final product was dark green-gray. The Alfin catalyst was siphoned by means of nitrogen pressure into a large pressure bottle which had been flushed with nitrogen and the bottle was capped with a Neoprene-lined self-sealing cap. This catalyst consisted of a 1:1 molar ratio of sodium isopropoxide to allylsodium.

Alfin catalysts of different compositions were prepared in a similar manner by varying the amount of isopropyl alcohol added to the amylsodium initially and then passing in propylene to convert the remaining amylsodium to allylsodium.

F. Titration of Alfin Catalyst.—The physical state of the Alfin catalyst was such that it was relatively easy to measure out aliquots directly into a hypodermic syringe, using a 20-gauge needle. The bottle was shaken to give a uniform dispersion, and several 1-ml. samples were removed and each was decomposed in 25 ml. of methanol. An equal volume of distilled water was added to each sample, and it was titrated with 0.1 *N* HCl to the phenolphthalein end-point. The strength of the Alfin catalyst, measured as total alkalinity, was 0.8 to 0.9 meq. per milliliter. The conversion of amylsodium to Alfin catalyst was quantitative.

Polymerizations.—All solvents used were dried over sodium wire. In a dry pressure bottle which had been flushed with dry nitrogen was placed 200 ml. of dry hexane. After the bottle was capped with a self-sealing cap, a dial thermometer was clamped to the side of the bottle with adhesive tape in such a manner that good thermal contact with the bottle below the liquid level was ensured. The desired amount of styrene was then injected through the cap. The catalyst was injected into the bottle, which was then shaken using a wrist-action shaker. The temperature was read at 5-minute intervals, and the polymerization was allowed to proceed until a maximum value had been passed. The average reaction time was about 45 minutes. Controlled temperature runs were carried out in water-baths using a tumbling device for agitation. For the −20° runs, the wrist-action shaker was placed in a freezer. When runs were carried out below room temperature, the reactants were precooled before the catalyst was added. After the polymerizations had been completed, the materials were placed in methanol and leached for several hours to decompose the catalyst, the precipitated polystyrene was dissolved in benzene and the solution filtered free of sodium chloride. The clear solution was then washed with dilute acetic acid, followed by several washes with distilled water. The polymer was precipitated in methanol, filtered and dried.

Crystallization of Polymers.—The dried polymer samples were placed directly in the crystallizing medium and refluxed or held at the desired temperature for the required period of time.

Acknowledgment.—The authors are indebted to E. E. Alden and L. E. Contois of the Physical Chemistry Department, Eastman Kodak Co., for intrinsic viscosity measurements and for crystallinity determinations.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND NUTRITION, GRADUATE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF PITTSBURGH]

The Relationship of Oxidation Rate and Molecular Conformation of Sugar Anomers[1]

BY RONALD BENTLEY

RECEIVED FEBRUARY 20, 1956

Methyl α-D-arabinopyranoside has been found to be more rapidly oxidized by chlorine in aqueous solution than the β-anomer. The conformationally related L-fucose (solid α-anomer and equilibrium solution) was oxidized with bromine water; β-L-fucose was the more rapidly oxidized anomer. The equilibrium solution of L-fucose was found to contain 31.6% of the slowly oxidized α-anomer from these measurements. These observations support the theory that without exception, those anomers of stable conformation in which the glycosidic substituent is in an equatorial position are the more readily oxidized. Frequently, such anomers are the β-forms, using the nomenclature of Hudson's rule, but arabinose is an exception. A generalization has been drawn correlating conformation, optical rotation, configuration at C_1 and relative reactivity for anomeric pairs.

The more rapid oxidation of β- than α-D-glucose with potassium permanganate,[2] sodium hypoiodite[3] and bromine water[4,5] has been interpreted through consideration of the preferred "chair" conformations of the pyranose ring.[6] Following Reeves,[7] these conformations (Fig. 1) will be referred to as C 1 and 1 C, as shown. By analogy with the cyclohexane system,[8] reactions involving an equatorial (*e*) anomeric hydroxyl group would be expected to be more rapid than the same reaction with the sterically hindered, axial (*a*) anomeric group—provided that the reaction mechanism was a direct attack on the anomeric substituent. In the oxidation of pyranoses with buffered bromine solutions (*p*H 5.4, 0°), free bromine is the oxidant, and the initial product is the δ-lactone, formed without breaking the pyranose ring.[9] Gluconic acid is subsequently formed by hydrolysis. A similar oxidation is that of the methyl pyranosides to the same products with chlorine.[10] Among the pentoses and hexoses so far studied in the bromine oxidation, the β-anomers are more rapidly oxidized than the α[4,5,9]: the former compounds are all found to have the anomeric OH group in the equatorial position. The only exception among these compounds is L-arabinose, where the α-anomer is the more rapidly oxidized. Since the hydroxyl groups on C_1 and C_2 of β-L-arabinose, the ordinary solid form, are in a *cis* relationship and since L-arabinose has the C 1 conformation, it follows that the anomeric OH group of this compound is axial. The more rapid oxidation of the α-anomer would therefore be expected from the considerations just outlined.

