and after reaction was examined via UV/Vis spectrophotometer. A temperature decrease of the cloud point from 58.8 to 50.2 °C was found after the linear polymer was reacted with CD-(SH)7 (Fig. S12[†]), which was also noticed in a previous report.¹⁰ The expected lower cloud point value for



Scheme 3 Schematic representation of the synthesis of poly (ϵ -CL) initiated by CD–(S–MA)₇.



Fig. 4 1 H (top) and 13 C (bottom) NMR spectra of PCL-CD-(S-MA)₇ in DMSO-d₆.

star polymers was attributed to the MW increase after reaction and also caused by the local high chain density on the surface of CD core, which lead to the chain aggregation at lower temperature. This phenomenon further indicated the successful thiol-ene reaction between $CD-(SH)_7$ and the CCTP polymer.

The hydroxyl groups on the secondary face of β -CD remained unreacted during the thiol-ene reactions as seen in the ¹H NMR and MALDI-ToF MS spectra. Recently, CDs have been used as co-initiators for the stannous octanoate (Sn(Oct)₂) catalyzed ROP of cyclic esters.^{26,27} To examine the application of thiol-ene CD products in ROP, a bulk polymerization of ϵ -CL in the presence of CD–(S–MA)₇ and Sn(Oct)₂was conducted at 120 °C overnight (Scheme 3).

After reaction, SEC analysis (Fig. 1) showed a polymer of $M_n = 8670 \text{ g mol}^{-1}$ and PDI = 1.32 was obtained in the absence of oligomers or the unreacted CD derivative. The ¹H NMR spectrum revealed major proton signals of PCL unit and also CD–(S–MA)₇ unit, Fig. 4. ¹³C NMR spectrum showed the carbon residues of CD–(S–MA)₇. FT-IR spectrum (Fig. S14[†]) revealed the enhancement of methylene absorbance compared with CD–(S–MA)₇ and new peak appeared at 732 cm⁻¹ due to the chain alkane from PCL and the MALDI-ToF MS spectrum showed a series of peaks belonging to CD initiated PCL. All of the results indicate that PCL-CD–(S–MA)₇ with designed structure has been successfully synthesized.

In conclusion, we report the first example of CD–(SH)₇ for base catalyzed thiol-ene reaction with different (meth)acrylic monomers and vinyl terminated polymers. The hydroxyl groups on the secondary face of CD were kept during the reaction and were employed as ROP initiator of ϵ -CL. Different CD-centred macromolecular architectures and star polymers have been prepared through the combination of CCTP, ROP and thiol-ene click reaction. This versatile strategy introduces the thiol-ene click reaction into modification of CD for polymer synthesis and future studies will focus on synthesis of miktoarm star polymers and polymers with covalently attached to CD.

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