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Synthesis of Hyperbranched Polysaccharide by Thermally Induced Cationic Polymerization of 1,6-Anhydrohexopyranose

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Summary: The thermally induced cationic polymerizations of 1,6-anhydro-β-D-glucopyranose (**1a**), 1,6-anhydro-β-D-mannopyranose (**1b**) and 1,6-anhydro-β-D-galactopyranose (**1c**) as a latent cyclic AB_4-type monomer were carried out using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**) as an initiator. The solution polymerization in propylene carbonate proceeded without gelation to produce the water-soluble hyperbranched polysaccharides (**3a-c**) with controlled molecular weights and narrow polydispersities. The degree of branching (DB), estimated by the methylation analysis of **3a-c**, was in the range of 0.38 – 0.49. The thermally induced cationic polymerization of **1a-c** using **2** is a facile method leading to a hyperbranched polysaccharide with a high DB value.

Keywords: cationic polymerization; hyperbranched; polysaccharides; ring-opening polymerization; water-soluble polymers

Introduction

Most chemically synthesized polysaccharides are linear macromolecules or have short branches, so that it is of great interest to synthesize and characterize hyperbranched polysaccharides. In this paper, we report the synthesis and characterization of a hyperbranched polysaccharide based on the strategy of the ring-opening multibranching polymerization of 1,6-anhydrohexopyranose. The ring-opening polymerizations of 1,6-anhydro-β-D-glucopyranose (**1a**), 1,6-anhydro-β-D-mannopyranose (**1b**) and 1,6-anhydro-β-D-galactopyranose (**1c**) as latent AB_4-type monomers were carried out in propylene carbonate as a solvent using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**) as a thermally induced cationic initiator, as shown in Scheme 1. The proton-transfer ring-opening

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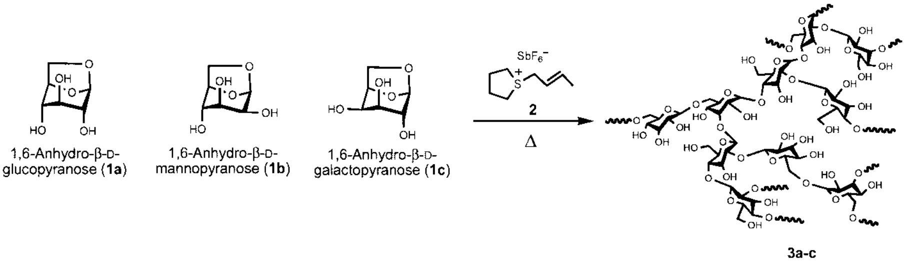
polymerization mechanism is discussed by determining the structure of the resulting polysaccharides (**3a-c**), such as the constitutional units and degree of branching. In addition, the three-dimensional property of the hyperbranched polysaccharides was characterized on the basis of static laser light scattering and viscosity measurements, which was compared with the linear polysaccharide.



Scheme 1. Thermally induced cationic polymerization of 1,6-anhydrohexopyranose (**1a-c**).

Polymerization

The ring-opening polymerization of 1,6-anhydrohexopyranose (**1a-c**) was carried out using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**) as a thermally induced cationic initiator at temperatures in the range of 130 - 210 °C. Table 1 summarizes the results of the polymerization. When propylene carbonate was used as the solvent, the polymerization proceeded homogeneously for 5 min, and then the reaction system gradually became heterogeneous as the reaction proceeded. The polymeric products were isolated by precipitation using water and methanol. The resulting polysaccharide was a gel-free white solid that was completely soluble in water and dimethyl sulfoxide, slightly soluble in pyridine and 1,3-dimethyl-2-imidazolidinone, and insoluble in toluene, chloroform, acetone and methanol. For the solution polymerizations of **1a-c** in propylene carbonate, the weight-average molecular weights ($M_{w,SLS}$) measured by static light scattering (SLS) and the yields of the resulting polysaccharide (**3a-c**) gradually increased with the rising polymerization temperature. The extension of the polymerization time also led to an increase in the $M_{w,SLS}$ and the yield. The $M_{w,SLS}$ of **3a-c** varied in the range from 2.2×10^4 to 6.4×10^5, which were significantly higher than the weight-average molecular weight values ($M_{w,SEC}$: 2.1×10^3 to 1.1×10^4) by size exclusion chromatography (SEC). In general, highly branched polymers, such as dendrimers, star polymers, and hyperbranched polymers, are known to have spherical conformations in a solution, and the $M_{w,SEC}$s of these polymers were often claimed to be too low because the hydrodynamic volumes of these polymers are smaller than the corresponding linear polymers used for the calibration. These results suggest that **3a-c** have a more compact form in solution when compared to the linear polymer. The polydispersities ($M_{w,SEC}/M_{n,SEC}$) for the resulting polysaccharide were found to be relatively narrow values in the range of 1.13 - 1.43 and increased with increasing monomer conversion. For all the polymerization conditions, the polymerizability of **1a-c** increases in the order of **1b** >> **1a** > **1c**. The melt polymerization of **1b** using **2** at 210 °C immediately occurred to produce a brown cake, and the precipitated polysaccharide was a light brown solid with the $M_{w,SLS}$ of 8.1 x 10^4 in 23.8 % yield. The $M_{w,SEC}/M_{n,SEC}$ (1.84) was broader than obtained from the solution polymerizations in propylene carbonate.

