and to the Alfred P. Sloan Foundation and the Public Health Service (GM-12595) for support. Mass spectrometers employed in these studies were obtained through support of the Public Health Service (CA-11388 and GM-16864). We are grateful to a referee for bringing reference 8 to our attention.

Solid-Phase Synthesis of Oligosaccharides. II. Steric Control by C-6 Substituents in Glucoside Syntheses

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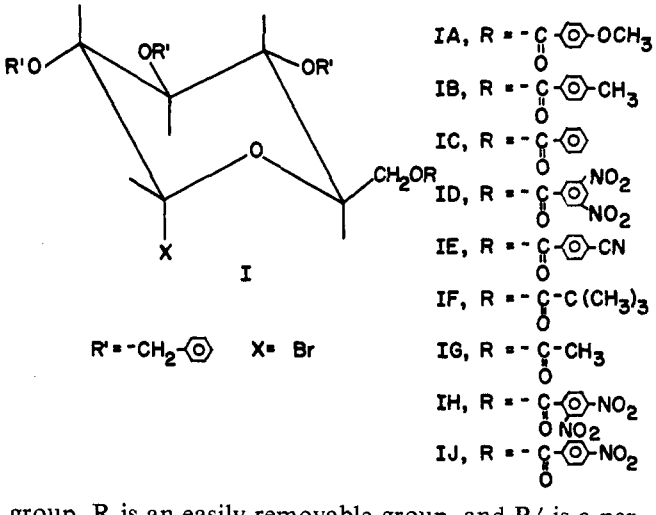
Abstract: A number of 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromides containing various acid residues on C-6 were prepared and tested in glycoside-forming reactions. The fraction of anomeric glucosides produced varied from over 90% α to over 90% β depending on the nature of the C-6 acyl group. In the para-substituted benzoic acid series the proportion of α-glucoside formed was shown to increase with increasing σ Hammett substituent constant value. This degree of steric control should be sufficient for the synthesis of lower 1→6 linked oligosaccharides and is probably due primarily to orbital overlap of the carbonyl function in the transition state. Reaction rates were measured polarimetrically and product composition was estimated by nmr spectrometry with the help of deuterated samples. A few glucopyranosyl chlorides tested were shown to react by a different mechanism. The difference between the chlorides and bromides may be due to the relative tightness of the intermediate ion pairs.

The feasibility of synthesizing oligosaccharides in a solid-phase system was suggested by our previous work[1] in which a suitably functionalized solid support was prepared and a reaction sequence leading to an oligomer of glucose was tested in an exploratory fashion. Among the requirements cited for application of the solid-phase method to the synthesis of 1→6-linked oligosaccharides was the use of a monomer having a structure such as I (Chart I) in which X is a leaving

Chart I



group, R is an easily removable group, and R′ is a persistent blocking group.

In order to exploit fully the advantages of the solid phase method, the steric outcome of the coupling reactions should be controlled and stereospecificity achieved. The addition of acid acceptors such as nucleophilic tertiary amines or catalysts such as metal ions[2,3] should be avoided if possible, since their use induces side reactions and complicates the reaction sequence.

One method most frequently used for control of the configuration of C-1 during glycoside formation involves the use of a participating substituent at C-2. This method has been applied to produce low yields of oligosaccharides by means of some variations of the Koenigs–Knorr method[2] or Helferich's modifications.[3] The products isolated have, however, invariably contained a mixture of anomers and side products. Furthermore, the C-2 participating substituent is usually an ester group which is most conveniently used as a temporary blocking group rather than one which is retained through several steps of a solid-phase synthesis. The obvious solution would seemingly reside in the use of a monomer possessing a more stable (persistent) participating group at C-2. Such monomers are, however, not presently available though their synthesis is being actively investigated.[4] We have followed another approach involving glucosyl halides of type I, since monomers of this type have been effectively used in glucoside-forming reactions to yield products containing a high percentage of α or β configuration, although no general method was found to control the steric outcome of the reaction.

To this date few glycosyl halides of this type have been studied. Zemplén, Csürös, and Angyal[5] were the first to prepare 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranosyl bromide and Pravdić and Keglević[6] prepared the corresponding chloride in their synthesis of glucuronic acid esters. Both groups used a modified Koenigs–Knorr synthesis to prepare the corresponding β-glycosides (isolated in 15 and 63% yields, respectively).

