Well-Defined Lactose-Containing Polymer Grafted onto Silica Particles

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Reversible addition-fragmentation chain transfer (RAFT) polymerization of 2-*O*-meth-acryloyloxyethoxyl-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (MAEL) was performed directly in $CHCl_3$ solutions using cumyl dithiobenzoate (CDB) as the chain transfer agent to give well-defined glycopolymers. The chemical composition and structure of the glycopolymer were characterized by ^{1}HNMR, FTIR, and SEC. The living glycopolymer chains were subsequently grafted onto γ-methacryloxypropyl-trimethoxy (MPTMS) modified silica particles. The acetyl groups of the poly(MAEL) grafted onto the silica gel particles were converted to the hydroxyl groups with CH_3ONa/CH_3OH, thus obtaining silica gel particles modified with well-defined lactose-carrying polymer.

Introduction

In recent years, much interest has been directed toward the synthesis of saccharide-containing synthetic polymers, due to their potential applicability in various fields of biotechnology, pharmacology, and medical materials.[1−6] Hence, a variety of synthetic polymers containing saccharide residues, herein referred to as "glycopolymers", have been reported. Glycopolymers are considered high-value polymeric materials due to their solubility in water and strong hydrogen bonding ability. Moreover, the sugar portion of glycopolymers has been found to play an essential role in the control of its biological functions.[7−11]

For the synthesis of well-defined glycopolymers, the great majority of reports focuses on the use of living cationic polymerization,[3,12,13] living anionic polymerization,[4,14] atom transfer radical polymerization,[15−17] nitroxide-mediated living radical polymerization,[5,18−20] living ring-opening polymerization,[21−23] and ring-opening metathesis polymerization.[24] Recently, reversible addition-fragmentation chain transfer (RAFT) mediated polymerization has proved to be a new and robust method to synthesize well-defined glycopolymers with low polydispersity under a broad range of experimental conditions.[25−29]

The elaboration of organic/inorganic composites by polymers provides a unique opportunity to engineer the interfacial properties of solid substrates.[30−32] Routes usually used to achieve the chemical bonding of functional polymers onto a solid substrate are the reaction of end-functionalized polymers with appropriate surface sites,[33] growth of polymer chains from preformed surface-grafted initiators,[34−36] and monomer graft on substrate by the introduction of surface active site.[37] Glycopolymers were grafted onto the surface of solid substrates, which is an efficient way to introduce the sugar functional groups to the solid substrates and further to obtain novel functional materials.[38] In this area, Fukada et al.[15] first reported the controlled grafting of a well-defined glycopolymer on a solid substrate by surface-initiated atom transfer radical polymerization, which is a good way to get a homogeneous graft polymer layer with a high graft density.

In our work, first, well-defined lactose-containing polymers were synthesized via the RAFT technique, and then the living glycopolymers with dithioester residues were grafted onto the γ-methacryloxypropyltrimethoxy (MPTMS) modified silica gel particles. This is a simple method to get well-defined lactose-containing glycopolymer grafted silica gel particles with some extent grafting ratio, which will have potential applications for separation materials in the analysis of substances with biological activity, such as, proteins.[39,40]

Experimental Section

Materials and Reagents. Silica gel particles (Meigao Chemical Co., Lid, Qingdao, China) with an average diameter of 10 μm and a specific surface area of 129 m^2/g (N_2 adsorbed, BET method) were boiled in 20% HCl, washed extensively with distilled water, and dried at 120 °C for 24 h. 2-Hydroxyethyl methacrylate (HEMA) (Tianjin Chemreagent Institute,China) was distilled under reduced pressure before use. Lactose octaacetate was synthesized by the reaction of lactose and acetic anhydride according to the literature.[41] Bromobenzene and α-methylstyrene purchased from QingPu Reagent Factory (Shanghai, China) were analytical grade. 2,2′-Azoisobutyronitrile (AIBN) purchased from Tianjin Fuchen Chemical Reagent Factory (China) as initiator was purified by recrystallization in ethanol. Toluene and diethyl ether were analytical grade and distilled over sodium metal under nitrogen. Other chemicals were analytical grade used as received.

