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Aqueous vinyl-insertion polymerization of lactamine-functionalized norbornene by palladium(II) chloride

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Abstract—Polymers of norbornene 4-*O*-(β-D-galactopyranosyl)-β-1′-((±)-*exo*-5-norbornene-2-carboxamido)-1′-deoxy glucitol were synthesized using $PdCl_2$ catalyst in water. Molecular weights were measured by MALDI and GPC with on-line MALLS and differential refractive index (DRI) detection. Polymer molecular weights were found to be dependent upon both the concentration of reagent monomer and catalyst ($PdCl_2$), while polydispersity was found to be independent of monomer and catalyst concentration. Molecular weights and polydispersity index derived from MALDI-MS were in good agreement with the MALLS-GPC method.

1. Introduction

Glycopolymers (synthetic polymer having sugar moieties as pendant groups) are useful in various biotechnologies[1] because they mimic structures in cell membranes.[2] For example, early glycopolymer applications were reported for lectin or antibody binding assays[3] and as matrices for cell culture.[4] More recent reports include applications of glycopolymer conjugates of various enzymes to give immobilized enzymes which show increased temperature stability and enhanced catalytic activity.[5] Glycopolymers have also been synthesized for application in drug design. For example, a polyoxanorbornene polymer bearing glucose pendant groups prevents erythrocyte agglutination at a glucose residue concentration at least 2000-fold lower than that required with the monomeric methyl-α-D-glucopyranoside[6a] and polyacrylamide polymers bearing sialic acid pendant groups inhibited the agglutination of chicken erythrocytes induced by influenza virus.[6b] Sialyl α-(2→3)-lactoside copolyacrylamide with different carbohydrate incorporation are also shown to possess antigenic properties.[6c]

To date, methods used to synthesize well defined glycopolymers[7] rely on conjugation of a polymerizable monomer with the desired sugar followed by free radical polymerization or ring-opening metathesis polymerization (ROMP) either in organic solvent or in water. The polymerizable moiety, which includes styrene,[4] (methyl)acrylate,[8] (methyl)acrylamide,[3a,3f,5] and (oxa)norbornene,[6a,9] and sugar are usually linked by either amide or ester functional groups. Moreover, the methods employed for monomer synthesis are often low yielding because a number of protecting and deprotecting steps are required[3a,10] and free radical polymerization usually gives poor control of polymer molecular weight (M_w) and polydispersity (PDI: 1.8–2.4). For (oxa)norbornene functionalized glycopolymers, well controlled polymer properties of M_w and PDI are obtained by ROMP,[11] but usually protection of monomers with silyl ethers, esters, or acetals is required.[9]

Norbornenes are known to undergo three different polymerization reactions depending upon the catalyst employed: (i) cationic polymerization initiated by $C_2H_5AlCl_2$;[12] (ii) ROMP polymerizations initiated by $Ru^{(III)}$,[13] and (iii) vinyl-insertion polymerizations initiated by $Pd^{(II)}$[14a,b] or $Ti^{(IV)}$.[14c] Although $Pd^{(II)}$-mediated norbornene polymerizations have been studied by several research groups, $Pd^{(II)}$-mediated sugar-functionalized norbornene polymerizations have, to our knowledge, not been reported. Therefore, we wish to report a facile and efficient method for the preparation of a new lactose-functionalized monomer **3** (Fig. 1) and its subsequent vinyl insertion homopolymerization to **4**.