(1) J. Frechet and C. Schuerch, *J. Amer. Chem. Soc.*, **93**, 492 (1971).
(2) W. Koenigs and E. Knorr, *Chem. Ber.*, **34**, 957 (1901).
(3) B. Helferich and J. Zinner, *ibid.*, **95**, 2604 (1962).
(4) R. Eby and C. Schuerch, unpublished results.
(5) G. Zemplén, Z. Csürös, and S. Angyal, *Chem. Ber.*, **70**, 1848 (1937).
(6) N. Pravdić and D. Keglević, *Tetrahedron*, **21**, 1897 (1965).

Table I. Preparation of 1,6-Diacyl-2,3,4-tri-*O*-benzyl-D-glucopyranose

Compd	Product composition β:α	Nmr spectrum[a] α	β	Crystalln solvent[b]	Crystalline form	Yield of crystalline material, %	Mp, °C	[α]²³D,[c] deg	Anal.[d] % C	% H	% N
A		*e*	6.02 (7.1)	1, 2	β	81	108–109	−10.4	71.85 71.86	5.89 5.77	
B	7:3	6.72 (3)	6.1 (7)	3, 2	β	65	109	−6.3	75.20 74.97	6.16 6.43	
C	2:1	6.68 (3)	6.06 (7)	3, 4	β	51	90–91	−6.2	74.76 74.99	5.81 5.86	
D	55:45	6.64 (3)	6.07 (7)	5, 6	β	50	118–119	−17	58.71 58.45	4.08 3.88	6.68 6.55
E	8:2	6.61 (3)	5.99 (7)	7, 8	β	67	127–128	−1.7	72.87 72.68	5.13 5.03	3.95 3.77
F	8:2	6.43 (3)	5.68 (7.3)	9, 10	β	70	76–77	+25	71.82 71.96	7.49 7.59	
G	3:8	6.41 (3.3)	5.70 (7.5)	3, 3	α	65[f]	63.5–65[f]	+68			
H	7:3	6.71 (3.5)	6.0 (6.5)						58.71 58.64	4.08 4.07	6.68 6.63
K[h]	7:9[g]	6.38 (3.3)	5.75 (7.3)								

[a] Upper line, chemical shift δ in parts per million; lower line, coupling constant in hertz. [b] First code number for crystallization solvent, second code number for recrystallization solvent: 1, methanol; 2, ethyl acetate–pentane; 3, ethanol; 4, ethanol–pentane; 5, ethyl acetate–petroleum ether; 6, methylene chloride–ethyl acetate; 7, carbon tetrachloride; 8, carbon tetrachloride–ethanol; 9, petroleum ether–pentane; 10, petroleum ether. [c] Measured in chloroform; *c* 1–2. [d] Upper line, calculated value; lower line, experimental value. [e] Anomeric proton covered by aromatic resonance of *p*-methoxybenzoyl group. [f] Pravdić and Keglević report 67–70% yield; mp 64–65.5°. [g] Pure α-K was obtained by reaction of 2,3,4-tri-*O*-benzyl-D-glucopyranose with trifluoroacetic anhydride in the presence of 2,4-dinitrobenzoic acid. [h] Acyl group, $-COCF_3$.

Ishikawa and Fletcher[7] in their investigation of the methanolysis of a number of α-D-glucopyranosyl bromides prepared 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide which anomerized in solution to the corresponding α-D anomer. Methanolysis of this α-D-glucosyl bromide yielded almost exclusively (96%) the methyl α-D-glucopyranoside. This result is of considerable interest to our work since it should be applicable to the solid-phase synthesis of α-linked oligomers of glucose. Recently Anderson and his coworkers[8] prepared a disaccharide mixture by condensing 3-phenylpropyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride in the presence of a silver salt. The thioglucoside unit was used by these authors as a model for a planned solid-phase synthesis on a resin containing a thiol functional group. Anderson's approach differs, therefore, from ours in the method of coupling to resin and the use of metal ion as catalyst.

Experimental Section

Nuclear magnetic resonance spectra were measured on a Varian A-60 or Jeolco 100-MHz spectrometer in deuterated chloroform or deuterated acetone with tetramethylsilane as internal reference. Optical rotations were determined in a Perkin-Elmer Model 141 polarimeter using jacketed 1-dm cells kept at a constant temperature with a thermostated water bath. All melting points recorded are corrected.

