Synthesis of a Well-Defined Glycopolymer by Nitroxide-Controlled Free Radical Polymerization

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ABSTRACT: This is the first report of the synthesis of a well-defined glycopolymer by free radical polymerization. *N*-(*p*-vinylbenzyl)-[*O*-*β*-D-galactopyranosyl-(1→4)]-D-gluconamide (VLA), a styrene derivative with an oligosaccharide moiety, was polymerized in *N*,*N*-dimethylformamide solution at 90 °C by the nitroxide-mediated free radical polymerization technique. Acetylated VLA gave polymers with a molecular weight from about 2000 to 40 000, an M_w/M_n ratio of about 1.1 in all cases, and a conversion of up to about 90%, where M_w and M_n are the weight- and number-average molecular weights. Indispensable for this success were (1) the use of di-*tert*-butyl nitroxide (DBN) rather than other nitroxides such as TEMPO, (2) the acetylation of VLA, and (3) the use of a radical initiator DCP (dicumyl peroxide) as an accelerator. DBN provided a well-controlled polymerization of VLA at 90 °C (VLA becomes unstable at higher temperatures, e.g., >120 °C). The acetylation effectively prevented the chain transfer that leads to dead polymers and broad polydispersities. DCP remarkably accelerated the rate of polymerization (the rate of chain extension), which otherwise was impractically slow, without causing any appreciable broadening of polydispersity.

Introduction

It is recognized today that carbohydrates represent an important class of informational biomolecules.[1] The new term "neoglycoconjugate" is widely used to designate conjugates of carbohydrates to proteins, lipids, polymers, or other solid materials.[2] Neoglycoconjugates are useful not only for basic understandings of protein−carbohydrate interactions but as a practical tool for the isolation and characterization of animal and plant lectins, the separation of cells, and the targeting of drugs.

Furthermore, the recent accumulation of detailed information on saccharide chemistry has urged the preparation of various types of glycopolymers.[3,4] However, the preparation of well-defined glycopolymers have been dealt with only in a few studies, which include the polymerization of a sugar-residue-carrying monomer with the protected hydroxyl groups by cationic polymerization,[5] ring-opening metathesis polymerization,[6] and ring-opening polymerization of *N*-carboxyanhydrides.[7] As far as we know, there has been no previous study in which a well-defined, low-polydispersity glycopolymer has been prepared by a free radical mechanism.

In this work, we have examined the applicability of nitroxide-mediated free radical polymerization to the synthesis of well-defined glycopolymers. The nitroxide approach has opened up a simple and robust route to the synthesis of narrow-polydispersity polymers[8,9] and found unique and important applications in random,[9i,10,11] block,[9i,12] and graft[13] copolymerization, suspension[8b] and emulsion[14] polymerization, aqueous solution polymerization,[15] and so forth. Effective initiating systems have been developed and applied.[9f−h,9j,16] The mechanism and kinetics of nitroxide-mediated polymerization, mainly of styrene systems, have also been explored in detail.[8h,17,18] The system studied here (the polymerization of a lactose-related oligosaccharide-carrying styrene derivative in *N*,*N*-dimethylformamide) is distinguished from those previously studied in that the monomer has a bulky sugar residue as a pendent group, the sugar residue has many hydroxyl groups (before protection), the thermal (spontaneous) polymerization of this monomer is unlikely or at least insignificant compared with that of styrene, and the solvent is a highly polar one. In this regard, this system is very interesting to study with respect to the availability of well-defined polymers as well as the kinetics of polymerization. It will be shown below that the nitroxide method is able to provide narrow-polydispersity, high-molecular weight glycopolymers with careful and unique design of experimental conditions.

