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Synthesis of star-glycopolymers by Cu(0)-mediated radical polymerisation in the absence and presence of oxygen†

Hui Xue,‡[a] Lun Peng,‡[b] Yishi Dong,[a] Yuqing Zheng,[b] Yafei Luan,[a] Xiang Hu,[a] Gaojian Chen*[ab] and Hong Chen*[a]

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In this paper, novel star glycopolymers were synthesized *via* Cu(0)-mediated radical polymerisation at ambient temperature. The reaction was fast with little star–star coupling. Moreover, star glycopolymers can be obtained without removing oxygen from the polymerisation mixture. The effects of solvent and the ratio of initiator/catalyst/ligand on polymerisation were investigated, and the optimal conditions for the synthesis of star glycopolymer were determined. In addition, the binding ability between synthesised glycopolymers and concanavalin A (ConA) was studied using a turbidity test and quartz crystal microbalance-dissipation (QCM-D). Compared with linear glycopolymers, star glycopolymers showed higher binding ability to specific lectins and the strongest binding was obtained when the molecular weight was medium.

1. Introduction

Carbohydrates are key molecules in life. They are not only the main energy source, but also the basis for cell identification and intercellular signalling, due to the specific interaction with proteins.[1–4] A number of diseases, such as cancer and immune disorders, are closely related to abnormal interactions between sugar and protein.[5–7] Although the interaction between individual sugar molecules and protein is weak, it can be greatly enhanced by the combination of a plurality of sugar molecules, resulting in what is called a 'glycoclusters effect'.[8,9] In order to study the interactions between carbohydrates and proteins, glycopolymers with multiple pendant sugar units have been synthesized and applied in many fields such as histological engineering, drug controlled release, biosensors, proteome analysis and so on.[10–16] It has been shown that dendritic sugar molecules and derivatives possess high protein binding ability due to higher local concentration of sugar units.[17–19] Many reports demonstrated the potential of star-polymers in medicine due to the unique structure, special hydrodynamics and multisite modification.[20–23] Compared with their linear counterparts, star polymers possess additional properties thanks to their compact structure and high arm density.[24] Therefore, it is of significance to develop robust and convenient synthetic methods for obtaining well-defined star glycopolymers.

Star glycopolymers have been successfully synthesized *via* Reversible Addition–Fragmentation Chain Transfer Polymerisation (RAFT)[25–27] and Atom Transfer Radical Polymerisation (ATRP).[28,29] However, there are disadvantages such as easily coupling between star molecules, producing linear by-product and needing high reaction temperature. Cu(0)-mediated Living Radical Polymerisation (LRP) possesses many advantages,[30–35] although the mechanism is under debate. Glycopolymers with narrow molecular weight distributions have been successfully prepared in a well-controlled manner *via* room temperature Cu(0)-mediated living radical polymerisation.[36,37] Cyclodextrin-based glycoclusters/star glycopolymers were synthesized by Haddleton and coworkers *via* the combination of CuAAC Huisgen coupling and copper-mediated living radical polymerisation.[38] More recently, Davis and Haddleton showed that well-defined PDMAEA stars with narrow molecular weight distributions can be obtained by copper(0) mediated living

[a]*State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren'ai Road, Suzhou 215123, P. R. China. E-mail: chenh@suda.edu.cn; Fax: +86 512 65880827; Tel: +86 512 65880827*

[b]*Center for Soft Condensed Matter Physics and Interdisciplinary Research, Soochow University, Suzhou 215006, P. R. China. E-mail: gchen@suda.edu.cn; Tel: +86 512 65884406*

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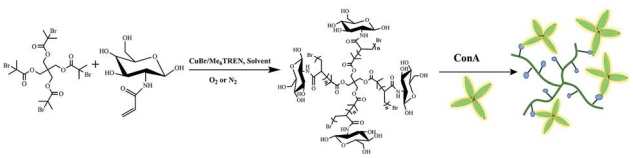
‡ These authors contributed equally to this work.



