Anionic Living Polymerization of Functional Monomers. Precise Synthesis of Various Functionalized Polystyrenes with Monosaccharide Residues by Anionic Living Polymerization and Living Functionalization Reaction

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SUMMARY: Precise syntheses of monosaccharide-functionalized polystyrenes with various molecular architectures are described. The polymers synthesized here are well-defined monosaccharide-functionalized polystyrenes, block copolymers, and polystyrenes functionalized with one or more (up to four) glucose residues at the chain ends and in chains which are synthesized by anionic living polymerization of styrenes substituted with acetal-protected monosaccharides and living functionalization reaction using a 1,1-diphenylethene substituted with two acetal-protected glucofuranoses.

Introduction

Anionic living polymerization of styrene and 1,3-dienes is undoubtedly one of the best established methods to realize precise polymer synthesis.[1] It permits synthesizing various polymers with predictable molecular weights and narrow molecular weight distributions as well as block copolymers and, in particular, shaped polymers with well-defined architectures. However, a difficulty generally arises in this method when one attempts to synthesize such polymers with useful functional groups, because the initiation and propagation reactions are not tolerant of these functional groups. In order to overcome this difficulty, we have been developing, since 1982, a general and versatile methodology which involves protection and anionic living polymerization of functionalized styrenes and dienes, followed by removal of the protecting groups from the resulting polymers.[2-4]

As part of our work to investigate more the generality and versatility of our methodology, we here pay attention to monosaccharides as functional groups or as such since they exhibit unique and interesting properties originating from multiplicity of hydroxy groups and chiral centers. If styrenes functionalized with monosaccharides are applied in our methodology, we can rationally design and precisely synthesize various monosaccharide-functionalized polystyrenes with well-defined architectures. These polymers should have a variety of potential applications from viewpoints of their solubility in water, strong hydrophilicity, hydrogen-bonding ability, biodegradability, chiral recognition, and pharmacological activity.[5,6] Moreover, their well-defined and precisely controlled structures make them advanced materials for elucidation and fundamental understanding how monosaccharide residues influence polymer functions, properties, and behavior.

In this paper, we report on the anionic living polymerization of several new styrenes substituted with monosaccharides whose hydroxy groups are protected by acetalization. We also report on the

 CCC 1022-1360/00/$ 17.50+.50/0

synthesis of well-defined polystyrenes functionalized with one or more (up to four) monosaccharide residues either at the chain ends or in desired positions in the chains by living functionalization reaction which combines anionic living polystyrenes and specially designed terminators containing the same acetal-protected monosaccharides.

Experimental part

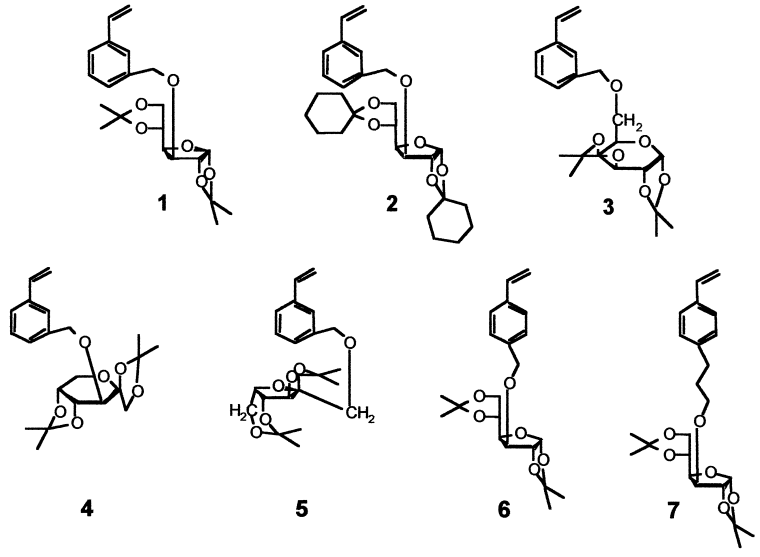
Experimental details were described in our previous papers.[7-9]

Monomer **7** was synthesized in 57 % yield by the reaction of 4-(3-bromopropyl)styrene with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in 50 % NaOH-CH_2Cl_2 in the presence of $Bu_4N^+HSO_4^-$ at 40 °C for 4 days.

