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Preparation of a Non-hydrolyzable Polysaccharide and Polygluconic Acid *via* Epoxide Polymerization

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Epoxide polymerization of 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose is unsuccessful with Lewis acids and certain anionic catalysts, but polymerization by strong bases such as potassium and cesium hydroxide results in products with degrees of polymerization up to twenty-five. The factors affecting this process are studied in detail and a mechanism of heterogeneous epoxide polymerization is proposed. The main new feature of the mechanism is an equilibrium chain inactivation with water and a distribution of un-ionized polymer between the catalyst surface and the liquid phase. Dilution by good solvents *including monomer* can thus favor chain inactivation with water and initiation over propagation and can decrease the degree of polymerization obtained. The observed optimum monomer to catalyst ratio for the formation of high molecular weight polymers is thus explained. The polymer is hydrolyzed quantitatively to a monomethylated non-hydrolyzable polysaccharide and oxidized to a polygluconic acid, although the oxidation appears to be complicated to a minor degree by a saccharinic acid rearrangement.

In recent years effort has been directed toward the chemical synthesis of high molecular weight polysaccharides.[1-9] Interest in this problem is generated not only by the challenge of the synthesis but also by the possible use of these substances in medicine or as model substances for the study of physiological processes involving macromolecules,[8] and by the possibility of correlating systematically chemical structure and biological activity. Among naturally occurring polysaccharides are many containing carboxylic acid functions, and these often exhibit dramatic viscosity effects and solution properties as would be expected of polyelectrolytes: the mucilages, pectin, gel formers and hyaluronic acid are examples. In addition, Mora has investigated the effect of polyglucoses containing carboxyl groups on the action of bacteriophage and certain enzymes,[9] and investigations of this type undoubtedly will be carried further.

This article deals with the investigation of possible routes to synthetic polysaccharides *via* the polymerization of 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose (I), and conversion of the product to a polygluconic acid derivative. These polymers have certain unique features for previously reported polysaccharides are all linked by a hydrolyzable acetal link while these are ether-linked and non-hydrolyzable. Other synthetic polysaccharides have highly branched structures and rather broad molecular weight distributions. These polymers in contrast are linear, and since the monomer is a substituted ethylene oxide, it will yield polymers of Poisson molecular weight distribution if a rapid initiation step and a method of propagation without termination or chain transfer can be found, although our systems do not appear to fulfil these latter conditions.

The synthetic sequence included the following steps: the preparation of 1,2,5,6-di-O-isopropylidene-D-glucofuranose, its methylation, partial hydrolysis and subsequent monotosylation on the 6-position. The 1,2-O-isopropylidene-3-O-methyl-6-O-tosyl-D-glucofuranose so formed was allowed to react with base to give 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose and this was subjected to a variety of polymerization catalysts and conditions and polymers of various degrees of polymerization were obtained. Some new insight into epoxide polymerization is suggested by the proposed mechanism. Hydrolysis of the polymer gave the corresponding non-hydrolyzable polyanhydroglucose monomethyl ether with no significant degradation of the chain and oxidation with hypoiodite gave a polyanhydrogluconic acid. These reactions are straightforward, but there are puzzling and interesting features to the polymerization mechanism and the oxidation apparently is accompanied by a minor side reaction. Both of these topics are discussed below.

Experimental

Preparation of 5,6-Anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose from D-Glucose.—Standard references to the synthesis of diacetone glucose can be misleading because they do not mention factors that can lead to failure: The heterogeneous reaction between glucose and acetone competes in rate with the homogeneous acid-catalyzed condensation of acetone. If the particle size of glucose is too large, the acid concentration too high or agitation too slight, water from the acetone condensation can reverse the equilibrium between the mono- and di-isopropylidene derivatives. Neutralization of the acetone solution is not satisfactory by insoluble alkali carbonates; ammonia gas should be used to prevent the extremely rapid partial hydrolysis. Benzene cannot be used to extract acetone condensation products preferentially because of the high solubility of the 1,2,5,6-di-O-isopropylidene derivative. By stirring 100 g. of anhydrous copper sulfate, 100 g. of anhydrous glucose, 2 l. of dry acetone and 15 ml. of concentrated sulfuric acid vigorously for 48 hours and working up in a conventional manner but with the above precautions, crude yields of 60–70% of product of m.p. 90–100° were obtained routinely. Purification by recrystallization gave 1,2,5,6-di-O-isopro-