Experimental Section

Materials. The sugar-carrying styrene derivative, *N*-(*p*-vinylbenzyl)-[*O*-*β*-D-galactopyranosyl-(1→4)]-D-gluconamide (VLA, Figure 1a),[19] was provided by NeTech. Commercially obtained styrene (Wako Pure Chemicals, Osaka, Japan) and benzoyl peroxide (BPO, Nacalai Tesque, Kyoto, Japan) were purified by the standard methods described elsewhere.[20,21] Di-

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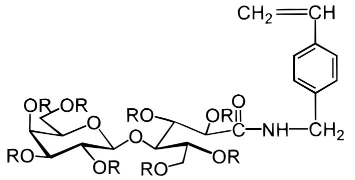
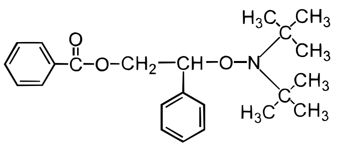


(a) VLA (R = H) (b) Ac-VLA (R = acetyl)



(c) BS-DBN

Figure 1. Chemical structures of (a) VLA, (b) Ac-VLA, and (c) BS-DBN.

tert-butyl nitroxide (DBN) was purchased from Aldrich and used without further purification. Dicumyl peroxide (DCP, Nacalai Tesque) was recrystallized from a chloroform/methanol mixture before use. *N*,*N*-Dimethylformamide (DMF) was dried over molecular sieves (4 Å) for several days before use. Other reagents were commercially obtained.

Preparation of *N*-(*p*-Vinylbenzyl)-2,3,5,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-D-gluconamide (Ac-VLA, Figure 1b). To a cold suspension of VLA (10 g) in dry pyridine (100 mL) with 4-(dimethylamino)-pyridine (100 mg) was added at 0 °C acetic anhydride (64 mL). The mixture was gradually warmed to room temperature and magnetically stirred in the dark for 2 days. The thus obtained clear solution was concentrated in vacuo, and the residue was diluted with chloroform (300 mL). The organic solution was washed twice with 1 N H_2SO_4 (2 × 200 mL), twice with saturated $NaHCO_3$ (2 × 200 mL), then twice with saturated brine (2 × 200 mL), and finally with pure water (200 mL). Drying over Na_2SO_4, filtration, and evaporation of the solvent produced a white solid, which was recrystallized from a mixture of ethanol and diethyl ether (15.1 g, 88%): ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6, 20.7, 20.8, 20.9, and 20.9 ($\mathit{C}H_3COO$), 43.0 (benzyl methylene), 60.9 (C-6), 61.6 (C′-6), 66.8 (C′-4), 77.2 (C-4), 101.7 (C′-1), 66.8, 69.0, 69.2, 69.8, 71.0, and 71.7 (the remaining pyranose carbons), 114.0 ($\mathit{C}H_2{=}CH-$), 126.4 and 127.7 {phenyl (*ipso*)}, 136.0 and 136.9 {phenyl (*meta* and *ortho*)}, 136.9 ($CH_2{=}\mathit{C}H-$) 166.8 (CONH), 169.0, 169.3, 169.5, 169.8, 169.9, and 170.2 ($CH_3\mathit{C}OO$). Anal. Calcd for $C_{37}H_{47}NO_{19}{\cdot}H_2O$: C, 53.68; H, 5.98; N, 1.69. Found: C, 53.98; H, 5.86; N, 1.70.