^{1}H NMR ($CDCl_3$): δ 7.32, and 7.15 (2d, 4H, J = 8.10 Hz, Ar), 6.69 (dd, 1H, -CH=), 5.55 (d, 1H, J = 5.10 Hz, α-pyranose H-1), 5.70, and 5.19 (2d, 2H, J = 17.7 and 11.1 Hz, CH_2=), 4.63 - 3.48 (m, 8H, H-2 - H-6, and $CH_2CH_2CH_2O$), 2.68 (t, 2H, J = 7.50 Hz, $ArCH_2$), 1.89 (m, 2H, $CH_2CH_2CH_2$), 1.54 1.46, 1.35, and 1.34 (four singlets, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 141.93, 135.24, 128.78, and 126.24 (Ar), 136.76 (-CH=), 112.99 (CH_2=), 109.28, and 108.61 (>$C(O)_2$), 96.45 (C-1), 77.30, 71.25, 70.48, 69.38, and 66.72 (C-2 - C-6), 70.71 ($CH_2CH_2CH_2O$), 32.02 ($ArCH_2$), 31.24 ($CH_2CH_2CH_2$), 26.18, 26.08, 25.04, and 24.52 (CH_3).

Results and discussion

Anionic Living Polymerization of Styrene Derivatives Substituted with Acetal-Protected Monosaccharide Residues. We previously attempted the anionic polymerization of styrenes **1** – **5**, meta-substituted with monosaccharide residues, whose hydroxy groups were protected by acetalization:



The monosaccharides employed were D-glucose, D-galactose, D-fructose, and L-sorbose. Typical results of polymerization of **1** - **5** in THF at –78 °C with *s*-BuLi as initiator are summarized in Table 1.

Table 1. Anionic polymerization of monomers **1-5** in THF at –78 °C for 30 min[a)]

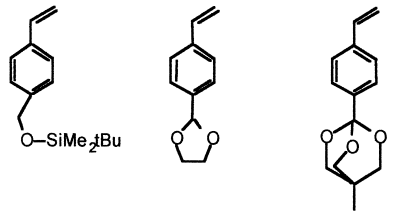
Monomer	*s*-BuLi mmol	Monomer mmol	$M_n \times 10^{-3}$ calculated[b)]	observed[d)]	M_w/M_n[d)]
1	0.0787	2.29	11	9.3	1.07
1	0.0364	3.00	31	33	1.08
2	0.0886	1.98	10	9.5	1.05
3	0.0715	2.08	11	9.4	1.08
4	0.0760	2.01	10	8.5	1.07
5	0.0377	2.50	25	20	1.07

[a)] The yields of polymers were quantitative; [b)] M_n(calcd) = [monomer] x $MW_{monomer}$ / [initiator] + $MW_{initiator}$; [c)] For M_n(calcd) $\leq 2 \times 10^4$, from the H^1 NMR area ratio of signals corresponding to the main chain and initiator fragments; for M_n(calcd) $> 2 \times 10^4$ from M_w (SLS) and M_w/M_n (SEC); [d)] from SEC calibration using polystyrene standards in THF solution.

