Preparation of High Polymers from 1,6-Anhydro-2,3,4-tri-*O*-Substituted β-D-Glucopyranose

ERWIN R. RUCKEL AND CONRAD SCHUERCH

Department of Chemistry, State University College of Forestry, Syracuse, New York 13210

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Cationic polymerization of three 1,6-anhydro-2,3,4-tri-*O*-substituted β-D-glucopyranose monomers (methyl, ethyl, and benzyl) was successful with Lewis acid catalysts and resulted in highly stereoregular polymers with degrees of polymerization as high as 300. All polymerizations were performed using high purity monomers and high vacuum technique. Optimum conditions of reaction included low temperature to avoid chain transfer and relatively high concentrations of phosphorus pentafluoride as catalyst. The optimum catalyst concentration varied with monomer. A trialkyl oxonium ion mechanism is postulated for the polymerizable monomers. The polydispersity of the polymers appears to reflect both variable initiation and propagation rates. The latter may be caused by differences in counter ion. Phosphorus pentafluoride failed to polymerize 1,6-anhydro-2,3,4-tri-*O*-acetyl-β-D-glucopyranose. Instead, a stable catalyst–monomer complex formed which precipitated from solution at high catalyst concentration. 1,6-Anhydro-2,3,4-tri-*O*-trifluoroacetyl and 2,3,4-tri-*O*-trimethylsilyl monomers failed to develop the yellow-green color observed during all successful polymerizations and which is believed to be characteristic of the reactive oxonium ions. Failure for a monomer to polymerize appears, therefore, to be the result of competition for the Lewis acid by nonpolymerizable functional groups in some cases, and in others steric or electronic effects.

During the past 4 or 5 years much effort has been directed toward the chemical synthesis of specific polysaccharides having a definite composition.[1,2] Interest in the problem has been generated not only by the challenge of the synthesis, but also by the use of these polymers in medicine and as model substances for the study of physiological processes involving macromolecules.[3] Dextrans, the polysaccharides to which the present work is most closely related, have a well-known value as blood plasma substitutes and very recently have been found to reduce high cholesterol levels in the blood.

Several groups[4,5] have worked on the addition polymerization of 1,6-anhydroglucose and observed that polymers of indefinite structure with variable branching and mixed anomeric configuration were obtained. In order to prepare a linear polysaccharide Korshak and coworkers[5] polymerized 1,6-anhydro-2,3,4-tri-*O*-methyl-β-D-glucopyranose. Tu and Schuerch[6] confirmed the work and first reported the high α-stereospecificity of this polymerization. However, the latter authors demonstrated that polymers of degree of polymerization of about 25 were obtained. Several review articles[1,2] mention unpublished work of groups[7,8] who have since reproduced the polymerization of the trimethyl ether of levoglucosan.

A related current investigation[9,10] is concerned with the synthesis of linear cellulose by condensation polymerization of 2,3,6-tricarbanilylglucose. Earlier work on condensation polymerization led to polysaccharides of mixed anomeric configuration.[11,12]

The following work had a twofold objective, namely, to find synthetic conditions by which a linear stereoregular polysaccharide could be prepared with a degree of polymerization comparable to the naturally occurring polymers and to investigate various blocking groups which could be removed subsequent to polymerization. The polymerization of 1,6-anhydro-2,3,4-tri-*O*-alkyl- (methyl- and ethyl-) β-D-glucopyranose monomers was studied to correlate synthetic conditions with polymer yield, stereospecificity, and number and weight average molecular weights (polydispersity). We have investigated the polymerization of four monomers with removable 2,3,4-substituted blocking groups, one of which formed high polymers.

Experimental Section

Preparation of Starting Materials. A. 1,6-Anhydro-2,3,4-tri-*O*-alkyl- (methyl- and ethyl-) β-D-glucopyranose.—Levoglucosan was prepared by pyrolysis of preferably ash-free[13] amylose. The tri-*O*-methyl ether was prepared in 65% yield by the three-fold methylation of levoglucosan with dimethyl sulfate.[14] The monomer, purified by either vapor phase chromatography (column 20 ft × 3/8 in. consisting of 20% fluorinated silicone, QF-1, as stationary phase on a solid support of 45/60 Chromosorb P) on a Wilkens Autoprep Model A-700 and subsequent recrystallization or zone refinement (Litton Co., Tallahassee, Fla.), had mp 57.5–58.5, $[\alpha]^{25}D$ −63.7 (*c* 2.0, H_2O).

The tri-*O*-ethyl ether was prepared in 37% yield by an analogous route utilizing diethyl sulfate. The monomer was purified by vapor phase chromatography followed by fractional distillation: bp 90° at (0.60 mm), $[\alpha]^{25}D$ −51.5 (*c* 2.8, $CHCl_3$), d^{23} 1.081.

Anal. Calcd for $C_{12}H_{22}O_5$ (246.30): C, 58.52; H, 9.00. Found: C, 58.50; H, 9.14.

B. 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose.—This monomer was obtained by 77% yield from 1,6-anhydro-2,3,4-tri-*O*-acetyl-β-D-glucopyranose[15] (mp 109.5–110.5°, $[\alpha]^{25}D$ −50.8) by employing a modification of the method of Zemplén, Csürös, and Angyal:[16] mp 89.5–90.5°, $[\alpha]^{25}D$ −30.8 (*c* 2.7, $CHCl_3$).