Preparation of the Glycomonomer (MAEL). MAEL was synthesized using similar methods as described by Chaikof et al.[17] To a 100 mL three-neck flask cooled with ice−water bath were added a stirred solution of lactose octaacetate (3.39 g, 5 mmol,) and 2-hydroxyethyl methacrylate (0.72 mL, 6 mmol) in dichloromethane (20 mL) and BF_3-etherate (3.20 mL), and the reaction mixture was stirred for 2 h at 0 °C. Then the solution was allowed to warm to room temperature and stirred for an additional 12 h. The mixture was washed with water and saturated aqueous sodium hydrogen carbonate and dried over Na_2SO_4. The mixture was evaporated using a rotatory evaporator under reduced pressure to get the residue, which was purified further by column chromatography (SiO_2) using acetone−petroleum ether (1:1.4, v/v) as eluent to afford the glycomonomer (1.88 g, 50.2%,wt). ^{1}H NMR

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Table 1. Summary of RAFT Polymerization Experiments[a]

run	[M]/[CDB]/[I]	reaction time (h)	conversion (wt %)	M_n (calcd)	M_n (^{1}H NMR)	M_n (SEC)	PDI
1	100/0/1	24	77.8			94529	2.99
2	100/1.05/1	24	35.5	25682	63451	21368	1.34
3	100/2/1	24	30.1	11487	37579	9294	1.22
4	100/3/1	24	23.1	5436	27863	6747	1.08
5	100/5/1	24	20.5	3340	18531	5286	1.07
6	30/2/1	24	33.2	4003		3856	1.13
7	60/2/1	24	30.9	7218	29934	6291	1.09

[a] Reaction temperature: 70 °C. For SEC: polystyrene as equivalent. PDI: M_w/M_n (SEC).

($CDCl_3$), δ_{ppm}: 6.13 (s, 1H), 5.60 (s, 1H), 5.38−4.85 (m, 5H), 4.58−3.60 (m, 13H), and 2.20−1.93 (m, 24H). MS/FAB, *m/z*: calcd for $C_{32}H_{44}O_{20}Na$, 771.57; found, 771.53$[M+Na]^+$.

Preparation of Cumyl Dithiobenzoate (CDB). The synthesis procedure of CDB has been reported in the literature.[42] Bromobenzene (26.76 mL, 255 mmol) was mixed with 60 mL of dried diethyl ether, and then the solution was added to magnesium turnings (6.2 g, 255 mmol, in diethyl ether) under a nitrogen atmosphere. The mixture was stirred for 30 min or more and then heated to reflux for 30 min. Carbon disulfide (6.04 mL, 255 mmol) was added slowly after the mixture was chilled with ice water. The reaction mixture was kept at 0 °C for 3 h under stirring and then carefully poured into ice water, and the product was extracted with diethyl ether. After removal of the ether, the crude dithiobenzoate acid was obtained as a dark red−brown oil.

Dithiobenzoate acid (3.0 g, 19 mmol), α-methylstyrene (4.0 g, 34 mmol), carbon tetrachloride (4 mL), and a small amount of acid catalyst (*p*-toluenesulfonic acid, 0.05 g) were combined under nitrogen and heated at 70 °C for 5 h. After evaporation of the solvent and excess monomer using a rotatory evaporator, the residue was purified twice by column chromatography on silica gel with petroleum ether as the eluent to give cumyl dithiobenzoate as a dark-purple oil (yield 10 wt %). ^{1}HNMR δ: 1.99 (s, 6H); 7.2−7.6 (m, 8H) and 7.85 (m, 2H).

Synthesis of Glycopolymer by RAFT Polymerization. In a typical experiment (Table 1), MAEL (1 g, 1.34 mmol) was dissolved with a $CHCl_3$ solution of 2,2′-azoisobutyronitrile (AIBN, 2.2 mg, 0.013 mmol) and cumyl dithiobenzoate (CDB, 7.3 mg, 0.027 mmol). The reactor was then sealed, degassed with three freeze−evacuate−thaw cycles, and transferred to an oil bath preheated to 70 °C. At the end of the reaction for 24 h, the reaction mixture was quenched in cold water, then precipitated in cold diethyl ether, and washed for several times. The obtained glycopolymer was dried in vacuo for 24 h (Table 1).

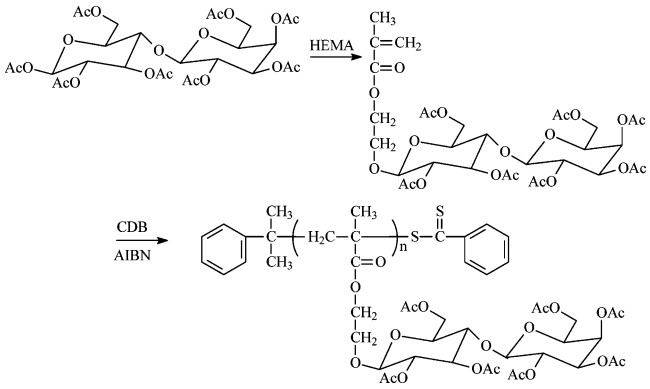
Grafted Reaction and Deprotection. Prior to the graft reaction on silica particles with the end-functionalized glycopolymer, the surface modification for the silica particles was carried out with γ-methacryloxypropyltrimethoxy (MPTMS). One gram of silica was first suspended in 15 mL of dry toluene, and then 1 g of MPTMS and a trace amount of triethylamine were added. This mixture was refluxed for 10 h under nitrogen. The silica was isolated by centrifugation and extracted by Soxhlet's extraction apparatus with acetone for 24 h to remove the physical adsorbed MPTMS.

