ACS Macro Letters

Letter

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Synthesis and Aggregation of Double Hydrophilic Diblock Glycopolymers via Aqueous SET-LRP

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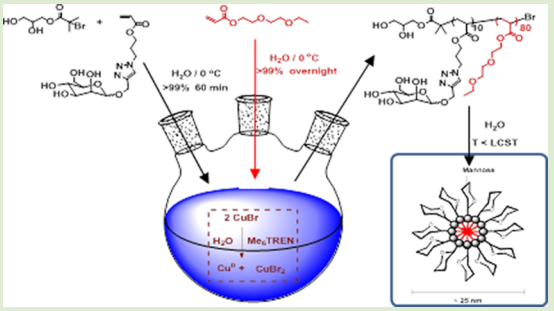
Supporting Information

ABSTRACT: A chemically unprotected mannose-containing acrylate (ManA) monomer was synthesized and polymerized by Cu(0)-mediated radical polymerization in water (SET-LRP). One-pot block copolymerization was achieved upon addition of a solution of *N*-isopropylacrylamide (NIPAm) or diethylene glycol ethyl ether acrylate (DEGEEA) forming thermoresponsive double hydrophilic diblock glycopolymers which revealed self-assembly properties in aqueous solution forming well-defined, sugar-decorated nanoparticles.



Controlled radical polymerization (CRP)[1−10] enables polymer chemists to design and construct synthetic polymers with excellent control over the chemical composition and conformation to achieve predefined chemical and physical properties. Synthesis of block copolymers is usually achieved either by coupling two, or more, end-functional homopolymers often via highly efficient "click" reactions[11−14] or by chain extension of synthetic polymeric macroinitiators/chain transfer agents.[15−18] Though both approaches have proved to be effective, low conversions during homopolymerizations and exhaustive purification can be required to ensure appropriate end-group functionality for subsequent coupling or chain extension reactions. This can be addressed in part by the use of Cu(0)-mediated radical polymerization, in which chain end fidelity can be retained throughout polymerization even at very high conversion (>99%).[19−21] Indeed this has been manipulated to achieve one-pot copolymerization, via sequential monomer addition, of acrylate monomers furnishing discrete and high molecular weight (multi)block poly(acrylate) systems.[22−25]

The incorporation of carbohydrate moieties into synthetic block copolymers is attractive given the key role they play in a variety of biological processes including (but not limited to) cell surface recognition and binding. The association constant between sugars and lectins benefits from multivalency ("cluster glycoside effect")[26] imposed by numerous copies of a particular sugar or sugar sequence designed to complement the "glycocode" of the cell surface.[27] Numerous multivalent carbohydrate ligands have been prepared, as glycodendrimers[28−31] and glycopolymers,[32−36] to investigate these interactions and probe the potential for such entities to intervene in significant cellular processes including recognition, binding, and signaling.

Multivalency can also be imposed by sugar-decorated polymer nanoparticles formed from the self-assembly of amphiphilic di- and triblock glycopolymers.[16,37−39] The challenge in synthesizing these amphiphilic systems is finding a solvent system compatible with hydrophilic sugars and the chosen hydrophobic comonomer(s).[40,41] This can and has been circumvented by the use of protected sugar monomers, with subsequent deprotection to unmask the desired hydrophilic sugars.[42−46] Alternatively, postpolymerization modification of functional polymer scaffolds with functionalized sugar moieties has also been successfully employed.[47−50] Nanoparticles have also been prepared from double hydrophilic block glycopolymers containing complementary block(s) designed to respond to changes in the local environment such as temperature and pH, thus modulating the assembly/disassembly process.[51−54] Synthetically, both classes of block glycopolymers have been prepared by free radical (FR)[55] and CRP techniques in a variety of solvent systems. However, there are only limited examples of the formation of block glycopolymers in aqueous or biologically relevant solvent systems.[56−58] We recently introduced a rapid and robust protocol for the Cu(0)-mediated polymerization (SET-LRP) of hydrophilic monomers in pure aqueous,[59−61] complex,[62] and biologically[63] relevant media. Homopolymerization and in situ chain extension/block copolymerization of hydrophilic monomers including *N*-isopropylacrylamide (NIPAm), 2-hydroxyethyl acrylate (HEA), and poly(ethylene glycol) methyl ether acrylate ($PEGA_{480}$) was demonstrated.[59,64] Moreover, for the first time the aqueous Cu(0)-mediated polymerization of *N*-acryloylmorpholine (NAM),[65] the synthesis of which has previously been limited to RAFT,[66−69] has

