Carbohydrate Research, 135 (1985) 195–202
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

STERIC CONTROL IN THE POLYMERIZATION OF 1,2-ANHYDRO-3,4,6-TRI-*O*-BENZYL-β-D-MANNOPYRANOSE

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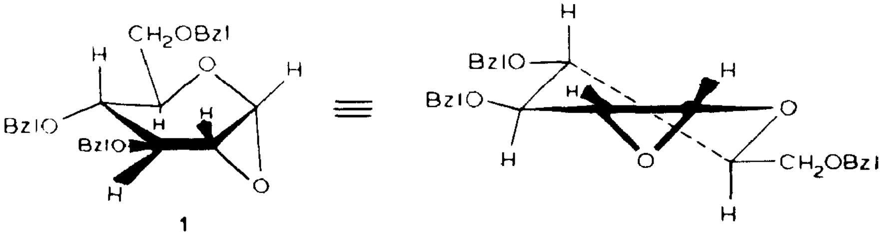
(Received December 15th, 1983; accepted for publication in revised form, April 5th, 1984)

ABSTRACT

Polymerization of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose under acid catalysis has led to a series of polymers varying in anomeric configuration from ~90% α to 70% β. Optical rotations follow ^{13}C-n.m.r. estimates of anomeric composition linearly over this range. Low-temperature polymerization with trifluoromethanesulfonic anhydride as initiator favors mainly *cis*-opening of the anhydro ring, presumably through the intermediary of a macroester. These results are compared with related glycosylation and polymerization reactions on 1,2-anhydro sugar derivatives, and some mechanistic conclusions are proposed.

INTRODUCTION

This laboratory has recently published syntheses of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose[1] (**1**) and 1,2-anhydro-3,4,5-tri-*O*-benzyl-β-D-man-



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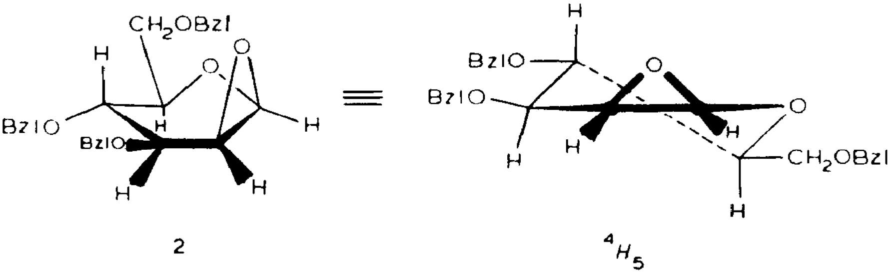

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$^4H_5$

nopyranose[2] (**2**), a study of their conformations[3], and preliminary investigations of their polymerization[4,5]. Acid-catalyzed polymerizations of **1** under appropriate conditions led to polymers with 90% β-configuration[4], corresponding to *trans*-opening, whereas with **2**, our current interest, the polymer configurations were generally random[5]. However, with base catalysis, compound **2** underwent *trans*-opening to give an essentially stereoregular, oligomeric product, corresponding to an α-linked hexamer[5]. Recent results with 1,3-anhydroglucose[6] and -mannose[7] derivatives have shown that high degrees of stereoregularity may be achieved in polymerizations of these monomers with trifluoromethanesulfonic anhydride as initiator at room temperature. This article reports the use of this and other catalyst or initiator systems that lead to (1→2)-D-mannopyranans of a wide range of stereoregularity, both α and β. The influence of reaction conditions and monomer structure is discussed relative to this and other glycosylation and polymerization reactions.