Preparation of 2-(Benzoyloxy)-1-(phenylethyl)-DBN (BS-DBN, Figure 1c). Freshly distilled styrene (100 mL), BPO (5.2 g), and DBN (4.1 g) were charged in a round-bottomed flask, degassed, and sealed off under vacuum. The mixture was incubated at 90 °C for 3 h. After unreacted styrene was evacuated off, the crude product was purified by flash chromatography on a column of silica gel with a 9:1 hexane/ethyl acetate mixture eluent and then with a 9:1 chloroform/hexane mixture eluent to yield a pale yellow oil as a final product (1.5 g): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.11 (s, 9H, *tert*-butyl group of DBN unit), 1.33 (s, 9H, *tert*-butyl group of DBN unit), 4.55 (q, 1H, C*H*H), 4.87 (q, 1H, CH*H*), 5.07 (q, 1H, C*H*), 7.21−7.53 (m, 8H, Ar*H*), 7.89 (d, 2H, ortho protons of benzoyl group); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.6 ($C(\mathit{C}H_3)_3$), 62.2 and 62.6 ($\mathit{C}(CH_3)_3$), 66.4 ($\mathit{C}H_2$), 83.8 ($\mathit{C}H$), 127.4, 127.6, 127.9, 128.1, 129.4, 130.0, 132.6, and 140.3 (phenyl), 166.0 (C=O). Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.75; H, 8.47, N, 3.79. Found: C, 75.00; H, 8.42; N, 3.76.

Gel Permeation Chromatography (GPC). The GPC measurements using DMF containing 5 vol % of water as eluent were made on a Tosoh GPC-8010 high-speed liquid chromatograph equipped with Tosoh gel columns G2000H and G4000H. The temperature was maintained at 40 °C. The column system was calibrated with standard poly(ethylene glycol)s (PEGs). Sample detection and quantification were made with a Tosoh refractive-index detector RI-8010. This system was used for the characterization of poly(VLA) (PVLA).

The GPC measurements using tetrahydrofuran (THF) as eluent were made on a Tosoh GPC-8020 high-speed liquid chromatograph equipped with Tosoh gel columns G2500H, G3000H, and G4000H. The temperature was maintained at 40 °C. The column system was calibrated with standard polystyrenes (PSs). Sample detection and quantification were made with a Tosoh refractive-index detector RI-8020. This system was used for the characterization of poly(Ac-VLA).

General Procedure for Polymerization of VLA or Ac-VLA. A solution of VLA (25 wt %) or Ac-VLA (60 wt %) in DMF containing a prescribed concentration of BS-DBN and DCP was charged in a Pyrex tube, degassed, and sealed off under vacuum. The tube was placed in a temperature-controlled oil bath for a prescribed time, quenched to room temperature, and subjected to a GPC analysis after appropriate dilution with DMF for the VLA system or with THF for the Ac-VLA system. The monomer conversion was estimated by comparing the GPC peak area of the produced polymers with that of a model polymer, poly(VLA) or poly(Ac-VLA), dissolved in DMF or THF, respectively, at a known concentration.

Results and Discussion

It has been established that the nitroxide-mediated polymerization of styrene is set under control by the dissociation−combination reversible reaction between the alkoxyamine P−X and the polymer and nitroxyl radicals P* and X*:

$$\mathrm{P{-}X} \underset{k_c}{\overset{k_d}{\rightleftarrows}} \mathrm{X^*} + \mathrm{P^*} \circlearrowright^{\,k_p}_{\,(\mathrm{M})} \qquad (1)$$

where k_d and k_c are the dissociation and combination rate constants and, in the presence of the monomer M, P* undergoes propagation with a velocity k_p[M] until it is blocked by X* to form the dormant species P−X. The polymerization rate, $R_p = k_p[P^*][M]$, in typical styrene/nitroxide systems was found to be essentially independent of alkoxyamine concentration.[9h,17a,b] This means that the stationary concentration of P* is determined, as in the conventional (alkoxyamine-free) system, by the balance of initiation and termination reactions, where initiation may occur either by thermal means (styrene undergoes significant thermal initiation at high temperatures, e.g., >100 °C) or by the decomposition of an initiator like BPO and DCP. Details of elementary reactions, including values of k_d and k_c, are now available for the styrene/TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) system.[18] The VLA/DBN and Ac-VLA/DBN systems studied here are different in many aspects from the styrene/TEMPO system, as will be described below.