Received: April 2, 2014
Accepted: May 2, 2014
Published: May 9, 2014

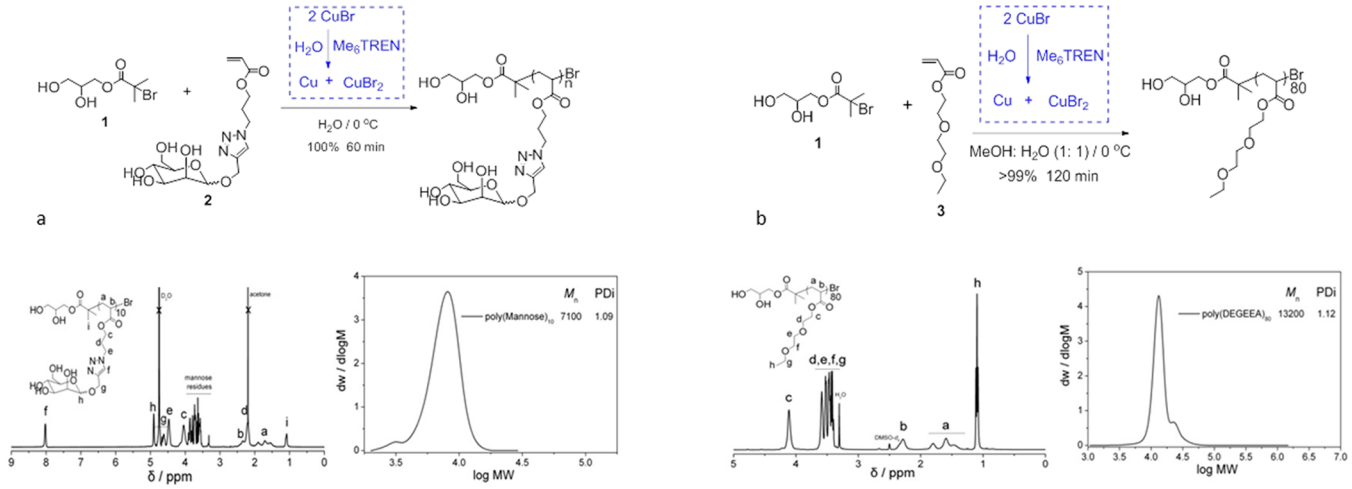


Figure 1. Synthesis and characterization of poly(ManA) and poly(DEGEEA) homopolymers by aqueous SET-LRP. ^{1}H NMR performed in D_2O (poly(ManA)) or d_6-DMSO (poly(DEGEEA)) and size exclusion chromatography (SEC) performed using DMF as eluent.

also been demonstrated. Herein, we report the translation of this technology to the synthesis of thermoresponsive double hydrophilic diblock glycopolymers which are shown to self-assemble in aqueous media into sugar-decorated nanoparticles predisposed for biochemical recognition and binding applications. This allows for the polymerization of unprotected sugar monomers, removing chemical complexity arising from the use of aqueous solvents.

