Carbohydrate Research, 184 (1988) 13–25
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

FURANOSE RING ANOMERIZATION: A KINETIC STUDY OF THE 5-DEOXYPENTOSES AND 5-*O*-METHYLPENTOSES

JOSEPH R. SNYDER AND ANTHONY S. SERIANNI
Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556 (U.S.A.)
(Received January 19th, 1988; accepted for publication, June 6th, 1988)

ABSTRACT

The anomerization of 5-deoxy-L-pentoses (**1–4**) and 5-*O*-methyl-D-pentoses (**5–8**) in aqueous solution has been studied by ^{13}C saturation-transfer n.m.r. (s.t.-n.m.r.) spectroscopy, using compounds substituted with ^{13}C at the anomeric carbon atom. Unidirectional rate-constants of ring-opening (k_{open}) and ring-closing (k_{close}) have been obtained for these compounds under identical solution conditions (50mM acetate buffer, pH 4.0 at 60°), and have been compared to those measured for the D-tetroses (**9** and **10**) and the four D-pentose 5-phosphates (**11–14**). Based on these comparisons, several correlations between furanose structure and reactivity have been revealed, and models have been proposed to explain the observed kinetic behavior of compounds **1–10**. The effect of exocyclic structure on acid-catalyzed rate-constants was also examined by comparing the behavior of 5-deoxy-L-(1-^{13}C)-lyxose and 5-*O*-methyl-D-(1-^{13}C)lyxose. Some consideration has been given to identifying the factors (enthalpic and entropic) that may play roles in determining the effect of structure on anomerization reactivity.

INTRODUCTION

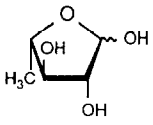
Recent studies of the unidirectional rate-constants of anomerization of such monosaccharides as D-erythrose and D-threose[1], D-idose[2], D-fructose[3], DL-apiose[4], and D-talose[5] have shown that anomeric configuration influences the ring-opening rate-constants (k_{open}) of neutral furanose sugars (*i.e.*, furanoses that do not contain an ionizable group such as phosphate or carboxylate). In the tetrofuranoses and idofuranoses, for example, anomers having O-1 and O-2 *cis* (*β-threo, α-erythro*, and *β-ido*) open at similar rates to, or faster than, anomers having these atoms *trans* (*α-threo, β-erythro*, and *α-ido*)[1,2], regardless of the relative thermodynamic stabilities of the anomers. Likewise, the ring-opening rates of β-D-fructofuranose and 6-*O*-methyl-β-D-fructofuranose, which have O-2 and O-3 *cis*, are greater than those of α-D-fructofuranose and 6-*O*-methyl-α-D-fructofuranose, respectively[3,6]. The ring-opening rate-constants of apiofuranoses also depend on the number and configuration of the substituents. For instance, 3-*C*-(hydroxymethyl)-β-L-threofuranose contains the greatest number of destabilizing interactions [two *cis*-1,2

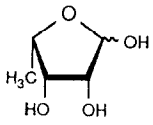
0008-6215/88/$ 03.50

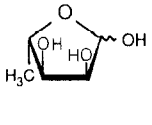
interactions (OH–OH, OH–CH_2OH) and one *cis*-1,3 interaction (OH–CH_2OH)], and its ring opening is the fastest of those of the four apiofuranose anomers[4].

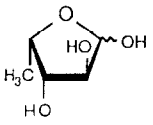
From observations to date, it appears that the number and nature of substituent interactions, particularly *cis*-1,2 interactions, affect the rate of ring opening of neutral furanoses, with kinetic instability increasing as the number of interactions increases. However, furanoses, such as the pentose 5-phosphates, that contain an ionizable functionality behave differently, with α anomers opening at rates similar to or greater than those of the β anomers at pH 4.2, regardless of the configuration of the other ring-carbon atoms[6]. This behavior was previously explained[6] by invoking the participation of the phosphate group as an intramolecular catalyst that acts more effectively when O-1 and C-5 of the pentofuranose ring are *trans*, an arrangement found only in their α anomers.