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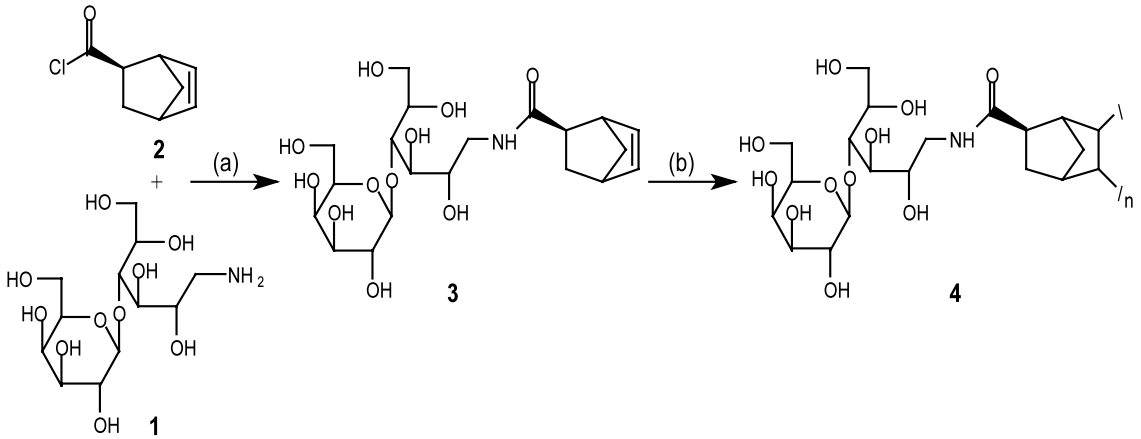

Figure 1. Synthesis of glycomonomer **3**, and its homopolymerization to **4**. (a) 2 M K_2CO_3, CH_2Cl_2, 0°C, 24 h. (b) $PdCl_2$, H_2O.

Our objective was to synthesize monomer **3** from lactamine **1** and *exo*-norbornene carbonyl chloride **2** via a protocol which did not require hydroxyl protection. The *exo*-isomer of norbornene carbonyl chloride was selected over the *endo*-isomer since *endo*-norbornenes typically undergo slow olefin-based polymerization due to steric hindrance.

By taking advantage of the increased reactivity of an acid halide toward a 1°-amine moiety over 1°- or 2°-hydroxyl moieties, the synthesis of **3** from **1** and **2** was accomplished under basic conditions in water at 0°C. Using excess acid chloride (**2**), which was destroyed by aqueous sodium hydroxide, **3** was obtained in nearly quantitative yield and found to be easily soluble in water, DMSO, methanol, and ethanol. The FAB mass spectrum of **3** shows a protonated molecular ion peak at 464.2114 m/z.

Polymerization of monomer **3** was achieved in the presence of $PdCl_2$ in water to give polymer **4**. This polymerization was confirmed by ^1H NMR of the final product, which clearly showed disappearance of the vinylic signals at 6.16–6.22 ppm. The polymerization was carried out with different concentrations of monomer (**3**) and catalyst ($PdCl_2$) giving the various molecular weight polymers presented in Table 1. These polymers were readily soluble in water, DMSO, and methanol, but poorly soluble in ethanol. The differential monomer versus polymer solubility in ethanol provided a convenient opportunity for separating polymer from monomer and other impurities.

In investigating the insertion polymerization of **4**, both monomer and $PdCl_2$ concentration effects were probed to bracket their effects on glycopolymer molecular weight, as determined by MALLS-GPC and MALDI-TOF. The molecular weight of glycopolymer **4** increased (7,831–15,800 Dalton) when the concentration of monomer **3** (22–110 mM) and the concentration of $PdCl_2$ (0.86–4.3 mM) was varied [reaction time (35 h), ratio of monomer ([M]) to $PdCl_2$ ([I]) ([M]/[I] = 25.7), and reaction temperature (ambient) held constant]. The relatively low molecular weights observed in these experiments were not surprising since $Pd^{(II)}$-catalyzed insertion polymerization usually results in low molecular weight polymers due to the rigid structure of the forming polymer.[15] The PDI of **4** remained low and with no substantive change (1.07–1.19; Table 1) under the various conditions.