Scheme 1 Schematic representation of four arms star glycopolymer *via* Cu(0)-mediated radical polymerisation and the specific interaction between glycopolymers and ConA.

radical polymerisation.[39] In aqueous media, copper(0)-mediated radical polymerisation wherein reactive Cu(0) and Cu(II)X_2 species, obtained by disproportionation of Cu(I)X species in the presence of a diversity of N-containing ligands, mediate an ultrafast living radical polymerisation of acrylates at room temperature or below. As being highlighted by Zhang *et al.*, it is able to rapidly achieve high molecular weights with excellent control of molecular weight distribution, with perfect retention of chain end functionality and low bi-radical termination ratio.[37,40,41] Herein we report the synthesis of star glycopolymers *via* room temperature Cu(0)-mediated radical polymerisation in aqueous media in the absence and presence of oxygen. Star glycopolymers were successfully synthesized with high reaction rate at room temperature without protecting sugar monomers and the polymerisation can still be carried out in the presence of oxygen (Scheme 1). This method provides a promising pathway for the synthesis of star glycopolymers in different situations without degassing. In addition, the specific binding ability of glycopolymers to ConA was measured by turbidity experiment and QCM-D, and it provides in-depth information for designing star glycopolymers with potential application in targeted drug delivery.[42,43]

2. Experimental

2.1 Materials

2-Bromoisobutyryl bromide (Sigma-Aldrich, 98%), 3-(2-amino ethyl methyl) amine (Me_6-TREN, Sigma-Aldrich, 97%), concanavalin A (ConA, Sigma-Aldrich), 11-mercaptoundecanoic acid (Sigma-Aldrich, 95%), *N*-hydroxysuccinimide (Sigma-Aldrich, 98%), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (Sigma-Aldrich, 98%), D-(+)-glucosamine hydrochloride (TCI, 98%) and acryloyl chloride (Aladdin, 96%) were used as received. Pentaerythritol (Aladdin, 98%) was used after dried in vacuum oven. Deuterated chloroform ($CDCl_3$, 99.8%) and deuterium oxide (D_2O, 99.9%) were purchased from Cambridge Isotope Laboratories, Inc. Cuprous bromide (CuBr, J&K, 98%) was used after purification (washed with glacial acetic acid and methanol, stirred for 30 min, filtrated and dried under vacuum for 24 h). Triethylamine, anhydrous magnesium sulfate ($MgSO_4$), potassium carbonate (K_2CO_3), concentrated ammonia solution, hydrogen peroxide (30 vol%), methanol, dimethylformamide (DMF) and other solvents were all purchased from the Sinopharm Chemical Reagent Co., Ltd. (China) and used as received. The dialysis membranes were purchased from Solarbio Life Science, Inc. The monomer acryloyl D-(+)-glucosamine (AGA) was synthesized according to the ref. 44.

2.2 Synthesis

Synthesis of star-initiator tetrakis(2-bromoisobutyryl) pentaery-thritolate. Dried pentaerythritol (1.36 g, 10 mmol), triethylamine (8.4 mL, 60 mmol), and tetrahydrofuran (THF, 30 mL) were added to a dry three-necked flask with a magnetic bar. The reaction mixture was bubbled with nitrogen for 10 min in an ice bath, the mixed solution of 2-bromoisobutyryl bromide (7.9 mL, 60 mmol) and THF (10 mL) was added dropwise in 15 min with constant pressure funnel. Then the mixture was stirred under nitrogen atmosphere overnight. The milky turbid liquid was diluted with CH_2Cl_2 and filtered to get yellow oily liquid. The filtrate was extracted with H_2O (1 × 30 mL), saturated NaOH solution (1 × 30 mL) and H_2O (3 × 30 mL) iteratively. The organic phase was dried with anhydrous $MgSO_4$ and recrystallized from methanol for three times. The product was obtained as a white solid and thoroughly dried in a vacuum oven for 36 h. Yield: 36.81%. ^{1}H NMR ($CDCl_3$), δ ppm: 4.31 (m, 8H, $-CH_2-$), 1.92 (m, 24H, $-CH_3$).

Synthesis of star poly(acryloyl-D-(+)-glucosamine). Typically, AGA (0.4662 g, 2 mmol) and four-arm star initiator (0.0092 g, 0.0125 mmol) were added to a round-bottom flask and dissolved in the solution with 3 mL DMF and 1 mL H_2O and the mixture was bubbled with nitrogen to remove oxygen. H_2O (2 mL) was degassed *via* nitrogen bubbling in other flask, and then Me_6-TREN (27.5 μL, 0.1 mmol) and CuBr (0.0143 g, 0.1 mmol) were added. Five minutes later, the former solution was transferred into the latter flask to react for 6 hours at ambient temperature. All operations in experiments were carried out in the glove box. Finally, the resulting solution was dialyzed for 48 hours and then freeze-dried. The conversion of the monomer was determined by gravimetry.