It is also noted that the polymerization of VLA with a TEMPO mediator did not work satisfactorily, presumably due to the partial decomposition of the monomer at the high temperatures (>120 °C) where the k_d of the VLA/TEMPO system is expected to be sufficiently large. Actually, the system was observed to become brownish after a prolonged polymerization at 125 °C. Reported model experiments[22] and molecular orbital calculations[22,23] suggest that DBN will give a larger k_d than TEMPO when other conditions are the same. This encouraged us to carry out VLA and Ac-VLA polymerizations at lower temperatures (90−105 °C) using DBN as a mediator. At these temperatures, no decomposition

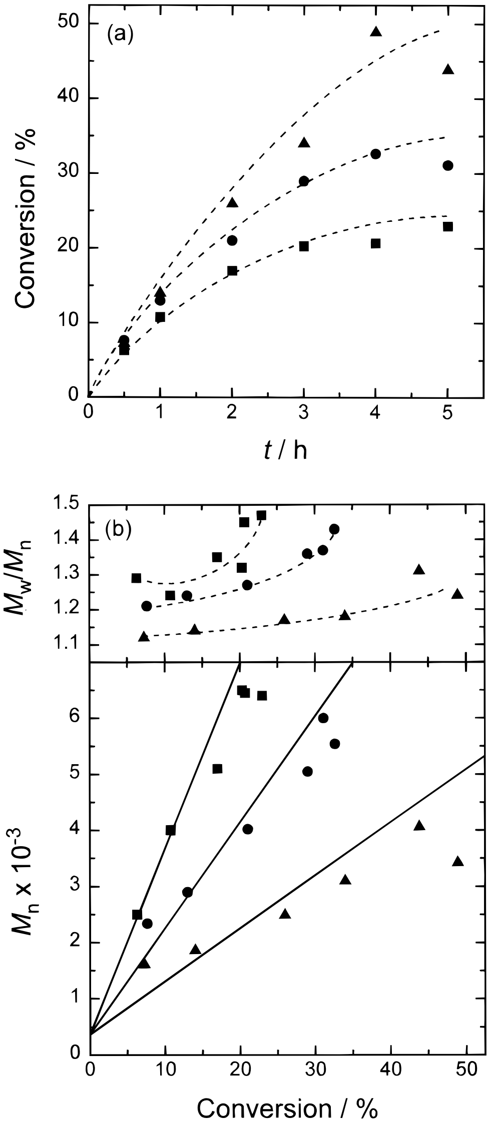


Figure 2. (a) Time−conversion plots for the polymerization of VLA and (b) values of M_n and M_w/M_n (estimated by PEG-calibrated GPC) as a function of monomer conversion. Solution polymerization in DMF with different BS-DBN concentrations at 105 °C: [M]/[BS-DBN] = 70/1 (■), 40/1 (●), and 20/1 (▲). The full lines in Figure 2b represent the theoretical predictions.

of the monomers was detectable in the time scale of the polymerizations.

System with VLA and BS-DBN. Figure 2a shows the time−conversion plot for the VLA polymerization in DMF at 105 °C with various concentrations of the alkoxyamine BS-DBN. Clearly, the rate of polymerization depends on [BS-DBN]: the conversion at a fixed polymerization time increases with increasing [BS-DBN]. However, the conversion seems to level off after some time that depends on [BS-DBN]. We also note that a polymerization with [BS-DBN] lower than about 1/100 of [VLA] gave no polymer even after 5 h of polymerization (data not shown) and that no thermal polymerization was detectable for the pure VLA (in DMF). The number-average molecular weight M_n and the polydispersity ratio M_w/M_n of the produced polymers are given in Figure 2b. The M_n increases nearly linearly with conversion, and it reasonably compares to the theoretical prediction calculated from the conversion/[BS-DBN] ratio (the solid lines in the figure), even though this comparison cannot be a rigorous one because of the use of the PEG-calibrated GPC. The M_w/M_n ratio increases with an increase in conversion when [BS-DBN] is fixed and with a decrease in [BS-DBN] when conversion is fixed.