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TABLE I

SELECTED POLYMERIZATIONS OF 5,6-ANHYDRO-3-O-METHYL-1,2-O-ISOPROPYLIDENE-D-GLUCOFURANOSE

Run	Temp., °C.	Catalyst	Weight % catalyst	$\frac{\text{Monomer}}{\text{Catalyst}}$	Time	Yield, %	M.p., °C.	$\overline{\text{D.P.}}_n$
1	100	NaOMe	10.0	2.0	2 wk.	84	87–122	2.0
2	100	NaOH	10.0	1.6		83	105–131	1.8
3	100	KOC_6H_5	10.0	5.0		88	110–130	4.0
4	100	KOH	10.0	2.3		91	135–170	9.8
5	75	KOH	5.0	4.6		92	145–168	11.0
6	50	KOH	5.0			81	100–130	11.0
7	50[a]	KOH	5.0			86	128–150	11.0
8	50[b]	KOH	5.0		2 wk.	83	122–140	18.0
9	50[c]	KOH	5.0			93	130–145	25.0
10	50[c]	KOH	0.5	46.0	1 mo.	n.r.[d]	.....	..
11	50[c]	KOH	1.0	23.0	1 mo.	n.r.	.....	..
12	50[c]	KOH	2.0	11.5	2 wk.	n.r.	.....	..
13	50[c,e]	KOH	4.0	5.8		63/72	95–106/101–113	5.0/7.0
14	50[c,e]	KOH	5.0	4.6		91/87	135–158/132–161	25.0/24.0
15	50[c,e]	KOH	6.0	4.0		90/89	145–168/139–171	24.0/25.0
16	50[c,e]	KOH	7.0	3.4		91/86	133–159/142–163	24.5/25.3
17	50[c,e]	KOH	8.0	2.9		91/86	141–159/133–161	24.0/23.5
18	50[c,e]	KOH	9.0	2.6		90/86	122–141/128–150	18.0/16.5
19	50[c,e]	KOH	10.0	2.3		85/90	121–133/126–141	11.0/10.0
20	50[c,e]	KOH	15.0	1.4		89/87	105–121/111–126	1.5/1.8
21	50	CsOH	2.0	32.0		20	92–108	2.3
22	50	CsOH	5.0	13.0		81	121–148	23.6
23	50[c]	CsOH	5.0	13.0		83	138–162	23.1
24	50[c]	CsOH	15.0	5.0	2 wk.	87	129–156	19.0

[a] One-quarter volume benzene added. [b] One volume benzene added. [c] One-half volume benzene added. [d] No polymer formed, only oil. [e] Duplicate runs.

pylidene-D-glucofuranose, m.p. 105–106°, $[\alpha]^{30}\text{D}$ − 16.3° (2.0, water); literature[10] m.p. 105–106°, $[\alpha]^{21}\text{D}$ − 16.9° (2.43, water).

Methylation by the method of Glen and co-workers[11] gave 1,2,5,6-di-O-isopropylidene-3-O-methyl-D-glucofuranose in 40% yield, b.p. 142–143° (13 mm.) and $[\alpha]^{26}\text{D}$ −31.85° (5.05°, ethanol); literature[12] b.p. 139–140° (12 mm.) and $[\alpha]^{20}\text{D}$ −32.17° (5.05, ethanol).