A required amount of MPTMS modified silica particles, PMAEL (0.25 g), toluene (10 mL), and AIBN (0.01 g) were introduced into a flask reactor under nitrogen atmosphere in which the reaction temperature was controlled at 70 °C for 8 h. The glycopolymer-grafted silica particles were isolated by centrifugation and extracted by Soxhlet's extraction apparatus with acetone for 24 h to remove the absorbed glycopolymer and solvent. The graft density of the PMAEL on the silica surface was estimated by thermogravimetric analysis (TGA) using the following equation:

$$\text{graft ratio (mg/m}^2) = \frac{100(W_{\text{glycopolymer}} - W_{\text{silane}})}{S_{\text{specific}}(100 - W_{\text{glycopolymer}})(100 - W_{\text{silane}})} \times 10^3$$

where $W_{\text{glycopolymer}}$ and W_{silane} are the % weight loss between room temperature and 800 °C corresponding to the decomposition of the PMAEL and MPTMS and S_{specific} is the specific surface area of the silica gel, 129 m^2/g.

Scheme 1. Synthesis Procedure for Glycopolymers by RAFT Polymerization



Then the glycopolymer grafted silica particles were suspended in dry methanol, added sodium methoxide and stirred for 50 min at room temperature. The suspension was isolated by centrifugation and dialyzed for 2 days with distilled water to obtain the silica gel particles grafted by well-defined lactose-carrying polymer.

Characterization. ^{1}H NMR spectra were recorded on a Varian UNITY-plus 400 spectrometer operated at 400 MHz with $CDCl_3$ or D_2O as a solvent and with the internal solvent peak as a reference.

The molecular weights and polydispersities (PDI) of the glycopolymers were determined with size exclusion chromatography (SEC) equipped with Waters 2414 refractive index detector and Waters 1525 Binary HPLC Pump, using Waters Styragel HT2, HT3, HT4 THF 7.8*300 mm columns. Calibration was based on low-polydispersity Shodex polystyrene standards. THF was used as the eluent at a flow rate of 1.0 mL/min operated at 35 °C.

IR spectra were recorded with a Bio-Rad FTS 135 Fourier transform infrared (FTIR) spectrometer in the range of 3500−500 cm^{-1} using KBr pellets.

Thermogravimetric analysis (TGA) was carried out with NETZSCH TG 209 (Germany) at a heating rate of 10 °C/min in N_2 atmosphere and the temperature range from 0 to 800 °C.

The surface composition and chemical state of silica gel particles were determined by X-ray photoelectron spectroscopy (XPS). The XPS measurements were performed on a PEKIN ELMER PHI 1600 spectrometer using an Mg Kα X-ray source. All binding energies (BE's) were referenced to the C_{1s} hydrocarbon peak at 284.8 eV.

Results and Discussion

RAFT Polymerization of Glycomonomer. The synthesis procedure for glycopolymer is shown in Scheme 1. In the first step, we chose a convenient method to synthesize the glycomonomer. Lactose octaacetate was used as glycosylation donor and reacted with 2-hydroxyethyl methacrylate to give corresponding lactose containing monomer under the catalysis of $BF_3{\cdot}Et_2O$. The mild reaction condition and the good yield after purification attracted us. The glycomonomer obtained in our lab was characterized by ^{1}H NMR and FTIR spectroscopy, as well as mass spectrometry.

The key to controlled RAFT polymerizations is the judicious choice of the couple of monomer/chain transfer agents (CTA). The effectiveness of the chain transfer agents depends on their chain transfer constant which is determined by the nature of the groups X, Z, and R, the monomer, and the polymerization conditions. The structures of X, Z, and R on the RAFT agent play a crucial role in controlling the molecular weight distribution and the rates of polymerization. The most effective reagents