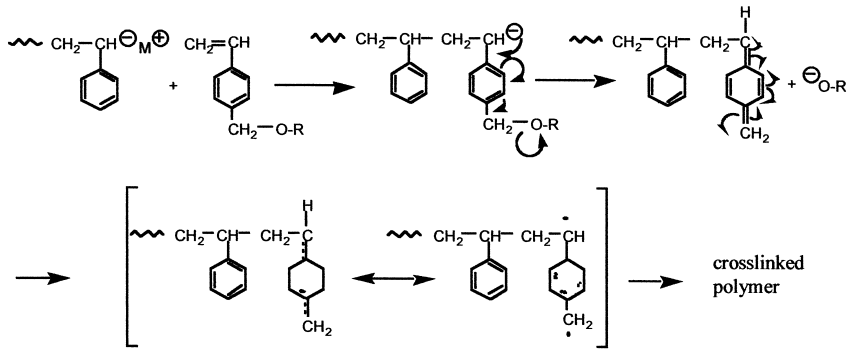
In each polymerization, a reddish orange color characteristic of polystyrene anion was always observed. The yields of polymers were quantitative in all cases.

All polymers had symmetrical unimodal SEC peaks with narrow distributions, M_w/M_n values being less than 1.1. As can be seen in Table 1, there is a fair agreement between M_n values observed and calculated from the [monomer]/[initiator] ratio. These results and the appearance of the reddish orange color strongly indicate the living character of the anionic polymerization of **1-5**. Accordingly, their acetal-protected functionalities and monosaccharide frameworks are stable under the conditions in THF at –78 °C for 0.5 h. Novel AB and BA types block copolymers of **1** with styrene were successfully synthesized by adding successively **1** and styrene in this order or *vice versa*. Their well-controlled structures were supported by SEC and NMR analyses of the resulting polymers.

By contrast, attempts to polymerize the para-substituted styrene **6** always failed under exactly the same conditions with either *s*-BuLi or potassium naphthalenide. An anomalous reaction behavior of **6** was also observed in the block copolymerization with difunctional polystyrene-potassium. Instead of the expected block copolymer, an insoluble gelatinous material was obtained, along with a small amount of THF-soluble polymer with a very broad molecular weight distribution. Most **6** was recovered from the polymerization mixture. IR analysis of the insoluble (probably crosslinked) material indicated that it consisted of polystyrene containing a few units of **6**. This behavior of **6** toward initiators and difunctional polystyrylanion is very similar to that of the functionalized styrenes with benzyl ether moieties previously reported by our group[10-12]:



In order to explain such reaction behavior of **6**, we have proposed the reaction pathway as shown in Scheme 1.



Scheme 1

The carbanion formed at the chain end underwent 1,6-elimination to generate a very reactive *p*-xylylene or biradical intermediate, which might readily react with each other to result in the crosslinked polymer formation. Note that this pathway can be applied to para- and possibly ortho-substituted styrenes, but not to the corresponding meta isomer.

To further investigate whether the reaction behavior of **6** arises from its benzyl ether structure, we have newly synthesized a similar para-substituted styrene[13] **7**, where the glucofuranose residue is separated from the styrene by three methylene units. **7** was then polymerized in THF at –78 °C with *s*-BuLi for 0.5 h. In this case, the polymerization mixture gained an intense red color characteristic of polystyrene anion. A polymer was obtained in 100 % yield. SEC analysis exhibited a unimodal peak with a narrow molecular weight distribution, the M_w/M_n value being 1.06. The observed M_n value (15 000) was found to fully agree with the calculated value (15 000). Thus, the anionic polymerization of **7** proceeded in a living manner without problems. Again, this result indicates that the benzyl ether structure in **6** is responsible for the anomalous behavior.

Stabilities of Anionic Living Polymers Produced from 1 and 7. Although all features of anionic polymerization of **1** are indicative of a "living" process, we did observe that the living polymer is problematic with respect to its stability. As mentioned in the preceding section, the molecular weight distribution of the polymer obtained after the 30 min polymerization was unimodal as shown in Figure 1a. The polymer obtained after 22 h, however, shows a higher molecular weight shoulder, which seems monodisperse having double molecular weight of the parent living polymer (Figure 1b). Judging from both peak areas, 40% of the starting living polymer dimerized after 22 h by unexpected coupling reactions.