One of the main reasons for the observed differences of the VLA system from the styrene and *p-tert*-butoxystyrene systems must be the absence (or insignificance) of thermal initiation in the VLA system. The radical concentrations in a nitroxide-mediated system may generally be described by

$$d[P^*]/dt = k_d[P-X] - k_c[P^*][X^*] + R_i - k_t[P^*]^2 \quad (2)$$

$$d[X^*]/dt = k_d[P-X] - k_c[P^*][X^*] \quad (3)$$

The k_d and k_c terms in eqs 2 and 3 come from the reversible reaction in eq 1, R_i is the initiation rate, and k_t is the rate constant of termination. When $R_i > 0$, [P*] and [X*] eventually reach the stationary values that are analytically obtained by solving the two equations $d[P^*]/dt = d[X^*]/dt = 0$. When $R_i = 0$, eqs 2 and 3 cannot be analytically solved rigorously. A computer simulation has shown that during an initial short time (typically, on the order of tens of nanoseconds), [P*] sharply increases and then begins to decrease, passing through a broad maximum, while [X*] increases sharply at first and then more slowly.[17c,24] These initial behaviors are virtually independent of R_i. When $R_i \neq 0$, [P*] and [X*] gradually approach the mentioned stationary values. When $R_i = 0$, [P*] and [X*] monotonically decrease and increase, respectively, reaching no stationary values. Fischer[25] noted for the first time that [P*] and [X*] in this time region show simple power-law behavior. In fact, eqs 2 and 3 (with $R_i = 0$) can be easily solved under the approximations that $[P-X] = [P-X]_0 - [X^*] \simeq [P-X]_0 \gg [X^*] \gg [P^*]$ and that $d[X^*]/dt \simeq 0$, which are usually valid for the main part of such a polymerization process of practical interest. With a modification of the Fischer model, in which it was assumed that $k_c = k_t$, we obtained

$$[P^*] = (K[P-X]_0/3k_t)^{1/3}t^{-1/3} \quad (4)$$

$$[X^*] = (3k_tK^2[P-X]_0^{\ 2})^{1/3}t^{1/3} \quad (5)$$

where $K = k_d/k_c$. Integration of the relation $-d[M]/dt = k_p[P^*][M]$ with eq 4 leads to

$$\ln([M]_0/[M]) = (3k_p/2)(K[P-X]_0/3k_t)^{1/3}t^{2/3} \quad (6)$$

Thus the logarithmic conversion index $\ln([M]_0/[M])$ in an initiation-free system is expected to show the characteristic 2/3-order dependence on time and 1/3-order dependence on the mediator concentration $[P-X]_0$.[25] This relation should be compared to the stationary-state equation valid for systems with nonzero R_i

$$\ln([M]_0/[M]) = (k_p/k_t^{\ 1/2})R_i^{\ 1/2}t \quad (7)$$

which is first order in t and zeroth order in $[P-X]_0$.[17a,b,18c]

Figure 3 shows the plot of $r^{-1/3}\ln([M]_0/[M])$ vs $t^{2/3}$ for the same data as in Figure 2a, where r $(=[P-X]_0/[M]_0)$ is approximately proportional to $[P-X]_0$ because the volume fraction of P−X is nearly zero in all studied cases (hence $[M]_0$ is nearly constant). For the first 2 h or so ($t^{2/3} < 1.6$), all the data points seem to form a common