Partial hydrolysis[13] yielded 68% of 1,2-O-isopropylidene-3-O-methyl-D-glucofuranose, b.p. 174–175° (0.3 mm.), $[\alpha]^{25}\text{D}$ −54.38° (4.0, chloroform); literature[13] b.p. 173–175° (0.1 mm.), $[\alpha]^{15}\text{D}$ −54.0° (4.0, chloroform).

Tosylation in 67% yield and reaction of crude product with alkali in 37% yield by the method of Vischer and Reichstein[14] gave 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose, b.p. 77–78° (0.15 mm.) and $[\alpha]^{21}\text{D}$ −62.65° (2.07, acetone); literature[14] b.p. 75–80° (0.1 mm.) and $[\alpha]^{15}\text{D}$ −64.8 ± 2° (2.0, acetone).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.50; H, 7.40. Found: C, 55.42; H, 7.38.

Polymerizations.—Potassium hydroxide, sodium hydroxide, potassium phenoxide and sodium methoxide were reagent grade materials. They were pulverized, dried for 5 days at 50° *in vacuo* and stored in a desiccator over phosphorus pentoxide. Lithium hydroxide and cesium hydroxide were fused, pulverized and stored over phosphorus pentoxide.

Pure 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose was prepared by storing thrice-distilled monomer over calcium hydride and distilling just prior to use. Polymerizations were carried out in sealed Pyrex tubes under reduced pressure. Monomer and catalyst (also solvent when used) were weighed into the tube, the tube was connected to a high vacuum line and the mixture degassed by freezing in Dry Ice–acetone and thawing several times. The tube was then sealed under vacuum and placed in a constant temperature oil-bath. Polymerization was accompanied by dark brown discoloration and by an increase in viscosity which began at the surface of the catalyst.

The product was isolated by dissolving the entire organic contents of the polymerization tube in benzene, washing with dilute aqueous hydrochloric acid, dilute aqueous sodium bicarbonate until basic and then with water until neutral. The discoloration passed into the aqueous phase. The benzene layer was separated and freeze-dried. The resulting material was redissolved in a minimum amount of benzene, filtered to remove inorganic material and again isolated by freeze-drying.

The polymers were all ash-free, white, fluffy powders. None of the polymers had a true melting point, rather they gradually softened and melted over a wide range. Regardless of molecular weight, all of the polymers were soluble in benzene, acetone and dioxane, and they were insoluble in water, methanol, ethanol, diethyl ether, petroleum ether, methyl ethyl ketone, ethyl acetate, chloroform and carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.50; H, 7.40. Found: C, 55.53; H, 7.50.

Molecular Weights.—Number-average molecular weights were determined using a thermoelectric vapor phase osmometer. The theory underlying the use of this apparatus is due to Hill[15] and Baldes,[16] while the design of the instrument was by Debye.[17,18]

Hydrolysis of Polymer.—Approximately 0.2 g. of polymer was dissolved in 15–25 ml. of 80:20 (v./v.) dioxane–water in a 50-ml. round-bottomed flask equipped with a thermometer, gas bubbler and condenser arranged for downward distillation. The tip of the condenser did not quite touch the surface of 50 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid in an erlenmeyer flask surrounded by an ice-bath. Two drops of concentrated sulfuric acid was added to the polymer solution and a slow stream of nitrogen was bubbled through the solution.

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[18] P. Debye and H. Coll, Tech. Rep. No. 2, *ibid.*, (1958).

By carefully controlling the heating, it was possible to hydrolyze the polymer quantitatively without distilling off any of the solvent. The 2,4-dinitrophenylhydrazine solution was allowed to stand in the ice-bath for an additional hour and then filtered through a tared, sintered-glass funnel. The precipitate was washed with cold 2 N hydrochloric acid and then with water and dried to constant weight. The amount of acetone liberated from the polymer was then calculated. In all cases, the experimental values agreed to within $\pm 0.5\%$ of the theoretical value.