Preparation of 1,6-Di-*O*-acyl-2,3,4-tri-*O*-benzyl-D-glucopyranose. The starting material for all the monomer syntheses was 2,3,4-tri-*O*-benzyl-D-glucopyranose prepared from 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose as described by Zemplén, *et al.*[5] While 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose was prepared as described by Zemplén, *et al.*[5] all the other monomers were prepared by the following general procedure.

To a cooled and stirred solution of 5 g (11.1 mmol) of 2,3,4-tri-*O*-benzyl-D-glucopyranose in 15 ml of dry pyridine was added an excess (23.6 mmol) of the desired acid chloride. A precipitate of pyridinium salt usually appeared after a few minutes and the colored reaction mixture was then stirred at room temperature overnight. The mixture was then poured into 300 ml of ice–water and the gummy precipitate which formed was extracted with chloroform. After extracting the aqueous phase with chloroform, the chloroform solutions were combined and washed successively with water, aqueous sodium bicarbonate solution, and water. The chloroform phase was dried on anhydrous magnesium sulfate, then evaporated to an oil. The nmr spectrum of the oil was recorded and the proportion of each anomer estimated from the area of the respective anomeric protons. On crystallization from the solvents indicated in Table I, the β isomer was obtained in every case. After recrystallizing from the proper solvent or solvent system (Table I), the melting point and specific rotation of the product were recorded with the results of the elemental analysis. These results are summarized in Table I.

Preparation of 6-*O*-Acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl Bromides. 2,3,4-Tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide (IJ) was prepared from its β isomer by anomerization in dichloromethane as described by Ishikawa and Fletcher.[7] All the other glucopyranosyl bromides were prepared as follows. One gram of 1,6-di-*O*-acyl-2,3,4-tri-*O*-benzyl-D-glucopyranose was dissolved in a saturated solution of hydrogen bromide in dichloromethane (10–20 ml) and dry hydrogen bromide was bubbled through the solution for 10–30 min at room temperature. When *p*-methoxybenzoic acid, *p*-methylbenzoic acid, *p*-cyanobenzoic acid, 3,5-dinitrobenzoic acid, and 2,4-dinitrobenzoic acid had precipitated, they were collected on a fritted glass filter. The solution was then concentrated *in vacuo* and succesive portions of dichloromethane were evaporated *in vacuo* from the residual syrup to remove any trace of hydrogen bromide. In three instances the remainder of the acid produced by the reaction was removed by precipitation from other solvents: from ethyl acetate–pentane in the case of *p*-methoxybenzoic acid and from carbon tetrachloride in the cases of *p*-methylbenzoic and *p*-cyanobenzoic acid. The total yield of acid collected was in each case 95% or higher. In another instance, acetic acid was eliminated by azeotropic distillation with anhydrous benzene. Finally, in all other cases where less than 80% of the acid could be collected by filtration (3,5-dinitrobenzoic acid and 2,4-dinitrobenzoic acid) or no acid precipitated (benzoic acid, 2,2-dimethylpropanoic acid) the syrup was dissolved in methylene chloride. The solution was then washed twice with cold aqueous

(7) T. Ishikawa and H. G. Fletcher, *J. Org. Chem.*, **34**, 563 (1969).
(8) P. J. Pfaffli, S. H. Hixson, and L. Anderson, Abstracts, Chemical Institute of Canada–American Chemical Society Joint Conference, Toronto, Ont., May 24–29, 1970, Carbohydrate Division, paper No. 15.

sodium bicarbonate solution, rinsed rapidly with water, and dried on anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. After drying under high vacuum the nmr spectrum and optical rotation of each sample were recorded and the data can be found in Table II. In all cases the high optical rotation and nmr data indicated that the α anomer had been obtained.

