GLYCOSIDATION OF SUGARS

II. METHANOLYSIS OF D-XYLOSE, D-ARABINOSE, D-LYXOSE, AND D-RIBOSE[1]

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Received April 30, 1963

ABSTRACT

Rates of methanolysis reactions of D-xylose, D-arabinose, D-lyxose, and D-ribose have been determined. It was found that methanolysis of a pentose proceeds to equilibrium through four distinguishable, competing reactions: (1) pentose → furanosides; (2) anomerization of furanosides; (3) furanosides → pyranosides; (4) anomerization of pyranosides. The glycoside compositions at equilibrium are interpreted in terms of stabilities of each of the four glycosides from each sugar as influenced by steric and ionic effects; a system of conformational analysis of furanoside rings is presented. The free energies of reaction in anomerization of pyranosides were in excellent agreement with values calculated from previously reported interaction energies in the pyranoid ring. The relative rates of the reactions were consistent with the view that non-bonded interactions in the methyl glycosides are relieved in the transition states for their interconversions.

The first paper (1) in this series described a study of the reactions of D-xylose in methanolic hydrogen chloride; the four methyl D-xylosides, products of the reaction, were analyzed at different times by gas–liquid chromatography of their fully methylated derivatives. The resulting rate data showed that four reactions could be distinguished: (1) xylose → methyl furanosides, (2) anomerization of furanosides, (3) furanosides → pyranosides, (4) anomerization of pyranosides; a tentative mechanism was proposed.

The present paper describes an extension of this work to the other pentoses, D-arabinose, D-lyxose, and D-ribose; some of the reactions in the D-xylose series were repeated to obtain comparable data. It is shown that the methanolysis of each pentose proceeds via the reactions given above. The equilibrium compositions can be interpreted in terms of relative stabilities of each of the four glycosides from each sugar and the relative reaction rates indicated that non-bonded interactions in the methyl glycosides are relieved in the transition states for their interconversions.

The conditions cited for the reactions were carefully controlled and products in the D-xylose and D-arabinose series were analyzed by gas–liquid chromatography of their fully methylated derivatives as described previously (1). Reaction products in the D-lyxose and D-ribose series were analyzed by gas–liquid chromatography of their fully acetylated derivatives because of the better separations obtained. The rate at which reducing sugar disappeared was measured by gas–liquid chromatography of the acetylated reaction mixture; the pentopyranose tetraacetates, arising from the reducing sugars, were widely separated from the methyl tri-*O*-acetyl pentosides. Separation of individual methyl tri-*O*-acetyl pentosides in this procedure, although not always complete, was sufficient to provide information about the early products of reaction. The use of acetylation avoided the correction required (1) when the methylation procedure was used on reaction mixtures in which reducing sugars were present. The retention volumes (R_v) in Tables I and II illustrate the separations pertinent to this work. The R_v values of derivatives from a single pentose are made relative to the fastest moving component ($R_v = 1.00$) in that series and are not related to the values in another pentose series. For example, the R_v values for the methyl tri-*O*-methyl-D-xylosides are related only to each other.

[1]*Issued as N.R.C. No. 7542.*

TABLE I

Retention volumes of methyl tri-*O*-methyl-D-pentosides[a]

	D-Xylose	D-Arabinose		D-Xylose	D-Arabinose
α-Furanoside	1.95	1.00	α-Pyranoside	1.40	2.26
β-Furanoside	1.60	1.31	β-Pyranoside	1.00	2.10

[a]Gas–liquid chromatography on column (4 ft×4 mm) of 10% Carbowax 6000 on Gas-Chrom A, 100–120 mesh; 125° C; 100 ml argon/min. Methyl tri-*O*-methyl-D-ribosides not resolved completely.

TABLE II

Retention volumes of methyl tri-*O*-acetyl-D-pentosides and pentopyranose tetraacetates

	D-Xylose[a]	D-Ribose[a]	D-Lyxose[b]
α-Furanoside	1.24	1.00	1.57
β-Furanoside	1.00	1.32	1.28[c]
α-Pyranoside	1.33	1.08	1.00
β-Pyranoside	1.33	1.48	1.13
Tetraacetates (α, β)	2.67, 2.89	3.35, 3.73	2.47, 3.19

[a]Gas–liquid chromatography on column (8 ft×4 mm) of 13% OF-1-0065 on Chromosorb W, 100–120 mesh (packing prepared by Applied Science Laboratories, State College, Pennsylvania, U.S.A.); 200° C; 80 ml helium/min. Separation of D-arabinose derivatives not attempted.
[b]Column (4 ft×4 mm) of 10% ethylene glycol isophthalate polyester on Gas-Chrom Z, 100–120 mesh; 195° C; 60 ml argon/min.
[c]Identified by inference as the only peak not corresponding to one from an authentic sample.

Methanolysis of a sugar proceeds to equilibrium through four distinguishable, competing reactions and a unified kinetic treatment of the complete process is therefore very complicated. However, it has been possible to establish conditions under which a single reaction predominated. Since the observations were made at constant hydrogen ion concentrations the bimolecular reaction could be expressed in terms of first-order rate kinetics. Compositions of reaction products at different times under specific conditions are given in Tables VIII–XI (see Experimental). Inspection of these results shows that a single reaction was predominant during the early periods and was characterized reasonably well by a first-order rate constant. Minor variations in these rate constants for the initial reactions were probably within experimental error. At later stages deviations from first-order kinetics became noticeable and analysis of the products showed that other reactions were occurring to a significant extent. The rate constants indicated in Table VIII–XI were averaged to give the k_1 values in Table III. To give measurable rates reactions 3 and 4 required 10 and 100 times respectively the concentration of hydrogen chloride used for reactions 1 and 2. No Hammett acidity functions have been reported for the methanol – hydrogen chloride system but it had been found (1) that the rates of all methanolysis reactions of D-xylose were approximately proportional to the acid concentrations. The average first-order rates for reactions 3 (Table X) and 4 (Table XI) were therefore reduced to 1/10 and 1/100 respectively to provide comparable k_1 values (Table III) all relative to 0.01% of hydrogen chloride in methanol. This undoubtedly introduced inaccuracies as far as absolute values were concerned; however, the relative orders of reactivity, of major interest in this work, were probably not disturbed. The equilibrium constants (K) in Table III were obtained from glycoside compositions after prolonged reaction periods (Table V) and the k_2 values were calculated from k_1 and K.