Synthesis of star glycopolymer in the presence of O_2. The polymerisations were carried out with different ratios of monomer to initiator. In a typical reaction, AGA (0.4662 g, 2 mmol) and four arms star initiator (0.0092 g, 0.0125 mmol) were added to a round-bottom flask and dissolved in the solution with 3 mL DMF and 1 mL H_2O. CuBr (0.0143 g, 0.1 mmol) and Me_6-TREN (27.5 μL, 0.1 mmol) were dissolved in 2 mL H_2O in another flask. Then the former solution was transferred into the latter flask to react for 2 hours at room temperature. All the steps were carried out without degassing. The resulting solution was dialyzed (3500 M_w cut-off) for 48 h, and then freeze-dried. The conversion of the monomer was determined by gravimetry.

2.3 Binding assay of glycopolymer and ConA

Glycopolymer (5 mg) and ConA (1 mg) were dissolved in 1 mL phosphate buffered saline (PBS, pH = 7.4, with 0.1 mM $CaCl_2$ and $MnCl_2$) respectively. Then both of the solutions (0.4 mL) were mixed with each other, and the absorbance data were obtained in 30 minutes by UV-spectrophotometer at 25 °C (λ = 360 nm).

The QCM-D chips (AT-cut, 5 MHz, 14 mm in diameter) were washed by ethanol and deionized water iteratively. Both sides of the chips were treated in ozone atmosphere for 30 minutes respectively and then cleaned with ethanol and deionized water. Mixture of concentrated ammonia solution, hydrogen peroxide solution and deionized water, with ratio of 1 : 1 : 5 in volume, was used to boil the chips at 75 °C for 10 minutes, followed by rinsing them with abundant deionized water. The chips were dipped in 1 mL ethanol solution of 11-mercaptoun-decanoic acid (0.2 M) overnight and then washed with ethanol. Dried chips were dipped in 1 mL PBS solution of *N*-hydroxysuccinimide and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.05 M respectively) and then rinsed with deionized water. The QCM-D chips were placed in

the fluid and exposed to the solution. Detection in QCM-D experiments was carried out in flow-through mode with a flow rate of 10 μL min^{-1} at 25 °C. The baseline was set up by passing the PBS (with 0.1 mM $CaCl_2$ and $MnCl_2$) that mentioned earlier through for about 4.5 hours. Then freshly prepared ConA solutions (PBS with 0.1 mM $CaCl_2$ and $MnCl_2$, 1 mg mL^{-1}) were passed through for about 3 hours to obtain the adsorption plateau. After that, the chips were washed with the former PBS to remove loosely attached protein.

2.4 Characterization

^1H NMR spectra of the polymers were recorded on an Agilent 400 MHz nuclear magnetic resonance (NMR) instrument, using D_2O as the solvent. ^{13}C NMR spectra of the polymers were recorded on an INOVA 300 MHz nuclear magnetic resonance (NMR) instrument using D_2O as solvent. The molecular weights and molecular weight distributions of the polymers were measured on a waters 1515 gel permeation chromatography (GPC) system equipped with a PL aquagel-OH MIXED-M column using PEG as the standard sample. A mixture of millipore water containing 70% of 0.2 M $NaNO_3$, 0.1 M NaH_2PO_4 with a pH of 7 and 30% methanol was used as the mobile phase and was delivered at a flow rate of 1 mL min^{-1}. GPC traces were acquired by an Agilent PL-GPC 50 gel permeation chromatograph system equipped with a refractive index detector and using a 5 μm Guard, 5 μm MIXED-D column. PMMA was used as the standard samples and DMF containing 0.05 mol L^{-1} lithium bromide was used as the eluent at a flow rate of 1 mL min^{-1}. The measurement was operated at 50 °C. The binding ability of glycopolymers and ConA was measured by Ultraviolet spectrophotometer on a Shimadzu (Kyoto, Japan) UV-3600. The quartz crystal microbalance-dissipation (QCM-D, HRBio, Suzhou, China) measurements primed with water or PBS at a speed of 10 μL min^{-1} and 25 °C were conducted using a Q-Sense-E4instrument (Q-Sense, Sweden) with control software (Resonant Probes GmbH, Goslar, Germany) to analyse the data.