(1) This work was supported in part by a Research Grant (A-725) from the National Institutes of Health, United States Public Health Service.

(2) R. Kuhn and T. Wagner-Jauregg, *Ber.*, **58**, 1441 (1925).

(3) K. Myrback, *Svensk. Kem. Tid.*, **52**, 293 (1940); K. D. Reeve, *J. Chem. Soc.*, 172 (1951).

(4) H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **10**, 337 (1932).

(5) H. S. Isbell and W. W. Pigman, *ibid.*, **18**, 141 (1937).

(6) R. Bentley, *Nature*, **176**, 870 (1955).

(7) R. E. Reeves, THIS JOURNAL, **72**, 1499 (1950).

(8) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(9) H. S. Isbell and C. S. Hudson, *J. Research Natl. Bur. Standards*, **8**, 327 (1932); H. S. Isbell, *ibid.*, **8**, 615 (1932).

(10) A. Dyfverman, B. Lindberg and D. Wood, *Acta Chem. Scand.*, **5**, 253 (1951).

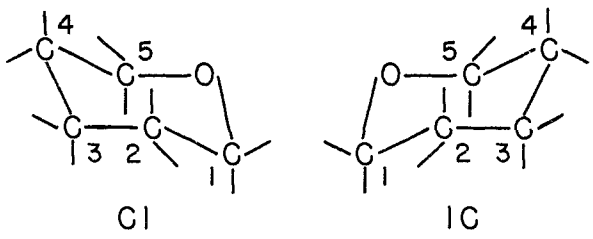


Fig. 1.—Chair conformations of the pyranose ring.

This paper reports the previously undescribed chlorine oxidation of the methyl α- and β-D-arabinopyranosides and the bromine oxidation of the conformationally related L-fucose. The bromine oxidations of D-arabinose, L-lyxose and L-xylose proceeded as predicted from previous studies with enantiomorphic compounds.

Unless otherwise indicated, all anomeric assignments in this paper are those derived by application of Hudson's rule.

Results

Chlorine Oxidation of Methyl α- and β-D-Arabinopyranosides.—These experiments were carried out at 37° to reduce the very lengthy reaction times needed for other pyranosides, previously oxidized at 20°. The oxidation of methyl α-D-arabinopyranoside was fairly rapid under these conditions; very slightly more than 1 mole of organic acid per mole of initial glycoside was formed within 20 hours (see Fig. 2), and this level of acid

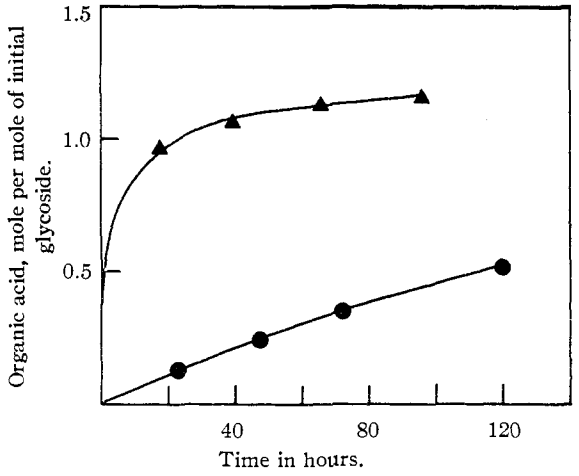


Fig. 2.—Oxidation of methyl α- and β-D-arabinopyranosides at 37°: α-anomer, ▲; β-anomer, ●.

remained constant despite prolonged chlorination. With methyl β-D-arabinopyranoside, the rate of oxidation was very much slower, less than 0.5 mole of organic acid per mole of initial glycoside being formed in the same time. In both cases the solutions contained relatively large amounts of HCl and it was possible that the arabinopyranosides might have been first hydrolyzed to arabinose which would then have been oxidized rapidly.