RESULTS AND DISCUSSION

1,2-Anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose was polymerized under a variety of conditions and with a number of catalyst systems. The conditions and results are summarized in Table I. The polymers were white powders with, for the most part, relatively low molecular-weights. As may be seen, fairly long polymerization-times were necessary to reach a reasonable conversion. In the previous work[5], the highest specific rotations obtained via cationic initiation were +4.0 to +8.1°, indicating that the polymers contained a mixture of α and β linkages with nearly equivalent proportions of each type of linkage. From the positive rotations listed in Table I, it is obvious that polymers having much higher degrees of α-stereoregularity had been produced by using the catalysts indicated. The highest positive values of $[\alpha]_D$ were produced by using triflic anhydride as initiator at ambient temperatures in either dichloromethane or benzene. What is most notable, however, is the effect temperature has on the polymer stereochemistry when the polymerizations are performed in dichloromethane. The percentage of α-linkages steadily increased with temperature from a low value (26%) until 90% was reached at room temperature. Polymerization conducted above ambient temperature (polymer number 12) also resulted in polymers having lower percentages of α-linkages. The nature of the mechanism is discussed later.

To estimate the relationship between optical rotation and percentage of α-linkages in the polymer, it was necessary to examine the ^{13}C-n.m.r. spectra of the various polymers used in this study. The resonances assigned to the anomeric carbon atom (C-1) were used to determine the proportion of α linkages, as two distinct absorptions, representing carbon atoms in α or β linkages ($\delta_{c\alpha}$ = 100.6–101.6 and $\delta_{c\beta}$ 97.0–100.0 p.p.m.)[5,8,9] may be discerned in this region of the ^{13}C-n.m.r. spectrum of the benzylated polymers. Spectra were determined under conditions comparable to those used elsewhere to determine anomeric content of carbohydrates[10]. The results of these measurements are presented in Table I. The

TABLE I

POLYMERIZATION OF 1,2-ANHYDRO-3,4,6-TRI-*O*-BENZYL-*β*-D-MANNOPYRANOSE

Expt. no.	*Catalyst*	*Mol % to monomer*	*Solvent*	*Monomer/-solvent ratio (g/100 mL)*	*Temp. (degrees)*	*Time (h)*	*Yield (%)*	*Mol. wt*[a]	$[\alpha]_D$ *(degrees)*[b]	*Configuration (%α)*[c]
1	$(CF_3SO_2)_2O$	2.5	CH_2Cl_2	11.9	−60	80	51	12,000	−7.0	26
2	$(CF_3SO_2)_2O$	2.7	CH_2Cl_2	12.1	−40	78	54	4,800	−4.6	38
3	$(CF_3SO_2)_2O$	2.7	CH_2Cl_2	13.1	−20	78	86	16,000	−2.0	45
4	$(CF_3SO_3)_2O$	3.0	CH_2Cl_2	9.5	0	80	71	5,000	+18.4	78
5	$(CF_3SO_2)_2O$	3.2	CH_2Cl_2	10.0	[b]	80	63	6,000	+22.9	91
6	$(C_6H_5)_3CClO_4$	2.0	C_6H_6	15.3	[b]	72	51	5,000	+5.3	57
7	$(CF_3SO_2)_2O$	2.5	C_6H_6	15.0	[b]	72	70	9,200	+22.0	88
8	$(C_6H_5)_3CCl$	2.1	C_6H_6	15.1	[b]	60	32	4,600	+14.1	71
9	$(C_6H_5)_3CBr$	2.0	C_6H_6	15.2	[b]	54	78	33,000	+10.6	62
10	$(C_6H_5)_3CCl$	2.1	$C_6H_5CH_3$	15.2	0	15	20	8,800	+17.6	78
11	$(CF_3SO_2)_2O$	2.5	C_6H_6	50.0	[b]	90	79	8,600	+22.4	89
12	$(CF_3SO_2)_2O$	2.5	C_6H_6	15.6	35°	90	45	3,600	+14.2	72
13	$(CF_3SO_2)_2O$	0.5	C_6H_6	15.5	[b]	92	7.1	28,000	+20.7	85
14	HCl	2.0	C_6H_6	10.0	[b]	70	29	6,000	+16.0	74

[a] As determined by gel-permeation chromatography with polystyrene standards. [b] At room temperature. [c] As determined from ^{13}C-n.m.r.