Table 1. Thermally induced cationic polymerization of 1,6-anhydrohexopyranose (**1a-c**) using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**)[a)]

run	M	[M] mol·L^{-1}	[M]/[2]	Time min.	Temp. °C	Yield[b)] %	$M_{w,SLS}$ x 10^{-3}	$[\alpha]_D$[c)]
1	**1a**	4.0	700	40	150	60.0	33.0	+99.5
2		6.4	350	20	130	35.9	24.5	+90.6
3	**1b**	6.4	350	20	130	61.6	80.5	+64.7
4		6.4	700	40	150	63.0	637	+64.4
5		Melt	350	<1	210	23.8	80.9	+51.9
6	**1c**	6.4	350	20	130	30.7	22.3	+95.8

[a)] Solvent, propylene carbonate.
[b)] Water-soluble but methanol-insoluble parts.
[c)] Measured in H_2O at 23 °C (*c* 1.0).

Viscosity measurements

In the viscosity measurement of **3a-c** in aq. $NaNO_3$ solution (0.2 mol·L^{-1}) as shown in Figure 1, a linear dependence between the reduced viscosity and the concentration was observed in the polymer concentration range for the SLS measurement, meaning that no aggregation occurred, and therefore, the measured $M_{w,SLS}$ corresponded to the absolute molecular weight of the polysaccharide. The solution viscosities of **3a-c** were very low, i.e., the intrinsic viscosities were in the range of 0.023 - 0.047 dL·g^{-1}. On the other hand, the intrinsic viscosity for the linear polymers of (1→6)-α-D-mannopyranan with the viscosity-average molecular weights of 8.1 x 10^4 was 0.41 dL·g^{-1}.[1] Therefore, these results of the SEC, SLS, and viscosity measurements suggested that **3a-c** were highly branched spherical molecules, i.e., hyperbranched polysaccharides.

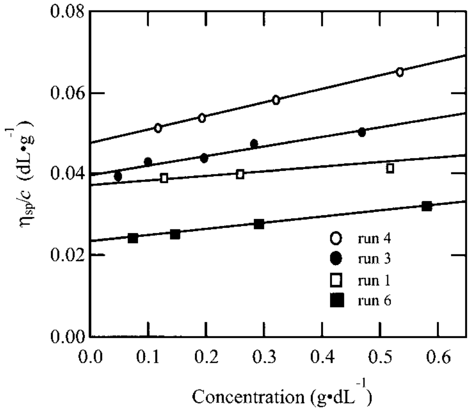


Figure 1. Viscosity-concentration plots for **3a-c** in aq. $NaNO_3$ solution (0.2 mol·L^{-1}) at 23 °C. Intrinsic viscosities [η]; 0.037 dL·g^{-1} for run 1, 0.040 dL·g^{-1} for run 3, 0.047 dL·g^{-1} for run 4, and 0.023 dL·g^{-1} for run 6.

Polymer structure

In order to investigate the polymer structure, the ^{13}C NMR measurement of polysaccharide **3b** was carried out in D_2O. The spectrum in Figure 2 consisted of a number of split and broad peaks, which should be caused by the different sequences of the D-mannopyranosyl units, such as (1→2)-, (1→3)-, (1→4)-, and (1→6)-linkages, and so on. The major signals for **3b**, which are asterisked in Figure 2, agreed fairly well with the chemical shifts of the carbons for methyl α-D-mannopyranoside (**4a**) and methyl β-D-mannopyranoside (**4b**), corresponding to the model compounds of terminal units in **3b**. These results indicated that **3b** was a highly branched polymer having numerous nonreducing D-mannopyranosyl terminal units, which is characteristic of a hyperbranched polymer. In addition, the ^{13}C NMR spectrum of **3b** exhibited the presence of the D-mannofuranosyl units, as shown by the open circle in Figure 2, i.e., the peaks at 79.83 and 63.67 ppm fairly agreed with the chemical shifts of the C-4 and C-6 carbons for methyl α-D-mannofuranoside (**5a**) and methyl β-D-mannofuranoside (**5b**). Therefore, these peaks should be assigned to the carbons of the nonreducing D-mannofuranosyl terminal units. Polysaccharides **3a** and **3c** also include the D-hexopyranosyl and D-hexofuranosyl terminal units. The ratio of the D-hexopyranosyl terminal units to the D-hexofuranosyl ones in **3a-c** calculated using quantitative ^{13}C NMR measurements was 94.2 mol % of the glucopyranosyl terminal unit and 5.8 mol % of glucofuranosyl terminal unit for **3a** (run 2), 93.0 mol % of the mannopyranosyl terminal unit and 7.0 mol % of the mannofuranosyl terminal unit for **3b** (run 3), and 84.3 mol % of the galactopyranosyl terminal unit and 15.7 mol % of the galactofuranosyl terminal unit for **3c** (run 6), respectively.