The rates of acid hydrolysis of the two anomers were therefore studied under conditions approximating those in the early stages of the oxidation (0.5 *M* glycoside in *N* HCl at 37°). The changes in optical rotation during hydrolysis and oxidation are compared in Fig. 3. It is apparent that the oxidations take place more rapidly than do the hydrolyses. The hydrolytic reactions were followed until an equilibrium value of optical rotation was reached by both anomers (50 days). Velocity constants (reciprocal hours, decimal logarithms) were calculated to be 0.00160 for the α- and 0.00145 for the β-anomer. This very slight difference in hydrolytic rates is noteworthy in view of the large difference in rates of oxidation of the methyl arabinopyranosides and in view of the more pronounced differences in hydrolytic rates of other anomeric pyranosides. Previously reported values for the velocity constants of the arabinopyranosides were 0.0026 (α) and 0.0018 (β) measured with the L-enantiomorphs in 0.5 *N* HCl at 75°[11]; and 0.0032 (identical values for both anomers) measured with the D-enantiomorphs in 0.05 *N* HCl at 98° (all values in reciprocal minutes and decimal logarithms).[12]

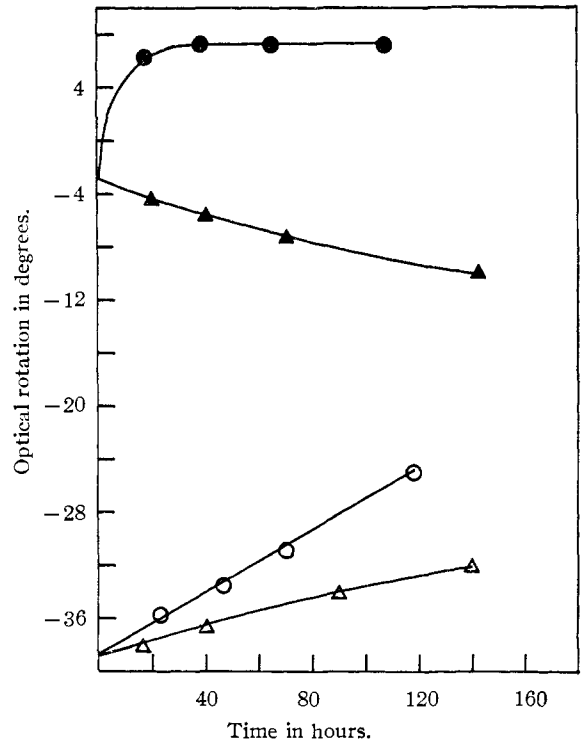


Fig. 3.—Changes in optical rotation (2-dm. tube) during hydrolysis and chlorine oxidation of methyl α- and β-D-arabinopyranosides at 37°; 0.5 *M* solution of arabinopyranoside in *N* HCl used for hydrolysis: α-anomer, ▲; β-anomer, △; 0.5 *M* solution of arabinopyranoside for oxidation: α-anomer, ●; β-anomer, ○.

Bromine Oxidation of L-Fucose.—Since the β-anomer of L-fucose has not been prepared, these oxidations were carried out with the solid α-anomer and with the equilibrium solution. The results of these oxidations are shown in Table I.

It was found that the equilibrium solution contained a rapidly oxidized component, and 74% of

(11) C. N. Riiber and N. A. Sorensen, *Det. Kgl. Norske Videnskab. Selskabs Skrifter*, No. 1, 1 (1938).

(12) E. M. Montgomery and C. S. Hudson, THIS JOURNAL, **59**, 992 (1937).

TABLE I

BROMINE OXIDATIONS OF L-FUCOSE AT 1°

Solid α-L-fucose			Equilibrium solution		
Time, min.	Sugar remaining, g.	Oxidized, %	Time, min.	Sugar remaining, g.	Oxidized, %
0	0.75	0.0	0	0.75	0.0
0.23	.67	10.7	1	.52	30.6
12	.60	20.0	3	.27	64.0
24	.54	28.0	4.5	.23	69.4
58	.34	54.8	6	.21	72.0
128	.14	81.5	15	.18	76.0
180	.06	92.0	30	.14	81.5
			65	.07	90.5
			120	.03	96.0

the total sugar in this solution was oxidized within 10 minutes. In the case of the freshly dissolved α-anomer, slightly less than 20% was oxidized in the same time. From the plot of log % fucose unoxidized against time, it was calculated by the method of Isbell and Pigman[4] that the equilibrium solution of L-fucose contained 31.6% of the α-anomer. There are apparently no calculations of the composition of the equilibrium solution on the basis of optical data.

From the oxidation results with the equilibrium solution, the rate ratio $k\beta/k\alpha$ was determined from values of $1/t \times \log A/A - X$, calculated for the slow and rapid oxidation (A = sugar initially, $A - X$ = sugar at time t). The calculation was carried out as described by Isbell and Pigman,[4,5] with the assumption that the concentration of free bromine was constant. These values for the oxidation of the α- and β-anomers, respectively, were 0.763×10^{-2} and 37.10×10^{-2} (reciprocal minutes and decimal logarithms). From the separate experiment with solid α-L-fucose, the value was calculated to be 0.767×10^{-2}. It follows that the rate ratio for this oxidation, $k\beta/k\alpha$, is therefore 48.6.