Table II. Preparation of 6-*O*-Acyl-2,3,4-tri-*O*-benzyl-D-glucopyranosyl Bromides

Substrate	Reaction time, min	$[\alpha]^{23}D$, deg in $CHCl_3$, *c* 1–2	—Nmr spectrum— δ, ppm	$J_{1,2}$, Hz
A	20	+123	6.43	3.7
B	45	+123	6.47	3.8
C	30	+124.5	6.46	3.6
D	10	+114	6.43	3.9
E	10	+129.5	6.46	3.9
F	30	+115	6.42	3.8
G	30	+123.5	6.41	3.9
H	15	+116	6.46	4

Preparation of 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl Chloride (IIG). This monomer was prepared from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose as described by Pravdić and Keglević.[6] The product had $[\alpha]^{23}D$ +88.5° (*c* 2, chloroform); Pravdić and Keglević report $[\alpha]D$ +90°. Its nmr spectrum included a doublet ($J_{1,2}$ = 3.6 Hz) centered at δ 6.07.

Preparation of 2,3,4-Tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl Chloride (IIJ). One gram of 2,3,4-tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranose,[7] dissolved in 25 ml of dichloromethane, was added to a saturated solution of hydrogen chloride in ether (10 ml). Dry hydrogen chloride was bubbled through the solution for 6 hr. The solution containing some precipitated *p*-nitrobenzoic acid was then placed overnight in a refrigerator. The reaction mixture was then filtered through fritted glass filter to remove the *p*-nitrobenzoic acid (212 mg, 95%). The filtrate was then concentrated and the residual syrup evaporated three times from dichloromethane at room temperature. After drying on high vacuum the product had $[\alpha]^{23}D$ +102° (*c* 1.7, chloroform). Its nmr spectrum showed the expected proton ratio and a doublet ($J_{1,2}$ = 3.1 Hz) centered at δ 6.11 indicating that the product was the α anomer.

Preparation of 6-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl Chloride (IIC). To a solution of 2.1 g of dry hydrogen chloride in 10 ml of absolute ether is added 2 g of 1,6-di-*O*-benzoyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranose. After thorough mixing the solution was kept 4 days in a refrigerator. The solvent was then evacuated *in vacuo* and the remaining hydrogen chloride removed by repeated evaporation from absolute benzene. The benzoic acid was removed by washing a dichloromethane solution of the product successively with cold aqueous sodium bicarbonate and cold water. After drying over magnesium sulfate the solvent was evaporated *in vacuo*. After drying under high vacuum the product had $[\alpha]^{23}D$ +104° (*c* 1.7, chloroform). Its nmr spectrum showed the expected proton ratio and a doublet ($J_{1,2}$ = 3.4 Hz) centered at δ 6.09 indicating that the product was the α anomer.

Solvolysis of the D-Glucopyranosyl Halides. The sample of glucopyranosyl halide (~30 mg or 0.047 mmol) was placed in a 1-ml volumetric flask and dissolved in dry acetone (0.2 ml). Methanol (0.15–0.75 ml or 3.7–18.5 mmol) was added and the solution brought to 1 ml by addition of dry acetone. The optical rotation of the solution as a function of time was followed polarimetrically in a 1-dm tube at 23°. When the reaction was complete the solvents were removed *in vacuo* at room temperature and the resulting product was evaporated from several portions of dichloromethane. After drying on high vacuum the product was dissolved in deuterated chloroform for nmr analysis. The various samples were then saponified or transesterified and the nmr spectra of the resulting 2,3,4-tri-*O*-benzylmethyl-D-glucopyranosides were recorded. An alternate work-up procedure included washing the methanolysis product with aqueous bicarbonate to neutralize the solution before processing. The reaction was frequently performed on a larger scale (fivefold). In some cases deuterated methanol and deuterated acetone were used for the methanolysis. When tetrabutylammonium halides were used in the methanolyses two additional washings with distilled water were necessary to eliminate the tetrabutylammonium halide from the reaction product prior to nmr analysis. When other alcohols were used the molar proportion alcohol–halide was kept constant. The nmr analysis was performed by comparison of the expanded spectra of the methyl D-glucopyranosides in the region δ 3–4 with the expanded spectra of corresponding deuterated samples in some cases prior to and in all cases after removal of the C-6 ester group. The anomeric composition determined by this method was most accurate for those samples having a high proportion of one isomer and the results were generally reproducible within 3–5%.

Results and Discussion

In an attempt to find a glucosyl halide susceptible of yielding a product of high stereospecificity when used in a glycoside forming reaction, a series of monomers of type I with benzyl substituents at C-2, C-3, and C-4 and esterified with various acid residues at C-6 was prepared by conventional methods from 2,3,4-tri-*O*-benzyl-D-glucopyranose.