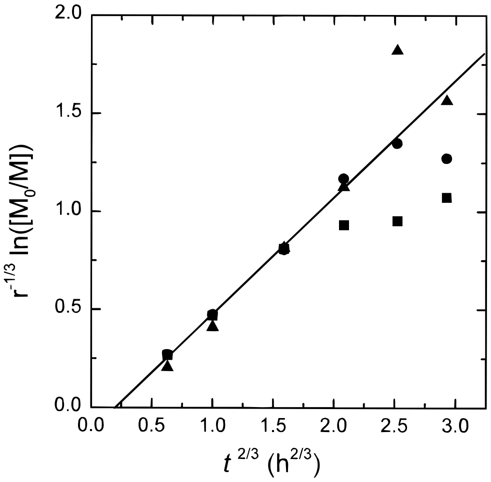


Figure 3. Plot of $r^{-1/3}\ln([M]_0/[M])$ vs $t^{2/3}$ for the VLA/BS-DBN system at 105 °C: [M]/[BS-DBN] = 70/1 (■), 40/1 (●), and 20/1 (▲).

straight line, as eq 6 predicts. For larger t, downward deviations from the straight line become evident for the runs with $r = 1/70$ and $1/40$, while the 1/20 run is still representable by the straight line. This suggests the presence of side reactions. A possible one may be the decomposition of the active chain end through the β-proton abstraction by the nitroxyl radical,[17c,26] forming a terminally unsubstituted PVLA and a hydroxyamine. If this is a main side reaction, however, the nonlinear behavior in Figure 3 should be independent of r, since the β-proton abstraction is a quasi-first-order reaction that is proportional to the frequency of dissociation (hence of combination) of the alkoxyamine. This conflicts with the experiments. Even though direct evidence is lacking at the moment, it is likely that the retardative (or degradative) transfer to the hydroxyl groups of VLA is responsible for the observed slowing down of the polymerization rate, which becomes more serious with a decrease in $[P-X]_0$ and hence an increase in chain length. This interpretation is supported by the observation that there seems to be a maximum M_n attainable in this system, which is about 6000, and that the M_w/M_n ratio increases with increasing M_n (Figure 2b).

System with VLA, BS-DBN, and DCP. To increase polymerization rate and chain length, we have attempted to add the radical initiator DCP to the VLA/BS-DBN system. In the styrene/nitroxide system, such an initiator was found to work very effectively for the mentioned purpose.[18c,27] Figure 4a shows the time–conversion plot, showing the effect of DCP. Clearly, the conversion at a fixed polymerization time increases with increasing [DCP]. The M_n increases approximately linearly with conversion (Figure 4b), indicating that the number of polymer chains does not significantly change despite the addition of DCP. However, again, the conversion showed a leveling-off trend (Figure 4a), and the M_n did not become much larger than about 7000 with the M_w/M_n value increasing with increasing M_n (Figure 4b). Thus, DCP plays the expected role of enhancing the stationary value of [P*] or R_p without a significant increase of the number of polymer chains, but it fails to increase M_n or conversion. This can be understood again in terms of a retardative (or degradative) transfer.

System with Ac-VLA, BS-DBN, and DCP. Since the transfer to the hydroxyl groups of VLA is likely to be the main cause for the undesirable features of the VLA systems, namely the relatively low M_n and conversion and the broadening of polydispersity with increasing M_n, we carried out the polymerization of the protected monomer Ac-VLA. Figure 5 shows the GPC curves of poly(Ac-VLA) synthesized with BS-DBN in the presence of a small amount of DCP. It can be seen that the molecular weight increases with increasing reaction time, and the M_w/M_n ratio remains remarkably small in all cases. Figure 6a shows the time–conversion first-order plot for the polymerization in the presence of a fixed amount of BS-DBN and varying concentration of DCP. The plots are linear, indicating that the radical concentration stays constant during the polymerization. Remarkably, a 90% conversion has been reached in 5 h with the highest concentration of DCP studied here. There seems to be a short induction period in the Ac-VLA/BS-DBN system (Figure 6a), the reason for which is unclear at this moment. Figure 6b shows that the M_n of the produced polymer linearly increases with