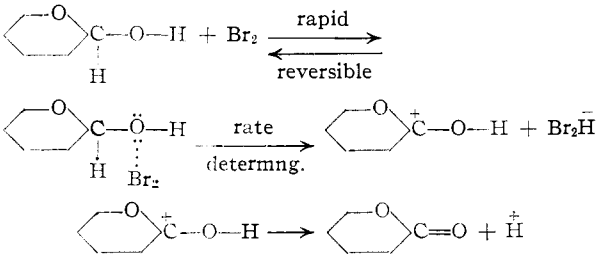
Other Bromine Oxidation Studies.—Bromine oxidation of β-D-arabinose and α-L-xylose, and their equilibrium solutions, under the standard conditions of Isbell and Pigman,[4,5] gave oxidation curves identical in each case with those obtained by these authors with the enantiomorphs. In the case of L-lyxose, the oxidation was carried out on a smaller scale and at a lower sugar concentration. The results of this experiment lead to a value for the rate ratio, $k\beta/k\alpha$, calculated from results with solid β-L-lyxose and α-anomer in equilibrium solution, of 2.7. This is in good agreement with the value of 2.9 obtained by Isbell and Pigman using the two solid, enantiomorphic anomers.[5]

Discussion

Mechanism of Halogen Oxidations.—With the exception of arabinose, the β-anomers of the pyranoses are the more rapidly oxidized by bromine. Similarly, with the exception of methyl β-D-arabinopyranoside, reported here, a higher reactivity of methyl β-pyranosides has been observed with all of the compounds studied in the chlorine oxidation (methyl D-gluco-, D-manno-, D-galacto- and D-xylopyranoside).[10,13] The detailed mechanism of the chlorine oxidations is not well understood; in particular, the fate of the methyl group is not known. Dyfverman, *et al.*,[10] have suggested that hydrolysis of the glycoside does not precede the oxidation. This is strikingly confirmed by the results of the present experiments, where the rates of hydrolysis of the anomeric pyranosides are only slightly different, despite the large difference in oxidation rates.

It was suggested previously that the bromine oxidation of the pyranoses involved an attack on oxygen, with formation of a hypobromite intermediate.[6] Further, an initial attack of halogen on the glycosidic oxygen, probably rapid and reversible, was suggested by kinetic studies of the chlorine oxidation of glucose; the formation of a hypochlorite was considered unlikely in this reaction.[14] Assuming attack of the oxidant at the C_1-hydroxyl, the decreased reactivity of axial OH groups was attributed to the steric hindrance of such groups, as originally suggested by Barton in connection with reactions in the cyclohexane series.[8]

An alternative explanation is possible, however, since it has been shown that the rate of oxidation of ethanol-1-*t* with bromine is less than that of ethanol.[15] This observation rules out the intermediate formation of ethyl hypobromite and has been interpreted as due to the transfer of a hydride ion to bromine. If a similar mechanism is involved in the oxidation of pyranoses by bromine, there may still be an initial, rapid and reversible formation of a pyranose–halogen complex, followed by a rate-determining transfer of a hydride ion as shown in the equations



In this case, the greater reactivity of those anomers in which the hydrogen on C_1 is axial is due to the fact that the rate-determining step is favored by the release of strain,[16] which is greatest when the H is axial. This is the reverse of the usual situation in cyclohexane compounds but, as Edward has pointed out, it is likely that in the pyranose series, axial OH groups on C_1 are in general more stable than equatorial OH groups, because of the repulsive forces associated with the unshared electrons of the ring oxygen atom.[17] In a similar manner, rate differences in the hydrolysis of anomeric methyl pyranosides have been considered from two points of view; the generally decreased reactivity of α-anomers is due either to the steric shielding of axially located glycosidic substituents from protonation[18] or to stability differences between the two

(13) B. Lindberg and D. Wood, *Acta Chem. Scand.*, **6**, 791 (1952).

(14) N. N. Lichtin and M. H. Saxe, THIS JOURNAL, **77**, 1875 (1955).

(15) L. Kaplan, *ibid.*, **76**, 4645 (1954).

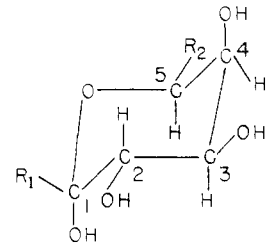
(16) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

(17) J. T. Edward, *Chemistry & Industry*, 1102 (1955).

(18) A. B. Foster and W. G. Overend, *ibid.*, 566 (1955).

