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Multiblock sequence-controlled glycopolymers *via* Cu(0)-LRP following efficient thiol-halogen, thiol-epoxy and CuAAC reactions

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The combination of copper(0) mediated living radical polymerization (Cu(0)-LRP) with thiol-halogen, thiol-epoxy and copper catalysed alkyne azide coupling (CuAAC) click chemistry has been employed to give a new route to multiblock sequence-controlled glycopolymers. Multiblock poly(glycidyl acrylate)-*co*-(acrylic acid 3-trimethylsilanyl-prop-2-ynyl ester) (poly(GA)-*co*-(TMSPA)) were obtained by Cu(0)-LRP in DMSO at ambient temperature *via* iterative monomer addition whereby the sequence of the multi blocks is attained in a designed way. Thiol-halogen and thiol-epoxy reaction of poly(GA) have been exploited, which suggested a preference for the reaction of the halogen rather than the epoxide for the thiol with triethyl amine as catalyst. The obtained multiblock poly(GA)-*co*-(TMSPA) were then used for sequential thiol-halogen, thiol-epoxy and CuAAC reactions to build functional glycopolymers in defined sequence.

Introduction

Carbohydrates, typically specific protein-linked oligosaccharides and synthetic carbohydrate ligands, take part in many protein recognition processes and are involved in intercellular recognition and interaction, pathogen identification *etc* and have potential therapeutic applications.[1-4] Carbohydrate sequence and conformation potentially supply a vast source of information and act as biological information transfer beyond genetic code, namely "sugar code" or "glyco code", which has been shown to play a critical role during evolution.[5-7] Since the introduction of Koenigs-Knorr and Fischer-Helferich type glycosylation reaction over one century ago, chemists have developed different synthetic protocols for oligosaccharide and glycoprotein synthesis, including chemical synthesis, enzymatic synthesis and automated solid-phase synthesis.[8-12] However, the efficient synthesis of oligosaccharides with specific composition and structure still remains a major challenge and limit for the progress of glycobiology. Synthetic carbohydrate-containing macromolecules, or glycopolymers, can also undergo similar recognition events as oligosaccharides due to the "cluster glycoside effect" and can be obtained in a relatively facile manner, which have been considered as alternative structures of oligosaccharides.[13-16] A current challenge for glycopolymer synthesis is to mimic oligosaccharides with selective binding property, which means it is important to encode the carbohydrate during synthesis and thus obtain a simulated glycopolymer code.[17] Precision polymer synthesis is needed in order to gain some degree of control of the carbohydrate sequence and conformation, which is very important in understanding the multivalent binding of oligosaccharide and sequence-controlled glycopolymers to different lectins.[18-20]

However, sequence control of both individual monomers and multiblocks in polymer synthesis is challenging, due to the difficulty in precise control and characterization during monomer sequencing.[21] In many cases in the application of synthetic polymers the control over the order of short blocks of monomers should be sufficient for enhanced performance. Since the important breakthrough of solid-phase synthesis in the 1960's, this technique has been widely applied in synthesis of many important high-ordered biopolymers and non-biological polymers.[22, 23] Templated polymerization and step-growth polymerization especially condensation polymerization could also result in sequence-specific polymers.[24-30] Chain-growth copolymerization offers a promising route for complex monomer sequence construction, including random, block, alternate and gradient microstructures.[26] Living polymerization, such as ring opening polymerization, has been applied for multiblock copolymerization of protected sugar-based cyclic olefins.[31] Transition metal-catalyzed living radical polymerization tolerates most functional groups and allows excellent control over the polymer architecture.[32-34] Recent progress in Cu(0)-LRP allows for facile synthesis of high-order multiblock copolymers *via* iterative monomer addition in an one-pot reaction featuring high yield, high chain end fidelity and requiring purification only at the last step.[35] The Cu(0)-LRP of different functional glycomonomers could produce glycopolymers with some control of sequence and distance between the oligosaccharides, which also supplied a route

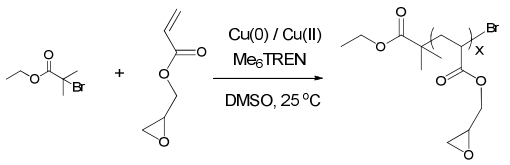
for polymerization of unprotected glycomonomers.[18] Optimization of polymerization conditions, typically amount of catalyst and ligands, allows synthesis of high molecular weight multiblock copolymers.[36] As one of the most prominent controlled radical polymerization, reversible addition fragmentation chain transfer polymerization (RAFT) also showed unprecedented ability in the control of polymer microstructure and multiblock (even up to 20 short blocks) copolymers have been synthesized. [37-39]

Besides direct polymerization of functional glycomonomers, post-polymerization modification is also an important strategy for glycopolymer synthesis.[20, 40, 41] This strategy has the advantage of introducing different functional groups along polymer backbones, especially when some functional groups maybe not suitable for the polymerization.