Non-bonded interactions impose certain conformations upon molecules and the principles of conformational analysis have been of considerable assistance in interpreting the physical and chemical properties of the pyranoid sugars (2–5). Although Kilpatrick *et al.*

TABLE III

Rate constants of methanolysis reactions[a]

Reaction	D-Xylose				D-Arabinose				D-Lyxose				D-Ribose			
	k_1	k_2	k_1+k_2	K	k_1	k_2	k_1+k_2	K	k_1	k_2	k_1+k_2	K	k_1	k_2	k_1+k_2	K
1. Pentose $\xrightarrow{k_1}$ furanosides	57	—	—	—	—	—	—	—	19	—	—	—	226	—	—	—
2. Furanoside: $\alpha \underset{k_2}{\overset{k_1}{\rightleftarrows}} \beta$	49	29	78	1.69	1.39	4.35	5.74	0.32	Very small	Very large	—	—	11.3	3.4	15.2	3.3
3. Furanosides $\underset{k_2}{\overset{k_1}{\rightleftarrows}}$ pyranosides	0.12	0.0004	—	320	0.088	0.011	—	7.9	0.84	0.001	—	650	0.069	0.008	—	8.8
4. Pyranoside: $\beta \underset{k_2}{\overset{k_1}{\rightleftarrows}} \alpha$	0.031	0.014	0.04	2.2	0.093	0.18	0.27	0.52	0.62	0.072	0.64	8.6	0.02	0.11	0.13	0.176

[a]Reaction 2: $K = [\beta]/[\alpha]$; reaction 3: $K = [\alpha\text{-pyr}][\beta\text{-pyr}]/[\alpha\text{-fur}][\beta\text{-fur}]$; reaction 4: $K = [\alpha]/[\beta]$. Concentrations of products for these calculations were taken from the equilibrium values given in Table V.

(6) showed in 1947 that the cyclopentane ring is puckered, the furanoid sugars have been regarded as essentially planar molecules. However, the fructofuranosyl portion of crystalline sucrose (7) and the ribofuranosyl moiety of crystalline cytidine (8) were both found to have non-planar ring structures. More recently specific conformations, based upon nuclear magnetic resonance spectroscopy, have been proposed for D-ribofuranose in purine and pyrimidine nucleosides (9), in thymidine (10), in certain deoxyribonucleosides (11) and nucleotides (12), and in 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose, methyl 2,3-anhydro-α-D-ribofuranoside, and its β-anomer (13). A specific conformation has also been proposed for a furanose ring having a cis-fused *O*-isopropylidene ring (14). However, no system of conformational analysis has been proposed for furanose sugars that permits the prediction of a preferred conformation and accounts for the chemical properties of the compounds concerned. The system shown in Fig. 1 was derived from a consideration of the non-bonded interactions which should be operative in these molecules.

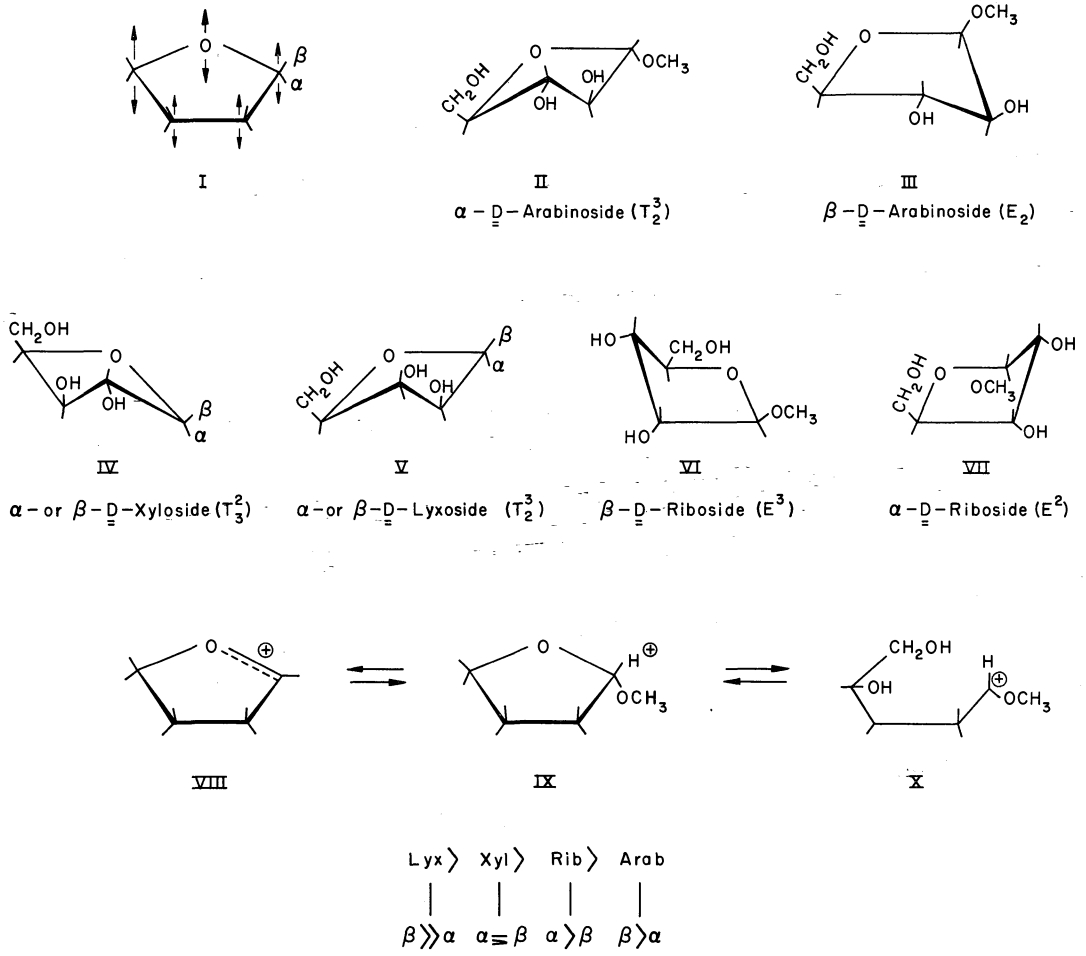

FIG. 1.