The polymer after the hydrolytic removal of the isopropylidene groups was isolated by neutralizing the sulfuric acid with barium carbonate and filtering. The filtrate was treated with decolorizing carbon, filtered and isolated by freeze-drying. A determination of the molecular weight of one sample of hydrolyzed polymer confirmed that the polymer itself had not been degraded.

Hypoiodite Oxidation.—Oxidation of the polymer after the hydrolytic removal of the isopropylidene groups was accomplished by suspending 0.6012 g. (3.43×10^{-3} mole) of the polymer in 50 ml. of water. To this suspension was added 10 ml. of 0.1 N iodine solution and 15 ml. of 0.1 N aqueous sodium hydroxide. The sodium hydroxide was added dropwise from a buret. The alternate addition was repeated until 100 ml. (5×10^{-3} mole) of iodine and 150 ml. (1.5×10^{-2} mole) of sodium hydroxide had been added. The flask was swirled vigorously during the course of the addition, and the polymer went into solution as the oxidation proceeded.

The solution was allowed to stand for an additional 15 minutes, and then a 10-ml. aliquot was withdrawn, acidified with 10 ml. of 2 N sulfuric acid and titrated to a thyodene end-point with 0.1 N sodium thiosulfate. The titration indicated that approximately 90% of the theoretical amount of iodine had been consumed.

Acidification of the solution with acetic acid produced a precipitate. This precipitate was filtered, washed thoroughly with water and dried to constant weight. The material was a white solid with a yellowish cast which melted at 200–210°, and it had a methoxyl content of 14.2%.

Preparation of the Calcium Salt of the Polygluconic Acid.—Approximately 0.3 g. of the polygluconic acid was dissolved rapidly in 10 ml. of 30% (v./v.) aqueous ammonium hydroxide. To this solution was quickly added 10 ml. of a 10% (w./w.) aqueous solution of calcium acetate. An immediate white precipitate was obtained. This precipitate was filtered, washed thoroughly with water and dried to constant weight.

Infrared Spectra.—The infrared spectra of all of the above products except 1,2-O-isopropylidene-3-O-methyl-6-O-tosyl-D-glucofuranose have been recorded in the Ph.D. thesis of R.S.N.

Results and Discussion

Polymerization.—The monomer, 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose, is a substituted ethylene oxide and it is in part polymerized by base even under the conditions of its preparation. Unfortunately and as was expected, Lewis acid catalysts, which are effective catalysts for the polymerization of simpler epoxides and some of which cause stereospecific polymerization,[19] are unsatisfactory with this monomer.

Ferric chloride, zinc chloride and zinc chloride–aluminum isopropoxide[20] cause decomposition, while aluminum chloride and aluminum isopropoxide do not react at all. Cleavage of the tetrahydrofuran nucleus or the 1,3-dioxolane nucleus probably occurs and the epoxide ring is not sufficiently reactive to permit specific attack. Exploratory experiments to effect polymerization with sodium–naphthalene,[21] *n*-butyllithium, strontium and barium carbonates[22] and calcium butylacetoacetate[23] were also unsuccessful under our conditions.

Initiation by strong bases, however, resulted in a slow polymerization as is the case with other epoxides. The main structural features of the polymers produced can be deduced from the method of synthesis. The reactions which they undergo and which are discussed later are consistent with a backbone of a substituted polyethylene oxide. Since other nucleophiles attack this monomer primarily or exclusively on the C_6-atom,[24,25] we assume polymerization is by this route and the product has a head-to-tail structure. We will qualify this statement slightly below.

Three factors were found to affect the polymerization markedly: the nature of the cation, the monomer to catalyst ratio and the presence or absence of a solvent. In the series lithium, sodium and potassium hydroxides, the larger cations are found to be more effective catalyst components. Lithium hydroxide does not cause polymerization, oligomers are formed with sodium hydroxide, while under our optimum conditions polymers of degree of polymerization twenty-five were formed with potassium hydroxide. Cesium hydroxide, however, produced polymers of no higher molecular weight than potassium and the optimum conditions were somewhat different. Since the initiation and propagation steps may be either dipole–dipole or ion–dipole reactions and the latter are expected to proceed more readily, it is not surprising that the larger cations with more ionic metal–oxygen bonds are the superior catalyst. Similar results have been observed with propylene oxide,[26] but have been interpreted as caused by the specific geometry of the potassium hydroxide lattice.