As illustrated in Table 2, glycopolymer **4** has a slightly higher molecular weight—but not PDI—at decreased [**3**]/[$PdCl_2$] ratio (constant [**3**] = 110 mM, reaction time = 35 h, and temperature = ambient). The low poly-

Table 2. M_w and PDI data for glyopolymer **4** with varying concentrations of **3** and $PdCl_2$

Entry	mM Concentration			LS-GPC	
	[**3**]	[$PdCl_2$]	[**3**]/[$PdCl_2$]	M_w	PDI
1	110	2.2	50	17,355	1.15
2	110	4.3	25.7	15,800	1.12
3	110	11	10	14,310	1.18

Table 1. M_w and PDI data for glyopolymer **4** with varying concentrations of **3** and $PdCl_2$

Entry	mM Concentration		LS-GPC		MALDI-TOF	
	[**3**]	[$PdCl_2$]	M_w	PDI	M_w	PDI
1	22	0.86	7,831	1.19	4,552	1.20
2	44	1.7	11,940	1.10	9,853	1.17
3	80	3.1	15,160	1.07	12,378	1.13
4	110	4.3	15,800	1.12	12,756	1.14

dispersities of these polymers indicate that the $PdCl_2$-catalyzed insertion polymerization in water generally gives living polymers with low chain termination and chain transfer during polymerization.

A total of six glycopolymer samples (**4**) were analyzed by MALDI. Fig. 2 displays positive ion MALDI-TOF mass spectra of glycopolymers from Table 1 (entries 1 and 2). A broad molecular ion distribution was observed ranging between $m/z = 1000$ and $m/z = 20000$. The molecular weight averages and PDIs were deduced directly from the spectrum—weight average $M_w = 9853$ and PDI = 1.172, respectively. The M_w and PDI of glycopolymer **4**, measured by MALDI and MALLS-GPC, are summarized in Tables 1 and 2. Although the molecular weights determined by MALDI are generally lower than those determined by GPC, these values are in good qualitative agreement. Additionally, the data confirm narrow PDI distributions (<1.2) for the synthesized glycopolymer products.

It is important to point out that molecular weights (M_n and M_w) determined by MALDI-MS are in qualitative agreement with chromatographic values only for polymers having narrow molecular weight distributions.[16] MALDI data from polydisperse polymers indicate that high-mass components are generally underrepresented with respect to lower mass oligomer peaks. Such mass discrimination effects are due to a combination of several factors including sample preparation, mass dependent desorption/ionization processes, and mass dependent detection efficiency. Indeed, caution must be exercised in interpreting average molecular weights and molecular weight distribution values deduced from MALDI data, especially for highly polydisperse polymers.

2. Conclusions

Monomer **3**, 4-*O*-(β-D-galactopyranosyl)-β-1′-((±)-*exo*-5-norbornene-2-carbox-amido)-1′-deoxy glucitol, is readily synthesized from lactamine without the requirement for hydroxyl protection/deprotection. This monomer is polymerized by $PdCl_2$ in an aqueous environment and the resulting polymers were characterized by both MALLS-GPC and MALDI mass spectrometry. The results obtained from MALDI and GPC are in good agreement, and provide evidence of a living insertion polymerization mechanism for norbornene polymerization by $PdCl_2$ in water.

3. Experimental

Lactamine **1**[17] and (±)-*exo*-5-norbornene-2-carbonyl chloride **2**[18] were synthesized according to literature protocols.