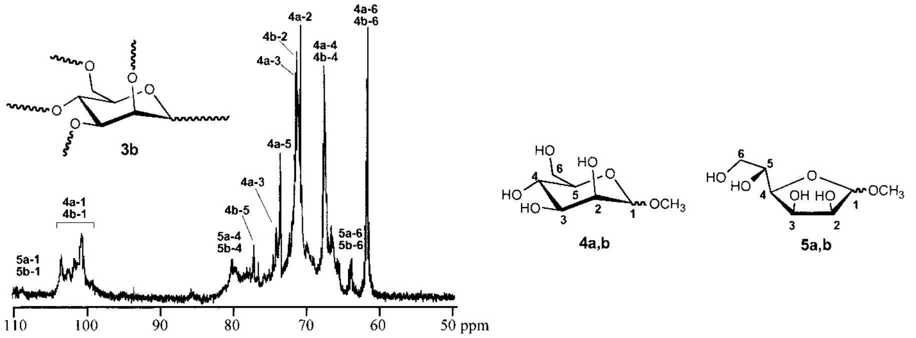


Figure 2. ^{13}C NMR spectrum of hyperbranched polysaccharide **3b** prepared from **1b**. The peaks shown by the asterisk and the open circle agreed with the chemical shifts of the carbons for **4a,b** and **5a,b**, respectively.

In order to confirm the branching and manner of linkage of the repeating units, the methylation analysis of **3a-c** was carried out according to a reported method.[2-5] These results were summarized in Table 2. The identified repeating units were classified into five categories of terminal units (T), linear units (L), two semi-dendritic units with three and four linkages ($s\mathrm{D}_1$ and $s\mathrm{D}_2$, respectively), and perfect dendritic units (D) with five linkages. The main components were D-hexopyranosyl terminal units and (1→6)-linked D-hexopyranosyl units. The terminal units increased and the (1→6)-linked units decreased with the increasing molecular weight of **3a-c**. The results of the methylation analysis showed that the reaction with the C-6 position was apparently favored. For the solution polymerization of **1a**, the C-3 hydroxyl groups was less reactive than the C-2 and C-4 hydroxyl groups, i.e., the reactivity increased in the order of C-6 >> C-2 = C-4 > C-3, while C-6 >> C-2 > C-4 > C-3 for **1b**, and C-6 >> C-3 > C-2 > C-4 for **1c**.

Table 2. Linkage analysis of polysaccharide (**3a-c**) obtained by thermally induced cationic polymerization of 1,6-anhydrohexopyranose (**1a-c**) using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**) [a)]

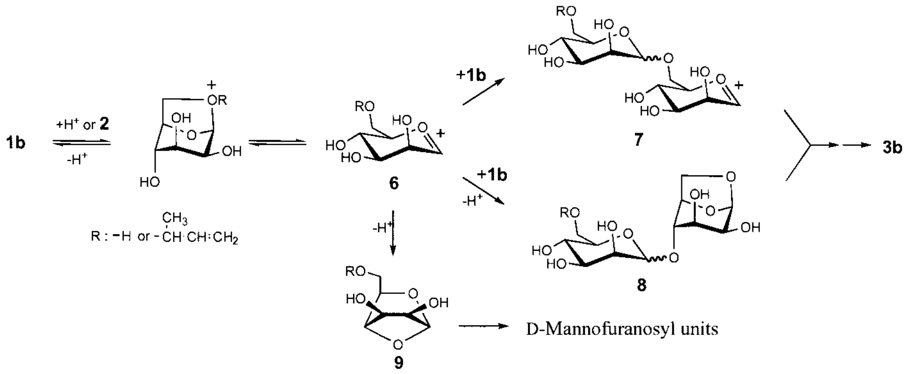
run	T	L	sD_1	sD_2	D	DB [b)]
1	33.6	45.7	16.5	2.5	1.7	0.38
2	35.8	43.0	17.7	2.4	1.1	0.38
3	29.1	43.4	21.8	5.1	0.7	0.43
4	31.5	41.3	20.9	5.6	0.7	0.44
5	36.2	39.2	19.1	4.8	0.8	0.44
6	31.8	38.2	21.5	7.7	0.7	0.49

[a)] Estimated by the methylation analysis of polysaccharide and the correction by molar response-factors.[6] The values were normalized by mol %.