C. 1,6-Anhydro-2,3,4-tri-*O*-trifluoroacetyl-β-D-glucopyranose.—The trifluoroacetylation procedure of Bourne and co-workers[17] was used for this synthesis. A mixture of 1.0 g of levoglucosan,

(1) J. Klar, *Chemiker Ztg.*, **87**, 731 (1963).
(2) I. J. Goldstein and T. L. Hullar, *Advan. Carbohydrate Chem.*, in press.
(3) P. T. Mora, B. G. Young, P. B. Maury, V. W. McFarland, T. L. Wilhelm, and J. W. Wood, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960.
(4) J. daS. Carvalho, J. W. Prins, and C. Schuerch, *J. Am. Chem. Soc.*, **81**, 4054 (1959).
(5) V. V. Korshak, O. P. Golowa, V. A. Sergew, N. M. Merlies, and R. Ya Sneer, *Vysokomolekul. Soedin.*, **3**, 477 (1961).
(6) C. C. Tu and C. Schuerch, *Polymer Letters*, **1**, 163 (1963).
(7) J. Klar, Dissertation, Freiburg, 1962, p S46.
(8) H. Bredereck and U. Hutten, unpublished data, cited in ref 1, p 737; U. Hutten, Ph.D. Dissertation, T. H. Stuttgart, 1961, pp S56 ff.
(9) E. Husemann and H. O. J. Müller, *Makromol. Chem.*, **49**, 238 (1961).
(10) E. Husemann and G. J. M. Müller, *ibid.*, in press. Private communication from E. Husemann to I. J. Goldstein.[2]
(11) F. Micheel and A. Böckmann, *ibid.*, **51**, 97 (1962).
(12) G. Schramm, H. Grötsch, and W. Pollmann, *Angew. Chem.*, **74**, 53 (1962).
(13) O. P. Golova and R. G. Krylova, *Dokl. Akad. Nauk. SSSR*, **135**, 1391 (1960); *Chem. Abstr.*, **55**, 12842*f*.
(14) T. C. Irvine and T. W. H. Oldham, *J. Chem. Soc.*, **127**, 2903 (1925).
(15) I. A. Wolff, *J. Am. Chem. Soc.*, **67**, 1623 (1945).
(16) G. Zemplén, Z. Csürös, and S. Angyal, *Ber.*, **70**, 1848 (1937).
(17) E. J. Bourne, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 1367 (1950).

TABLE I

SELECTED POLYMERIZATIONS OF 1,6-ANHYDRO-2,3,4-TRI-*O*-SUBSTITUTED β-D-GLUCOPYRANOSE[a]

Expt no.	Monomer	Catalyst	[cat.]100/[monomer]	Solvent	Monomer/solvent ratio (g/100 ml)	Temp, °C	Time, hr	% yield	$\bar{M}_n$	$\overline{DP}_n$	$\bar{M}_w$	$[\alpha]_D$	$[\phi]$	$[\eta]$	k'	s_0	$\bar{M}_w/\bar{M}_n$
R-1	Me_3	$BF_3 \cdot Et_2O$	3.2	C_6H_6	10	+25	157	28.1	4,700	23	...	+194		0.08			
R-2	Me_3	$BF_3 \cdot Et_2O$	3.2	C_6H_6	10	+25	280	26.6	3,950	19	...	+189		...			
R-3	Me_3	$BF_3 \cdot Et_2O$	3.6	CH_2Cl_2	10	−78	157	0	...	...	...			...			
R-4	Me_3	$BF_3 \cdot Et_2O$	3.0	CH_2Cl_2	10	+25	157	6.0	1,400	8	...	+183		...			
R-5	Me_3	PF_5	3.7	CH_2Cl_2	10	+17	144	11.1	2,960	14	...	+141		...	...		
R-6	Me_3	PF_5	3.7	CH_2Cl_2	10	−28	144	85.3	19,950	98	...	+202		0.21	0.508		
R-7	Me_3	PF_5	3.7	CH_2Cl_2	10	−78	144	91.9	*[b]	*	...	+196		0.68[c]	1.06		
R-8	Me_3	PF_5	3.7	C_7H_8	10	−78	144	0[d]	...	...	...	...		...	...		
R-9	Me_3	PF_5	1.2	CH_2Cl_2	10	−78	144	0	*[b]	*	...	...					
R-10	Me_3	PF_5	2.5	CH_2Cl_2	10	−78	144	30	*[b]	*	...	+202					
R-11	Me_3	PF_5	9.1	CH_2Cl_2	10	−78	144	72.5	*[b]	*	...	+195					
R-12	Me_3	PF_5	18.2	CH_2Cl_2	10	−78	144	85	*[b]	*	...	+195					
R-13	Me_3	PF_5	3.7	CH_2Cl_2	10	−78	18	28.9	*[b]	*	...	+199	...				
R-14	Me_3	PF_5	3.7	CH_2Cl_2	10	−78	48	85.6	*[b]	*	$1.09 \times 10_6$	+208	+425				
R-15	Me_3	PF_5	3.7	CH_2Cl_2	10	−78	245	85.5	*[b]	*	...	+198	...				
R-16	Et_3	PF_5	3.9	CH_2Cl_2	10	−78	227	0	...	...	...	...	...				
R-17	Et_3	PF_5	9.5	CH_2Cl_2	10	−78	185	5.0	...	...	...	...	...	...			
R-18	Et_3	PF_5	11.8	CH_2Cl_2	10	−78	167	70.0	14,800	60	...	+181	+447	0.12	...	...	...
R-19	Et_3	PF_5	19.7	CH_2Cl_2	10	−78	29	88.6	28,200	114	$4.75 \times 10_5$	+198	+490	0.38	0.173	11.11	16.8
R-20	Et_3	PF_5	19.0	CH_2Cl_2	20	−78	12	51.0[e]	47,200	192[f]	$2.94 \times 10_6$	+178	+440	0.85	0.434	28.6	62.5
R-21	Et_3	PF_5	20.0	CH_2Cl_2	20	−78	19	76.5	37,600	152	$1.86 \times 10_5$	+184	+454	0.32	0.537	6.45	4.95
R-22	$(CH_2Ph)_3$	PF_5	20.2	CH_2Cl_2	20	−78	88	90.5	41,800	97	...	+109	+472	0.38	0.29		
R-23	$(CH_2Ph)_3$	PF_5	20.2	CH_2Cl_2	20	−78	136	90.3	44,400	103	...	+110	+476	0.25	0.29		
R-24	$(CH_2Ph)_3$	PF_5	20.2	CH_2Cl_2	33	−78	72	91.6	56,600	131	...	+110	+476	0.28	0.45		
R-25	$(CH_2Ph)_3$	PF_5	20.2	CH_2Cl_2	33	−78	87	86.4	56,100	130	...	+111	+480	0.33	0.23		
R-26	$(CH_2Ph)_3$	PF_5	10.6	CH_2Cl_2	20	−78	91	94.5	75,750	178	...	+113	+489	0.38	0.34		
R-27	$(CH_2Ph)_3$	PF_5	85.3	CH_2Cl_2	20	−78	94	53.1	4,050	9	...	+109	+472	0.08	...		