The strain inherent in a five-membered ring, cyclopentane or furanoid (I), can be relieved by a slight puckering brought about by movement of one or two atoms out of the plane of

the ring. For cyclopentane, in which all atoms are equivalent, this results in two possible conformations (6): (*a*) the C_s conformation in which a single atom is displaced from the plane of the other four, (*b*) the C_2 conformation in which two atoms are displaced, one above and the other below the plane of the remaining three adjacent atoms. In the furanoid sugars a more definitive designation of conformation is required because of the specific stereochemistry of the carbon atoms in the ring. Jardetzky (12) used a system for the ribofuranose ring in which the carbon atoms displaced from the plane were designated by number and the direction of displacement was related to the orientation of the C_4—C_5 bond by the terms *endo-* or *exo-*. Hall (13) has proposed a system in which the conformation with four atoms coplanar is designated by E (envelope), that with three atoms coplanar by T (twist). The atoms out of plane can then be indicated as subscripts or superscripts to show respectively displacement below or above the plane of reference; carbon atoms are given as numbers, the ring oxygen by "o". This system is simple, fully descriptive, adaptable to general use, and will be used in the present publication.

In the furanoside ring the effective interactions are those between eclipsed groups on adjacent carbon atoms and the most favored conformations will allow maximum staggering. Conformations with C_1, C_4, or O displaced have a fully or nearly fully eclipsed pair of carbon atoms and should be less stable than those in which C_2 or C_3 or both are displaced from the plane. Methyl α-D-arabinofuranoside (II) has all of its large substituents in trans orientation and the strain in the ring can therefore be relieved by the maximum staggering afforded by a T_2^3 or T_3^2 conformation. In methyl β-D-arabinofuranoside (III) there is an eclipsed interaction between the C_1- and C_2-substituents which should force them away from each other, giving an E_2 conformation. The methyl-D-xylofuranosides have large eclipsed groups at C_3 and C_4 with the bulky hydroxymethyl group at C_4 contributing to a greater repulsive force. The net result of the deformation in which the hydroxymethyl group forces the C_3-hydroxyl down and away will be that C_2 is pushed up, giving the conformation T_3^2 (IV). An important consequence of this conformation is that the C_2-hydroxyl is oriented in an almost ideal skew position with respect to the anomeric substituents and is only slightly closer to the C_1-α than the C_1-β bond angle in a projection along the C_2—C_1 bond. A possible alternate conformation for the methyl β-D-xylofuranoside is E_3. The methyl-D-lyxofuranosides have eclipsed interactions between C_2–C_3 and C_3–C_4 substituents. The molecule should therefore adopt a T_2^3 conformation V which provides for the maximum distance between the *O*-substituents within an ideally staggered form. An alternative for the methyl α-D-lyxofuranoside could be E_3. The interaction between the C_2- and C_3-hydroxyls in the methyl-D-ribofuranosides should result in an E^3 conformation (VI) or its equivalent E^2. The latter should be preferred for the methyl α-D-ribofuranoside (VII) because it would also relieve the interaction between the C_2-hydroxyl and the anomeric substituent. Table IV contains the preferred conformations for the methyl pentofuranosides and the hydroxyl interactions in each compound. On present evidence it is impossible to decide between alternative conformations for a single furanoside.

Analyses of products showed that furanosides were the first compounds formed in the methanolysis of a pentose (Table VIII). This reaction must be regarded as essentially irreversible because of the large excess of methanol present. The quantitative data obtained for three of the sugars showed that higher k_1 values for this reaction were associated with higher furanoside concentrations at equilibrium (Table V). The k_1 for D-arabinose in reaction 1 could not be measured because of the low solubility of that sugar in methanol. However, D-arabinose showed the largest amount of furanoside at equilibrium

TABLE IV

Preferred conformations of methyl pentofuranosides

Methyl-D-pentofuranoside		Conformation	Hydroxyl interactions (total)	
Arabinoside	α	T_2^3 T_3^2	—	0
	β	E_2	C_1–C_2	(1)
Riboside	β	E^3	C_2–C_3	(1)
	α	E^2	C_1–C_2, C_2–C_3	(2)
Xyloside	α	T_3^2	C_3–C_4	(1)
	β	T_3^2 (E_3)	C_3–C_4	(1)
Lyxoside	α	T_2^3 (E_3)	C_2–C_3, C_3–C_4	(2)
	β	T_2^3	C_1–C_2, C_2–C_3, C_3–C_4	(3)

and should have the largest k_1 based on the correlation observed for the other three sugars. The relative rates in reaction 1 therefore reflected the relative stabilities of the pentofuranosides. In reactions 2, 3, and 4 the rate-controlling steps may be assumed to be the formation of ionic intermediates; since the anomerization of furanosides (reaction 2) and the furanoside to pyranoside conversion (reaction 3) proceed from the same initial products at different rates it is likely, although not proved, that the reaction routes are different. Possible intermediates for the furanoside anomerization (VIII) and for the furanoside to pyranoside conversion (X), both arising from the protonated furanoside (IX), are shown in Fig. 1. The non-bonded interactions between large eclipsed groups in the furanosides (II–VII) will be relieved in X by the opening of the ring. These same interactions will be relieved in VIII if it has a puckered form with C_3 being above or below the plane of the other four atoms. Thus, in VIII, dissociation at C_1 removes any interaction between C_1- and C_2-substituents and displacement of C_3 in an E_3 or E^3 conformation relieves interactions between substituents on that carbon atom and those on C_2 and C_4. The relative orders of reactivity for the four pentoses should therefore be the same for reactions 2 and 3 and should depend on the strength and number of eclipsed interactions in the furanosides. The same argument holds if reactions 2 and 3 proceed through a common intermediate which decomposes at different rates into furanoside and pyranoside. The order predicted from the proposed furanoside conformations is given in Fig. 1. The experimental values confirm this prediction. Thus, the lyxofuranosides, with two adjacent eclipsed interactions, should be the most reactive furanosides (see k_1 values, reaction 3). The xylofuranosides, also with only one eclipsed interaction, should be less reactive than the lyxofuranosides but more reactive than the ribofuranosides because the C_3–C_4 eclipsed interaction involving the hydroxymethyl group is stronger than the C_2–C_3 eclipsed interaction. The arabinofuranosides are free of eclipsed interactions, except at the anomeric position in the β-glycoside, and therefore should be the least strained and slowest reacting of the pentofuranosides.