TABLE II

COMPARISON OF COMPOUNDS WITH THE SAME CONFORMATION AND THE SAME CONFIGURATIONS AT C_2, C_3 AND C_4



R_1	R_2	Name	Conformation[a]	Anomeric assignment on basis of Hudson's rule	Specific rotation[b] Pyranose	$[\alpha]^{20}D$ Methyl-pyranoside	Relative reaction rate Br_2 oxidation of pyranose	Relative reaction rate Hydrolysis of methyl pyranoside
H	H	D-Arabinose	1 C	β	$-190.6 \rightarrow -104.5°$	$-245.5°$	$\alpha > \beta$[c]	$\alpha \geq \beta$[d]
H	CH_3	L-Fucose	1 C	α	$-152.6 \rightarrow -75.9$	-197.4	$\beta > \alpha$[c]	
H	CH_2OH	L-Galactose[e]	1 C	α	$-150.7 \rightarrow -80.2$[f]	-179.3	$\beta > \alpha$[g]	$\beta > \alpha$[h]
H	CHOH-CH_2OH	D-*glycero*-L-*glacto*-Heptopyranose	"1 C"	β	$-120.5 \rightarrow -65.1$		$\alpha > \beta$[i]	
H	CHOH-CH_2OH	L-*glycero*-L-*glacto*-Heptopyranose[e]	"1 C"	α	$-120.0 \rightarrow -64.7$		$\beta > \alpha$[i]	
CH_2OH	H	D-Fructose	"1 C"	β	$-132.2 \rightarrow -92.4$	-172.1		$\alpha > \beta$[j]
CH_2OH	CH_2OH	L-*glacto* heptulose (Perseulose)	"1 C"	α	$-90 \rightarrow -80$[i]			

[a] Where the conformation is predicted from consideration of the instability factors, it is indicated as "1 C." All determined conformations (1 C) from Reeves (footnote 7). [b] These values are taken from Bates, *et al.* (footnote 25). [c] This paper. [d] Footnotes 11, 12 and this paper. [e] Results derived from enantiomer. [f] Hydrate. [g] Footnote 4, 5. [h] Footnote 11. [i] Footnote 19. [j] L. J. Heidt and C. B. Purves, THIS JOURNAL, **66**, 1385 (1944).

anomeric forms.[17,19] At present, in the absence of information on the reaction mechanism, it is probably not possible to specify the precise influence of the steric situation in the halogen oxidations.

Relationship Between Relative Oxidation Rates and Conformation.—In view of the greater reactivity of α-arabinose and methyl α-arabinopyranosides, and since the proposal of Isbell and Pigman[4,5,20] to change the anomeric assignments for arabinose has not been accepted, it is not possible to make the generalization that all β-anomers are the more rapidly oxidized. A further difficulty is that among the aldoheptopyranoses, in four cases (D-*glycero*-L-*gluco*-, D-*glycero*-L-*manno*-, D-*glycero*-L-*galacto*-, D-*glycero*-L-*talo*heptopyranose) the α-anomers are the more rapidly oxidized if the anomeric assignments for these compounds are made on the basis of Hudson's rule. In these cases, Isbell's nomenclature, which is partly based on the results of bromine oxidations, has been generally accepted; this results in the β-anomers of these compounds being the more readily oxidized. However, despite such nomenclatural problems, it is apparent that in all cases where the compounds are conformationally stable, the more rapidly oxidized member of an anomeric pair is that compound where the anomeric substituent, OH or OCH_3, is equatorial.

Compounds studied in the present work (L-fucose and D-arabinose) are related to L-galactose and are all of 1 C conformation. Table II summarizes the anomeric assignments on the basis of Hudson's rule, specific rotations and relative reaction rates for anomers of these and other related compounds. This table emphasizes the fundamental importance of the conformational type in considering the similarities frequently observed in the sugars. Early attempts by Isbell[20] to use conformations in discussing such similarities, and the reactivity of anomeric forms, were hampered by the lack of knowledge of the shapes of these six-membered rings. For compounds of the same ring conformation, substitutions at C_1 and C_5, while maintaining the same configurations of the other carbon atoms, do not markedly affect the specific rotation of the compounds. All of the compounds shown in Table II have axial glycosidic substituents; they are all less reactive than the equatorially substituted compounds, despite the differences in the anomeric assignments.

From consideration of such comparisons, it seems that a correlation can be made between the conformation of the entire molecule, the configuration at C_1, the optical rotation and the relative reactivity of the anomers. The following generalization may be drawn. "For any pyranose of stable C 1 conformation, regardless of membership in the D- or L-configurational series, the more dextrorotatory member of the anomeric pair will have the anomeric substituent in the axial position. Similarly, for any pyranose of stable 1 C conformation, regardless of membership in the D- or L-configurational series, the more levorotatory member of the anomeric pair will have the anomeric substituent in the axial position. The anomer with the glycosidic substituent in the axial position will in general be the least reactive."