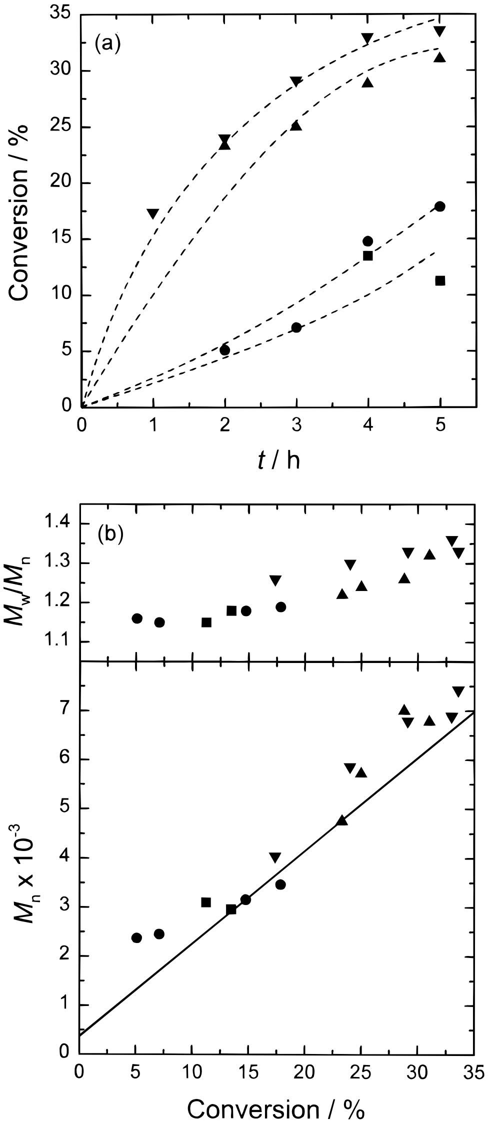


Figure 4. (a) Time–conversion plots for the polymerization of VLA and (b) values of M_n and M_w/M_n (estimated by PEG-calibrated GPC) as a function of monomer conversion. Solution polymerization in DMF with different DCP concentrations at 90 °C: [M]/[BS-DBN]/[DCP] = 40/1/6 (▼), 40/1/3 (▲), 40/1/0.3 (●), and 40/1/0 (■). The full line in Figure 4b represents the theoretical prediction.

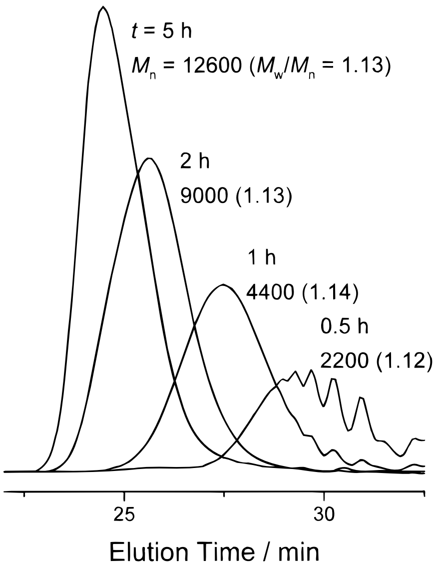


Figure 5. GPC curves for the polymerization of Ac-VLA in DMF at 90 °C: [M]/[BS-DBN]/[DCP] = 40/1/2.2.

conversion, independent of DCP concentration, and the M_w/M_n ratio stays around 1.1 at all conversions. Particularly noteworthy is the essential role played by the radical initiator.[17b,18c,27] It increases R_p (by more than 15 times when [DCP]/[BS-DBN] = 2.2) without causing appreciable broadening of polydispersity. On the basis of the reported decomposition rate constant of DCP in cumene,[28] the cumulative number of the polymer molecules originating from the decomposition of DCP is estimated to be less than about 5% of those of the BS-DBN origin even for the run with the highest DCP concentration ([DCP]/[BS-DBN] = 2.2) and the longest polymerization time (5 h). Obviously, the R_p of the DCP-free system is impractically too small (Figure 6a).