A similar prediction of the reactivities of the anomeric forms in reaction 2 is shown in Fig. 1 and this was also in complete agreement with the experimentally determined rates (see k_1 and k_2, reaction 2). Starting with the most reactive pentose, the methyl β-D-lyxofuranoside should anomerize at a much faster rate than the α-anomer because of the extra interaction at C_1–C_2. In fact, no methyl β-D-lyxofuranoside could be detected in any of the reactions and the rate of reaction 2 for lyxose could not be determined experimentally. It is apparent, then, that k_1 for this reaction must be smaller and k_2 larger than any of the other rate constants in Table III. In the methyl-D-xylofuranosides (IV) the C_2-hydroxyl bond very nearly bisects the angle made by the bonds of the anomeric substituents being

oriented slightly more toward the α- than the β-position. This accounts for the slightly greater (1.69 times) rate of anomerization of the α-form. In the D-ribofuranosides the α-glycoside has one more eclipsed interaction than the β- and should therefore be more reactive; for the same reason methyl β-D-arabinofuranoside should anomerize at a faster rate than its α-anomer. It is noteworthy that the one additional eclipsed interaction causes a 3-fold increase in the rate of anomerization in both the ribofuranosides and the arabinofuranosides. Another comparison which substantiates the predicted behavior of these compounds is the approximately equal rates of anomerization of methyl β-D-arabinofuranoside and methyl β-D-ribofuranoside, each having one eclipsed interaction in an envelope (E) conformation. This indicates that the eclipsed interactions at C_1–C_2 and at C_2–C_3 are of nearly the same strength. The rates for reaction 2 are greater than those for reaction 3 for each pentose. It should be emphasized that VIII and X are given only as possible intermediates for reactions 2 and 3 respectively. They are offered primarily to illustrate that any intermediate considered must be of a form that permits relief of the non-bonded interactions in the methyl pentofuranosides.

The differences in rates of pyranoside anomerization (reaction 4) can be explained by principles that are already familiar (2–5). If the pyranoside anomerization proceeds through a cyclic, half-chair carbonium ion, as postulated earlier for the xylopyranosides (1), the conformational changes shown in Fig. 2 must be involved (15). Formation of the

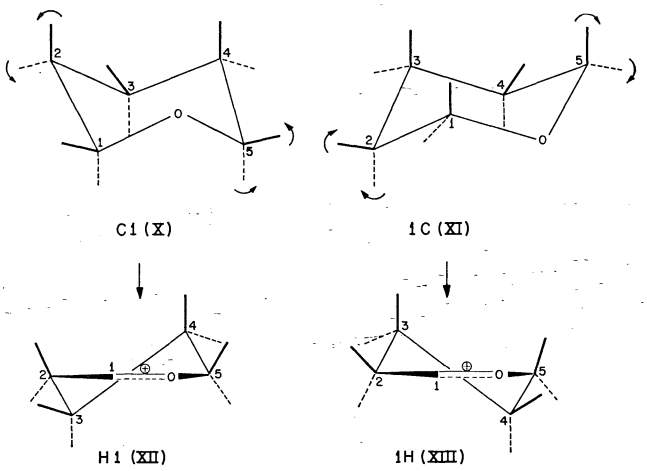

FIG. 2.

H1 (XII) or 1H (XIII) (4) carbonium ions from the C1 (X) or 1C (XI) chair forms (2) respectively requires rotation about the C_2—C_3 and C_4—C_5 bonds as shown. This will be hindered by increased opposition of C_2–C_3 substituents and of C_4—C_5 substituents but these will be of the same magnitude for all pentosides. However, the change will be helped by recession of an axial group on C_2 away from one on C_4 and by the recession of the C_5-axial group from that on C_3. The preferred conformations of the pentopyranosides (2) are shown in Fig. 3 together with the predicted order of reactivity. The xylosides, with no axial substituents, should anomerize at the slowest rate; the ribosides and arabinosides, each with one axial hydroxyl, should anomerize more rapidly than the xylosides but more slowly than the lyxosides, which have either two axial hydroxyls (1C conformation) or one axial hydroxyl and Reeves' $\Delta 2$ effect (2) (axial hydroxyl at C_2 bisects the

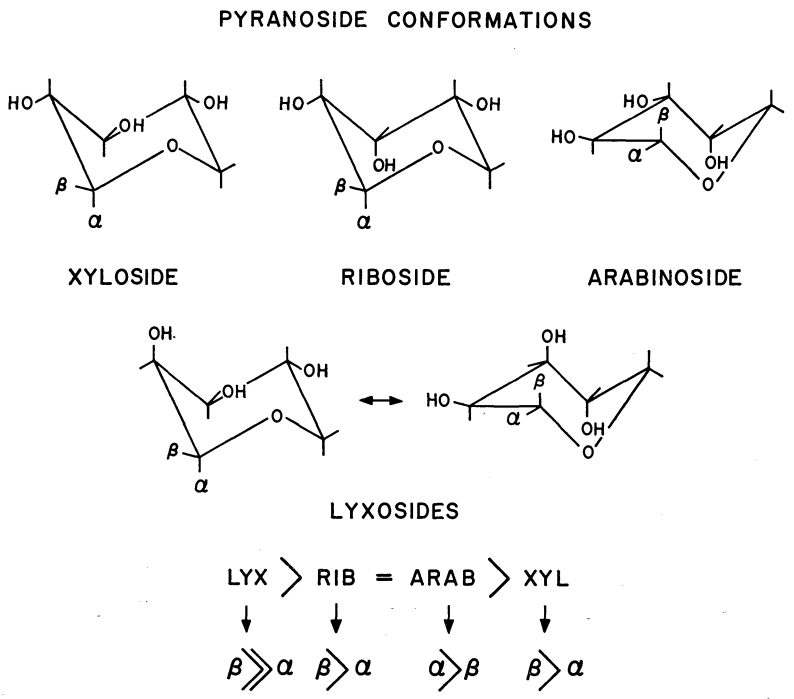

FIG. 3.

angle of the two C—O bonds at C_1). The rates in Table III (k_1+k_2, reaction 4) agree with this interpretation. The ribosides anomerize more slowly than the arabinosides because formation of the H_1 carbonium ion from the former causes increased eclipsing of the hydroxyls on C_2 and C_3.