On the other hand, the living polymer produced from **7** is very stable under the same conditions. As can be seen in Figures 1c and 1d, the molecular weight distributions of both polymers obtained

after the 0.5 and 22 h polymerizations, respectively, are symmetrically unimodal; no shoulders were observed on both the SEC peaks.

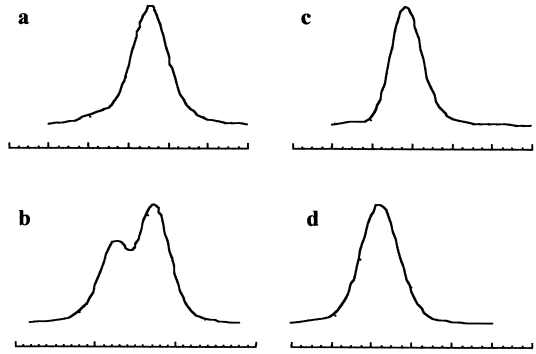


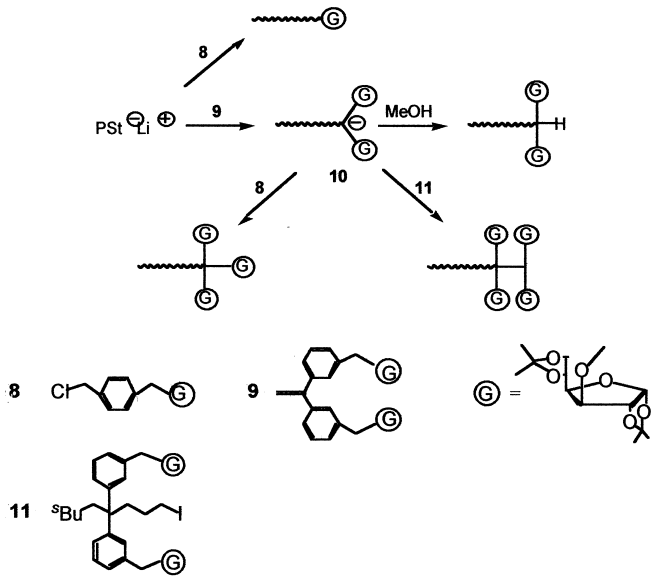
Fig. 1: SEC curves (differential refractivity index vs. elution count) of poly(**1**)s obtained at (a) –78 °C, 0.5 h, M_n(obsd) = 9 300, M_w/M_n = 1.07; (b) –78 °C, 22h, M_n(obsd) = 12 000, M_w/M_n = 1.16 and SEC curves of poly(**7**)s obtained at (c) –78 °C, 0.5 h, M_n(obsd) = 15 000, M_w/M_n = 1.06; (d) –78 °C, 22 h, M_n(obsd) = 8 900, M_w/M_n = 1.06.

To further ascertain the stability of living polymer of **7**, styrene was added to it after the 22 h polymerization of **7**. The SEC peak of the resulting polymer shifted completely toward the higher-molecular-weight side after addition of styrene and no peak corresponding to the starting living polymer of **7** was present. The values of M_n and composition observed agreed with those calculated within experimental error. This result clearly indicates that the living polymer produced from **7** is stable enough at –78 °C even after 22 h. The stability difference between living polymers of **1** and **7** is thus apparent. It is again likely that the benzyl ether moiety in **1**, although meta-substituted in this case, may play a key role in this difference. We are tentatively considering that an elimination of chain end anion similar to that illustrated in Scheme 1 might gradually occur as dimeric products were only formed, although the exact reactions are not clearly understood at present.

Synthesis of Functionalized Polystyrenes with a Definite Number of Monosaccharide Residues at the Chain Ends or in the Chains. By reacting polystyrene-lithium with the benzyl chloride derivatives **8** containing acetal-protected monosaccharide residues, various monosaccharides including not only D-glucose, but also D-galactose, D-fructose, and L-sorbose residues could be introduced at the chain ends. Their end-functionalization degrees in all cases were higher than 95 %. Similarly, 1,1-diphenylethene substituted with two acetal-protected glucose residues (**9**) was an effective agent for introducing two glucose residues at the polystyrene chain ends because **9** underwent monoaddition reaction with polystyrene-lithium quantitatively.