The M_n values obtained by GPC were significantly smaller than those calculated from the conversion/alkoxyamine ratios. Apparently, the PS-calibrated GPC does not work accurately for this particular system. Thus, we have carried out an ultracentrifuge sedimentation equilibrium (UCSE) analysis with one of the samples. Its M_w was found to be 40 000, about 2.7 times as large as the GPC value but reasonably close to the theoretical value. These results show that the protection of the hydroxyl groups of the monomer suppresses side reactions to provide the polymerization system with better "living" characters. Since the deacetylation of poly(Ac-VLA) can be achieved easily and quantitatively by treatment with hydrazine in DMF solution,[29] the proposed polymerization procedure will open up a new and practical route to the preparation of well-defined glycopolymers.

Conclusions

The free radical polymerization of VLA in DMF in the presence of a BS-DBN adduct proceeds in a "living" fashion under limited conditions, giving relatively narrow polydispersity PVLA. However, the monomer conversion does not become high enough, and polymers with a high enough molecular weight cannot be obtained. The polymerization of the monomer with protected hydroxyl groups (Ac-VLA) in the presence of BS-DBN as mediator and DCP as accelerator proceeds in a better-defined "living" fashion, giving higher-molecular weight, narrower polydispersity polymers with a high conversion. Thus this work has broadened the practical synthetic route to well-defined glycopolymers and the applicability of the nitroxide-mediated "living" radical polymerization. The "living" radical polymerization of Ac-VLA will also find important applications in, e.g., the preparation of amphiphilic block and graft copolymers. This will be the topic of a forthcoming publication.

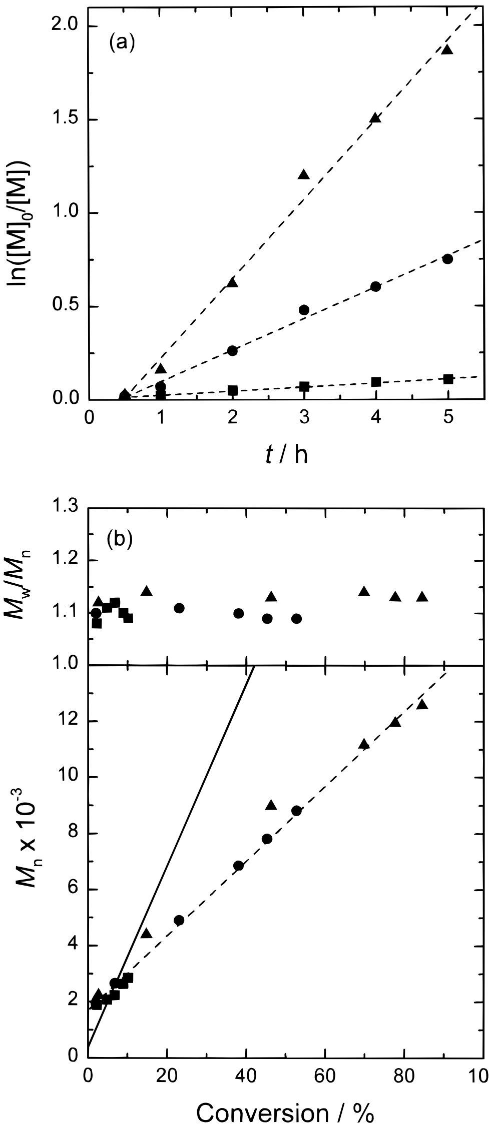


Figure 6. (a) Time−conversion plots for the polymerization of Ac-VLA and (b) values of M_n and M_w/M_n (estimated by PS-calibrated GPC) as a function of monomer conversion. Solution polymerization in DMF with different DCP concentrations at 90 °C: [M]/[BS-DBN]/[DCP] = 40/1/2.2 (▲), 40/1/1.1 (●), and 40/1/0 (■). The full line in Figure 6b represents the theoretical prediction.

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