The relative rates of anomerization of the anomeric pairs can be explained by principles enunciated by Edward (15). The unshared pair of electrons on the ring oxygen of the pyranosides impart a polar character to the C_5-ring oxygen bond and the negative end of this dipole is oriented so that the electrostatic repulsive forces with the C_1-*O*-substituent are stronger when that substituent is equatorially oriented. Those anomers should therefore be less stable and should display a faster rate of reaction; the predicted order of reactivity of anomeric pairs is given in Fig. 3. The k_1 and k_2 values for each pentopyranoside in reaction 4, Table III, confirm the prediction for the anomeric lyxopyranosides, arabinopyranosides, and xylopyranosides. The difference in rate between anomers is greater for the lyxopyranosides because of the additional repulsive force applied to the β-anomer by the axial hydroxyl at C_2. The anomeric ribopyranosides showed reactivities which were the reverse of those predicted on the basis of dipole interaction. Probably the axial–axial interaction between the C_3-hydroxyl and the C_1-α-substituent of anomeric ribopyranosides is stronger than the dipole interaction at the β-position and results in greater reactivity of the α-anomer.

Table V shows the glycoside compositions at equilibrium of the four pentoses and of some *O*-methyl derivatives of D-xylose and D-arabinose. Substitution of the C_2- and C_3-hydroxyl groups in D-xylose or D-arabinose by *O*-methyl groups greatly increased the concentrations of furanoside forms at equilibrium. This can be explained by considering the projections (Fig. 4) of the C_2—C_3 bond with trans *O*-substituents for pyranoside and

TABLE V

Glycoside compositions at equilibrium[a]

Sugar	α-Furanoside	α+β	β-Furanoside	α-Pyranoside	α+β	β-Pyranoside
D-Xylose	1.9		3.2	65.1		29.8
3-*O*-Methyl-D-xylose		9.0			91.0	
2-*O*-Methyl-D-xylose		12.8			87.2	
2,3-Di-*O*-methyl-D-xylose		16.4			83.6	
D-Arabinose	21.5		6.8	24.5		47.2
3-*O*-Methyl-D-arabinose		50.7			49.3	
2-*O*-Methyl-D-arabinose		66.7			33.3	
2,3-Di-*O*-methyl-D-arabinose		75.4			24.6	
D-Lyxose	1.4		Not detected	88.3		10.3
D-Ribose	5.2		17.4	11.6		65.8

[a]Sugar (2%) in 1% methanolic hydrogen chloride at 35° C.

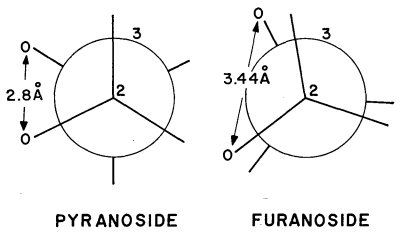

FIG. 4.

furanoside ring forms. Equatorial–equatorial *O*-substituents at C_2 and C_3 in the pyranoside ring are 2.8 Å apart while trans *O*-substituents on a furanoside ring are 3.44 Å apart. An increase in the size of the *O*-substituents will therefore result in a stronger repulsive interaction in the pyranoside than in the furanoside form and the equilibrium will be shifted toward the latter.

The free energies (Table VI) calculated from the equilibrium constants reflect the relative stabilities of the compounds concerned. In the conformation T_3^2 proposed for the

TABLE VI

Free energies for methanolyses of pentoses

	Δ*F* (reaction) (cal/mole)		Δ*F* (reaction) (cal/mole)
Xylose		Lyxose	
α-Furanoside ⇄ β-furanoside	− 320	α-Furanoside ⇄ β-furanoside	Very large
Furanoside ⇄ pyranoside	−3530	Furanoside ⇄ pryanoside	−4080
α-Pyranoside ⇄ β-pyranoside	480	α-Pyranoside ⇄ β-pyranoside	1310
Arabinose		Ribose	
α-Furanoside ⇄ β-furanoside	695	α-Furanoside ⇄ β-furanoside	− 740
Furanoside ⇄ pyranoside	−1260	Furanoside ⇄ pyranoside	−1330
α-Pyranoside ⇄ β-pyranoside	− 400	α-Pyranoside ⇄ β-pyranoside	−1060

xylofuranosides anomerization involves the substitution of one skew orientation for another and no strong interactions. The small Δ*F* for this reaction is consistent with this proposal. Anomerization of arabinofuranosides and of ribofuranosides introduces or removes an eclipsed interaction between the C_1- and C_2-*O*-substituents which can be relieved somewhat because the ring is free to adopt a less strained conformation. The Δ*F* of reaction for these two anomerizations should therefore be nearly the same, greater

than for the xylofuranoside anomerization, but less than that of the lyxofuranosides where the C_1–C_2 interaction in the β-anomer cannot be relieved because of the fixed conformation imposed by the other interactions in the ring.

The ΔF of reactions for the furanoside to pyranoside conversions reflect the relative stabilities of the two ring forms in these sugars. In arabinose and ribose the furanoside forms have only one or two easily relieved cis interactions while the pyranoside forms each have an axial hydroxyl group. The ΔF for the ring conversions is therefore less for these two pentoses than for xylose or lyxose because the former has the best possible conformation in the pyranoside form and the latter has the worst possible furanoside conformation.

Similarly, the energy differences between the anomeric pyranosides of xylose and arabinose are very nearly the same; this indicates that the axial C_4-hydroxyl of arabinose has little effect on the relative stabilities of the two anomers. In lyxose and ribose the differences between the anomeric pyranosides are larger than for xylose or arabinose. These larger differences were undoubtedly caused by increased repulsions at the β-anomeric position in lyxose by the axial C_2-hydroxyl and at the α-anomeric position in ribose by the axial C_3-hydroxyl.