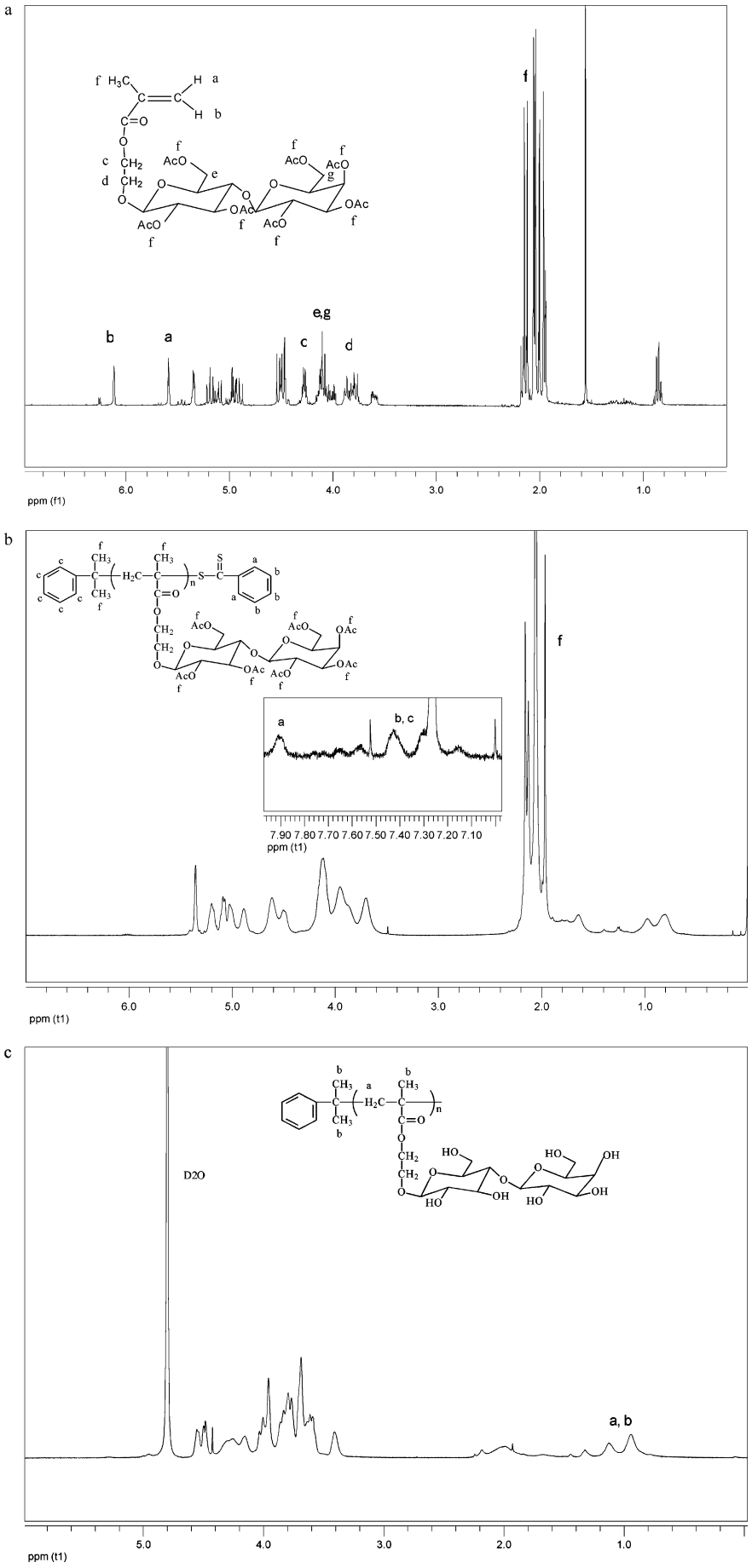


Figure 1. [1]HNMR spectra of (a) glycomonomer, (b) glycopolymer (run 3), and (c) glycopolymer after deprotection.

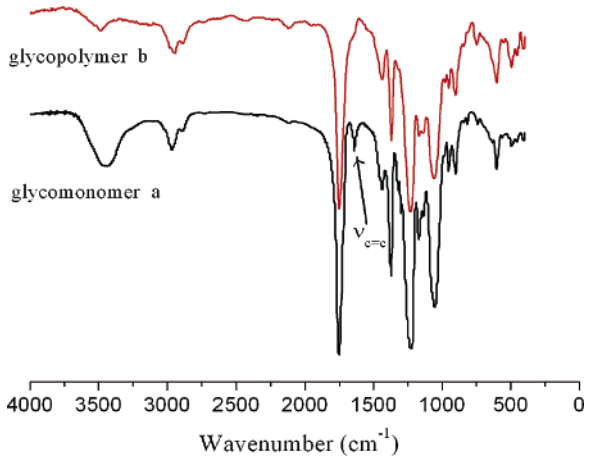


Figure 2. FT-IR spectra of (a) glycomonomer and (b) glycopolymer (run 3).