Methanolysis of the various glucosyl halides was used as a model for the glucoside forming reaction since solvolyses using other alcohols showed that the reaction rate was practically independent of the nature of the primary alcohol chosen (Table III). Furthermore, the stereospecificity of the methanolyses could conveniently be estimated by nuclear magnetic resonance as the methoxyl resonances of methyl 2,3,4-tri-*O*-benzyl-D-glucopyranosides appear at different chemical shifts for the α and β isomers (δ 3.37 and 3.55 ppm, respectively). Fully deuterated methanol was also used in parallel experiments and the reaction products were examined by nmr to determine the exact area of the spectrum which could be assigned to the methoxyl resonance of each anomer. As can be seen in Table IV, drastic differences in product composition were observed for the methanolyses of the glucopyranosyl bromides containing different C-6 acyl groups. A product containing a high proportion (93%) of methyl β-D-glucopyranoside was obtained by methanolysis of 6-*O*-*p*-methoxybenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide in sharp contrast with the high hield (96%) of the corresponding methyl α-D-glucopyranoside obtained by Ishikawa and Fletcher[7] from the 6-*O*-*p*-nitrobenzoyl derivative. When the C-6 acyl groups were other substituted benzoates, intermediate results were obtained.

When the C-6 acyl group was an acetyl or 2,2-dimethylpropanoyl group, similar results were obtained with the higher β stereospecificity observed in the case of the 2,2-dimethylpropanoyl group (86 *vs.* 65% methyl β-D-glucopyranoside). In this series a trifluoroacetyl group would have been expected to cause formation of a

Table III. Rates of Alcoholysis of 6-*O*-*p*-Methoxybenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl Bromide (IA) and 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl Chloride (IIG)

Substrate	Alcohol	Half-life, hr	—*k*— ln	sec^{-1}
IA	Methanol[a]	2.14	9	10^{-5}
IA	1-Butanol[a]	2.77	7	10^{-5}
IA	2-Methylpropanol[a]	2.85	6.7	10^{-5}
IA	Methanol[a,b]	0.23	8.2	10^{-4}
IIG	Cinnamyl alcohol[c]	34	5.6	10^{-6}
IIG	Methanol[c]	32	6	10^{-6}

[a] Molar ratio, alcohol:monomer, 156:1. [b] 4 mol of Bu_4NBr added/mol of substrate. [c] Molar ratio, alcohol:monomer, 67:1.

Table IV. Methanolysis of α-D-Glucopyranosyl Bromides[a]

Substrate	k, ln	k, sec⁻¹	$t_{1/2}$, min	Methyl D-glucopyranosides formed, β:α
IA	8.7	10^{-4}	12.8	93:7
IA[b]	2.5	10^{-3}	4.5	
IB	8	10^{-4}	14.4	88:12
IB[b]	2.1	10^{-3}	5.4	40:60
IC	9.8	10^{-4}	11.8	84:16
IC[b]	2.1	10^{-3}	5.4	43:57
ID	5.4	10^{-4}	21.3	75:25
ID[b]				16:84
IE	6.2	10^{-4}	18.5	63:37
IE[b]	2.2	10^{-3}	5.1	30:70
IF	9	10^{-4}	13.5	86:14
IF[b]	2.2	10^{-3}	5	
IG	2	10^{-3}	6	65:35
IG[b]	3.9	10^{-3}	3.1	
IH	4.9	10^{-4}	23.7	55:45
IH[b]	1.5	10^{-3}	7.5	30:70
IJ	6.5	10^{-4}	17.9	8:92[c]
IJ[b]	2.6	10^{-3}	4.5	*d*

[a] Reaction temperature, 23°; molar ratio, methanol:monomer, ~390:1. [b] Indicates reaction in which 4 mol of tetrabutylammonium bromide was added for each mole of substrate. [c] Ishikawa and Fletcher[7] report 4:96. [d] Ishikawa and Fletcher[7] report 10:90.

higher percentage of the methyl α-D-glucopyranoside. However, the reaction of 2,3,4-tri-*O*-benzyl-1,6-di-*O*-trifluoroacetyl-D-glucopyranose with methanol was found to be difficult to control and 2,3,4-tri-*O*-benzyl-D-glucopyranose was the major product. The methanolysis of glucopyranosyl halides having a C-6 acetyl group was also complicated by loss of the C-6 acetyl group.