To avoid the need for post polymerization modification and to ensure optimal control over the sugar sequence and epitope density, an unprotected mannose acrylate monomer (ManA, **2**) was prepared.[35] Initially, aqueous polymerizations were then performed at ambient temperature using Cu(0)-wire in the presence of $CuBr_2$ and Me_6-Tren (20 mol % with respect to the water-soluble initiator **1**). High conversions (93%) were obtained within 4 h, and polymerizations were found to proceed with a high degree of control ($Đ$ = 1.09, Figure S3, Supporting Information). The prerequisite for aqueous Cu-mediated polymerization (SET-LRP) is exploitation of the instability of Cu(Me_6-Tren)Br via in situ disproportionation to form Cu(0) and Cu^{II}(Me_6-Tren)Br_2 prior to the addition of a deoxygenated aqueous solution of monomer and initiator. Addition of a solution of ManA (**2**) and initiator (**1**) (DP_n = 10) to an aqueous solution of Cu(0) particles and Cu^{II}(Me_6-Tren)Br_2 at 0 °C resulted in an acceleration of the rate of polymerization relative to that observed when Cu(0)-wire was employed. Full (>99%) conversion was obtained within 1 h according to ^{1}H NMR with retention of the control exhibited in the Cu(0)-wire system ($Đ$ = 1.09, Figure 1a), representing a successful translation of the aqueous polymerization system to the synthesis of glycopolymer scaffolds.

The narrow molecular weight distribution exhibited by poly(ManA) includes a small low molecular weight tail/shoulder region that was reproducibly obtained during polymerizations of both ManA and NIPAm. To probe the cause of this discrepancy and identify any potential side reactions and byproducts, poly(NIPAm) (DP_n = 80, $M_n \approx 9300$ g·mol^{-1}) was prepared and dialyzed using a 1000 g·mol^{-1} nMWCO membrane against H_2O (500 mL) for 2 days. The dialysis water was then collected and removed by lyophilization to yield a solid product. Characterization by ^{1}H NMR and MALDI-ToF-MS identified oligo(NIPAm) (M_n < 1000 g·mol^{-1}) as the major side product, formed as a result of premature termination due to nucleophilic substitution at the chain end in the presence of H_2O, as well as an unidentified small molecule derived from NIPAm (Figures S6–S7, Supporting Information).

Despite the small amount of termination observed during homopolymerization, in situ block copolymerization of the poly(ManA) macroinitiator was achieved within 330 min at 0 °C upon addition of a deoxygenated solution of NIPAm ($DP_{n,th}$ = 80), without any prior purification steps. Efficient block copolymerization was confirmed by SEC, with evidence for the competing termination reaction manifest again as a small shoulder peak corresponding to "dead" chains of the homoglycopolymer (Figure S8, Supporting Information). The dispersity of the double hydrophilic block glycopolymer remained low ($Đ$ = 1.13), and ^{1}H NMR confirmed complete conversion (>99%). The presence of the poly(ManA) block was confirmed by the triazole signals at 8.0 ppm, with signals at 1.1 and 3.8 ppm indicative of the poly(NIPAm) block (Figure S9, Supporting Information). UV–vis allowed the comparison of lower critical solution temperatures (LCSTs) of the poly(ManA)$_{10}$-*b*-(NIPAm)$_{80}$ diblock glycopolymer to that of a poly(NIPAm)$_{100}$ homopolymer. The poly(NIPAm)$_{100}$ homopolymer prepared by aqueous SET-LRP exhibited a LCST ≈ 40.2 °C which is higher than expected (≈ 32 °C, Figure S11, Supporting Information). The increased LCST was attributed to the hydrophilic nature of the α-(vic-diol) and ω-(OH following dialysis) end groups. The hydrophilicity was further enhanced upon incorporation of sugar residues in the poly(ManA)$_{10}$-*b*-(NIPAm)$_{80}$ diblock glycopolymer which exhibited an increased LCST (42.6 °C).