[a] Polymerizations of the tri-*O*-methyl and tri-*O*-ethyl derivatives were on an 0.5-g scale; those of the tri-*O*-benzyl derivatives on a 1.0-g scale. Exceptions are polymerizations R-21 and -25 which represent a 2.5 scale-up of these quantities. Rotations were recorded in chloroform at concentrations of 25 g/l. ϕ represents the molecular rotation. k' is the Huggins constant determined from the intrinsic viscosity plot. s_0 is the sedimentation constant determined by ultracentrifuge. [b] Polymer has too high $\bar{M}_n$ to be measured accurately by Mechrolab vapor pressure osmometer. Polymer could not be measured by using membrane osmometers, since it was not completely soluble and coated the membrane. [c] Value represents $[\eta]$ after removal of insoluble gel fraction. The yield of chloroform soluble polymer was 53.8% (R-7). [d] Monomer is insoluble in toluene at −78°. [e] Very rapid polymerization occurred during warming from −196 to −78°. The lower yield was the result of gel formation before all monomer went into solution. [f] Further fractionation of this polymer by precipitation yielded a material of $\bar{M}_n$ 73,600, $\overline{DP}_n$ 298.

1.66 g of sodium trifluoroacetate, and 11.1 g of trifluoroacetic anhydride was stirred and refluxed until complete solution resulted (*ca.* 3 hr). Excess trifluoroacetic anhydride and trifluoroacetic acid were removed *in vacuo* and three 15-ml portions of carbon tetrachloride were then distilled from the residue to remove traces of anhydride or acid. The solid reaction residue was next extracted with 75 ml of hot carbon tetrachloride to give 2.7 g (97%) of desired product on concentration: mp 63.5–65.0°, $[\alpha]^{25}D$ −39.9 (*c* 2.1, $CHCl_3$). The infrared spectrum indicated no hydroxyl absorption. It is necessary to store the product in the cold under nitrogen atmosphere to avoid decomposition.

Anal. Calcd for $C_{12}H_7F_9O_8$ (450.17): C, 32.02; H, 1.57; F, 37.98. Found: C, 31.82; H, 1.47; F, 37.77.

D. 1,6-Anhydro-2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranose.—This unreported anhydro sugar was prepared by employing the trimethylsilylation procedure for carbohydrates described by Sweeley and co-workers.[18] To a solution of 4.05 g of levoglucosan in 50 ml of dry pyridine was added 24.4 g of hexamethyldisilazane. To this solution was slowly added 12.2 g of trimethylchlorosilane which resulted in a slightly exothermic reaction accompanied by immediate precipitation of ammonium chloride. The reaction mixture was cooled to room temperature and allowed to stir overnight. The ammonium chloride was filtered off and the filtrate concentrated to an oily residue. The latter was fractionally distilled collecting the fraction: bp 87–87.5° (0.05 mm); yield 8.5 g, 85%, $[\alpha]^{30}D$ −33.8 (*c* 3.6, $CHCl_3$); d^{30} 0.9914. The infrared spectrum showed no hydroxyl absorption and the vapor phase chromatograph indicated just one component.

Anal. Calcd for $C_{15}Si_3H_{34}O_5$ (378.69): C, 47.57; H, 9.05. Found: C, 47.77; H, 9.21.

Polymerizations.—All polymers were prepared using a high vacuum line capable of maintaining a vacuum of 1×10^{-5} mm. For isolation of dry solvent a 20-ml ampoule with breakseal and constricted opening was attached through a second constriction to a high vacuum system. Under a stream of nitrogen, bone dry barium oxide and a given volume of methylene dichloride were added, chilled, and the system was sealed. The solvent was degassed by freezing and thawing three times and the tube was removed by melting off under high vacuum. An identical setup was used for isolation of the catalyst precursor, excepting the substitution of a 5-ml ampoule. The calculated amount of dried benzene- or *p*-chlorobenzenediazonium hexafluorophosphate (Ozark Mahoning Co., Tulsa, Okla.) was added under a stream of nitrogen and the system was sealed. The diazonium salt was evacuated for 1 hr and the tube was removed as described above.

The ampoules containing solvent and diazonium salt were then fused on to a combination of monomer and polymerization tubes of 5 and 25-ml vol, respectively. Glass-coated iron magnets were sealed and magnetically anchored behind the two breakseals. The total polymerization apparatus is illustrated in Figure 1.

The polymerization apparatus was next evacuated, usually overnight with intermittent flameouts. Under a stream of nitrogen the monomer was then added. Solid monomers were introduced directly into the polymerization tube and subjected to a 15-min interval of evacuation at 10° without loss. Liquid monomers were added to the monomer tube, degassed five times, and distilled into the polymerization ampoule. This final distillation was intended to remove any hydroxyl compound which might have arisen, *e.g.*, as by hydrolysis of a trimethylsilyl group. Monomer tubes were melted off at their constriction subsequent to distillation of the liquid monomers. The nondistillable fraction (usually a speck of color) weighed <0.0001 g.

The solvent was chilled, the adjoining breakseal was broken, and the solvent was distilled into the polymerization tube maintained at liquid air temperature. The solvent section was next melted off at the constriction. The remaining breakseal was broken and the catalyst ampoule heated to 155–160° thus liberating phosphorous pentafluoride. The phosphorus pentafluoride catalyst was generated from this precursor as described by Campbell.[19,20] After condensation of all catalyst in the polymerization ampoule, the catalyst section was melted off at the constriction.