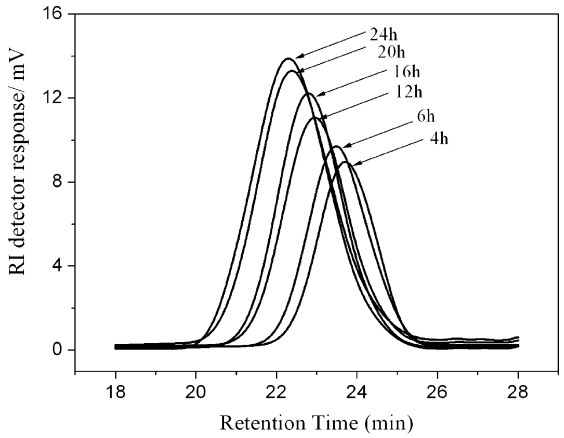


Figure 3. SEC profiles of the products at different reaction time in the synthesis of PMAEL by RAFT at 70 °C with [M]/[CDB]/[I] = 100:2:1.

for RAFT polymerization are dithioester compounds, where X is sulfur, R is a free radical leaving group that is capable of reinitiating polymerization, and Z is a group that modifies the activity of the RAFT agent.[43−45] In our experiment, since there is a huge side group for our lactose containing glycomonomer, we chose $-C(CH_3)_2Ph$ as the R group which had been confirmed that it has a bigger chain transfer constant for MMA[45]. For same reason, we also chose −Ph as the Z group which should have a stronger activation ability[45] to the glycomonomer. Thus, cumyl dithiobenzoate (CDB) was chosen as the CTA in our work. For the synthesis of CDB, we choose bromobenzene and dithiobenzoate acid as starting reagents, which is an effective way to get the target product, but the drawback of this reaction is the lower yield of 10 wt %.

The polymerization of MAEL in $CHCl_3$ was carried out using CDB as the RAFT agent and AIBN as the initiator. These experiments were conducted using different RAFT agent concentrations or reaction times while holding all other parameters constant, and their results are summarized in Table 1. The glycomonomer and glycopolymer were characterized by ^{1}HNMR spectroscopy. Figure 1 shows the ^{1}H NMR spectra of MAEL and PMEAL in $CDCl_3$. All of the saccharide signals can be identified in the region 3.5−5.6 ppm in Figure 1b and easily correlated with those of the starting monomer (Figure 1a). The signals of the double bond protons (6.1, 5.6 ppm) disappeared in Figure 1b. Enlargement of the aromatic area clearly displays the signals from the end-of-chain dithiobenzoyl group, whereas polymer backbone alkyl protons can be seen at 0.8−1.2 ppm. The deprotection of acetyl groups of glycopolymer were treated with CH_3ONa/CH_3OH. For the sake of easy characterization, we carried out the deprotection reaction for glycopolymer under the same reaction conditions as those of glycopolymer-grafted silica particles. Figure 1c shows a typical ^{1} H NMR spectrum after the hydrolysis. The acetyl group protons (around 2 ppm) have disappeared after the hydrolysis, which indicates the deprotection reaction was complete. Figure 2 shows the FTIR spectra of the glycomonomer (Figure 2a) and glycopolymer (Figure 2b). The spectrum in Figure 2a shows the characteristic vibrations ($\nu_{C=O}$ 1754 cm^{-1}) and the aliphatic groups (ν_{CH} = 2963, δCH = 1371 and 1436) of the saccharide. The double bond ($\nu_{C=C}$ = 1638) in MAEL from 2-hydroxyethyl methacrylate showed clearing in the figure, whereas in Figure 2b, no trace of the double bond ($\nu_{C=C}$ = 1638) in PMAEL is present in the spectrum.

The molecular weight and molecular weight distribution of the obtained glycopolymers were measured by SEC and ^{1}H NMR, respectively. The variations in polymer molecular weight and polydispersity as a function of the reaction conditions are shown in Table 1. It can be seen from Table 1, the final molecular weights of glycopolymers from runs 1−5 as measured by SEC were lower somewhat than the theoretical values calculated from the formula

$$M_n = M_m \frac{[M]_0}{[RAFT]_0} C + M_{RAFT}$$

where M_m and M_{RAFT} are the molecular weights of monomer and RAFT agents, respectively, C is the conversion, and $[M]_0$ and $[RAFT]_0$ are the initial concentrations of monomer and RAFT agent. This is most probably due to the inadequacy of polystyrene equivalents to approximate the hydrodynamic volume of PMAEL in THF.[47] The final molecular weights of glycopolymers as determined by ^{1}H NMR also did not agree with the theoretical values since the integral errors, but the two groups of data are very close in variation regularity. The homopolymers show narrow polydispersity in the range of 1.07−1.34, lower than 2.99 for a classical free-radical polymerization under the same reaction conditions. The glycopolymer shifted to the low molecular weight region with the increasing CDB concentration, so that a higher CDB concentration probably caused a dramatic slowing of the overall polymerization rate.[46,47]