3. Results and discussion

3.1 Effect of solvent in the polymerisation

Cu(0)-mediated LRP is a robust technique for polymer synthesis. As previously reported the complex Cu(I)/Me_6-TREN possess the best disproportionation efficiency in H_2O, and efficiently mediated the polymerisation process.[45,46] Considering the solubility of the initiator and disproportionation efficiency of catalyst, the experiments were carried out in the mixed solvents of DMF/H_2O or DMSO/H_2O. In order to determine the optimal condition for the synthesis of four-arm star glycopolymers, polymerisations with different solvent compositions and ratios of bromine/cuprous bromide/ligand (Br/Cu/L) ratios were conducted in the present work.

It can be seen from Table 1 that for the same polymerisation time, the conversion increases with increasing water content of the solvent, indicating that Cu(0) is formed more efficiently in water and then enhances the initiation of the polymerisation. For example, when DMF/H_2O is 1 : 1, polymer with molecular weight of 18 700 and PDI = 1.45 was obtained after 6 h. Meanwhile, with the increasing of water content in the mixed solvent, the polymer's GPC trace shows that the shoulder peaks at high molecular weight portion taper and disappear in Fig. 1a. It seems that couplings between star molecules are significantly inhibited, which offer an effective solution to the termination problem in the synthesis of star glycopolymers. However, when the water content increases to 75%, the polymer molecular weight is much higher than theoretical value with lower conversion rate within the same reaction time, no matter in the mixture of H_2O with DMF or DMSO. Moreover, the PDIs become high (>2.2). It is possibly due to the poor solubility of the initiator in water. At the very beginning, few initiator molecules dissolve in the solvent, and more initiators dissolve with the progress of polymerisation. Since the propagation time of each initiator is different, tails appear at the low molecular weight part of GPC curves, and PDIs broaden. From this we can draw a conclusion: when the volume ratio of DMF/H_2O is 1 : 1, the solvent is suitable for the synthesis of star glycopolymers (Fig. 2).

3.2 Influence of ratios of initiator/catalyst/ligand

Br/Cu/L ratio is a key parameter in the activation/deactivation process, and thus has an effect on the polymerisation rate and controllability. To make sure full complexation of Cu(0) with Me_6-TREN, the ratio 1 : 1 (Cu/L) was used. Experiments with different ratios of initiator/catalyst were carried out to investigate the effect of catalytic ratio on the synthesis of

Table 1 The glycopolymers obtained by polymerisation in different solvents with certain ratios of Br/Cu/L

Solvent	Solvent ratios (V)	Time (h)	$[M]/[I]^a$	Br/Cu/L[b]	Conversion (%)	$M_{n(th)}$	M_n[c] (g mol^{-1})	PDI[c]
DMF/H_2O	1 : 0	6	40	1 : 2 : 2	21.0	8500	Bimodal	
	9 : 1	6	40		29.1	11 500	9000	1.85
	3 : 1	6	40		34.2	13 400	10 400	1.67
	1 : 1	6	40		36.7	14 400	18 700	1.45
DMF/H_2O	1 : 1	2	40	1 : 1 : 1	75.7	28 900	29 200	1.55
DMF/H_2O	1 : 3	2	40		11.0	4800	34 600	2.20
DMSO/H_2O	1 : 3	2	40		13.5	5800	37 300	2.33

[a] Monomer/initiator. The initial concentration of monomer $[M(AGA)]_0$ is 0.33 mmol mL^{-1}. [b] (Initiator × 4)/catalyst/ligand. [c] Obtained by aqueous GPC.

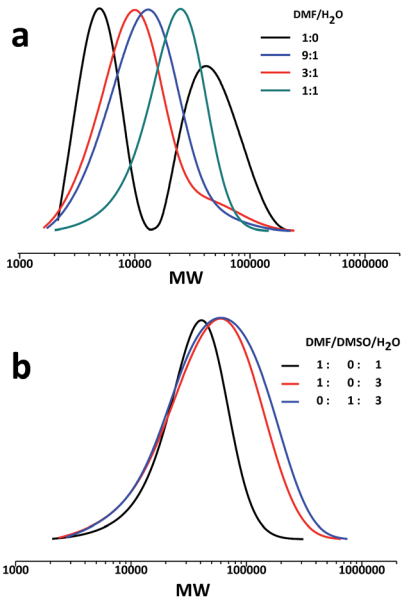


Fig. 1 (a) Aqueous GPC traces of star-polymers polymerised in solvent with different DMF/H_2O ratios and Br/Cu/L = 1 : 2 : 2, polymerisation time = 6 hours. (b) GPC traces of star-polymers polymerised in different solvent with Br/Cu/L = 1 : 1 : 1, polymerisation time = 2 hours. $[M(AGA)]_0$ = 0.33 mmol mL^{-1}.