Herein, we introduce a polymerization-first and subsequent efficient reaction modification strategy to the synthesis of glycopolymers with some monomer/block sequence control to give sugars in a pre-determined order. Alkyne and epoxide groups, which could be used for different click/efficient reactions such as azide alkyne cycloaddition, thiol-yne reaction or epoxy ring opening reaction with sodium azide, thiols and acid etc., were introduced along the polymer backbone *via* multiblock Cu(0)-LRP and subsequently used for multistep chemical modification to get sequence and spatially defined glycopolymers with control over the arrangement of the different carbohydrate within the polymer.

Results and discussions

Synthesis of poly(GA) *via* Cu(0)-LRP.



Scheme 1. Synthesis of poly(GA) *via* Cu(0)-LRP.

Epoxide containing acrylic (co)polymers *via* free radical polymerization of glycidyl (meth)acrylate have been seen as important precursors for synthesis of thermosetting polymers, which have wide applications in high performance coatings, adhesives, floorings and electric laminates.[42] Catalytic chain transfer polymerization (CCTP) of glycidyl methacrylate is highly efficient in synthesis of functional oligomers carrying terminal vinyl groups and side epoxy rings for post-polymerization modification.[43] The copper mediated living radical polymerization of glycidyl (meth)acrylate has been performed mainly using nitrogen-containing ligand/copper(I) halide as the catalyst, of which the Cu^{I} halide is either commercially available or generated in-situ *via* reduction of a Cu^{II} halide. [44-48] Recent research on Cu^{0} mediated living radical polymerization suggests that almost instantaneous disproportionation of copper(I) halide into Cu^{0} and Cu^{II} halides facilitates a very rapid LRP of various functional monomers under mild reaction conditions, namely single electron transfer living radical polymerization (SET-LRP).[34, 49-53] This robust methodology utilizes commercial Cu^{0} wire or powder as the activator (thus SET-LRP is also termed Cu(0)-LRP) and good solvents are usually polar including DMSO, alcohols, ionic liquids, water and even blood serum.[34, 54, 55] Initially addition of Cu^{II} halides has also been proved to be necessary for the effective deactivation and suppression of any induction period.[56-58] Thus in this current work poly(GA) was synthesized *via* Cu(0)-LRP in DMSO at ambient temperature using Cu^{0} wire as the activator and additional $CuBr_2$ as the deactivator and Me_6TREN as the ligand, Scheme 1.

The concentration of initiator relative to monomer, Cu^{0} wire, $CuBr_2$ and Me_6TREN was set as $[EBiB]_0:[GA]_0:[Cu]_0:[CuBr_2]_0:[Me_6TREN]_0$=1:20:0.3:0.1:0.18. At the beginning of the polymerization, there tends to be an induction period of approximately 1.5 h with the conversion reaching 17% and SEC analysis only revealing the existence of oligomers with M_n = 370 and M_w/M_n = 1.25, Figure 1 & 2. Subsequently, the polymerization became faster and conversion reached 87% in 3.5 h and 97% in 6 h. The first order kinetic plots after 1.5 h were almost linear with respect to monomer conversion, indicating that concentration of active species remained relatively constant throughout the fast polymerization period, Figure 2. The molecular weights of polymers as determined by DMF SEC against PMMA standards agreed well with the theoretical values. A good linear increase of M_n relative to conversion (Figure 2) was also observed, suggesting that termination during the polymerization was low. The M_w/M_n has a slight decrease with conversion but remained low (< 1.3) throughout the polymerization and the final dispersity was = 1.15, even including a small shoulder peak at higher molecular weight position, which may be caused by possible radical coupling termination at high conversion.

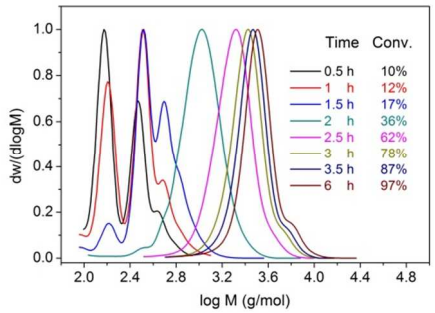


Figure 1. DMF SEC elution traces of poly(GA) synthesized *via* Cu(0)-LRP.