Figure 3 shows an overlay of the RI traces from the SEC analysis for the homopolymerization of MAEL at a [M]/[CTA]/[I] ratio of 100/2/1. Aliquots were withdrawn at various time intervals, precipitated in cold diethyl, washed several times, and then analyzed with SEC. It clearly illustrates the observed increase in molecular weight with elution time, and the traces are unimodal and symmetrical. The plots of M_n and M_w/M_n versus conversion are shown in Figure 4a. The molecular weights increase with the increasing conversion, and the measured PDIs are very low and change slightly from an initial value of 1.05 to a final value of 1.27. The higher concentration of CDB can control the polymerization reaction to lower PDIs but also decrease the reaction rate. The $\ln([M]_0/[M])$ vs time curves were linear after 4 h, but the extrapolated lines did not pass through the origin at zero time. The reason can be interpreted as being the hybrid behavior between conventional and living free radical polymerization for this work. For example, in this work, we chose chloroform as the polymerization solvent, since it is a good solvent both for glycomonomer and glycopolymer in the commonly used solvents, but chloro-

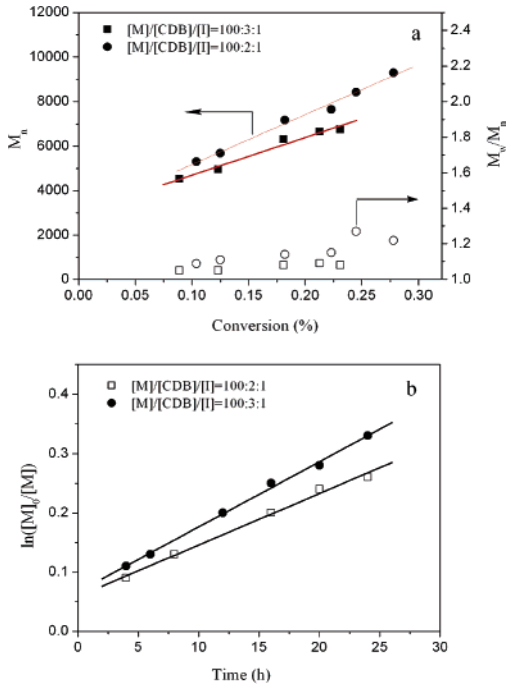
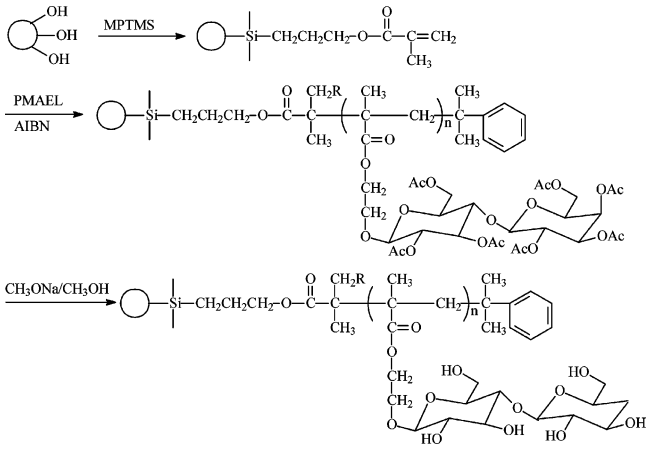


Figure 4. Plots of (a) M_n and M_w/M_n vs conversion and (b) corresponding pseudo first-order rate plots for the homopolymerization of PMAEL by RAFT.

Scheme 2. Schematic Illustration of Grafting Glycopolymers onto Silica Gel Particles



form has a radical transferring tendency to a certain extent. In addition, the result of the use of a polystyrene calibration is maybe another reason.[47,48]

Glycopolymer Grafted onto the MPTMS Modified Silica. The grafting process is depicted in Scheme 2. To carry out the grafting reaction onto the silica particles with the aforementioned glycopolymer, we mixed the PMAEL and the MPTMS-pretreated silica particles in toluene overnight under stirring, and then the initiator (AIBN) was added to the reactor. This is a different method than that reported by Barner et al.'s.[49,50] In their method, they first introduced the active group of RAFT agent on the surfaces of the grafted substrates to form macro-RAFT agents, and then the monomer graft polymerization on the surface took place.

The FTIR spectra of pristine MPTMS-modified and -grafted silica particles are shown in Figure 5. The spectrum of Figure 5b shows characteristic vibrations of the carbonyl ($\nu_{C=O} = 1721$ cm^{-1}), the double bond ($\nu_{C=C} = 1637$ cm^{-1}), and the aliphatic groups ($\nu_{CH} = 2846$, 2895, and 2955 cm^{-1}) of the MPTMS molecule. Compared to MPTMS-modified silica, the spectrum