[b)] Calculated by Frey's equation.[7]

Polymerization mechanism

Hyperbranched polysaccharides **3a-c** consisted of many kinds of α- and β-D-linked hexopyranosyl and hexofuranosyl repeating units. The mechanism for the thermally induced cationic polymerization, therefore, should proceed through a ring-opening mechanism with a proton transfer reaction, as shown in Scheme 2. For example, in the polymerization system with **1b**, the 1,6-ether oxygen atom was rapidly protonated and the protonated **1b** underwent the ring-opening to afford the carbenium-oxonium ion (**6**). When **6** reacted with the 1,6-ether oxygen atom of a second monomer, two kinds of α- and β-D-linked disaccharides (**7**) were formed. The process produced a terminal unit and a (1→6)-linkage. On the contrary, when **6** reacted with the hydroxyl group of another monomer, a disaccharide monomer (**8**) with a terminal residue and a (1→2)-, (1→3)-, or (1→4)-linkage was obtained along with the regeneration of a proton. A branched structure was obtained by the reaction of **6** (or **7**) with a hydroxyl group of the resulting oligo- and polysaccharides. Because the results of the NMR spectroscopic measurement and the methylation analysis indicated the presence of D-hexofuranosyl units, a portion of **6** was probably converted to 1,4-anhydro-α-D-hexofuranose derivative (**9**), as shown in Scheme 2. These reactions mentioned above simultaneously occurred in the polymerization systems and consequently produced the hyperbranched polysaccharides **3b**.



Scheme 2. Proposed mechanism for the thermally induced cationic polymerization of **1b**.

Degree of branching

For determining the degree of branching (DB) for a hyperbranched polymer, we assumed **1a-c** as latent AB_4-type monomers, which has one anhydro moiety capable of ring-opening and three hydroxyl groups, even though the reactivity of their hydroxyl groups was expected to be different for each other. The DB of **3a-c**, therefore, can be calculated from the numbers of T, L, sD_1, sD_2, and D units.[7] Table 2 summarizes the calculated DB values, where the DB values of 0 and 1 mean a linear polymer and a dendrimer, respectively. Assuming that the B groups has the same reactivity leading to the random polycondensation reaction, the DB value for the polymerization of the AB_4-type monomers is 0.42. For the thermally induced cationic polymerization of **1a-c**, the DB values were in the range of 0.37 - 0.50. As a result, the thermally induced cationic polymerization of **1a-c** with **2** is a facile method leading to a hyperbranched polysaccharide with a high DB value.

Conclusion

The thermally induced cationic polymerization of 1,6-anhydrohexopyranose (**1a-c**) using (*S*-2-butenyl)tetramethylenesulfonium hexafluoroantimonate (**2**) proceeded without gelation to produce a water-soluble hyperbranched polysaccharide (**3a-c**) with a high degree of branching. For the polymerization using propylene carbonate as the solvent, the weight-average molecular weights of **3a-c** can be controlled by the polymerization conditions, such as the ratio of monomer to initiator, the monomer concentration, the polymerization time, and the temperature. The results of the ^{13}C NMR, SLS, and viscosity measurements indicated that **3a-c** were highly branched spherical macromolecules, i.e., hyperbranched polysaccharides. The thermally induced cationic polymerization is a useful method for preparing a hyperbranched polysaccharide having numerous nonreducing D-hexopyranosyl terminal units, which can be expected for use in medical and medicinal applications.

[1] J. S. Tkacz, J. O. Lampen, A. D. Schuerch *Carbohydr. Res.* **1972**, *21*, 465.

[2] T. Satoh, T. Imai, H. Ishihara, T. Maeda, Y. Kitajyo, A. Narumi, H. Kaga, N. Kaneko, T. Kakuchi, *Macromolecules* **2003**, *36*, 6364.

[3] R. Gonda, M. Tomoda, M. Kanari, N. Shimizu, H. Yamada, *Chem. Pharm. Bull.* **1990**, *38*, 2771.

[4] M. Paterson-Beedle, J. F. Kennedy, F. A. D. Melo, L. L. Lloyd, V. Medeiros, *Carbohydr. Polym.* **2000**, *42*, 375.

[5] E. Lau, A. Bacic, *J. Chromatogr.* **1993**, *637*, 100.

[6] D. P. Sweet, R. H. Shapiro, P. Albersheim, *Carbohydr. Res.* **1975**, *40*, 217.

[7] D. Hölter, A. Burgath, H. Frey, *Acta Polym.* **1997**, *48*, 30.