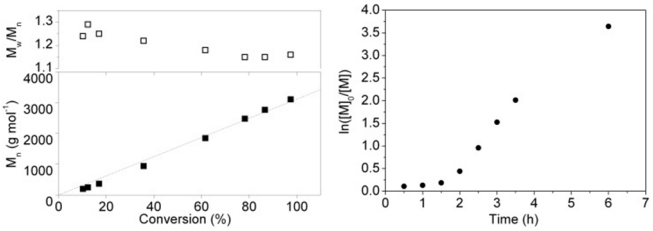


Figure 2. Number average molecular weight (M_n) and molecular weight distributions (M_w/M_n) as a function of monomer conversion for the Cu(0)-LRP of GA (left) and first-order kinetic plots for the Cu(0)-LRP of GA initiated by EBiB, catalysed by Cu(0)/$CuBr_2$/Me_6TREN in DMSO at ambient temperature (right).

^{1}H NMR of the final product revealed that the epoxide remained unreacted during the polymerization, as shown by the

typical peaks from the epoxide ring at 2.6, 2.8 and 3.2 ppm, Figure 3. The initiator residues could be seen at 1.1, 1.2 and 4.1 ppm and the polymer terminal end group could be distinguished at 3.7 ppm and the ratio of $\int_h$: $\int_f$: $\int_i$: $\int_d$ = 3: 6: 1.07: 18.5, which is in good agreement with the theoretical molecular weight and thus proved the high chain end fidelity even at full (>99%) conversion polymerization.

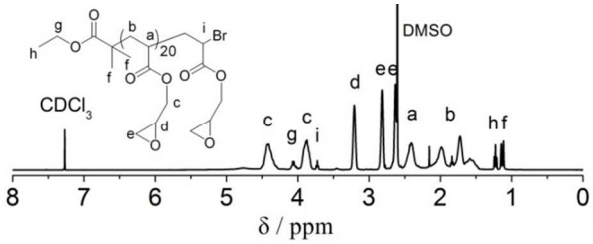


Figure 3. ^{1}H NMR spectrum of poly(GA) in $CDCl_3$. The numbering of the hydrogen atoms for the NMR peak assignment is shown in the scheme.

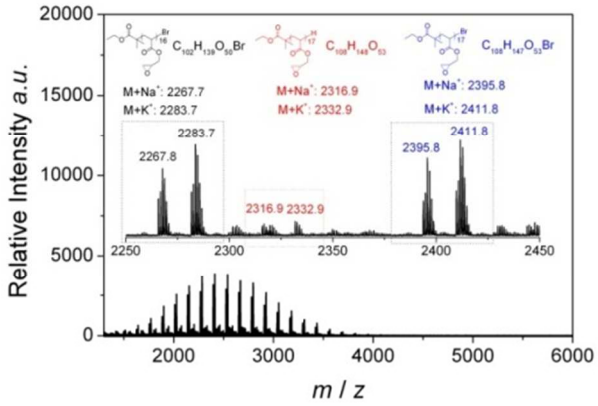


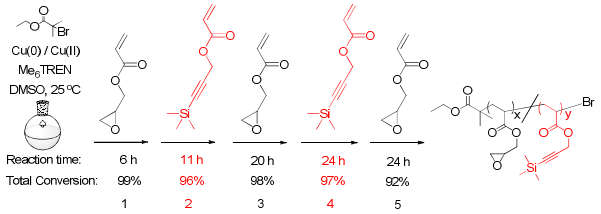
Figure 4. MALDI-ToF MS spectrum of poly(GA).

The degree of control in the Cu(0)-LRP of GA was also confirmed by linear-mode MALDI-ToF MS analysis, which revealed an expected single distribution from polymer chains initiated by EBiB and terminated with bromine, Figure 4. Peaks from hydrogen-terminated polymers, which may be caused by disproportionation, were also observed, however, the intensity ratio compared with that of the bromine-end polymers was much smaller, Figure 4. In summary, all of the data presented indicates that the polymerization proceeds in a controlled/living manner and well-defined poly(GA) with high chain end fidelity could be synthesized at ambient temperature *via* Cu(0)-LRP.