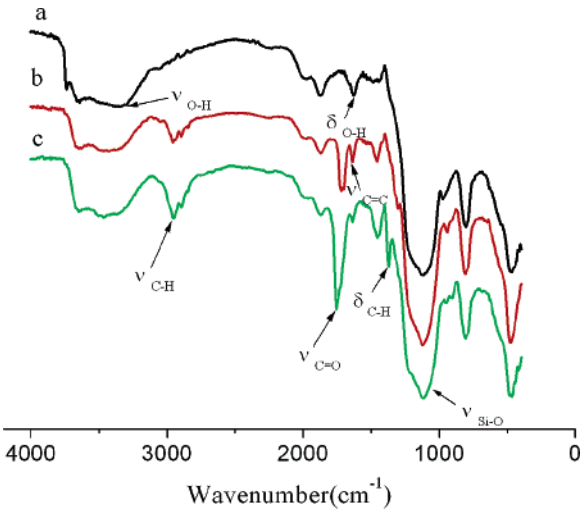


Figure 5. FT-IR spectra of (a) pristine silica; (b) MPTMS modified silica; (c) glycopolymer-grafted silica (Table 2, run 2).

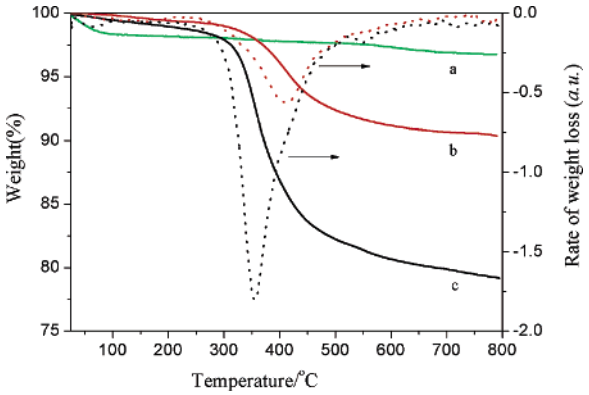


Figure 6. Thermogravimetric analysis (TGA) curves of (a) pristine silica; (b) MPTMS modified silica; (c) glycopolymer-grafted silica.

of Figure 5c gives clear evidence of grafting polymer with the absorption peaks at the aliphatic groups ($\nu_{CH} = 2894-2951$ cm^{-1}, $\delta_{CH} = 1370$ and 1454 cm^{-1}) and the strong absorption bond at the carbonyl ($\nu_{C=O} = 1754$ cm^{-1}) of the glycopolymer. The quantitative determination of MPTMS-modified and -grafted silica particles was determined by TGA analysis. TGA measurements were performed by heating at 10 °C/min from room temperature to 800 °C. The result (Figure 6) shows the weight loss of pristine MPTMS-modified and -grafted silica particles, with corresponding values of 3.3%, 9.61% and 20.83%, and the peak pyrolysis temperatures of MPTMS-modified and -grafted silica particles are 408.4 and 354.1 °C. To illustrate that the glycopolymers were grafted on the silica gel particles, not physical adsorbed on the particles, we took a certain amount of glycopolymer dissolved and adsorbed on the modified silica particles. Drying the physical adsorbed particles and then extracted by the Soxhlet's extraction apparatus using acetone for 24 h, with the glycopolymer grafted sample at the same conditions. The TGA result of the physical adsorbed sample was same as the MPTMS-pretreated silica before adsorption. This indicates that the increased weight of the glycopolymer-grafted particles was not the result of physical adsorption. The PMAELs with different molecular weights grafted onto silica gel particles are shown in Table 2. The data in Table 2 show that we have obtained better grafted numbers of PMAEL with different molecular weights on inorganic substrates, where the efficiency confirms retention of dithioester chain-end functionality as well as quantitative reactivation of