The solvolyses of all the halides were performed under identical conditions with the same alcohol:halide ratio and the reactions were followed polarimetrically. The polarimetric data from the various solvolyses were plotted against time and the first-order rate constants calculated from the classical polarimetric expression $k = 1/t \ln (\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$. The rate constants for the methanolyses of the various glucopyranosyl halides are shown in Tables IV and V. In general the

Table V. Methanolysis of α-D-Glucopyranosyl Chlorides[a]

Substrate	k, ln	k, sec⁻¹	$t_{1/2}$, hr	Methyl D-glucopyranosides formed β:α
IIC	4.8	10^{-5}	4	94:6
IIG	6.7	10^{-5}	2.85	94:6
IIJ	3.6	10^{-5}	5.2	84:16

[a] Reaction temperature, 23°; molar ratio, methanol:monomer, ~390:1.

initial rate was found to be slightly lower than the rate at half-life, probably due to the effect of the bromide ion liberated by the reaction. All the methanolyses were accompanied by levomutarotation and reaction rates were increased by the addition of halide ion. The largest rate increase was observed when the added ion was bromide or iodide rather than chloride and when the concentration of alcohol was low. As can be seen in Table IV, the addition of halide ion always caused also a change in product composition with a tendency to yield a product of lower stereospecificity.

As expected, changes in temperature were accompanied by changes in reaction rates as evidenced by the methanolysis of 6-*O*-*p*-methoxybenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide for which the relative reaction rates were the following: 1 at 22°, 0.085 at 0°, and 6.4 at 45°.

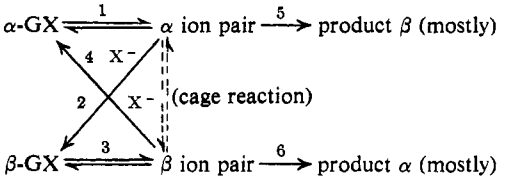
In some cases, it was possible to increase the stereospecificity of the reaction by decreasing the reaction temperature. The methanolysis of 6-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide at −15° yielded a product containing 90% of the methyl β-D-glucopyranoside *vs.* 84% at 22° and 76% at 60°. Similarly, the corresponding 6-*O*-*p*-toluoyl derivative yielded 91% of the methyl β-D-glucopyranoside at −15° *vs.* 88% at 22°.

In all cases the glucopyranosyl chlorides were found to solvolyse approximately 20–30 times slower than the corresponding bromides under the reaction conditions chosen (Tables IV and V). Their methanolysis yielded products having a different anomeric composition, the most striking difference occurring in the case of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl chloride which upon methanolysis yielded 84% of the methyl β-D-glucopyranoside, while the corresponding bromide yielded 96% of the methyl α-D-glucopyranoside. These results indicate that the two types of halides must react by different mechanisms.

Mechanism

The mechanism of solvolysis of glycosyl halides with nonparticipating groups at C-2 was first studied on 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl and mannopyranosyl chlorides by Rhind-Tutt and Vernon.[9] These authors found that the methanolysis of the glucopyranosyl chloride proceeded by an SN1 mechanism with essentially complete inversion by backside attack on a specifically oriented ion pair to yield 94% of the methyl β-D-glucopyranoside. The formation of the small amount of α anomer was explained by a mechanism involving chloride ion exchange to yield the β ion and therefore some α product (Scheme I). The possi-

Scheme I. Possible Configuration Control in Glycoside Synthesis (Modified from Reference 9)