There is an on-going debate on the mechanism of SET-LRP. Recently research has been reported on reversible-deactivation radical polymerization in the presence of metallic copper, including experiments investigating comproportionation-disproportionation equilibria and kinetics, kinetic simulation, activation of alkyl halides by Cu^0 and solvent effects on the activation rate constant.[59-62] It is reported that the [Cu^I] even represents approximately 99.95% of all soluble Cu species with $[Me_6TREN]_0/[Cu^{II}]_0$=6/1, this work does not address the situation when this ratio of $[Me_6TREN]_0/[Cu^{II}]_0$ is < 2.[5961] However, it is clear that the disproportionation becomes significant when the ratio of $[Me_6TREN]_0/[Cu^{II}]_0$ < 4/1 and there is a dramatic change when the ratio is < ~ 2.5/1.[59]

It is noted that in this current work the ratio of $[Me_6TREN]_0/[Cu^{II}]_0$ = 1.8/1, and the rate and extent of Cu^I disproportionation is also reported to be very dependent on the conditions.[63] Based on our observations the data suggests that the main process existing in these polymerizations are consistent with SET-LRP rather than supplemental activator and reducing agent (SARA) ATRP case as reported for the higher $[Me_6TREN]_0/[Cu^{II}]_0$ ratios.

Synthesis of multiblock poly(GA)-co-(TMSPA) *via* Cu(0)-LRP.



Scheme 2. Synthesis of multiblock poly(GA)-*co*-(TMSPA) *via* Cu(0)-LRP.

High chain end fidelity was retained in this Cu(0)-LRP system and could be utilized for efficient synthesis of high-order multiblock copolymers with relative low DP *via* iterative monomer addition.[18, 35, 64, 65] Under optimized conditions, high molecular weight multi block copolymers could also be synthesized *via* Cu(0)-LRP in DMSO at high conversions (92-99% for each block).[36] In order to introduce different functional groups along the polymer backbone with specific order, GA and TMSPA monomers were sequentially added to the reaction when the previous block polymerization had reached full or close to full conversion, Scheme 2.

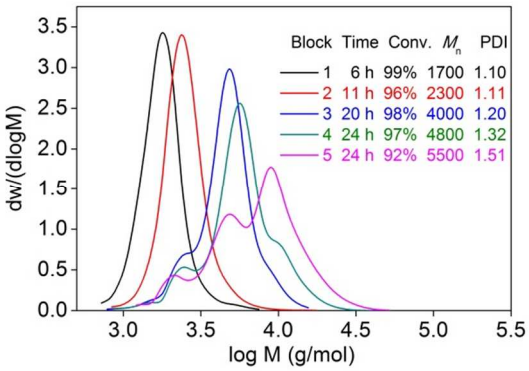


Figure 5. Molecular weight distributions of multiblock poly(GA)-*co*-(TMSPA) obtained by Cu(0)-LRP via iterative chain extension. Reaction time and conversion for each block were listed in the figure.

The ratio of [initiator]$_0$:[GA]$_0$:[TMSPA]$_0$:[GA]$_0$: [TMSPA]$_0$ was set as 1:8:4:8:4 and NMR and SEC analysis was used to follow the polymerization reactions. Firstly, long reactions times were employed in an attempt to ensure the conversion of each block copolymerization was close to full conversion (96%-99%). With the addition of each new monomer solution *via* cannula transfer, thus the reaction is unavoidably diluted increasing reaction times in order to reach high conversions.

Poly(GA) macroinitiator was achieved with dispersity as low as 1.10 and total elution trace-shift after polymerization of new added TMSPA monomer for 11 h, Figure 5. No tailing or shoulder peak, which could be caused by termination *via* disproportionation or coupling, was observed until the third chain extension. At this point the M_w/M_n increased to 1.32 when chain extension was conducted for the fourth time and 1.51 after polymerization for almost 4 days, which also showed evidence of termination in the SEC during the previous polymerization by the presence of multimodal peaks.

This suggests that under these experimental conditions, termination becomes more prevalent when the system gets more diluted and the rate of polymerization becomes slower. In order to alleviate this effect it is possible to minimise DMSO dilution, to add monomer prior to full conversion or to modify the amount of catalyst.

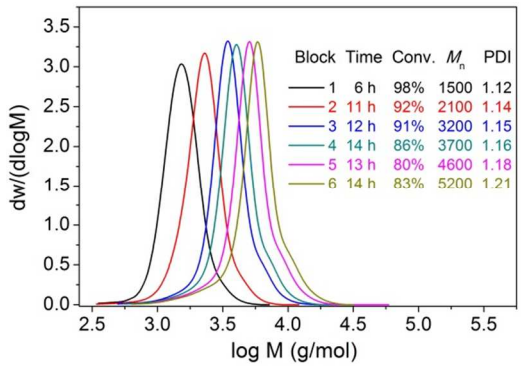


Figure 6. Molecular weight distributions of multiblock poly(GA)-*co*-(TMSPA) obtained by Cu(0)-LRP *via* iterative chain extension. Reaction time and conversion for each block are listed in the figure.