Angyal (16) has proposed a system of quantitative conformational analysis for the pyranoid sugars based on interaction energies derived from the equilibrium reactions of cyclitols (17, 18) and the anomeric equilibria of glucopyranose and mannopyranose (19). A similar system was given for acetylated sugars by Lemieux and Chu (20). Total interaction energies for the pyranoid pentoses in the two chair forms are shown in Table VII and were calculated from the following values in kcal/mole: O_1:O_2 = 0.50 (skew

TABLE VII

Interaction energies (kcal/mole) in pyranoid pentoses

	α		β		$\Delta F\ \alpha \rightleftarrows \beta$	
	C1	1C	C1	1C	Calc.[a]	Found
Lyxose	2.2	3.4	3.5	4.3	1.3	1.31
Xylose	2.3	5.0	2.7	5.0	−0.4	−0.48
Arabinose	3.8	3.1	3.8	2.7	−0.4	−0.40
Ribose	4.4	5.2	3.5	3.9	−0.9	−1.06

[a]For the more stable chair forms.

interaction between *O*-substituents on adjacent carbon atoms): O_a:H_a = 0.40 (axial–axial interaction between a hydrogen and an *O*-substituent); O_a:O_a = 2.1 (interaction between two axial *O*-substituents); $\Delta 2$ effect (2) = 0.40 (interaction of axial *O*-substituent at C_2 on equatorial anomer); anomeric effect (15, 21) = 1.20 (interaction of C_5-ring oxygen dipole on equatorial anomer). These values have been reported by Angyal *et al.* (17–19) for aqueous systems and agree substantially with those given by Lemieux and Chu (20) for acetates in an acetic acid – acetic anhydride system. The value for the anomeric effect has been given as 1.45 kcal/mole for methyl glycosides (19) and as 1.3–1.5 kcal/mole for different aglycons in sugar acetates (21). We have found that a value of 1.20 kcal/mole for the anomeric effect gave calculated differences in free energy between anomers that were in excellent agreement (see Table VII) with those found from the glycoside compositions at equilibrium.

The results of the present work are in general support of the sequence of reactions and the mechanism proposed earlier for the methanolysis of D-xylose (1). Only for D-lyxose

was there any evidence for pyranosides being formed early in the reaction (Table VIII. C). It is possible that lyxopyranosides were formed directly from the free sugar as has been proposed by Mowery (22) for D-mannose and L-arabinose. The highly unfavorable conformations of the furanoside forms of lyxose and mannose would be expected to favor the direct formation of some pyranosides from the free sugars. The only example of the reverse reaction, furanoside → pentose, occurred in the D-lyxose series with methyl α-D-lyxofuranoside as the initial compound (see Table X.C), a further indication of the instability of the furanoside forms of this pentose. Although rate data could not be obtained for the reaction of D-arabinose, qualitative examination of the early products of reaction showed that only arabinofuranosides were present.

The present results are also consistent with the proposed mechanisms for the anomerizations of furanosides and pyranosides for which two different cyclic carbonium ion intermediates were postulated. However, the mechanism tentatively proposed earlier for the furanoside → pyranoside ring expansion in D-xylose, which has been criticized (23), must still be regarded as an open question. Further work on this aspect of glycosidation is in progress.

EXPERIMENTAL

Reagents

Sugars were purified products obtained from commercial sources; no impurities were detected by paper chromatography. Methanol was reagent grade and was distilled from magnesium–iodine immediately before use. Hydrogen chloride was dried by passage through calcium chloride.

Apparatus

An F and M Model 500 Chromatograph or a Pye Argon Chromatograph were employed for gas–liquid partition chromatography. Conditions used are cited in Tables I and II.

Preparation of Methyl Pentosides

Methyl pentosides were prepared by methods described in the literature. The physical properties of these compounds and the reported values were as follows:

	Found		Reported		
	m.p. (°C)	$[\alpha]_D$	m.p. (°C)	$[\alpha]_D$	Ref.
Methyl α-D-xylofuranoside	83–84	+181°	84	+182°	24
Methyl β-D-xylofuranoside	Sirup	− 80°	45	− 89.5°	24
Methyl α-D-xylopyranoside	89–91	+151°	91–92	+153.9°	25
Methyl β-D-xylopyranoside	155.5–156.5	− 65°	156–157	− 65.5°	26
Methyl α-D-ribofuranoside	Sirup	+146°	Sirup	+146.8°	27
Methyl β-D-ribofuranoside	80	− 63°	80 (ref. 28)	− 62.4°	27
Methyl α-D-ribopyranoside	25	+103°	Sirup	+103.3°	27
Methyl β-D-ribopyranoside	83–84	−105°	83	−105.0°	29
Methyl α-D-arabinofuranoside	64–66	+123°	65–67	+123°	24, 30
Methyl β-D-arabinofuranoside	56	−117°	56–57	−119°	24
Methyl α-D-arabinopyranoside	131	− 17°	131	+ 17.3°	31[a]
Methyl β-D-arabinopyranoside	169	−242°	169	+245.5°	31[a]
Methyl α-D-lyxofuranoside	94.5–96	+160°	97	+129°	32
Methyl β-D-lyxofuranoside[b]					
Methyl α-D-lyxopyranoside	108–109	+ 59°	108–109	+ 59.4°	33
Methyl β-D-lyxopyranoside	116.5–117.5	−127°	118	−128.1°	34

[a]For the L-enantiomorphs.
[b]Not isolated in amounts sufficient for characterization. The fully acetylated or methylated derivative of each glycoside gave only one peak on gas–liquid chromatography.

Reactions and Analysis of Products

Reaction vessels were screw-capped bottles fitted with silicone rubber septums and maintained at 35±0.01°. Samples (0.4–0.5 ml) were removed by a hypodermic syringe, neutralized by sodium methoxide, and evaporated to dryness. Fully methylated derivatives were prepared from these samples as described previously

(1). When acetylated derivatives were required (lyxosides, ribosides, and all samples containing reducing sugar) the dry residues were dissolved in 0.3 ml of a mixture of pyridine – acetic anhydride (1:1) at room temperature; acetylation was complete after 1 hour. The solutions from methylation and acetylation were analyzed directly by gas–liquid chromatography, the components being identified by comparison with authentic samples prepared from the glycosides listed above. Amounts of individual components were determined by tracing the peaks from the chromatogram onto glassine paper from which they were then cut out and weighed.