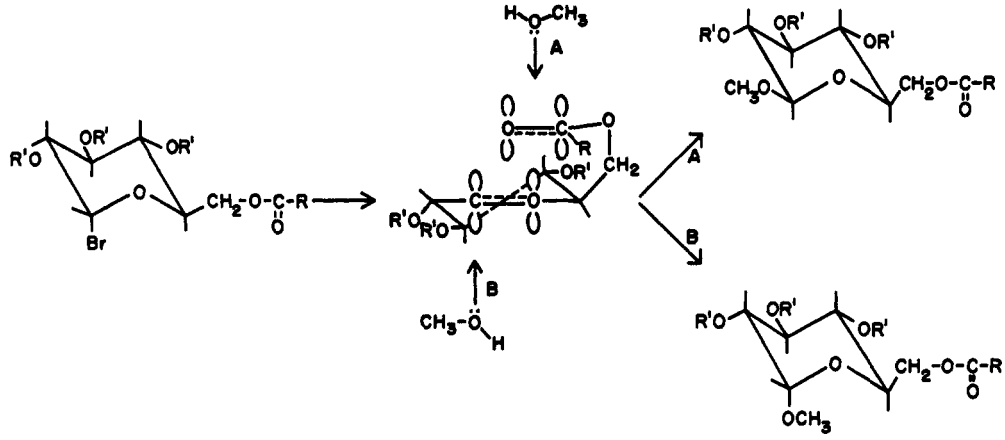


bility of inversion of β to α ion within a solvent cage was not discussed by the authors.

Ishikawa and Fletcher[7] in their investigation of the methanolysis of a number of α- and β-D-glucopyranosyl bromides having a benzyl group at C-2 used a somewhat similar mechanistic interpretation to explain the formation of their products which were mainly the methyl α-D-glucopyranosides. They suggest that these products were obtained from the β-bromides which were either present in small quantities in the starting material or formed rapidly in a concurrent anomerization presumably by reaction with bromide ion. Both groups

(9) A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 4637 (1960).

Scheme II



thus interpreted the steric course of the reaction in terms of the same equilibria although the products they obtained were opposite in C-1 configuration.

Although the mechanism used by these authors undoubtedly interprets successfully several features of these reactions, it appears not to be a complete explanation. Specifically, it is difficult to explain the wide differences in the configuration of products from quite similar starting materials, unless one considers the probable structure of the intermediate ions in more detail. Why, for example, should 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride produce nearly pure methyl β-D-glucopyranoside whereas 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide yields essentially a 50:50 mixture of both methyl D-glucopyranosides? Similarly, why should the product derived from 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl chloride be nearly as sterically pure β-glucoside as that from the fully etherified glucopyranosyl chloride, while on the other hand the 6-O-acetylated glucopyranosyl bromides yield products varying from 95% α to 95% β under apparent electronic control? The mechanism shown in Scheme I suggests that the results are due to widely different relative rates of reaction of very similar ion pairs with two nucleophiles, halide ion and methanol, or perhaps are due to unrealistic differences in equilibria. Neither interpretation clarifies the results.

We suggest that the results are more interpretable if one postulates that the glucopyranosyl chlorides generate tight ion pairs which react as postulated by Rhind-Tutt and Vernon by backside approach either by halide ion or alcohol, but that the glucopyranosyl bromides generate loose or solvent-separated ion pairs. In that case, the carbonium ion derived from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide is most probably in a half-chair conformation and approach from either the α or β direction is nearly equally probable. Since the substituents on asymmetric centers on the ion do not effectively block either mode of attack, the product mixture is nearly 50:50 α:β.

As indicated above, however, the methanolyses of 6-*O*-*p*-methoxybenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide and of the corresponding 6-*O*-*p*-nitrobenzoyl derivative yielded products of high stereospecificity and opposite configuration. Since the starting materials (IA and IJ) differ only in the nature of the para substituent on the C-6 benzoyl group and the substituents are separated from the reaction center by a number of single (as well as some conjugated double) bonds, their effect cannot be ascribed to a simple inductive effect. We propose that the changes in product composition can be attributed to the polar effects of the substituents on the carbonyl group in the following manner. As the glucopyranosyl bromides are converted into loose ion pairs of half-chair conformation, overlap between the vacant orbital on the C-1 atom and the filled orbitals of ring oxygen develops (Scheme II). The Lewis acid character of the electron-deficient center serves to attract the carbonyl group of the C-6 substituent into a position in which there is substantial overlap with the p orbitals of the C-6 carbonyl. Although this position is not the most probable rotamer, it can be readily stabilized by Lewis acid–base coordination with no distortion of the ring conformation.