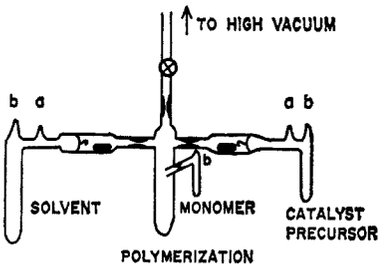


Figure 1.—Polymerization apparatus.

The polymerization ampoule was next melted off from the vacuum line and the contents of the ampoule were melted, mixed by agitation and placed in a bath of the appropriate temperature. Successful polymerizations were accompanied by yellow-green color formation after melting of the ampoule contents.

The polymerization was stopped by addition of an excess of methanol. After the color was discharged the mixture was diluted with chloroform, warmed to *ca.* 0° and neutralized with a 10% excess of sodium bicarbonate solution. The organic layer was washed with distilled water until neutral, treated with charcoal, and dried over anhydrous sodium sulfate. The polymer solution was concentrated and the polymer was precipitated, then redissolved and reprecipitated twice more by dropwise addition into 10 vol of petroleum naphtha. Tri-*O*-methyl and tri-*O*-ethyl-substituted dextrans were insoluble in solvents suitable for freeze drying and were, therefore, dried under high vacuum. Tri-*O*-benzyl-substituted dextran was freeze-dried from benzene. None of the polymers had a true melting point; rather they softened and melted over a wide range. The details of polymerization and results of characterization are reported in Table I.

Methanolysis of Polymers and Chromatography.—Polymer samples of tri-*O*-methyl and tri-*O*-ethyl dextrans were refluxed for 24 hr in 15 ml of 0.7 *N* methanolic HCl containing 1 g of drierite. The reaction mixture was cooled, Ag_2CO_3 added until neutral, solids filtered, and the mixture was concentrated to approximately 3 ml by blowing dry nitrogen over the clear liquid. The solutions were lightly spotted on a thin layer of Kieselguhr G, prepared according to Stahl, coated on glass to establish the location of the sugar, and thereafter heavily spotted to determine if dimeric species could be observed at lower R_f. The solvent system used for chromatography was benzene–methanol–ammonium hydroxide (80:20:0.3, v/v). After drying, the plate was developed by spraying with 25% sulfuric acid and placing in an oven at 110°. With each polymer only two spots were evident which represented the α and β anomers, the β anomer having the higher R_f value.[21] The mixture of anomers prepared by methanolysis of the appropriate anhydro sugar served as the standard. The vapor phase chromatographs[22] of the hydrolyzed polymers were obtained using a 6-ft column of diethylene glycol succinate polyester on ST 53 (AW) programmed for 120–180° at 2°/min and 45 cc of helium flow/min. Again the α and β anomers were present, but in addition a third component shown to be the anhydro sugar, the latter formed under the thermal conditions employed. Results are reported in Table II.

TABLE II

CHROMATOGRAPHIC RESULTS ON DEGRADED POLYMERS

Substance	R_f	Retention time, min
Methyl-2,3,4-tri-*O*-methyl-α-D-glucopyranoside	0.46	18.61
Methyl-2,3,4-tri-*O*-methyl-β-D-glucopyranoside	0.51	14.18
Methyl-2,3,4-tri-*O*-ethyl-α-D-glucopyranoside	0.53	18.96
Methyl-2,3,4-tri-*O*-ethyl-β-D-glucopyranoside	0.57	16.02
1,6-Anhydro-2,3,4-tri-*O*-methyl-β-D-glucopyranose	0.58	15.18
1,6-Anhydro-2,3,4-tri-*O*-ethyl-β-D-glucopyranose	...	13.61

(18) C. C. Sweeley, R. Bentley, M. Makita, W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).

(19) E. L. Wittbecker, H. K. Hall, and T. W. Campbell, *ibid.*, **82**, 1218 (1960).

(20) W. R. Sorensen and T. W. Campbell, "Preparative Methods of Polymer Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, p 253.

(21) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **40**, 1043 (1962); **41**, 1801 (1963).

(22) E. Bayer and R. Widder, *Anal. Chem.*, **36**, 1452 (1964).

Physical Methods.—Number-average molecular weights up to 15,000 were determined with a Mechrolab thermoelectric vapor pressure osmometer, Model 301A; values from 15,000–76,000 with a Mechrolab high speed membrane osmometer, Model 501. Trichloroethylene and toluene were used as solvents with the latter instrument for the perethylated and perbenzylated dextrans, respectively. Chloroform or methylene dichloride, although superior solvents, were too volatile to use in this instrument at 37°. Membranes were made of 300-gauge gel cellophane. Weight-average molecular weights were determined with a Beckman Spinco ultracentrifuge Model E using sedimentation velocity.

Nmr spectra were determined with a Varian A-60A analytical nmr spectrometer, infrared spectra with a Model 11 Baird infrared spectrometer.

Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter.

Results and Discussion

Although the polymerization of 1,6-anhydro-2,3,4-tri-*O*-methyl-β-D-glucopyranose has been previously reported,[5,6] the $\overline{DP}_n$ that has been attained previously is only *ca.* 25. Repetition of this work by us confirmed the low molecular weight reported.[6] It was thus necessary to make a systematic study of the polymerization in an attempt to find conditions for preparation of a high polymer. The low $\overline{DP}_n$ polymers obtained in prior work could have been caused by chain-transfer reactions or termination by impurities, catalyst, solvent, monomer, or polymer. To avoid chain termination by impurities, highly purified monomer and reagents and high vacuum technique were used throughout.

The use of a solvent of higher dielectric constant is believed in some systems to decrease transfer to gegen ion. However, the use of methylene chloride with BF_3–Et_2O or PF_5 catalysts (R-4, -5, Table I) at room temperatures gave a lower $\overline{DP}_n$ as well as lower yield than the use of toluene or benzene under the same conditions.