Results

The following tables show the percentage compositions at various times from which the rate constants used in the discussion were obtained. The tables are grouped according to reaction, the conditions for which are specified at the beginning of each section. For each reaction the initial compound is cited as the title of the table. The k values are based on the rate of decrease of initial product except for reaction 3, where they are based on decrease of total ($\alpha+\beta$) furanoside. The rate constants marked with an asterisk (*) were used to give the average values cited in the discussion (Table III).

Reaction 1.—Pentose → furanosides (Table VIII). Conditions: 2% of initial compound in 0.01% methanolic hydrogen chloride at 35±0.01° C.

TABLE VIII

Time (hr)	Unreacted pentose	Methyl glycoside: Furanoside α	Furanoside β	Pyranoside α	Pyranoside β	$k\times10^6$ (sec^{-1})
		A. D-Xylose				
0.25	95.2	3.2	1.7	0.0[a]		*56
0.75	84.7	9.4	5.9	0.0		*61
1.66	72.4	15.7	11.9	0.0		*54
3.0	63.9	20.7	15.5	0.0		42
6.0	35.5	34.5	29.4	0.6		48
22	12.7	40.8	43.7	2.8		26
		B. D-Ribose				
0.25	79.7	2.9	17.4	0.0	0.0	*253
0.50	64.4	4.2	28.3	0.0	0.0	*244
1.0	52.3	6.6	41.0	0.0	0.0	*180
1.5	20.0	10.7	69.3	0.0	0.0	*298
4.5	8.1	14.8	77.2	0.0	Trace	*155
6.0	Trace	18.5	81.5	Trace	Trace	—
24.0	0.0	24.2	73.3	0.5	2.0	—
		C. D-Lyxose				
0.5	96.4	2.1	0.4	1.1	—	*21
1.0	94.8	4.9	Trace	0.2	Trace	*15
1.5	91.2	7.8	—	0.9	Trace	*17
2.0	85.0	13.1	—	1.2	0.8	*23
4.5	71.2	24.7	—	2.7	1.5	*21
7.5	66.4	29.5	—	2.8	1.5	*15
24	12.4	75.8	—	8.1	3.7	
48	1.3	84.9	—	10.4	3.5	
120	1.1	76.8	—	15.6	6.5	
216	—	70.0	—	21.2	8.8	

[a]For α- plus β-pyranoside.

Reaction 2.—Anomerization of furanosides (Table IX). Conditions: 2% of initial compound in 0.01% methanolic hydrogen chloride at 35±0.01° C.

TABLE IX

Time (hr)	Methyl glycoside: Furanoside α	Furanoside β	Pyranoside α	Pyranoside β	$k\times10^6$ (sec^{-1})
	A. Methyl α-D-xylofuranoside				
0.2	96.5	1.4	0.8	1.3	*48
1.0	80.4	16.1	1.4	2.0	*60
2.0	67.2	30.5	0.6	1.7	*56
3.0	59.8	40.2	Trace	Trace	*48
4.0	54.4	45.6	0.0	0.0	*42
6.0	49.0	51.0	0.0	0.0	33
8.0	44.2	55.8	0.0	0.0	28
12	41.5	58.5	0.0	0.0	12
24	41.1	57.9	0.6	0.4	10
48	40.7	57.5	1.0	0.9	5
	B. Methyl β-D-ribofuranoside				
2	3.1	96.9	0.0	0.0	*4.2
7	10.4	89.6	0.0	0.0	*4.3
24	23.3	76.7	Trace	Trace	*3.1
48	23.6	74.2	0.5	1.6	1.7
72	23.1	74.6	0.6	1.7	1.1
96	22.7	74.1	0.8	2.5	0.9
	C. Methyl α-D-arabinofuranoside				
1	99.8	0.2	0.0	0.0	—
2	99.4	0.6	0.0	0.0	0.67
3	99.3	0.7	0.0	0.0	0.58
5	97.9	2.1	0.0	0.0	*1.10
8	96.7	3.3	0.0	0.0	*1.20
24	92.5	7.5	0.0	0.0	*1.89
48	87.1	12.8	Trace	Trace	0.80
79.5	83.0	17.0	Trace	Trace	0.65
120	79.3	19.2	1.0	0.5	0.56
168	77.9	19.8	1.5	0.8	0.41
216	77.7	19.4	2.0	0.9	0.33
288	73.6	23.5	2.2	0.8	0.25
360	72.6	23.2	2.8	1.4	0.25

Reaction 3.—Furanosides → pyranosides (Table X). Conditions: 2% of initial compound in 0.1% methanolic hydrogen chloride at 35±0.01° C.

TABLE X

Time (hr)	Methyl glycoside: Furanoside α	Methyl glycoside: Furanoside β	Methyl glycoside: Pyranoside α	Methyl glycoside: Pyranoside β	Lyxose	$k\times10^6$ (sec^{-1})
	A. Methyl α-D-xylofuranoside					
2	43.7	55.3	0.4	0.6		*1.34
4	43.7	54.2	0.7	1.4		*1.41
6	45.7	52.4	0.7	1.1		*0.94
8	42.7	53.9	1.3	2.1		*1.13
24	41.7	48.3	4.9	5.2		*1.10
96	26.6	35.5	14.9	23.1		*1.38
	B. Methyl β-D-ribofuranoside					
4	24.2	74.5	0.6	0.7		*0.85
24	23.4	70.5	1.4	4.7		*0.72
48	22.3	67.0	2.2	8.6		*0.65
72	20.2	64.7	3.1	12.0		*0.63
108	20.0	60.1	3.9	16.0		*0.57
144	18.9	57.7	4.5	18.9		0.51
192	18.0	52.6	5.8	23.7		0.50
	C. Methyl α-D-lyxofuranoside					
1	97.0	—	1.4	0.2	1.4	*8.3
2	94.2	—	3.6	1.2	1.0	*8.3
3	91.2	—	5.5	2.2	1.2	*8.9
5	85.9	—	9.9	3.2	1.0	*8.3
8	78.5	—	14.7	5.7	1.1	7.3
24	48.2	—	38.8	12.2	0.8	4.8
	D. Methyl α-D-arabinofuranoside					
1	93.9	6.1	0.0	0.0		—
3	83.1	15.9	0.5	0.5		*0.92
5	78.4	20.1	0.7	0.8		*0.87
24	70.7	22.1	2.8	4.5		*0.88
48	63.9	20.8	5.2	10.2		*0.96
79.5	60.7	19.5	6.8	13.0		*0.77
120	50.0	17.7	11.0	21.4		*0.90
168	47.4	15.6	12.9	24.1		0.77
216	45.4	15.5	13.8	25.4		0.64
288	43.2	14.2	14.7	27.8		0.54

Reaction 4.—Anomerization of pyranosides (Table XI). Conditions: 2% of initial compound in 1.0% methanolic hydrogen chloride at 35±0.01° C.