To reduce the LCST of the diblock glycopolymer, diethylene glycol ethyl ether acrylate **3** (DEGEEA) was used as an alternative comonomer for block copolymerization from the poly(ManA) macroinitiator. The compatibility of alcoholic solvent systems with the aqueous SET-LRP of NIPAm was efficiently applied to the polymerization of DEGEEA due to monomer solubility requiring the addition of methanol. The homopolymerization of DEGEEA (DP_n = 80) was thus performed in a H_2O/MeOH (1:1) solvent system, to ensure the solubility of the monomer and polymer during the reaction, and reached high conversion (>99%, Figure 1b) within 120 min. Good agreement between $M_{n,exp}$ (13 200 g·mol^{-1}) and $M_{n,th}$ (15 300 g·mol^{-1}), coupled with the low dispersity ($Đ$ =

dx.doi.org/10.1021/mz5001724 | ACS Macro Lett. 2014, 3, 491–495

1.12, Figure 1b), supports the controlled nature of the polymerization. The small high molecular weight shoulder evident in the SEC trace of poly(DEGEEA) can be ascribed to a small amount of diacrylate impurity in the monomer which is commercially available with limited purity (>90%, note the diacrylate does not constitute the other 10% and is present in very small quantities).

To attain block copolymerization, deoxygenated DEGEEA ($DP_{n,th}$ = 80) in H_2O/MeOH (1:2) was added to a reaction mixture containing poly(ManA)$_{10}$ at complete conversion (>99%, $Đ$ = 1.06), prepared in a purely aqueous system. The resulting polymerization mixture was left overnight after which full conversion (>99%) of the DEGEEA monomer was confirmed by ^{1}H NMR. The reaction solution was dialyzed against water for 3 days, and the polymer was obtained as a white solid after lyophilization of the resulting colorless solution. Successful block copolymerization was implied by ^{1}H NMR, revealing both the ManA block, through the presence of the triazole signal at 8.1 ppm, and the DEGEEA block via the pendent methyl group signal at 1.1 ppm. Confirmation was attained by SEC which revealed a complete shift in the molecular weight distribution while retaining low dispersity ($Đ$ = 1.13, Figure 2). UV−vis furnished an LCST of ≈13.1 °C for

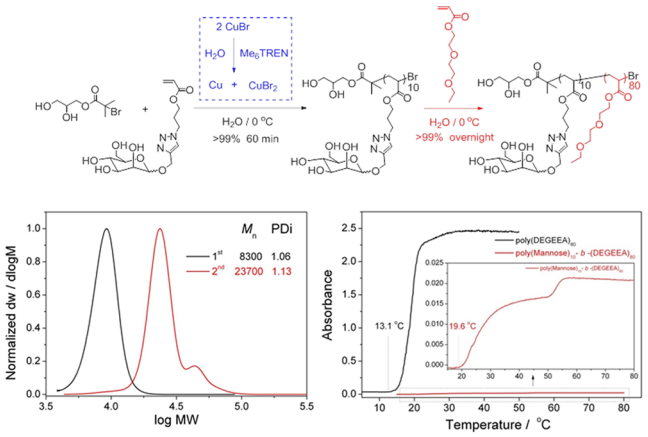


Figure 2. Synthesis and characterization of poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ by SEC (DMF) and UV−vis analysis.

the poly(DEGEEA)$_{80}$ homopolymer which increased to ≈19.6 °C upon incorporation of the hydrophilic ManA block in the poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ copolymer (Figure 2).