This generalization is of wider application than one previously proposed by Fieser[21] in connection with bromine oxidations, which in any case cannot be applied to pentoses. It holds true for those compounds where conformational instability is not a factor, in all of the hydrolytic and oxidative reactions so far reported. The available data for the

(19) G. Huber, *Helv. Chim. Acta*, **38**, 1224 (1955).

(20) H. S. Isbell, *J. Research Natl. Bur. Standards*, **18**, 505 (1937); **20**, 97 (1938).

(21) L. F. Fieser, THIS JOURNAL, **72**, 623 (1950).

TABLE III

RESULTS ILLUSTRATING APPLICATION OF PROPOSED RULE

D-Series sugar	Conformation[a]	Pyranose[b] More dextro (if conformation is C 1) or more levo (if conformation is 1 C) anomer $[\alpha]^{20}D$	Anomeric assign.[c]	Methyl pyranoside[b] More dextro (if conformation is C 1) or more levo (if conformation is 1 C) anomer $[\alpha]^{20}D$	Anomeric assign.[c]	Actual position of anomeric subst.	Relative reaction rates: Bromine oxidn. of free pyranose k_e/k_a[d]	Relative reaction rates: Acid hydrolysis of methyl pyranoside k_e/k_a[d]	Relative reaction rates: Chlorine oxidation of methyl pyranoside[e]
Pentoses									
Arabinose	1 C	$-190.6 \rightarrow -104.5°$	β	$-245.5°$	β	a	17.5[f]	1.45 (0.5 *N*, 75°)[g]	$e > a$[h]
Lyxose	C 1 ⇄ 1 C[i]	$+5.6 \rightarrow -13.8$	α	$+59.4$	α	$a \rightleftarrows e$	2.9	3.6 (0.05 *N*, 98°)[j]	
Ribose	C 1			$+103.3$[k]	α	a	5.2[l]		
Xylose	C 1	$+93.6 \rightarrow +18.8$	α	$+153.9$	α	a	18.0	2.0 (0.5 *N*, 75°)[g]	$e > a$[m]
Hexoses									
Allose	"C 1"								
Altrose	C 1 ⇄ 1 C			$+125.8$[n]	α	$a \rightleftarrows e$			
Galactose	C 1	$+150.7 \rightarrow +80.2$	α	$+179.3$[o]	α	a	37.9	1.8 (0.5 *N*, 75°)[g]	$e > a$[m]
Glucose	C 1	$+112.2 \rightarrow +52.7$	α	$+158.9$	α	a	39.2	1.9 (0.5 *N*, 75°)[g]	$e > a$[h]
Gulose	C 1[p]	$+37.1 \rightarrow -10$[q]	α	$+109.4$[p]	α	a	5.9	0.33 (0.5 *N*, 75°)[r]	
Idose	1 C[s]			-81.1,[t] -40.8[u]	β	a			
Mannose	C 1	$+29.3 \rightarrow +14.2$	α	$+79.2$	α	a	15.3	2.4 (0.5 *N*, 75°)[g]	$e > a$[m]
Talose	"C 1"	$+68 \rightarrow +20.8$	α			a	10.8		

[a] All experimentally determined conformations are from Reeves, footnote 7; conformations in quotation marks are predicted from consideration of instability factors. [b] All optical rotations are taken from Bates, *et al.*, footnote 25, unless otherwise indicated. [c] Hudson's rule. [d] k_e and k_a are the velocity constants for the anomer with substituent in the equatorial and axial position, respectively. [e] Precise velocity constants have not been determined for these reactions. [f] Ratios for bromine oxidations from Isbell and Pigman, footnote 5; the value for D-arabinose is taken from their results with the L-enantiomorph and is confirmed by the present work. [g] Riiber and Sorensen, footnote 11; other values for arabinose are discussed in the text. [h] This paper. [i] C 1 assumed to predominate. [j] Footnote 18. [k] G. R. Barker and D. C. C. Smith, *J. Chem. Soc.*, 2151 (1954). [l] Ratio for rapidly oxidized component in equilibrium solution compared to crystalline D-ribose. [m] Footnote 13. [n] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941). [o] Hydrate. [p] Footnote 10. [q] Methyl α-D-gulopyranoside favors the C 1 conformation though some instability is to be anticipated. [r] α-D-Gulose·$CaCl_2 \cdot H_2O$. [s] Methyl α-D-idopyranoside is definitely 1 C conformation. The conformation of methyl β-D-idopyranoside has not been determined experimentally, but the β-D-idopyranosides probably show C 1 ⇄ 1 C instability. [t] E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945). [u] L. F. Wiggins, *J. Chem. Soc.*, 1590 (1949).