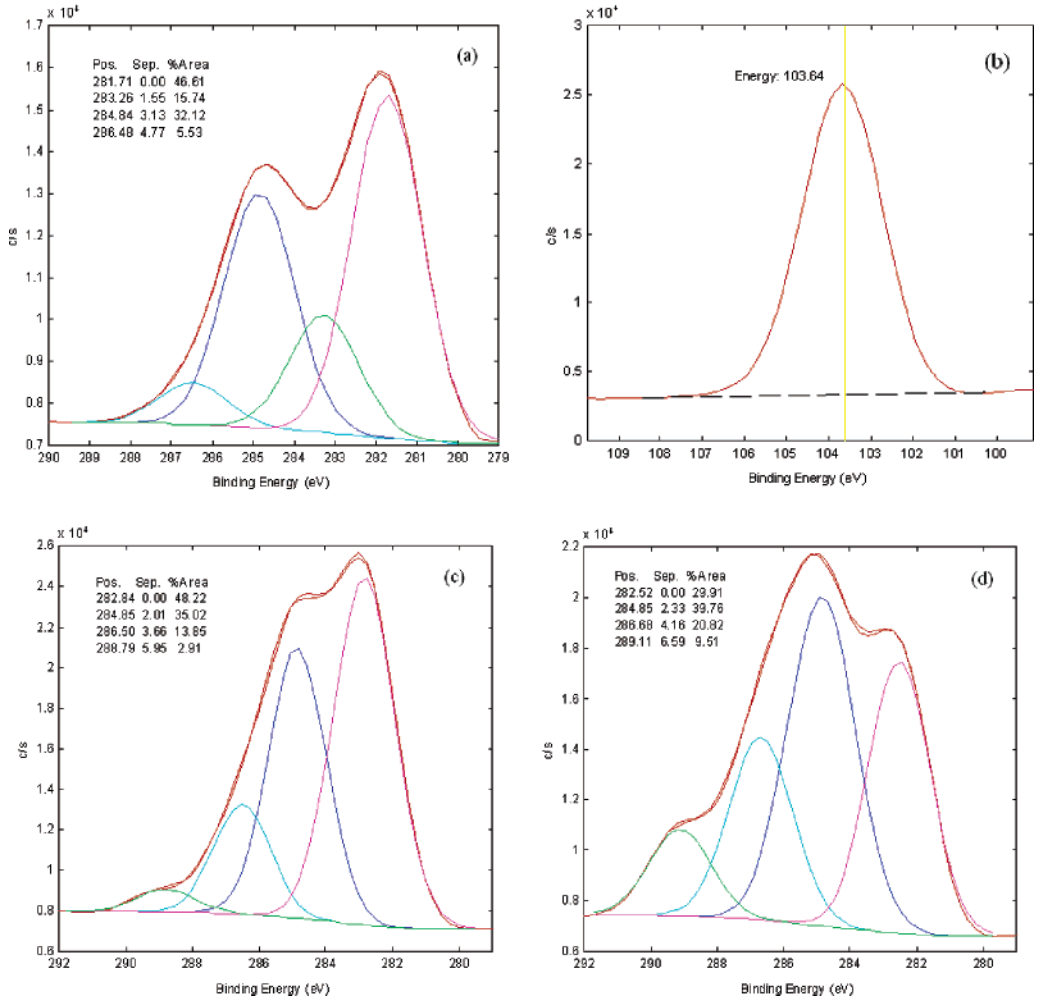


Figure 7. XPS spectra of (a) C_{1s} spectra for the pristine silica particles; (b) Si_{2P} spectra for the surface of pristine silica particles; (c) C_{1s} spectra for MPTMS modified; and (d) C_{1s} spectra for surface grafted silica particles (Table 2, run 2).

Table 2. Summary of Grafted PMAEL on Silica Experiments[a]

	PMAEL		weight loss	estimated graft density
run	sample	M_n	(wt %)	(mg/m^2)
1′	run 6	3856	20.21	1.14
2′	run 2	21365	20.83	1.21
3′	run 4	6747	22.14	1.38

[a] Reaction conditions: modified silica gel 0.2 g; PMAEL 0.25 g; AIBN 0.01 g; reaction time 8 h.

the well-defined glycopolymers. However, grafting reactions are very sensitive to experimental conditions (moisture content, silane chemical composition and functionality, washing procedures and curing treatments, etc.); such sensitivity makes it difficult to ensure reproducible surface coverages.[31]

To better understand the glycopolymer grafted silica particles from another angle, we used XPS to characterize the surface groups of silica particles (seen in Figure 7). Figure 7, panels a and b, shows the C_{1s} and Si_{2p} spectra of the pristine silica particles, respectively. The C_{1s} spectrum of the pristine silica surface was curve-fitted with four peak components, which are probably attributed to the remaining carbon on the pristine silica particles during the preparing procedure. The Si_{2p} spectrum is one peak component at the binding energies (BEs) of about 103.6 eV and attributed to Si−O species. Figure 7, panels c and d, shows the C_{1s} spectra of MPTMS-modified and -grafted silica particles. From Figure 7c, it is clearly seen that the peak component at the BE of about 288.8 eV is attributable to the O−C═O species of MPTMS. After the grafted glycopolymer, there still are four peak components from the Figure 7d. The peak components at binding energies (BEs) of about 289.1, 286.7, 284.8, and 282.5 eV are assigned to the O−C═O, C−O, CH_2, and remaining carbon, but the spectral peak component areas of the O−C═O, C−O, and CH_2 species have clearly increased with respect to the remaining carbon peak, which is attributable to the introduction of the glycopolymer.

Conclusions

In conclusion, RAFT polymerization using CDB as the chain transfer agent proves to be a viable method for the synthesis of well-defined glycopolymers with pendant lactose residues. Then well-defined glycopolymer-coated silica gel particles were prepared by the grafting onto reaction, where end-functionized glycopolymers react with appropriate surface sites. The versatility of the grafting technique, combined with the advantages of controlled polymerization processes, provide a route to elaboration of silica particles with potential applications in materials science, such as novel separation materials for analysis of substances with biological activity.

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