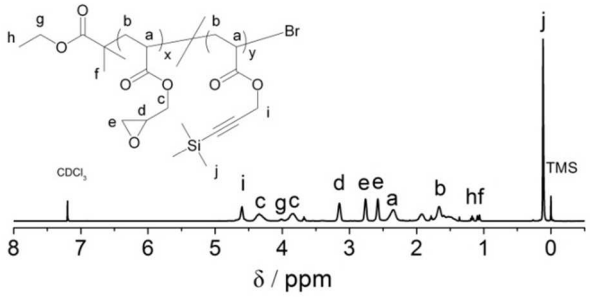
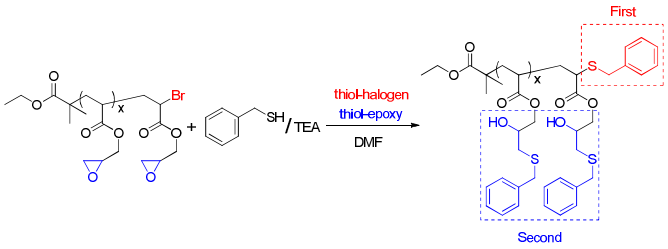


Figure 7. ^{1}H NMR spectrum of multiblock poly(GA)-*co*-(TMSPA) in $CDCl_3$.

In this work we first tried to add monomer into the system following polymerization for 11~14 h, at which point the conversion had reached 80% to 92%. In that case, the MW distribution of obtained copolymer became narrower and only increased to 1.21 after 6 chain extension reactions, Figure 6. Although the polymer is not really a strict multiblock copolymer different functional groups are sited along the polymer backbone in a high order according to the design. The ^{1}H NMR spectrum of the obtained poly(GA)-*co*-(TMSPA) copolymer revealed peaks from the epoxy ring, protected propargyl groups and terminal EBiB groups, Figure 7. In summary, multiblock poly(GA)-*co*-(TMSPA) copolymers with relatively short DP could be synthesized by Cu(0)-LRP *via* iterative addition of GA and TMSPA monomers.

Thiol-halogen and thiol-epoxy reaction of poly(GA) with benzyl mercaptan.



Scheme 3. Thiol-halogen and thiol-epoxy reactions of poly(GA) with benzyl mercaptan.

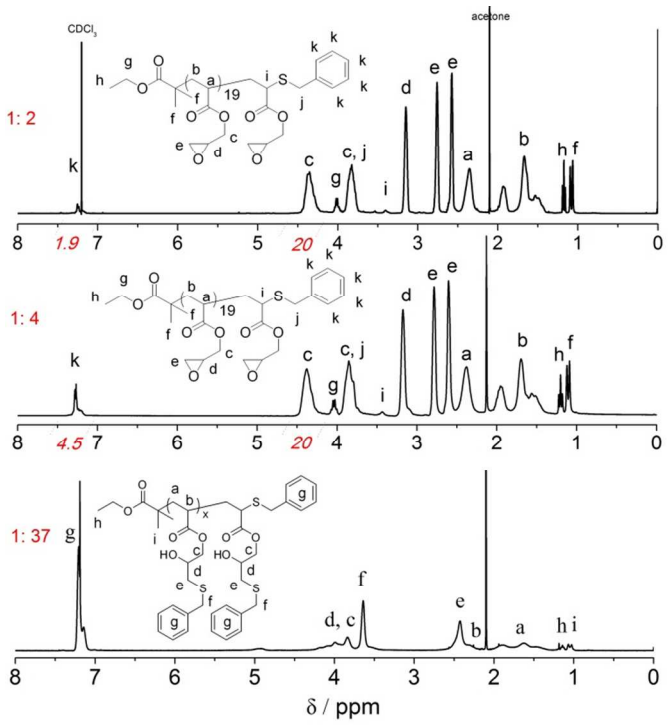


Figure 8. ^{1}H NMR spectra in $CDCl_3$ for the products obtained *via* reaction of poly(GA) with different amounts of benzyl mercaptan under the presence of TEA in DMF. $[poly(GA)]_0$: $[benzyl\ mercaptan]_0$ = 1: 2, 1:4 and 1: 37 as listed in the spectra from top to the bottom. The DP of $poly(GA)_0$ was 20 and the $M_{n,\,NMR}$ = 2800 and $M_w/M_{n,SEC}$ = 1.15.