simple pentoses and hexoses are listed in Table III, and it will be seen that the generalization holds for arabinose, ribose, xylose, galactose, glucose, mannose and talose. No data are available for allose (C 1 conformation), altrose (C 1 ⇄ 1 C) or idose (instability in the β-idopyranosides), either in oxidative or hydrolytic reactions. For lyxose (C 1 ⇄ 1 C) and gulose (anticipated conformational instability) a low rate ratio is observed in the bromine oxidation. For gulose, the hydrolytic rate of the methyl α-D-gulopyranoside is more rapid than that of the β-anomer. This interesting observation has been discussed by Foster and Overend[18] and by Edward.[17] The proposed rule would not be expected to be valid if the two anomeric forms of the same pyranoside were both conformationally stable but of different conformation.

Although no examples have been reported in which both members of an anomeric pair are oxidized at the same rate, the rate ratios vary in the bromine oxidation from a low value of 2.9 (lyxose) to a high value of 66 (D-*glycero*-L-*gluco*-heptopyranose). In the bromine oxidations of pyranoses, the rate ratios have the following variations: pentoses, 2.9–17.5; hexoses, 5.9–39.2; deoxyhexoses, 8.6–48.6; heptoses, 9.0–66.0. In general, there is a progressive increase in both the low and high values with increase in the size of the substituent at C_5 in the following order; $H < CH_2OH < CH_3 < CHOH \cdot CH_2OH$. This is in agreement with the principle that a large substituent on C_5 will, wherever possible, be accommodated in the equatorial position, thus stabilizing that particular conformation. It is of interest that among the compounds so far studied, the highest rate ratio in the bromine oxidation (66.0) is observed with D-*glycero*-L-*gluco*-heptopyranose. A high degree of stability would be expected for this compound; it has 1 C conformation, and the OH groups at C_2, C_3 and C_4, as well as the $CHOHCH_2OH$ group at C_5, are all equatorial.

Conversely, the lowest rate ratios in the pentose, hexose and heptose series are observed with lyxose (2.9), gulose (5.9) and D-*glycero*-D-*gulo*-heptopyranose (9.0). These low rate ratios probably result from the observed conformational instability in lyxose and the predicted conformational instability in gulose derivatives. Although, for example, solid α- and β-D-lyxose probably have a fixed C 1 conformation in the crystal structure, both C 1 and 1 C conformations (or possibly other boat conformations) are present in solution, as shown by Reeves' study of the cuprammonium complex forming properties of the methyl α- and β-D-lyxopyranosides.[22] In C 1 conformation, β-D-lyxose (anomeric OH = *e*) would be the more rapidly oxidized; but in 1 C conformation the anomeric OH will be in the axial position and β-D-lyxose would then be the more slowly oxidized. If a mixture of both conformations exists in solution, the net effect will be to increase the rate of oxidation of the α-anomer and to decrease that of the β-anomer, leading to a low rate ratio. The fact that the β-anomer is still more rapidly oxidized suggests that the C 1 conformation must predominate in the mixture. Other compounds where conformational instability

(22) In a personal communication, Dr. R. E. Reeves has informed me that he no longer regards C 1 ⇄ 1 C interconversion as a direct possibility. Where cuprammonium behavior led to this suggested interconversion, Dr. Reeves is now inclined to look for boat forms. The precise nature of the conformational instability is, however, relatively unimportant for the present problem since either C 1 ⇄ 1 C, or C ⇄ B instability will have the same effect on the rate ratio.

is observed are the methyl α- and β-D-altropyranosides and probably methyl β-D-idopyranosides (although not in methyl α-D-idopyranosides). The only result available for these compounds is the observation of a significantly low rate ratio ($k\beta/k\alpha$ = 12) in bromine oxidation of D-*glycero*-D-*ido*-heptopyranose.

In some cases, a low rate ratio is found in compounds where conformational instability is neither observed nor predicted. These cases are probably associated with the formation of isomers other than the α- and β-pyranoses in solution and may be suspected, though not always, when the sugar shows a complex mutarotation. For ribose, the rate ratio $k_{\text{rapidly oxid. component in equil. soln.}}/k_{\text{cryst. sugar}}$ has been determined as 5.2 (D-ribose) and 7.5 (L-ribose). Ribose has a complex mutarotation,[5] and the equilibrium solution is known to contain large amounts of isomer reducible at the dropping mercury electrode.[23] A similar situation may hold for D-talose ($k\beta/k\alpha$ = 10.8), D-*glycero*-D-*talo*-heptopyranose ($k\beta/k\alpha$ = 10.0) and D-*glycero*-L-*talo*-heptopyranose ($k\beta/k\alpha$ = 13.6), all of which show complex mutarotation.[5,20] Although no experimental determination of the conformation of talose is available, consideration of the instability factors suggests that talose will have a stable C 1 conformation. A further consequence is that in these cases the composition of the equilibrium solution, calculated from the optical data, does not agree with that calculated from the results of bromine oxidation. In the case of talose, for example, the equilibrium solution has the following compositions: optical data, 25% α, 75% β[24]; bromine oxidation, 55.9% α, 44.1% β.[5]