In the potassium hydroxide-catalyzed systems, dilution of the monomer with one-half its volume of benzene results in a substantial increase in the molecular weight of the polymer produced, while dilution beyond that ratio again resulted in lower degrees of polymerization. Dilution with tetrahydrofuran, however, did not favor higher molecular weights, and with cesium hydroxide the use of benzene did not improve the results obtained.

The most surprising characteristic of this polymerization is the dependence of molecular weight on the monomer to catalyst ratio. The optimum amount of catalyst corresponded to five to eight per cent. of the weight of the monomer used or a molar ratio of monomer to potassium hydroxide of from three to five. Obviously, all of the catalyst is not active in this polymerization. Initiation must be at the solid–liquid interface. It would be expected that larger amounts of catalyst could decrease the molecular weight of the polymer by making initiation more probable, but it is less obvious why a decrease in the amount of catalyst will likewise decrease the size of the polymer molecules produced. However, this was found to

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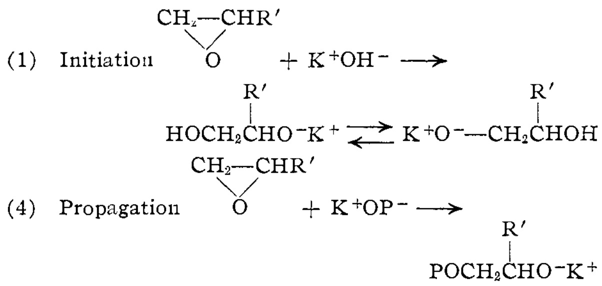
be the case with duplicate series of polymerizations using potassium hydroxide (Fig. 1) and similar less complete results were obtained with cesium hydroxide. Purification of the monomer by pre-polymerization and distillation did not change these results in any way. Furthermore, large amounts of alkali have also been used on simpler epoxides, but we are unaware of an explanation. Another feature of these polymerizations that bears emphasis is the fact that these results correspond to high conversions. The low degrees of polymerization obtained with small amounts of catalyst are not due to slow rates of propagation and incomplete reaction but must be explained by the fact that under these conditions a chain transfer or termination process competes effectively with propagation.

In spite of a number of recent publications on the heterogeneous polymerization of epoxides[26-30] there seems to be no published observation of this phenomenon or any explanation in terms of previous mechanisms. However, we believe these and other results can be qualitatively explained by a simple extension of the conventional mechanism of base-catalyzed epoxide polymerization as defined by the following equations (P represents polymer residue)



(3) Equilibrium chain inactivation $K^+OP^- + H_2O \rightleftharpoons HOP + K^+OH^-$

(3a) Distribution HOP (reaction site) $\rightleftharpoons$ HOP (solvent)

(4) Termination $K^+OP^- \longrightarrow$ P inactive $+ K^+OH^-$

The initiation process consists of a nucleophilic attack of the hydroxide ion on the primary carbon atom of the epoxide forming a secondary alkoxide ion. Since a secondary alcohol is usually less acidic than the primary, an equilibrium will be set up probably favoring primary over secondary alkoxide ion. Furthermore, the rate of reaction of the primary anion with epoxide will be faster than that of the secondary for obvious steric reasons and therefore it is to be expected that in any hydroxide-catalyzed secondary alkylene oxide polymer there will be at least one head-to-head unit near the center of the chain. Furthermore, polymerization will occur at both ends of the polymer chain, and there will thus be a statistical factor favoring growth of long chains if hydroxide or sulfhydryl is used as the catalyst rather than phenoxide, alkoxide or mercaptides. This seems to be in line with general experience.