relationship of the percentage of α linkages measured in this manner to optical rotation is expressed by the equation: $[\alpha]_D^{25}$ = 0.51 (% α-linkages) −22.4. The relationship is linear with a 0.99 correlation coefficient. If the line is extended, the intercepts are the optical rotations reasonably expected for polymers containing 100% α linkages or 100% β linkages. These values are +28.6 and −22.4°, respectively. The former value is consistent with that of a stereoregular low-d.p. polymer (P14)[5] prepared by anionic polymerization[5], and the latter is consistent with expectations for a perbenzyl ether of (1→2)-β-D-mannopyranan of $[\alpha]_D$ −50° reported by Gorin *et al.*[11]. In order to clarify the structure of the polymers, a polymer of high α-content was debenzylated (polymer 11). The ^{13}C-n.m.r. spectrum of the resulting material, together with peak assignments, is presented in Fig. 1. The optical rotation of this material is $[\alpha]_D^{25}$ +50.6°, which is somewhat lower than the previous high of +61.1° obtained by debenzylation of a polymer

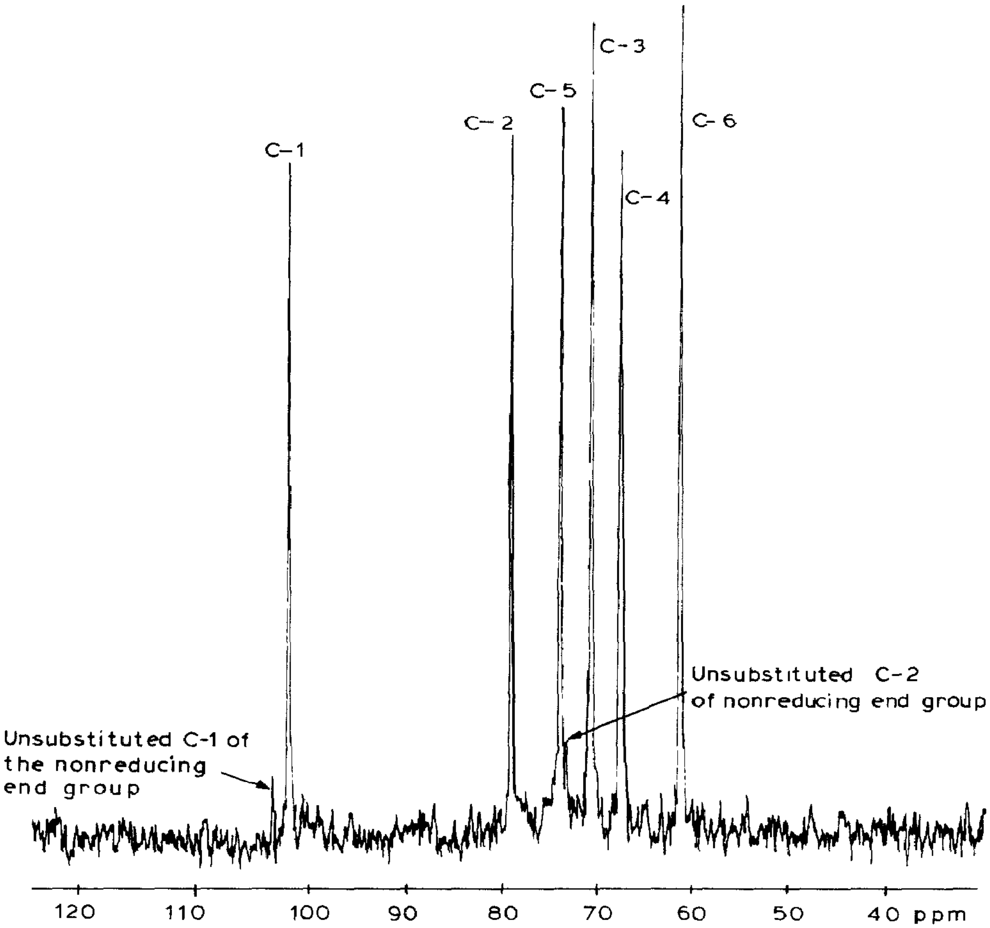

Fig. 1. ^{13}C-N.m.r. spectrum of (1→2)-D-mannopyranan. Estimated configurational purity ~90% α.