Since transfer processes are usually of higher activation energy than propagation, polymerizations were performed at increasingly lower temperatures (R-5–7, Table I). Lower temperatures resulted in a remarkable increase in $\overline{M}_n$ when methylene dichloride was the solvent and PF_5 the catalyst. This catalyst has been claimed to be very effective for cyclic ether polymerization.[23] The yellow-green color characteristic of oxonium ions[19] persists at −78° even after polymerization is complete but at higher temperatures chain-transfer or termination reactions occur and the color disappears. BF_3–OEt_2 was ineffective at −78°, which indicates no active monomer–catalyst complex was formed (R-3, Table I).

In an effort to determine the optimum catalyst concentration, a series of polymerizations was performed using varying amounts of PF_5 (R-7, -9–12, Table I). A "threshold" catalyst to monomer mole ratio of 0.025 was observed; that is, at this catalyst level a drastic reduction to 30% conversion occurred while the $\overline{DP}_n$ remained essentially the same. Yields of 85% were obtained when the catalyst to monomer mole ratio was 0.037 or greater. An increase in PF_5 concentration beyond conventional limits did not decrease $\overline{M}_n$, in contrast to the usual situation where large amounts of catalyst decrease the $\overline{M}_n$. These observations suggest that only a fraction of the catalyst was available as active catalyst for polymerization and at the lower concentration much of the catalyst was bound in an inactive form, perhaps with the oxygenated functions of monomer or polymer.

The tri-*O*-ethyl (R-16–21, Table I) and tri-*O*-benzyl (R-22–26, Table I) ethers of levoglucosan required a higher catalyst concentration for attainment of a $\overline{M}_n$ comparable with that obtained with the tri-*O*-methyl ether. A "threshold" catalyst to monomer mole ratio of 0.118 was observed with the tri-*O*-ethyl ether (R-18, Table I).

The rate of polymerization was found to be dependent on the kind of monomer, monomer concentration and catalyst concentration. In general, the tri-*O*-ethyl levoglucosan was found to polymerize at a faster rate than the other two tri-*O*-substituted ethers under the best conditions for the respective monomers. These rates were qualitatively measured by the time required for a polymer solution to become immobile and were observed to vary somewhat in identical runs. After the solutions became immobile, *ca.* 85–90% of polymer was isolated by the work-up mentioned, together with a small quantity of unreacted monomer.

The stereoregularity of the polymers could conveniently be estimated by optical rotations.[6] The high molecular rotations of all polymers suggests they are predominantly, if not exclusively, α linked. The molecular rotation of the perethylated and perbenzylated dextrans was 10–15% higher than the permethylated analog. This difference may reflect a slightly altered conformation in solution or small difference in structure. When the dielectric constant of the polymerization medium was lowered by having a high monomer concentration in solution, a lower $[\alpha]_D$ was observed with the tri-*O*-ethyl ether (R-19–21, Table I), but not with the tri-*O*-benzyl ether.

Polymers prepared from 1,6-anhydro-2,3,4-tri-*O*-ethyl-β-D-glucopyranose were found to be highly polydisperse, the polydispersity varying from 5 to 62.5. Fractionation of the material of $\overline{M}_w/\overline{M}_n = 62.5$ gave some fractions of M_n from 47,200 to 73,600. The lack of direct correlation of intrinsic viscosity with $\overline{M}_n$ also can qualitatively be attributed to the polydispersity of the perbenzylated products.

Hydrolysis studies showed no evidence for branching in the permethylated or perethylated synthetic dextran-like polymers. Both thin layer chromatography and vapor phase chromatography indicated only the α and β anomers of the appropriate monomers. A chain-transfer reaction during polymerization might have given rise to a carbonium ion at C-2, -3, or -4 which could initiate a new chain thereby creating a nonhydrolyzable ether linkage. The branch point so formed would survive the hydrolysis and subsequently give rise to a dimeric species. Neither mode of chromatography disclosed the presence of dimeric units.

The high $\overline{M}_n$ polymers prepared from tri-*O*-methyl levoglucosan at −78°, although homogeneous gels prior to work-up, were not completely soluble in any of a dozen different solvents or solvent mixtures after the polymers were isolated. The close packing of the polymer chains formed crystallites which had a limited solubility even in methylene dichloride or chloroform which were found to be the best solvents. This pre-

(23) E. Muetterties, U. S. Patent 2,856,370 (Oct 14, 1958); E. Muetterties, T. A. Bither, M. W. Farlow, and D. D. Coffman, *J. Inorg. Nucl. Chem.*, **16**, 52 (1959).

vented determination of exact molecular weights. As was expected, the triethyl derivative formed a polymer with a less tightly packed crystal lattice which was more soluble and accurate $\overline{M}_n$ data could be obtained on it. The X-ray powder patterns of the permethylated and perethylated synthetic dextrans indicate a very high degree of crystallinity, whereas the perbenzylated derivative was amorphous even on digesting with a poor solvent or film stretching. In this case, the polymer chains are more widely separated owing to bulkier side groups and thus have greater difficulty in forming the structural regularity needed for a unit cell.

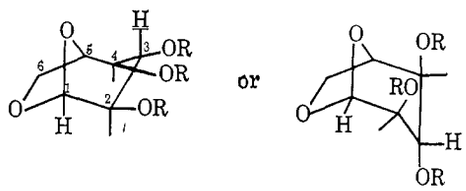
Various other monomers were investigated in our attempt to prepare a persubstituted linear α-(1→6)-linked polysaccharide with blocking substituents that were removable after polymerization. Attempted polymerization of 1,6-anhydro-2,3,4-tri-*O*-acetyl-β-D-glucopyranose using the PF_5 catalyst system at −78° was ineffective. No color indicative of an oxonium ion developed at a catalyst to monomer mole ratio of 0.10, thus no active species was formed. At a catalyst to monomer mole ratio of 3.10 a crystalline material precipitated from solution presumably a carbonyl–catalyst complex. The carbonyl group has a sufficiently high degree of basicity to compete successfully with the anhydro ring of the monomer as the coordination site with the Lewis acid. Work-up gave a 90% yield of recovered monomer.