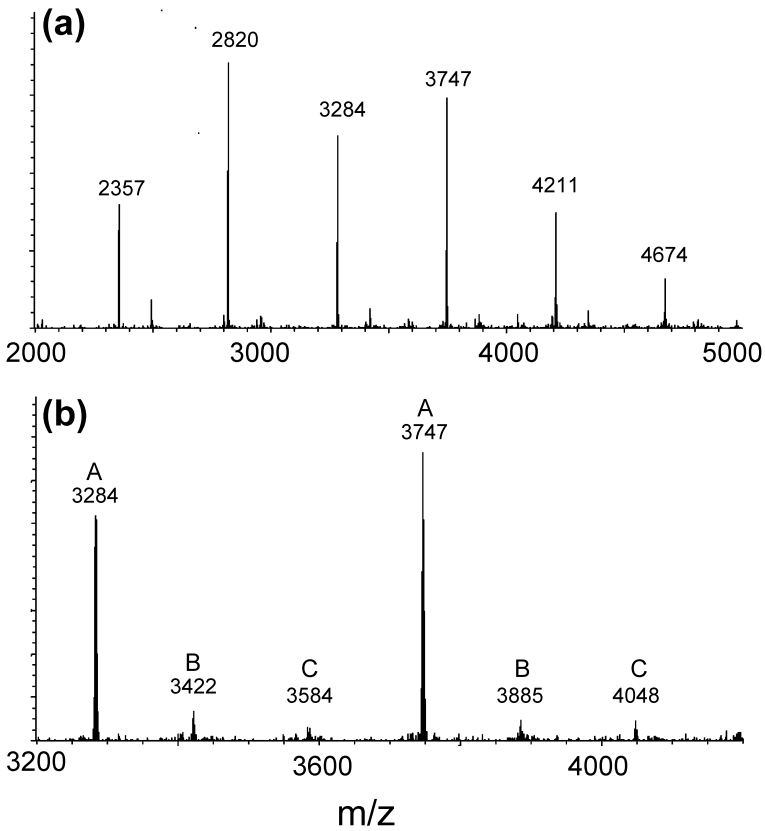

Figure 2. Positive ion low molecular weight range MALDI-TOF mass spectra of glycopolymer **4** from: (a) Table 1, entry 2—2000–5000 m/z range; (b) Table 1, entry 1—3200–4100 m/z range.

3.1. 4-*O*-(β-D-Galactopyranosyl)-β-1′-((±)-*exo*-5-norbornene-2-carboxamido)-1′-deoxy glucitol (3)

Aqueous K_2CO_3 (2 M, 35 mL) and 4-*O*-(β-D-galactopyranosyl)-β-1′-amino-1′-deoxy glucitol [lactamine **1**, 12.8 g, 37.3 mmol] were added to a 250 mL of three-neck round bottom flask and the contents cooled to −5°C. A CH_2Cl_2 (100 mL) solution of (±)-*exo*-5-norbornene-2-carbonyl chloride (7.0 g) was added slowly using a syringe pump so that the internal temperature of the solution never exceeded −2°C. The resulting mixture was stirred at 0°C for 24 h and the crude mixture was concentrated (roto-evaporation) and slowly poured into ethanol to precipitate the salts. Following filtration, the filtrate was passed through a mixed bed resin (BIO-RAD® AG 501-X8), concentrated, and freeze-dried to give an off-white solid in 91% yield (15.6 g): ^{1}H NMR ($CDCl_3$) δ 6.23–6.17 (m, 2H), 4.51 (d, 1H), 4.02–3.51 (m, 13H), 3.41–3.38 (m, 2H), 2.93 (bs, 2H), 2.23–2.18 (m, 1H), 1.77–1.71 (m, 1H), 1.52–1.32 (m, 3H). ^{13}C NMR (dioxane) δ 30.09, 41.27, 41.91, 43.88, 45.94, 46.57, 60.60, 61.96, 68.37, 70.08, 70.15, 70.98, 71.14, 72.49, 74.88, 79.40, 102.97, 136.15, 138.20, 179.28. Calcd for $C_{20}H_{33}NO_{11}$ $(M+H)^+$: m/z 464.2132. Found: 464.2114.

3.2. Polymer synthesis

In ratios delineated in Tables 1 and 2, monomer **3**, $PdCl_2$, and deionized water were placed in a 25 mL of round bottom flask. The reaction mixture was stirred at various temperature for 35 h. The reaction mixture was then concentrated (via freeze-drying) and the polymer was precipitated from ethanol. The dry polymer powder was dissolved in 0.1 M NaN_3 for molecular weight analysis by MALLS-GPC and MALDI analysis.

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