Most of the terminal bromide groups remain at the terminus during the Cu(0)-LRP and thus are available for post modification reactions such as thiol-halogen substitution.[35, 66] Thiol chemicals are also able to react with the epoxides, however, this reaction proved to be less efficient than the thiol-ene reactions.[43, 67] Triethyl amine (TEA) has been used as catalyst or reagent for the reaction of thiol with halogen and epoxy containing chemicals.[35, 68] Thus it proved interesting to check the relative order and rates of the thiol-halogen and thiol-epoxide reactions for poly(GA) under the presence of TEA. Different amounts of benzyl mercaptan were then reacted with poly(GA) in DMF, Scheme 3.

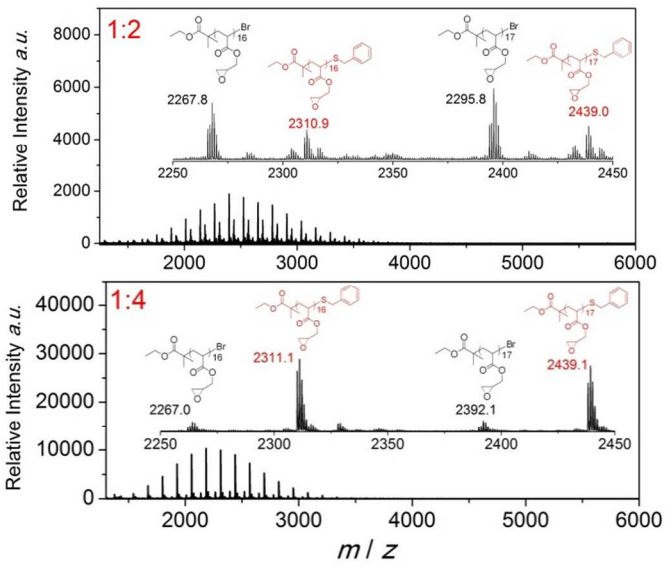


Figure 9. MALDI-ToF MS spectra for the products obtained *via* reaction of poly(GA) with different amounts of benzyl mercaptan under the presence of TEA in DMF. $[poly(GA)]_0$: $[benzyl\ mercaptan]_0$ was 1: 2 and 1: 4 as listed in the spectra.

For the reaction of poly(GA) with benzyl mercaptan in the ratio of $[poly(GA)]_0$:$[benzyl\ mercaptan]_0$ = 1:2 catalysed by TEA in DMF, no significant thiol-epoxide reaction was observed as demonstrated by the remaining of epoxide-related peaks, Figure 8. Benzyl ring-related peaks at 7.1-7.4 ppm were apparent following the reaction and its integral ratio compared with the integral of CH_2 adjacent to the epoxide ($\int_k$: $\int_c$) was ~ 1.9: 20, suggesting that only ~ 38% of the terminal bromide groups reacted with benzyl mercaptan. This was also shown by the appearance of new peaks in the MALDI-ToF MS spectrum belonging to the benzyl mercaptan terminated poly(GA), Figure 9. However, the peak height is less than that of bromine-terminated poly(GA), further indicating only a partial reaction.

As the ratio of $[poly(GA)]_0$:$[benzyl\ mercaptan]_0$ was increased to 1:4, no significant thiol-epoxy reaction was detected, according to the ^{1}H NMR spectroscopy as the integral ratio of epoxy ring protons to initiator residue protons ($\int_e$: $\int_f$) remained unchanged compared with raw poly(GA), Figure 8. However, $\int_k$: $\int_c$ increased to ~ 4.5: 20, indicating that ~ 90% of the terminal bromide groups reacted with benzyl mercaptan. The MALDI-ToF MS spectrum showed the main peaks from benzyl mercaptan-terminated poly(GA) and a small ratio of peaks from bromide-terminated poly(GA), Figure 9, further demonstrated that most of the terminal bromide groups could be substituted *via* the mild thiol-halogen reaction with the increase of benzyl mercaptan. No significant elution trace shift was observed *via* SEC analysis as the MW change after thiol-halogen reaction was small, S Figure 1.