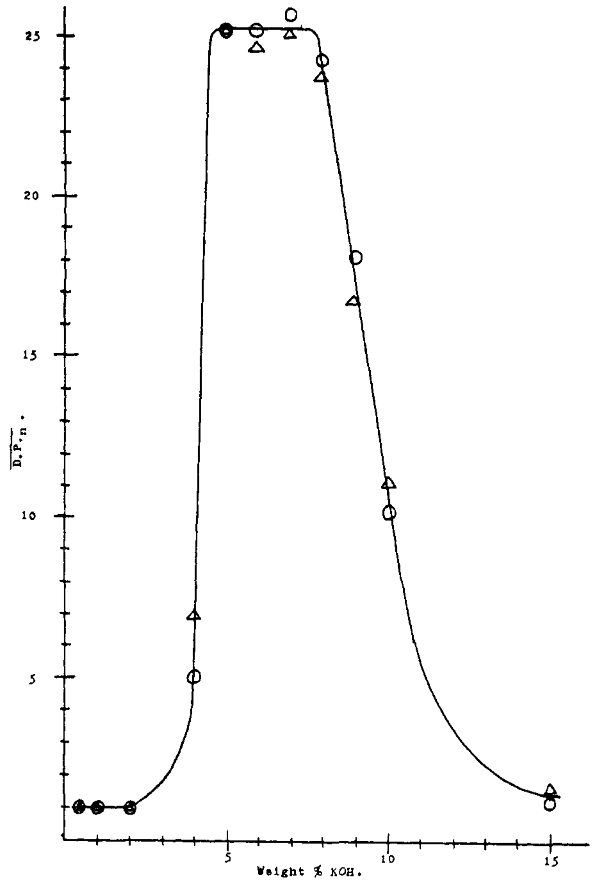


Fig. 1.—Number-average degree of polymerization of polymers of 5,6-anhydro-3-O-methyl-1,2-O-isopropylidene-D-glucofuranose: ○, first run; △, second run.

The propagation process (2) is obvious. The reaction of alkoxide with bound water in the catalyst we have called "equilibrium chain inactivation" (3). Other chain transfer processes are possible but since these systems are not anhydrous, chain transfer to water will be most important. The system is heterogeneous and any factor which favors removal (3a) of the alcohol from the locus of the reaction, *viz.*, the alkali surface, will shift equilibrium 3 to the right and cause initiation at the expense of propagation. Catalyst–monomer ratios and the presence or absence of a solvent—and its nature—will thus affect 3a. In general, then any factor favoring initiation, chain inactivation or termination over propagation will result in the production of low molecular weight products, and the relative rates of termination and propagation will place an upper limit on the degree of polymerization obtainable in this reaction.

Consider now our results. As reaction proceeds the viscosity of the medium increases rapidly and the mixture sets to a brittle resin around the catalyst making agitation ineffectual. We believe that under these conditions diffusion of the monomer through the rigid glass to the locus of reaction may become the rate-determining step in the propagation process and may thus permit termination (4) to be favored. Moderate dilution by benzene reduces the viscosity and permits propagation to

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(29) D. M. Simons and J. J. Verbanc, *J. Polymer Sci.*, **44**, 303 (1960).

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compete favorably with termination. (This effect is not noted with cesium hydroxide, perhaps because of the larger atomic volume of cesium, its greater possibility of coördination with monomer and the lower concentration of hydroxide ion per unit area of catalyst surface.) Further dilution with benzene decreases the concentration of monomer to such an extent that the rate of initiation and propagation are decreased and termination favored. Furthermore, excessive dilution will remove alcohol from the reaction site (3a) and shift the chain inactivation equilibrium to the right. As a result initiation will be favored over propagation. Excellent solvents for the polymer will favor extraction away from the reaction site and will disfavor propagation. This is in agreement with the expected solvent behavior of benzene and tetrahydrofuran and their effect on molecular weight.