There exists an unpublished claim[8] to polymerization of the above monomer using a catalyst system of bromoacetylglucose and acetyl chloride in the presence of silver perchlorate. This system illustrates a catalyst in which coordination does not prevent polymerization.

In order to reduce the likelihood of complex formation between the carbonyl groups and PF_5, the 1,6-anhydro-2,3,4-tri-*O*-trifluoroacetyl-β-D-glucopyranose monomer was prepared which should have had sufficiently reduced carbonyl electron density to obviate carbonyl–catalyst complex formation. This monomer was subjected to various polymerization conditions including catalyst to monomer mole ratios of 0.09:0.67, temperatures ranging from −78 to +28°, and from 5 to 10% monomer concentration. The latter concentration corresponds to nearly a saturated monomer solution in methylene dichloride. No characteristic color was formed in this system and presumably the active complex species did not form perhaps owing to unfavorable dipole–dipole repulsion that would exist in the active catalyst–monomer complex. Recovery of monomer (or levoglucosan following an aqueous work-up) was 95%.

A monomer with nonpolar blocking groups, 1,6-anhydro-2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranose, was also prepared and subjected to various polymerization conditions. No polymerization could be effected under the following conditions: (a) 20% monomer solution in methylene dichloride solvent, PF_5 catalyst to monomer mole ratios from 0.186 to 0.78, and temperatures ranging from −78 to +28°; (b) BF_3 catalyst to monomer mole ratios from 0.25 to 0.30, with or without trifluoroacetic acid cocatalyst at above temperatures and monomer concentration. The addition of monomer, alone or as a 40% solution in carbon tetrachloride, to trifluoroacetic acid at temperatures ranging from −28 to +28° produced only a trace of the trifluoroacetic acid addition product. In all these polymerization attempts no characteristic color was apparent, indicating that an active species was not formed. Monomer recoveries were *ca.* 90%.

The nmr spectra of the monomers were recorded in order to determine the conformation of the pyranose ring. If the anomeric hydrogen shows no coupling



with either H_2 or H_3, the pyranose ring does not exist in the chair conformation.[24] H_1 and H_3 will exhibit long range coupling of ~1 cps only if they are diequatorial.[25] The spectra of the tri-*O*-methyl, tri-*O*-ethyl, and tri-*O*-trimethylsilyl derivatives show no anomeric hydrogen coupling, indicating another conformation of the pyranose ring. Hall and Hough[24a] have shown that the pyranose ring of 1,6-anhydro-2,3,4-tri-*O*-acetyl-β-D-glucopyranose exists in the chair conformation on the basis of H_1 coupling. The spectrum of the tri-*O*-trifluoroacetyl analog is essentially the same as that of the tri-*O*-acetyl spectrum except that the resonance frequencies of H_1–H_5 are at lower field because of deshielding by the trifluoroacetyl clusters. For example, H_1 and H_3 for the tri-*O*-acetyl levoglucosan resonate at δ 5.45 and 4.85, respectively, whereas in the tri-*O*-trifluoroacetyl analog, the respective δ values are 5.62 and 5.12. Thus, the pyranose rings in both the tri-*O*-trifluoroacetyl and tri-*O*-acetyl levoglucosan are in the chair form. It thus appears that dipole–dipole interaction is relatively more important than steric interaction in determining molecular conformation.[26] It is likely that the pyranose ring in 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose is also in the chair conformation, since the anomeric hydrogen shows a coupling constant of ~1 cps.

Mechanism

The cationic polymerization of cyclic ethers is generally regarded[27] as proceeding through tertiary oxonium ions with nucleophilic attack of monomer at the α carbon. Any strong electrophile could conceivably act as a polymerization catalyst if the counter ion were a very poor nucleophile. However, PF_5 is the preferred catalyst[23] for cyclic ether polymerization and does not require a cocatalyst. This catalyst has given very high molecular weight polymer with tetrahydrofuran[28] but has repeatedly given irreproducible kinetics[29] and is apparent very sensitive to trace amounts of impurities.

(24) Personal communication with L. D. Hall, The University of British Columbia.

(25) L. D. Hall and L. Hough, *Proc. Chem. Soc.*, 382 (1962); L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964).

(26) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).

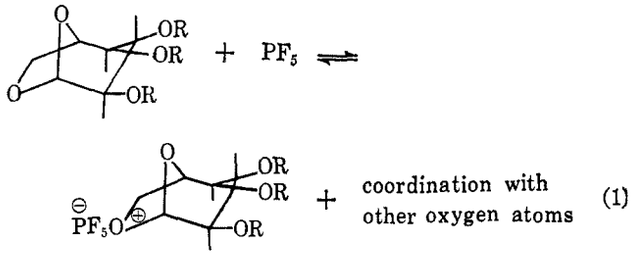
(27) J. Furukawa and T. Saegusa, "Polymerization of Aldehydes and Oxides," Interscience Publishers, Inc., New York, N. Y., 1963, Chapters 3–4.

(28) R. C. Burrows, *Polymer Preprints*, **6**, 600 (1965).