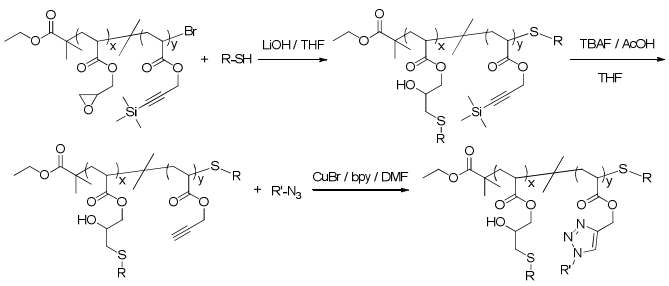
Subsequently, the ratio of $[poly(GA)]_0$:$[benzyl\ mercaptan]_0$ was increased to 1:37 (such that the ratio of $[epoxy]_0$: $[benzyl\ mercaptan]_0$ was ~ 1:2) and following overnight reaction, no epoxide residues were observed, indicating the thiol-epoxy reaction had occurred, Figure 8. SEC analysis revealed a total shift of elution trace due to significant MW increase following the reaction, S Figure 3.

Besides TEA, LiOH was also used as the catalyst for thiol-epoxide reaction and similar NMR spectrum and a similar MW change via SEC were obtained after reaction, S Figure 2 & 3.

In summary, a clear preference for the thiol-halogen substitution was observed by thiol over the epoxide ring opening reaction under these conditions. The large reactivity difference of the bromide end group and pendant epoxy group could be exploited for selectively modification with different thiol compounds.

Synthesis of multiblock glycopolymers *via* sequential efficient reactions.

Dual functional polymer brushes have been synthesized *via* sequential thiol-epoxy and thiol-yne reactions, during which the protected alkyne groups, could survive through the thiol-epoxide reactions.[69] Thus in order to attach different monosaccharide groups along the polymer backbone with a defined sequence and spatial resolution, thiol-halogen and thiol-epoxy reactions were first carried out prior to the deprotection of the alkyne groups following the CuAAC reactions with azide functionalized monosaccharides, Scheme 4.



Scheme 4. Synthesis of multiblock glycopolymers via sequential thiol-halogen, thiol-epoxy and CuAAC click reactions.

Firstly, 1-thio-β-D-glucose tetraacetate was reacted with the multiblock poly(GA)-*co*-(TMSPA). After the reaction ^{1}H NMR revealed that the epoxide related peaks totally disappeared with the appearance of peaks from the protected glucose, e.g. the acetate groups at ~ 1.9-2.2 ppm and the ring protons between 3.5 and 5.4 ppm, although it is difficult to assign each peak due to the overlap with the pendant groups, Figure 10. SEC analysis revealed a significant increase in M_n from 7400 to 14200 g mol^{-1}, S Figure 4, suggesting the successful thiol-epoxide reaction changes the hydrodynamic volume of the obtained product. FTIR analysis also showed a broad peak at around 3500 cm^{-1} due to the OH absorbance following thiol-epoxide reaction, S Figure 5.

Subsequently, the TMS protection groups were removed by treatment with TBAF/AcOH according to previous procedures.[70] ^{1}H NMR revealed the disappearance of TMS groups from ~0.2 ppm and retention of glucose residues, Figure 10. Interestingly, DMF SEC revealed a slight increase in M_n even with the loss of TMS groups, S Figure 4, suggesting an unusual hydrodynamic volume change in DMF solvent.