TABLE XI

Time (hr)	Methyl glycoside: Furanoside α	Furanoside β	Pyranoside α	Pyranoside β	$k \times 10^6$ (sec^{-1})
	A. Methyl β-D-xylopyranoside				
3	0.0	0.0	3.2	96.8	*3.0
7	0.4	0.3	6.5	92.9	*3.0
30	1.3	1.3	28.8	68.5	*3.5
72	1.2	1.8	49.0	47.9	*2.8
144	1.3	2.0	59.3	37.4	1.9
240	1.9	3.2	65.1	29.8	1.4
	B. Methyl β-D-ribopyranoside				
4	0.4	2.3	1.7	95.6	*3.2
24	2.4	7.6	6.0	83.9	*2.0
48	3.5	12.8	8.3	75.5	*1.6
72	4.2	14.8	8.9	72.1	*1.3
108	5.2	15.0	9.4	70.5	0.9
144	4.9	16.0	10.2	68.9	0.7
192	5.2	17.4	11.6	65.8	0.6
	C. Methyl β-D-lyxopyranoside				
0.25	0.4	—	4.7	94.9	*58
0.5	1.3	—	9.3	89.5	*61
0.75	1.8	—	14.1	84.1	*64
1.0	1.4	—	18.2	80.4	*61
1.5	2.2	—	28.1	69.8	*64
2	3.0	—	35.9	61.1	*69
3	2.5	—	49.3	48.1	*58
4	2.5	—	57.2	40.6	*64
7	2.3	—	61.7	35.9	42
24	1.8	—	84.6	13.6	
192	1.4	—	88.3	10.3	
	D. Methyl β-D-arabinopyranoside				
8	9.8	3.0	15.3	71.9	*11.4
24	16.2	6.1	24.5	53.2	*7.3
79.5	21.3	6.6	23.8	48.4	2.5
120	21.5	6.5	24.3	47.8	1.7
216	21.5	6.8	24.5	47.2	1.0

ACKNOWLEDGMENTS

We are very grateful to Dr. E. Berner, University of Oslo, Blindern-Oslo, Norway, for seed crystals of a number of the methyl pentofuranosides.

REFERENCES

1. C. T. Bishop and F. P. Cooper. Can. J. Chem. **40**, 224 (1962).
2. R. E. Reeves. Advan. Carbohydrate Chem. **6**, 107 (1951).
3. R. U. Lemieux. Advan. Carbohydrate Chem. **9**, 1 (1954).
4. R. J. Ferrier and W. G. Overend. Quart. Rev. (London), **13**, 265 (1959).
5. B. Capon and W. G. Overend. Advan. Carbohydrate Chem. **15**, 11 (1960).
6. J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer. J. Am. Chem. Soc. **69**, 2483 (1947).
7. T. R. R. McDonald and C. A. Beevers. Acta Cryst. **3**, 394 (1950).
8. S. Furberg. Acta Cryst. **3**, 325 (1950).
9. C. D. Jardetzky. J. Am. Chem. Soc. **82**, 229 (1960).
10. R. U. Lemieux. Can. J. Chem. **39**, 116 (1961).
11. C. D. Jardetzky. J. Am. Chem. Soc. **83**, 2919 (1961).
12. C. D. Jardetzky. J. Am. Chem. Soc. **84**, 62 (1962).
13. L. D. Hall. Chem. Ind. (London), 950 (1963).
14. R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan. J. Chem. Soc. 3699 (1962).
15. J. T. Edward. Chem. Ind. (London), 1102 (1955).
16. S. J. Angyal. Abstracts of Scientific Papers, 18th International Congress of Pure and Applied Chemistry, Montreal. 1961. D7, p. 275.
17. S. J. Angyal and D. J. McHugh. Chem. Ind. (London), 1147 (1956).
18. S. J. Angyal, P. A. J. Gorin, and M. Pitman. Proc. Chem. Soc. 337 (1962).
19. S. J. Angyal. Personal communication.
20. R. U. Lemieux and P. Chu. Abstracts of Papers, 133rd Meeting of the American Chemical Society. 1958. 31N.
21. R. U. Lemieux. Abstracts of Papers, 135th Meeting of the American Chemical Society. 1959. 5E.
22. D. F. Mowery. J. Org. Chem. **26**, 3484 (1961).
23. B. Capon, G. W. Loveday, and W. G. Overend. Chem. Ind. (London), 1537 (1962).
24. I. Augestad and E. Berner. Acta Chem. Scand. **8**, 251 (1954).
25. E. Fischer. Ber. **28**, 1145 (1895).
26. E. Fischer. Ber. **28**, 1157 (1895).
27. G. R. Barker and D. C. C. Smith. J. Chem. Soc. 2151 (1954).
28. I. Augestad and E. Berner. Acta Chem. Scand. **10**, 911 (1956).
29. E. L. Jackson and C. S. Hudson. J. Am. Chem. Soc. **63**, 1229 (1941).
30. E. D. Montgomery and C. S. Hudson. J. Am. Chem. Soc. **59**, 992 (1937).
31. C. S. Hudson. J. Am. Chem. Soc. **47**, 265 (1925).
32. S. Zurberg and S. Hammer. Acta Chem. Scand. **15**, 1190 (1961).
33. F. P. Phelps and C. S. Hudson. J. Am. Chem. Soc. **48**, 503 (1926).
34. H. S. Isbell and H. L. Frush. J. Res. Natl. Bur. Std. **24**, 125 (1940).