(29) H. K. Hall, Jr., *ibid.*, **6**, 535 (1965). Discussion of H. K. Hall, Jr., and A. Ledwith, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

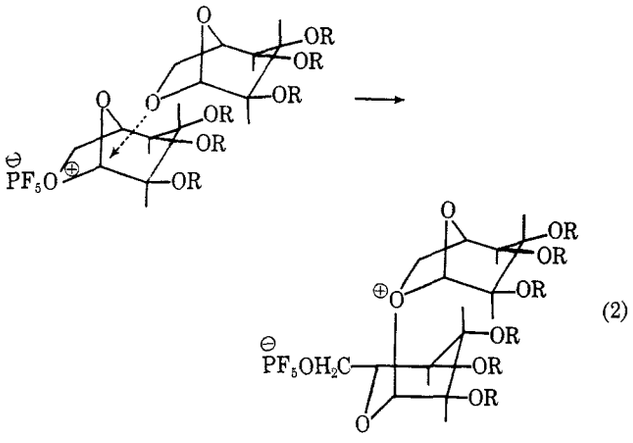
The polymerization of a 1,6-anhydropyranose monomer by PF_5 can likewise be visualized to proceed by a trialkyl oxonium ion mechanism,[5] and the observed high stereoregularity of the product requires the assumption of this mechanism. The Lewis acid would be expected to partition itself among the available oxygen atoms of the monomer and the concentration required to form the reactive complex with the 1,6-anhydro ring should, therefore, be comparatively high and should vary significantly with each monomer. A higher catalyst concentration was, in fact, required to form the reactive complex with the tri-*O*-ethyl and tri-*O*-benzyl monomer than with the tri-*O*-methyl monomer and all monomers required substantially more catalyst than the trace needed for tetrahydrofuran polymerization.[30a]

A reasonable initiation reaction may be described in three steps. In the first, the strongly electrophilic PF_5 coordinates with the oxygen of the 1,6-anhydro ring.



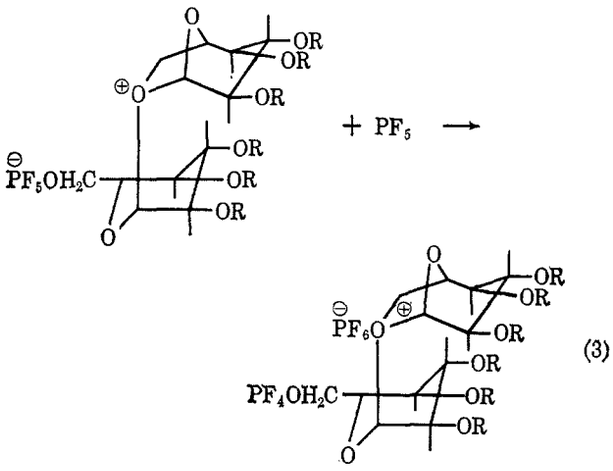
(1)

This species is now sufficiently reactive to initiate the second step, nucleophilic attack on the 1-carbon of the oxonium by ether oxygen of the monomer anhydro ring. This attack opens the anhydro ring and generates a new oxonium ion as shown in reaction 2.



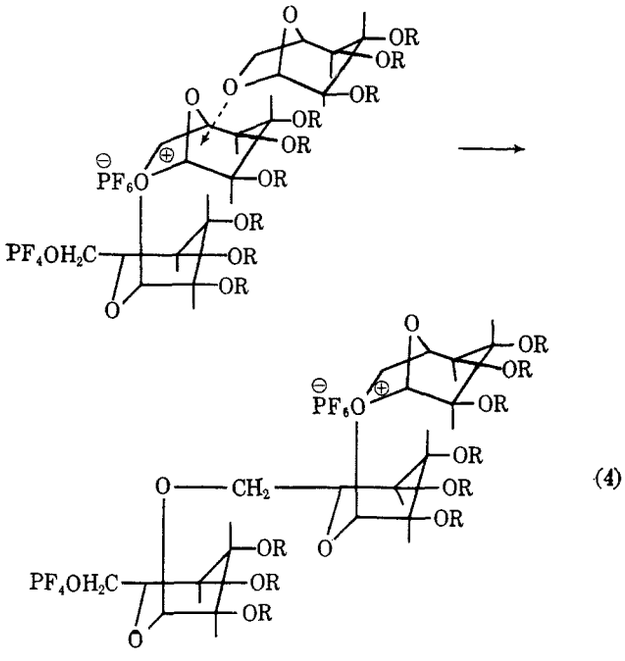
(2)

Propagation by this species would, however, require increasing separation of charge, which would be energetically unsatisfactory at low $\overline{DP}$ levels. At higher $\overline{DP}$ levels coiling of the chain might permit the formation of a cyclic ion pair. A preferred third step of the initiation would involve abstraction of a fluoride ion by another molecule of PF_5 (reaction 3 following). M. P. Dreyfus[30b] suggested such an initiation step with BF_3 or PF_5 catalysts to accommodate the fact that high-mole concentrations of catalyst (5–20%) polymerize tetrahydrofuran to a high-molecular weight product. The autoionization process $2PF_5 \rightleftarrows PF_4^+ + PF_6^-$ appears to be a less likely prospect, although it has been observed with PCl_5 or $SbCl_5$ in the solid state.[31]



(3)

The propagation reaction 4 is very similar to reaction 2, column 1.



(4)

If traces of water were present, an alternate mode of initiation could occur. A proton would arise from reaction of PF_5 with cocatalyst water and could effect initiation in two analogous steps. A second molecule of PF_5 might also convert the $^-PF_5OH$ counter ion to the extremely weak nucleophile $(PF_5OHPF_5)^-$.[28]

$$PF_5 + H_2O \longrightarrow H^{+-}PF_5OH$$

The high polymer polydispersities could be explained in part by multiple possibilities for the initiation step. The different electrophilicities of H^+ and PF_5 would lead to different rates of initiation.[28] However, rather elaborate precautions were observed to avoid this cause of variability and it is probably of less importance than the ability of catalyst to coordinate with multiple sites on the monomer or polymer and the influence of the various possible gegen ions on the rate of polymerization and extent of termination. The reactivity and

(30) (a) *Polymer Preprints*, **6**, No. 2, 608 (1965); (b) M. P. Dreyfus, Discussion at Symposium on Cyclic Ether Polymerization, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(31) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 381.

lifetime of the living end will probably be different for PF_6^-, PF_5OH^-, and $(PF_5OHPF_5)^-$ or $^-PF_5O$ polymer since the rates of polymerization with a PF_6^- gegen ion are known to be faster than with $SbCl_6^-$, *e.g.*, and PF_6^- is known to hinder transfer reactions.[32]

The polymerization solutions of the three dextran-like polymers at −78° maintained the characteristic color of the oxonium ion which was immediately discharged on adding a terminating agent such as water or methanol. The polymers thus appear to be living[33] in that at least part remain indefinitely active at this temperature.