acrylamide star glycopolymers. Since a four-arm initiator was used, Br/Cu here refers to the initial molar ratios of (initiator × 4)/catalyst. It can be seen that the polymerisation rate increases and PDI broadens slightly when the ratio of Br/Cu changes from 1 : 2 to 1 : 0.4. Low Br/Cu ratio is in favour of polymerisation regulation, while high Br/Cu ratio helps to accelerate the polymerisation. There's no shoulder in all of the three GPC curves, which indicates that this polymerisation system can reduce star–star coupling.

a

Solvent	Br/Cu/L	Conversion (%)	$Mn_{(th)}$	$Mn_{(GPC)}$ (g mol^{-1})	PDI
DMF/H_2O = 1:1	1:2:2	36.7	14400	18700	1.45
	1:1:1	75.7	28900	29200	1.55
	1:0.4:0.4	92.5	35200	31300	1.58

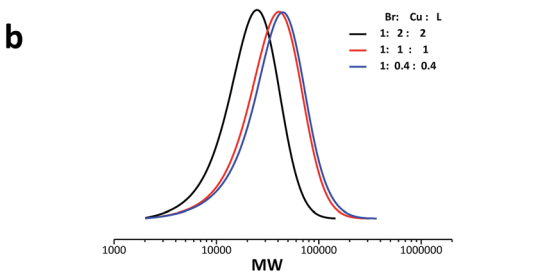


Fig. 2 (a) Molecular weight results measured by aqueous GPC and (b) the GPC curves of star-glycopolymers polymerised with different ratios of Br/Cu/L. Conditions: DMF/H_2O = 1 : 1, polymerisation time = 2 hours. $[M(AGA)]_0$ = 0.33 mmol mL^{-1}.

3.3 Kinetic of the polymerisation of AGA

Polymerisation system with Br/Cu/L (1 : 1 : 1) in the solvent of DMF/H_2O (1 : 1) was chosen for kinetic investigation, which possesses moderate polymerisation rate and controllability. $\ln([M_0]/[M])$ shows a linear relationship with time in (Fig. 3a), and the first order kinetics indicate that the radical concentration is constant. Molecular weight of the polymer increases linearly with the conversion and slightly diverges (especially at higher conversion) from the theoretical molecular weight. The reason is that the hydrodynamic radii of star molecules are smaller than linear ones with the same molecular weight in solution. As linear PMMA is used as standard samples in DMF GPC, the measured molecular weights by GPC are lower than the theoretical molecular weights. We found that the measured molecular weights by NMR are slightly higher than the GPC values and are close to the theoretical molecular weights (Table S1 and Fig. S5†). During the whole polymerisation, the polydispersity index remains at about 1.5.

3.4 Synthesis of star glycopolymers in the presence of O_2

For the synthesis of sugar macromolecules in living organism, the presence of oxygen is unavoidable. However, removing oxygen from the polymerisation mixture is required for the