($[\alpha]_D$ +29°) obtained by anionic polymerization[5]. The percentage of α linkages, as measured by ^{13}C-n.m.r. after debenzylation, increased from 89 to 91%, possibly because of loss of a small proportion of low-molecular-weight material of lower α-content, but the two values are consistent and within experimental error.

The polymerization of this monomer (**2**) has some unusual stereochemical features not found in glycosylation or polymerization reactions of other 1,2-anhydro sugar derivatives. It is instructive, therefore, to compare them with previous results on compounds **1** and **2** and on the Brigl anhydride, 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose.

Most information is available on the glycosylation of the Brigl anhydride, and the reactants used have included alcohols[12-16], phenols[13,17], and cyclic hemiacetals[18-20], in some cases with acid catalysis. Early claims[12,13] for the stereospecific synthesis of β glycosides by solvolysis with simple alcohols in uncatalyzed reactions are incorrect, as some proportion of α glycosides is surely formed[21]. Uncatalyzed and acid-catalyzed reactions of more-complex alcohols, phenols, and cyclic hemiacetals at elevated temperatures lead to α glycosides as the isolated product. However, as the yields are invariably low, the β glycoside is probably also formed. A number of mechanisms may be invoked to explain the overall *cis*-opening of the anhydro ring. Either the α-products derive from attack on a C-1 cationic intermediate, with thermodynamic preference for the α linkage, or the reaction involves double inversion at C-1 with participation of the 6-*O*-acetyl group, as proposed by Lemieux[19], or perhaps equally probably, the 3-*O*-acetyl group. There seems, moreover, to be no reason to assume a single mechanism in all cases and under all conditions.

Polymerizations of the Brigl anhydride follow a similar course. Little steric preference is observed on thermal polymerization[22], whereas acid-catalyzed polymerizations favor a predominance of α-linkages[23,24]. The proportion of α-linkages in the product polymer is somewhat higher at higher temperatures, presumably because of more bond-breaking before bond formation. The counterion or degree of complexation with Lewis acid also plays some role, for variations in α-content are observed with different Lewis acids and different quantities of the same Lewis acid.

The polymerizations of perbenzylated 1,2-anhydro-α-D-glucopyranose and -β-D-mannopyranose are free of the complication of neighboring-group participation, but there are striking differences in their steric course. The results of PF_5-catalyzed polymerizations of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose[4] are consistent with those of other perbenzylated monomers. At −60°, the product is predominantly β (90%), formed by *trans*-opening of the anhydro ring. At higher temperatures with this or similar Lewis acids, the product polymers contain increasing amounts of α-linkage. Presumably at low temperature, the monomer reacts in a conformation similar to its ground-state ($^4H_5$) conformation[3]. In this form, approach to C-1 is essentially unhindered and *trans*-opening of the propagating trialkyloxonium ion predominates. At higher temperatures, more bond-breaking precedes bond-formation and a larger proportion of the thermodynamically favored α-product results.

In contrast, polymerization of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose with the same catalysts proceded with little steric preference, even at low temperatures[5]. Inspection of Dreiding models suggests that *trans* (α) approach of a bulky reactant to C-1 of a monomer or its trialkyloxonium ion is hindered by H-5 when the molecule is in its favored ($^4H_5$) conformation[3]. The propagating onium ion presumably must be converted into a C-1 cation for reaction, and both α and β approaches are then relatively unhindered. The present results with triflic anhydride are strikingly different, and emphasize the role that may be played by catalyst or counterion. At room temperature, the product is predominantly α-linked (90%), as would be expected from reaction on a trialkyloxonium ion or a C-1 cation shielded by leaving group. The results at low temperature are much more surprising, as the high β preference in ring opening (70%) is contrary to both steric shielding and to thermodynamic preference. It therefore appears necessary to invoke double inversion by counterion.