The most striking characteristic of this polymerization is, of course, its high stereoregularity. The band at 891 ± 7 cm^{-1} in the infrared region characteristic of a β-anomeric linkage[34] is absent and the high optical rotation characteristic of an α linkage is even more convincing evidence. Rotations of +195 to +208 compare favorably with the value of +215 at 25° (*c* 0.53, HCl_2CCCl_2H) for the methylated natural dextran containing 95% α-(1→6)-D-glucosidic linkages.[35] The small amount of α-(1→3)-D-glucosidic linkages presumably increases the dextrorotatory power of the methylated natural polymer as it does the unsubstituted dextran.[36] Additional evidence for exclusive α linkage was also obtained from the nmr of the perethylated dextran. No observable C_1 axial proton resonance, which would be present if β linkages were present, was observed δ 0.45 upfield[37] from the very intense C_1 equatorial hydrogen resonance at δ 4.97.[38] Of the carbon atoms adjacent to the trialkyloxonium ion, the C-1 atom is the most electropositive and would be the expected site of attack. Apparently not only is attack on C-6 essentially absent but randomization *via* carbonium ion formation during propagation also must be nearly negligible.

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(32) A. Ledwith, discussion at Symposium on Cyclic Ether Polymerization, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.
(33) M. Szwarc, *Advan. Polymer Sci.*, **2**, 275 (1960).
(34) T. H. Barker, E. J. Bowne, M. Stacey, and D. H. Whiffen, *Chem. Ind.* (London), 196 (1953).
(35) J. W. Van Cleve, W. C. Schaefer, and C. E. Rist, *J. Am. Chem. Soc.*, **78**, 4435 (1956).
(36) A. Jeanes, W. C. Haynes, C. A. Wilham, J. C. Rankin, E. H. Melvin, M. J. Austin, J. E. Cluskey, B. E. Fisher, H. M. Tsuchiya, and C. E. Rist, *ibid.*, **76**, 5041 (1954).
(37) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).
(38) W. M. Pasika and L. H. Craig, *Can. J. Chem.*, **41**, 293 (1963).

Formation of Fructosazine

SHOJI FUJII, REIKO KIKUCHI, AND HIDEO KUSHIDA

Kyoto General Medico Chemical Laboratory, Bessho-cho 95, Misasagi, Yamashina, Kyoto, Japan

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Condensation of 2 moles of 2-amino-2-deoxy-D-glucose (D-glucosamine) or 2-amino-2-deoxy-D-mannose (D-mannosamine) in hot methanol gave, in each case, 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine (fructosazine). The yield of fructosazine derived from 2-amino-2-deoxy-D-mannose at 37° was about three times as large as that derived from 2-amino-2-deoxy-D-glucose. The presence of 2-amino-2-deoxy-D-mannose was observed together with fructosazine in a methanolic alkaline solution of 2-amino-2-deoxy-D-glucose.

The formation of fructosazine was studied at first with 2-amino-2-deoxy-D-glucose[1] (D-glucosamine), and with D-fructose and ammonia[2] in methanol. Stolte[3] identified this product as a pyrazine derivative, on the basis of the formation of pyrazine-2,5-dicarboxylic acid by oxidation of this product, and he named it as fructosazine having a formula of $C_{12}H_{20}N_2O_8$. Later Taha[4] carried out an experiment with 2-amino-2-deoxy-D-glucose and aqueous ammonia, and separated the fructosazine from the reaction mixture after 6 months by cellulose column chromatography in the yield of 4.6%, and Kuhn, Krüger, Haas, and Seeliger[5] synthesized fructosazine from 1-amino-1-deoxy-D-fructose in a yield of 26%.

It takes many days or sometimes even several months for the formation of fructosazine under the mild conditions which were employed by the previous investigators. We have found that fructosazine is formed during 4 hr by bubbling air into the methanolic solution of 2-amino-2-deoxy-D-glucose in the presence of a slight excess of sodium methoxide at 70°. Fructosazine prepared from 2-amino-2-deoxy-D-glucose under the new reaction conditions showed an infrared spectrum and physical constants identical with those of fructosazine prepared from 1-amino-1-deoxy-D-fructose. The compound was converted into pyrazine-2,5-dicarboxylic acid,[6] mp 253° dec, and its dimethyl ester, mp 169°. Identity of this ester was established by mixture melting point and comparison of the infrared spectrum with that of the authentic sample prepared[6] from 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline.[7]

Fructosazine showed an absorption maximum at 274 mμ and spectroscopic determination of the compound was possible. Table I shows the yields of fructosazine as determined by spectroscopy at 40 and 70°. When the crude compound was purified by treatment with a cation ion-exchange resin, the yield was diminished,[8] and the eluate with 3 *N* hydrochloric acid produced

(1) C. A. Lobry de Bruyn, *Ber.*, **31**, 2476 (1898).
(2) C. A. Lobry de Bruyn, *Rec. Trav. Chim.*, **18**, 72 (1899).
(3) K. Stolte, *Beitr. Chem. Physiol. Pathol.*, **11**, 19 (1908).
(4) M. I. Taha, *J. Chem. Soc.*, 2468 (1961).
(5) R. Kuhn, G. Krüger, H. J. Haas, and A. Seeliger, *Ann.*, **644**, 122 (1961).
(6) H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **77**, 829 (1958).
(7) F. Weygand and C. Bergmann, *Ber.*, **80**, 255 (1947).
(8) The fructosazine previously reported, without cation ion-exchange resin treatment, appears to be the mixture and is not pure fructosazine.