The resulting living functionalized polystyrene anion bearing two glucose moieties (**10**) is a key intermediate for the synthesis of end-functionalized polystyrenes with three and four glucose residues.

For example, a polystyrene end-functionalized with three glucose residues was obtained by reacting it with **8**. The degree of end-functionalization was 100% in this case. When using the benzyl chloride with acetal-protected D-galactose instead of **8**, two D-glucose and one D-galactose residues were simultaneously introduced at the chain end. More interestingly, four glucose residues could be introduced at the polystyrene chain end by reacting **10** with **11** readily prepared from **9**, *s*-BuLi, and 1,3-diiodopropane as illustrated in Scheme 2.



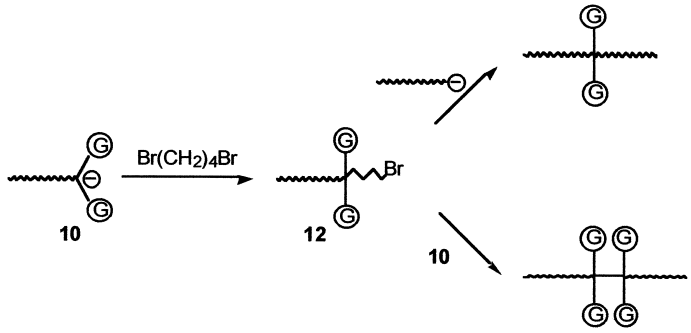
Scheme 2

Polymer **10** might also be a versatile precursor for the synthesis of well-defined functionalized polymers as was previously reported by Quirk and coworkers.[14] They were successful in synthesizing several polymers functionalized in the chains and block copolymers functionalized between two blocks.[14-16]

Polystyrene with two protected glucose and one 4-bromobutyl termini (**12**) was obtained from **10** with a ten-fold excess of 1,4-dibromobutane. It was then reacted with another polystyrene-lithium to afford the well-defined polystyrene functionalized with two glucose residues in the chain. Using this route, we can place two glucose residues at any position in the polymer molecule just by changing the molecular weights of both polystyrenes (see Scheme 3).

Similarly, polystyrene functionalized with four glucose residues in the chain was synthesized by coupling **12** with **10**. These functionalized polystyrenes were fractionated with HPLC since the reaction mixtures were always contaminated with small amounts of polymers used in excess in the reactions. Their isolated yields were usually more than 90 %. Table 2 summarizes the functionalized

polystyrenes with one or more monosaccharide residues at the chain ends or in the chains. As can be seen, all the polymers synthesized possess the desired structures with respect to molecular weights, molecular weight distributions, degrees of functionality, and the functionalized positions.



Scheme 3

Table 2. Synthesis of functionalized polystyrenes

Functionalization position	Polystyrene			Functionality (^{1}H NMR)
	M_n(calcd) x 10^{-3}	M_n(obsd)[a] x 10^{-3}	M_w/M_n[a]	
End	2.6	2.4	1.10	1.00
	3.3	3.1	1.07	1.88
	3.2	3.1	1.06	3.09
	6.6	6.9	1.04	4.00
Middle	12	12	1.04	2.00
	12	12	1.05	4.00

[a] By SEC calibration using polystyrene standards in THF solution.

In conclusion, we have successfully synthesized monosaccharide-functionalized polystyrenes and block copolymers with well-controlled structures by anionic living polymerization of styrenes functionalized with protected monosaccharides. We have also synthesized various well-defined polystyrenes functionalized with one to four glucose residues at the chain ends and in the chains. Studies on their solution behavior and microphase-separated structures with relation to well-defined structures of the polymers are now in progress.

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