We propose that, at low temperatures, triflic anhydride is unable to cleave the anhydro ring to form a reactive cation, and α-approach of a bulky monomer is probably hindered by H-5. The triflate counterion has, however, less steric requirement and has a strong tendency for covalent bond-formation[24]. Macroesters of ClO_4^-, FSO_3^-, $F_3CSO_3^-$, and I_3^- are recognized intermediates in cationic polymerization[24–26]. At low temperatures, therefore, the favored, though slow, reaction is for triflate ion to attack C-1 from the α-direction. The resulting C-1 α-triflate is sufficiently reactive to permit β-attack by monomer to form polymer with a predominance of β-linkages. This result appears therefore to provide unusual stereochemical evidence for the intermediary of a propagating macroester.

EXPERIMENTAL

General methods. — ^{13}C-N.m.r. spectra were determined with a Varian XL-100-15 spectrometer in the pulsed Fourier-transform, proton-noise-decoupled mode. The spectral width was 6000 Hz, acquisition time 0.666 sec., with 83,165 accumulations, and 8192 data points. The benzylated polymers were observed as $CDCl_3$ solutions with Me_4Si as internal standard. The debenzylated polymer was observed in D_2O, with the central resonance-signal of internal Me_2SO (δ_c −39.50 p.p.m.) as the standard. Optical rotations were measured in $CHCl_3$ at room temperature with a Perkin–Elmer 141 photoelectric polarimeter. Molecular-weight measurements were performed with a Waters model 200 chromatograph using 5 columns packed with Microstyragel (1×10^5, 1×10^4, 1×10^3, 1×500, and 1×100 A). Calibration curves were made by using standard polystyrene samples (Waters). [For (1→3)-linked polysaccharides, this technique gave low values[7].] N.m.r. peak-areas were measured by tracing on high-quality paper, cutting and weighing, and by a computer program.

Monomer synthesis. — The monomer, 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose, was synthesized and purified by published procedures[2]. Material having $[\alpha]_D^{25}$ +5.0° (*c* 1, $CHCl_3$), lit.[5] $[\alpha]_D^{25}$ +4.6° (*c* 1, $CHCl_3$) m.p. 89–90°, lit.[5] m.p. 89.5–90°, was used for all polymerizations.

Polymerization. — The polymerizations were all conducted with high-vacuum techniques. The triflic anhydride was distilled into calibrated receptacles and these were attached to the polymerization vessel via a breakseal. The triflic anhydride was then distilled *in vacuo* into a frozen solution of monomer, and the polymerization vessel was sealed under vacuum and brought to the desired polymerization temperature. The other initiators, with the exception of HCl, were solids and these were added directly to a frozen solution of monomer under a positive pressure of nitrogen. A saturated solution of HCl in benzene was prepared. The required amount of this solution was added to a frozen solution of monomer under a positive pressure of nitrogen. Polymerizations were terminated by addition of dry methanol. The precipitated polymers were dissolved in $CHCl_3$ and precipitated into dry hexane three times. The polymers were then freeze-dried from benzene. In several experiments, the hexane-soluble components were characterized by ^{1}H-n.m.r. spectroscopy and found to be mixtures of unreacted monomer and some low oligomers, apparently dimers and trimers.

Debenzylation. — Isolated polymer was debenzylated by a published method[27]. The polymer solution was purified by dialysis until ion free by using a UM-02 membrane (Diaflo Ultrafilter Amicon Co.) and isolated by freeze-drying from distilled water.

ACKNOWLEDGMENT

This work was supported by a research grant (5 ROI GM-06168) from the National Institute of General Medical Sciences, National Institutes of Health, U.S. Public Health Service.

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