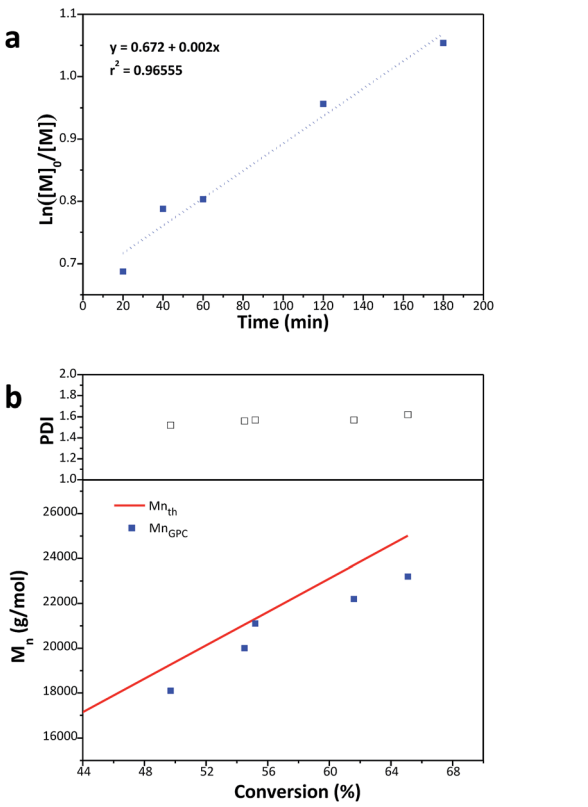


Fig. 3 (a) Kinetic plots of polymerisation of star poly(acryloyl-D-(+)-glucosamine) at 25 °C. (b) Dependence of the theoretical molecular weights, the molecular weights and PDIs on conversions of star polymer. Polymerisation conditions: DMF/H_2O = 1 : 1, Br/Cu/L = 1 : 1 : 1, M_n and PDI obtained by DMF GPC. $[M(AGA)]_0$ = 0.33 mmol mL^{-1}.

traditional free radical polymerisation or living radical polymerisation systems, which is bound to affect the researches on *in situ* synthesis of sugar macromolecules in biological systems. Previous studies have shown that AGET, ATRP and other polymerisation systems containing reducing components have a certain ability to endure oxygen.[47–49] Cu(0) is a good reductant which will react with oxygen, so we wonder whether the present system can still proceed in the presence of oxygen, since much Cu(0) will be produced in the disproportionation process.

To ensure the amount of Cu(0) is enough to catalyse the system in the presence of oxygen, the ratio of Br/Cu/L (1 : 2 : 2) was chosen. As shown in Fig. 4, the polymerisation can still move on with a high conversion in the presence of oxygen. Polymers with different molecular weights (from 7500 to 25 000) were easily obtained by changing the monomer/initiator (*M*/*I*) ratios, and the molecular weight distributions were kept reasonably narrow. Previous reports of the molecular weight distributions of star glycopolymers synthesized by RAFT polymerisation could reach to 1.9.[25] Relatively narrow molecular weight distributions of star glycopolymers ranging from 1.1 to 1.5 can be obtained *via* ATRP and the combination of SET-LRP/click chemistry, whose polymerisations were carried out for 15 to 24 hours in the absence of oxygen.[29,38] The tolerance to oxygen and shorter polymerisation time guarantee our approach more possibilities in complex systems.

3.5 Effects of different glycopolymers on specific binding to lectin

The specific interaction between sugar and lectin is the basis for intercellular signal transduction, and plays a vital role in many life activities.[11] The strength of binding between multiple ligands and lectin depends on ligand structure, molecular skeleton freedom,[50] binding-site density[51,52] and molecular weight.[53,54]

The binding abilities between synthetic star glycopolymers and lectins were first investigated through detecting changes of the mixed solution's turbidity, and the experimental results are shown in Fig. 5. The figure shows that the absorbance of star glycopolymer solution increases obviously, on the contrary, no change appears in linear molecules with a similar molecular weight and concentration, which indicates that the star glycopolymers possess a better specific binding ability with lectin. Chances are that star molecules tend to form crosslinkings with different lectins, and thereby more particles precipitate from

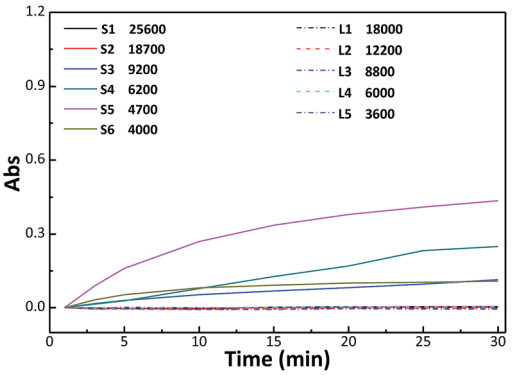


Fig. 5 Turbidity measurement of glycopolymers with ConA. S means star glycopolymers and L means linear glycopolymers. The number behind means the molecular weight.

a

[M]/[I]	Presence of O_2	Conversion (%)	$Mn_{(th)}$	$Mn_{(GPC)}$	PDI
40	NO	36.7	14400	18700	1.45
10	YES	30.2	3600	7500	1.28
40	YES	34.1	13400	18900	1.59
80	YES	67.6	51100	25600	1.58