Experimental

Preparation of Compounds.—D-Arabinose, L-xylose and L-fucose were obtained from Nutritional Biochemicals Corporation, Cleveland, Ohio. Their physical constants (m.p. and specific rotation) were in agreement with recorded values. Methyl β-D-arabinopyranoside was prepared by the Fischer method as described by Bates, *et al.*[25]; m.p. 170°, $[\alpha]^{25}D$ −243° (water, *c* 8). Methyl α-D-arabinopyranoside was prepared as described by Fletcher and Hudson[26]; m.p. 130–131°, $[\alpha]^{25}D$ −17.3° (water, *c* 8).

L-Lyxose was synthesized from L-galactonic acid[27] using the hydrogen peroxide degradation described by Hockett and Hudson for the enantiomorph.[28] The crude material was treated with Amberlite Monobed (MB 2) in aqueous solution; filtration and evaporation yielded a clear sirup. Crystallization took place on standing for several months at room temperature; the crystals were washed out with isopropyl alcohol and recrystallized by solution in hot isopropyl alcohol, followed by slow evaporation. The crystalline β-L-lyxose had m.p. 117–118°, $[\alpha]^{25}D$ +14.2° (water, *c* 5.08). Paper chromatography using phenol–water as solvent showed only one spot reacting with the aniline phthalate reagent and with the same R_f as that obtained from D-lyxose.

Bromine Oxidations.—The oxidations of D-arabinose, L-xylose and L-fucose were carried out essentially as described by Isbell and Pigman[4,5] except that 0.75 g. of sugar was used; the components of the buffer solution were 80 ml. of barium bromide solution (15 g. per 250 ml. water), 6 g. barium carbonate, 2 ml. bromine and either 20 ml. of water in the case of the solid anomers or 20 ml. of the equilibrium sugar solution. The final volume was 104 ml. The internal temperature of the reaction flask was maintained at 1° with an ice-bath, and the sugars were added at zero time either as solids or as equilibrium solution previously cooled in ice. A slow stream of carbon dioxide saturated with bromine vapor was passed through the well-stirred mixture throughout the reaction. Samples were removed at intervals and treated with a solution of corn oil in chloroform to remove bromine. The reducing sugar remaining was determined using Benedict solution.

The oxidations of L-lyxose were carried out on a smaller scale as follows. The L-lyxose (either solid β-anomer, 100.6 mg., or equilibrium solution, 2 ml. containing 101.6 mg.) was added to a mixture of barium bromide solution (20 ml.), barium carbonate (1.5 g.), bromine (0.5 ml.) and water (5 ml. in the case of the solid β-anomer and 3 ml. for the equilibrium solution). Approximately 2-ml. samples were removed at intervals; after removal of bromine and appropriate dilution, pentose analyses were carried out using the orcinol method.[29]

Chlorine Oxidations.—0.5 *M* solutions of the methyl arabinopyranosides in water were treated with a slow stream of chlorine at 37°. The chlorine was first bubbled through water, also at 37°, to minimize evaporation losses. The following determinations were carried out on samples removed at one or two daily intervals and aspirated with air until chlorine free: optical rotation, total acidity (the titrations with alkali were carried out with warming until a stable end-point was reached in order to hydrolyze the lactone present) and HCl (determined by titration with 0.1 *N* $AgNO_3$ using Mohr's method).

PITTSBURGH 13, PENNSYLVANIA

(23) S. M. Cantor and Q. P. Peniston, THIS JOURNAL, **62**, 2113 (1940).

(24) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 189 (1937).

(25) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," United States Government Printing Office, Washington, D. C., 1942, p. 514.

(26) H. G. Fletcher and C. S. Hudson, THIS JOURNAL, **72**, 4173 (1950).

(27) R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith and M. Stacey, *J. Chem. Soc.*, 1419 (1933).

(28) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **56**, 1632 (1934).

(29) W. W. Umbreit, R. H. Burris and J. F. Staufer, "Manometric Methods and Related Techniques for the Study of Tissue Metabolism," Burgess Publishing Co., Minneapolis, Minn., 1945, p. 166.