The ability of the two block glycopolymers to form higher ordered nanoparticles was investigated by dynamic light scattering (DLS). The UV−vis analysis of the poly(ManA)$_{10}$-*b*-(NIPAm)$_{80}$ block glycopolymer revealed a staggered phase transition between the LCST (≈42.6 °C, Figure S11, Supporting Information) and maximum temperature preset to 80 °C. Accordingly, DLS was conducted separately at 46 and 70 °C to ascertain whether the staggered phase transition was associated with a change in particle size. At both temperatures nanoparticles with an average diameter of ≈250 nm and low dispersities were observed ($Đ$ = 0.053 and 0.064, respectively, Table S1, Supporting Information). A similar staggered absorbance profile was obtained from UV−vis analysis of poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ (Figure 2). Particle size determination by DLS at 40 °C showed formation of nanoparticles of ≈48 nm with reasonable dispersity ($Đ$ = 0.119, Table S2, Supporting Information). The poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ was designed to exhibit a LCST below ambient temperature to allow self-assembly at room temperature and facilitate transition electron microsocpy (TEM) imaging. Thus, samples were prepared for TEM analysis to explore the morphology of the nanoparticles formed in aqueous solution. Staining with uranyl acetate exposed micellar nanoparticles, smaller than those predicted by DLS (≈25 nm, Figure 3).

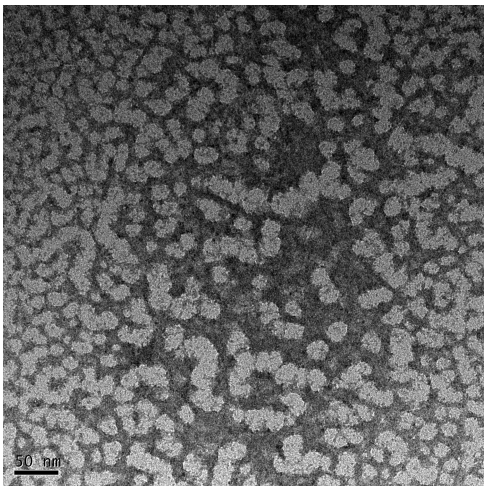


Figure 3. TEM of poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ displays sugar-decorated nanoparticle micelles ≈25 nm.

Finally, variable-temperature ^{1}H NMR (VTNMR) was conducted to probe how the polymer morphology varied as a function of temperature (Figure S16, Supporting Information). Below the LCST (≈19.6 °C) of the poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ diblock glycopolymer, unimers are present with both blocks being well solvated by the solvent (D_2O). However, as the temperature passes the LCST, the DEGEEA block becomes increasingly dehydrated, and the signals broaden and become indistinguishable. This coincides with the formation of micelles consisting of a dehydrated hydrophobic core (DEGEEA) and a well-solvated hydrophilic corona (ManA), verifying the DLS and TEM data obtained.

In summary, aqueous (and aqueous/alcoholic) SET-LRP has been applied for the synthesis of the double hydrophilic, thermoresponsive diblock glycopolymers. The thermoresponsive nature of the glycopolymers was demonstrated by self-assembly into polymeric nanoparticles above their LCST. Self-assembly of poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ was confirmed by DLS, TEM, and VTNMR revealing formation of well-defined polymeric micelles benefitting from a glycopolymer corona equipped with the potential for targeting and binding applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Materials, instruments and analysis, aqueous SET-LRP of D-mannose glycomonomer at 0 °C via disproportionation of CuBr/Me$_6$TREN, copper(0) wire mediated SET-LRP of D-mannose glycomonomer in H_2O at ambient temperature, aqueous SET-LRP of DEGEEA at 0 °C via disproportionation of CuBr/Me$_6$TREN, identification of side reactions during aqueous SET-LRP, synthesis of poly(mannose)$_{10}$-*b*-(NIPAM)$_{80}$ by aqueous SET-LRP, and synthesis of poly(mannose)$_{10}$-*b*-

dx.doi.org/10.1021/mz5001724 | ACS Macro Lett. 2014, 3, 491−495

$(DEGEEA)_{80}$ by aqueous SET-LRP. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We appreciate financial support from the University of Warwick and China Scholarship Council (Q.Z.). Equipment used in this research was supported by the Innovative Uses for Advanced Materials in the Modern World (AM2), with support from Advantage West Midlands (AWM), and partially funded by the European Regional Development Fund (ERDF). D.M.H. is a Royal Society/Wolfson Fellow.

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