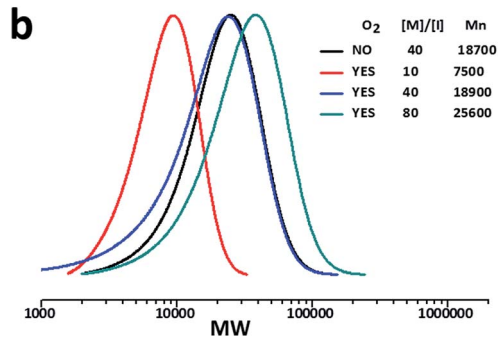


Fig. 4 (a) Molecular weight results measured by aqueous GPC and (b) the GPC traces of star-glycopolymers polymerised in the absence or presence of O_2. Polymerisation conditions: DMF/H_2O = 1 : 1, Br/Cu/L = 1 : 2 : 2, 2 h. $[M(AGA)]_0$ = 0.33 mmol mL^{-1} (DP = 40, 80), $[M(AGA)]_0$ = 0.0825 mmol mL^{-1} (DP = 10).

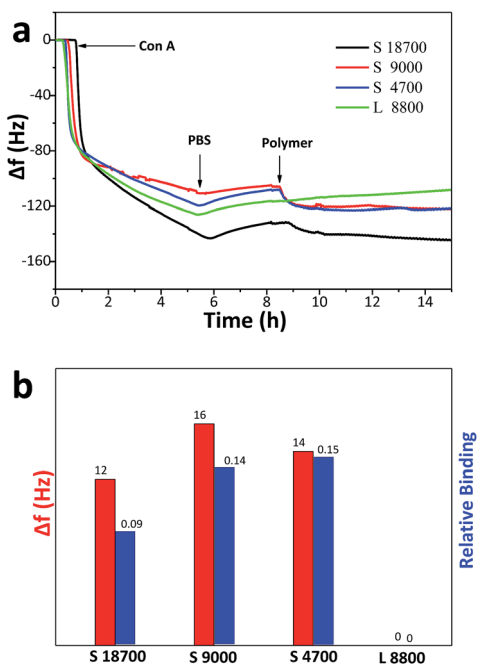


Fig. 6 (a) Plots of the frequency changes and (b) protein absorption of QCM in response to ConA (0.1 mg mL^{-1}), PBS, and glycopolymers (1 mg mL^{-1}).

the solution, leading to more obvious turbidity change. Furthermore, the star glycopolymer with $M_n = 4700$ shows the highest binding rate to ConA, and with the further increasing of molecular weight, the changing rate of turbidity gradually decreases, which coincides with the results from previous studies.[9,27] Both results of the present work and other reports show that higher molecular weights do not always enhance binding with proteins, and molecular weight optimization is necessary. To obtain more information about the interactions between glycopolymer and ConA, QCM-D data (Fig. 6) were used. For better comparison, we calculated the relative binding (the frequency change after polymer injection divided by the frequency change before polymer injection) of different polymers. It shows that star glycopolymers show higher binding potency to ConA than linear ones. And the star glycopolymers with $M_n = 4700$ and 9000 present higher relative binding value than the star glycopolymer with $M_n = 18\,700$, indicating that medium molecular weight is better for lectin binding.

4. Conclusion

A series of star glycopolymers were synthesized *via* Cu(0)-mediated radical polymerisation. The effects of solvent composition and ratio of initiator/catalyst/ligand were investigated and the optimized condition was determined. When a mixed solvent of DMF : H_2O = 1 : 1 is used, both good dissolution of the oil-soluble initiator and efficient disproportionation of Cu(I) can be achieved. A fast polymerisation rate and relatively good controllability can be obtained when the ratio of Br/Cu/L is 1 : 1 : 1. In the present work, we find that the polymerisation can still proceed and star glycopolymers with different molecular weights are able to be obtained in the presence of oxygen. The turbidity and QCM-D results show that star glycopolymers possess better specific binding ability to lectin than linear ones, and the star glycopolymers with medium molecular weights show higher specific binding potency. The star glycopolymers conveniently synthesized can find applications in the delivery of drugs, the study of the biomolecular interactions between carbohydrates and proteins, and for the fabrication of other sugar-based functional materials. The approach to prepare glycopolymers in the presence of oxygen provides a facile way for *in situ* polymerisations that can guarantee more possibilities in complex biological systems.

Acknowledgements

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