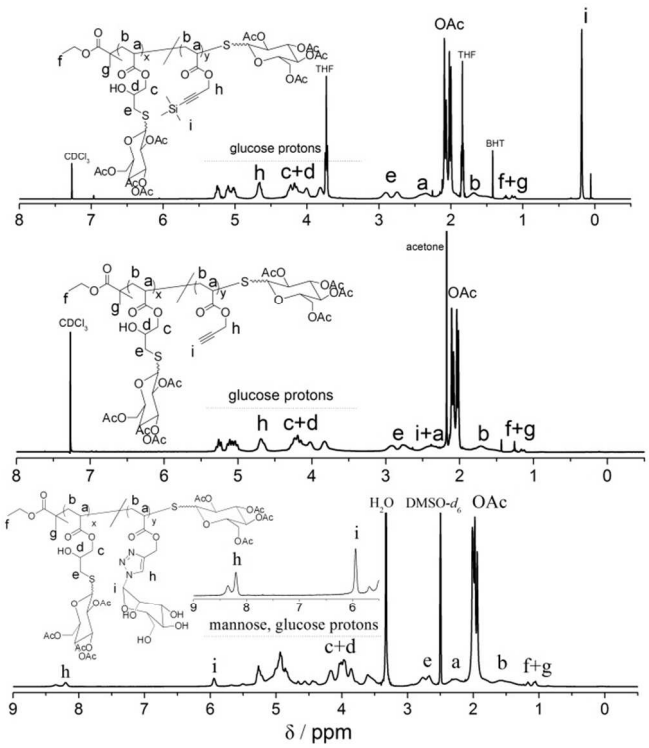


Figure 10. ^{1}H NMR spectra for the products after sequential thiol-epoxide reaction, deprotection of trimethyl silyl groups and CuAAC reaction. The numbering of the hydrogen atoms for the NMR peak assignment is shown in the scheme.

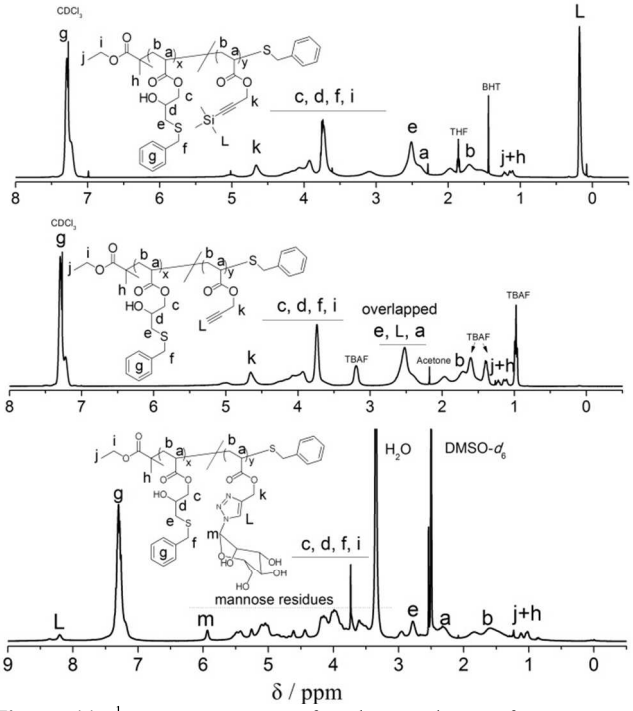


Figure 11. ^{1}H NMR spectra for the products after sequential thiol-epoxide reaction, deprotection of trimethyl silyl groups and CuAAC reaction. The numbering of the hydrogen atoms for the NMR peak assignment is shown in the scheme.

Following the reaction, ^{1}H NMR showed typical peaks from a triazole ring proton at ~ 8.2 ppm and mannose proton at ~ 6.0 ppm, Figure 10, clearly demonstrating the successful CuAAC reaction. FTIR spectroscopy revealed an OH absorbance increase at ~ 3500 cm^{-1} due to the addition of OH-rich mannose, S Figure 5.

In order to investigate the versatility of sequential reactions to glycopolymers, multiblock poly(GA)-*co*-(TMSPA) was also used to react with benzyl mercaptan and azide-functionalised mannose. Following the reaction with benzyl mercaptan, disappearance of epoxide groups was shown by ^{1}H NMR (Figure 11) and FTIR (peak at ~ 900 cm^{-1}, S Figure 7). Following deprotection of the TMS groups and reaction with azide-functionalised mannose ^{1}H NMR also showed similar peaks from a triazole ring proton at ~ 8.2 ppm and mannose proton at ~ 6.0 ppm, Figure 11.

Conclusions

In summary, Cu(0)-LRP has been utilized for the synthesis of poly(GA) with controlled MW, narrow dispersity and high chain end fidelity. Multiblock poly(GA)-*co*-(TMSPA) copolymers have been synthesized by Cu(0)-LRP *via* iterative monomer addition at full or close to full conversions. Thiol-halogen and thiol-epoxy reactions of poly(GA) with benzyl mercaptan suggest a significant preference of halogen rather than the epoxide for the thiol, which can be potentially used for selective modification. The obtained multiblock poly(GA)-*co*-(TMSPA) was subsequently used for sequential thiol-halogen, thiol-epoxy and CuAAC reactions to build functional glycopolymers with a defined sequence and spatial orientation. The Cu(0)-LRP and use of efficient reaction methodology were performed under mild reaction conditions to give high-order glycopolymers with sequence-control that are obtained in gram-scale. The recognition of such glycopolymers with appropriate lectins will be presented later.

Acknowledgements

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Notes and references

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