When the C-6 acyl group is the *p*-methoxybenzoyl group, the electron density on the carbonyl group is enhanced through resonance and the positive charge is concentrated more on the C-6 carbonyl group where it is best stabilized. Attack by the nucleophile will, therefore, proceed in the direction A shown in Scheme II and cause collapse of the carbonium ion with formation of the methyl β-D-glucopyranoside. (An alternate interpretation would involve hydrogen bonding of the alcohol with the more electron-rich oxygen followed by nucleophilic attack as in A.) The small amount of α isomer is presumably produced by direct attack of the nucleophile on C-1. If, however, the C-6 acyl group contains a relatively electron-deficient carbonyl (as in a *p*-nitrobenzoyl group), the positive charge will remain concentrated on C-1 and attack by the nucleophile will proceed from the least shielded side in direction B as shown in Scheme I to yield mainly the methyl α-D-glucopyranoside. In an intermediate case such as that of a benzoyl group on C-6 the reaction is less stereospecific as the electron density is balanced and does not cause localization of the positive charge on either site.

In all cases in which the C-6 acyl group was a para-substituted ester of benzoic acid, the steric outcome of the reaction could be predicted qualitatively from the value of the substituent constant as defined by σ in the classical Hammett equation. The proportion of methyl β-D-glucopyranoside produced decreased in the series: *p*-methoxybenzoyl > *p*-methylbenzoyl > benzoyl > *p*-cyanobenzoyl > *p*-nitrobenzoyl. Disubstitution on the benzene ring apparently introduces additional complexities for the product composition in

these cases is not so readily interpretable. However, the same electronic influence was evident in the behavior of the bromides IG and IF in which the C-6 acyl group was an acetyl and a 2,2-dimethylpropanoyl group. The highest proportion of methyl β-D-glucopyranoside was obtained in the case of the second halide (IF) for which dispersion of the positive charge on the carbonyl group is facilitated by the inductive effect of the three methyl group.

The electronic interaction visualized in this mechanism differs from the participation expected of carbonyl functions at C-2. In the latter case, sp^3 hybridization of C-1 and tetrahedral geometry results. If sp^3 hybridization of C-1 occurred with participation of a C-6 substituent, it appears that the ring conformation would have to be a boat form or a chair with all substituents axial. The energetics of these conformations are too unfavorable to be considered.

When bromide ion is added to the reaction mixture the reaction mechanism becomes much more complex and presumably takes on the character of the reactions shown in Scheme I. The change in product composition observed in every case is probably due to both direct attack of bromide ion on the glucopyranosyl bromide and nucleophilic attack on the carbonium ion.

The degree of steric control achieved by using monomers such as 6-*O*-*p*-methoxybenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide and 6-*O*-*p*-nitrobenzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide is probably sufficient for the synthesis of 1,6-linked oligosaccharides through classical or solid-phase synthesis. These monomers are now being tested in the synthesis of some otherwise relatively inaccessible α-glycosides and oligosaccharides of complex structure.

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Cyclic Peptides. II. Solution Conformations of *cyclo*(Prolylserylglycylprolylserylglycyl) from Nuclear Magnetic Resonance

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Abstract: The synthesis of *cyclo*(Pro-Ser-Gly-Pro-Ser-Gly) [*retrocyclo*(Ser-Pro-Gly-Ser-Pro-Gly)] is reported. Nmr data suggest that in water and in dimethyl sulfoxide this cyclic hexapeptide rapidly interconverts between two conformations designated β_D and β_L. In β_D Gly (ϕ, ψ) angles approximate those found for a β structure containing a D residue, while in β_L the Gly angles approximate those appropriate to an L residue β structure. Ser and Pro (ϕ, ψ) angles remain essentially unchanged on transformation from β_D to β_L. Both conformations contain two Gly–Gly intramolecular hydrogen bonds and two trans Gly–Pro peptide bonds. The nmr data also indicate the presence of an asymmetric conformation separated from β_D and β_L by a high free energy barrier. This conformation has a single Gly–Gly intramolecular hydrogen bond and nmr evidence suggests the asymmetric structure is the consequence of one cis and one trans Gly–Pro peptide bond in the cyclic hexapeptide.

Several reports have appeared recently in which high-resolution nmr is used to elucidate the secondary structure of cyclic peptides. The biologically active cyclic peptides gramicidin S,[2-6] oxytocin,[7,8] ferrichrome,[9] and antamanide[10,11] have been studied by nmr, as have cyclic tripeptides,[12,13] cyclic tetra-

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