The effect of catalyst to monomer ratio can be explained similarly. At high catalyst to monomer ratios, an excessive number of chains is initiated and degree of polymerization is consequently low. Increase in amount of monomer increases the chain length up to a point. Too large an excess of monomer will, however, extract un-ionized polymer from the locus of reaction and by shifting equilibrium 3 favor initiation over propagation.

The effect of temperature on this polymerization was not studied systematically but it was noted that no polymerization occurred over a period of three months at 25° while an observable increase in viscosity occurred in a few hours at 50°. A study of the effect of time of polymerization on the molecular size would give further insight into the importance of the termination process. However, since cesium and potassium hydroxides at optimum conditions produce polymers of degree of polymerization twenty-five, we believe that this probably corresponds to an optimum ratio of the rates of propagation and termination of the alkoxide ion.

Polymer Properties and Conversion.—The polymers prepared were characterized by infrared spectra, acetone content (by hydrolysis), carbon-hydrogen analysis, number average molecular weight and intrinsic viscosity. The relationship between molecular weight and intrinsic viscosity was reasonably linear (Table II).

TABLE II

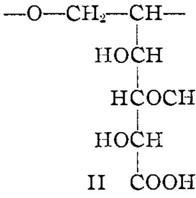
INTRINSIC VISCOSITY AND MOLECULAR WEIGHTS OF POLYMERS OF 5,6-ANHYDRO-3-O-METHYL-1,2-O-ISOPROPYLIDENE-D-GLUCOFURANOSE

[η] benzene, 25°	Degree of polymerization
0.021	2
.034	4
.042	9, 8
.050–0.053	11
.080	18[a]
.10	25[a]

[a] Values obtained by extrapolation to zero concentration.

The polymer was next hydrolyzed with sulfuric acid in dioxane–water. Acetone was removed quantitatively and after neutralization with barium carbonate, the hydrolysis liquors were removed by sublimation. The methylated polysaccharide was a white solid with m.p. ~190–200°. It was a "crumbly" material, in contrast to the polymer which was powdery. It was soluble in dioxane–water (~50:50, depending on $\overline{M}.\overline{W}.$) and pyridine–water and some of the lower $\overline{D}.\overline{P}.$ samples were soluble in acetone. The hydrolyzed polymer was, however, insoluble in water alone and it was necessary to carry out the hypoiodite oxidation heterogeneously. Preliminary experiments with 3-O-methyl-D-glucose indicated that the oxidation did not proceed quantitatively in neutral or acidic solution, but did so in basic solution.

Determination of iodine consumption by the polymer, however, indicated that only 90% of the theoretical amount of iodine was consumed under optimum conditions. Since aldoses undergo rearrangement in basic solution to saccharinic acids and alkylation on the 3-position increases the rate of rearrangement,[31,32] it seems probable that the oxidized polymer contains units not only of II but also of III in a ratio of about 9 to 1. The methoxyl content is also consistent with this interpretation (Table III). The infrared spectrum of the oxidized polymer showed a strong broad peak at 1740 cm.$^{-1}$ that was shifted to 1600 cm.$^{-1}$ on conversion to the calcium salt under conditions which should not hydrolyze a lactone. The polymer reacts rapidly with base, and there is no clear indication of the presence of lactone in the infrared spectrum, although the carboxyl absorption in both the ionized and un-ionized form is too diffuse to exclude it completely. On the basis of this evidence, then, we conclude that a free polygluconic acid is formed which contains about nine moles of II per mole of III.


II

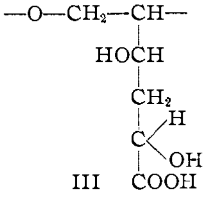

III

TABLE III

METHOXYL CONTENT OF POLYMERIC GLUCONIC ACIDS

	%
Experimental	14.2
Formula II	16.1
9 II:1III	14.7
Lactone II	17.8
Lactones of 8II:2III	14.7

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