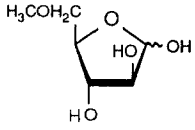
To explore the effect of pentofuranose structure on ring-opening and ring-

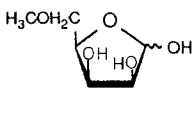

1

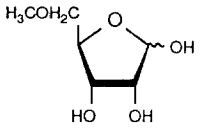

2

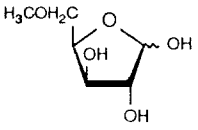

3

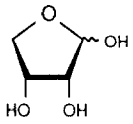

4

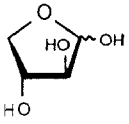

5

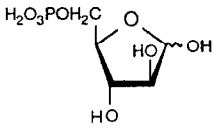

6

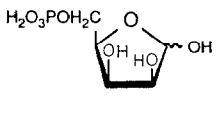

7

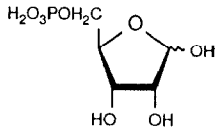

8

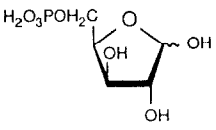

9


10


11


12


13


14

closing rates further, we have studied the behavior of the 5-deoxypentoses (**1–4**) and 5-*O*-methylpentoses (**5–8**) having the *arabino* (**1** and **5**), *lyxo* (**2** and **6**), *ribo* (**3** and **7**), and *xylo* (**4** and **8**) configurations. These compounds are similar in structure to the pentose 5-phosphates **11–14**, but lack the ionizable phosphate moiety at C-5, allowing an assessment of the effect of a nonionizable, exocyclic C-5 substituent on the anomerization kinetics of pentofuranoses.

EXPERIMENTAL

Materials. — $K^{13}CN$ (99 atom-% ^{13}C) and ^2H_2O (98 atom-% ^2H) were purchased from Cambridge Isotope Laboratories. The 5-deoxy-L-pentoses **1–4**, 5-*O*-methyl-D-pentoses **5–8**, and the tetroses **9** and **10** were synthesized with ^{13}C-enrichment at C-1, and purified according to procedures described previously[7–9].

Instrumentation. — Saturation-transfer (s.t.) ^{13}C-n.m.r. spectra were recorded with a Nicolet NT-300 300-MHz, superconducting, F.t.-n.m.r. spectrometer operated at 75 MHz for carbon, and equipped with quadrature phase-detection and a 293B pulse programmer. Spectrometer-hardware modifications and the pulse program used to obtain s.t.-n.m.r. spectra on the NT-300 spectrometer, and data analysis, have been described previously[1,2]. S.t.-^{13}C-n.m.r. spectra were recorded with saturation times ranging from 0.1 to 20 s and relaxation delays of >20 s. At least 10 saturation times were employed in each experiment (64 transients per spectrum), and signal intensities were plotted semi-logarithmically as described previously[1,2], in order to obtain τ_1 from the slope. Using T_1 (spin–lattice relaxation-times) and τ_1 values, ring-opening rate-constants in s^{-1} were determined from the relationship[1,2] $1/\tau_1 = k_{open} + 1/T_1$. The assignments of the ^{13}C-n.m.r. spectra of the 5-*O*-methyl- and 5-deoxy-pentoses have been published previously[9].

Measurements of pH were made with an n.m.r. combination micro-electrode purchased from Microelectrodes, Inc. and a Corning Model 125 pH-meter. Temperature measurements (±1°) were made with a Fluke Model 2160A digital thermometer equipped with a copper–constantan thermocouple. Solution temperatures in the n.m.r. probe were determined by securely placing the thermocouple in a duplicate, unenriched-sample solution in a 10-mm, n.m.r. tube, lowering the tube into the probe, and recording the observed temperature after equilibration (~15 min).

RESULTS

Ring-opening rate-constants for the 5-deoxy- and 5-O-methyl-pentoses. — The ring-opening rate-constants (k_{open}) for the 5-deoxy- and 5-*O*-methyl-pentoses at pH 4.0 in 50mM acetate buffer at 60° are given in Table I. Within each structure, the anomer having O-1 and O-2 *cis* (*β-arabino, β-lyxo, α-ribo*, and *α-xylo*) opens at approximately the same rate as, or greater than, that having these atoms *trans*. This behavior differs markedly from that of the pentose 5-phosphates **11–14**, in which α anomers open at rates similar to, or greater than, those of β anomers,

TABLE I

RING-OPENING RATE-CONSTANTS FOR TETROSES[a], C-5-SUBSTITUTED PENTOSES[a], AND PENTOSE 5-PHOSPHATES[b]

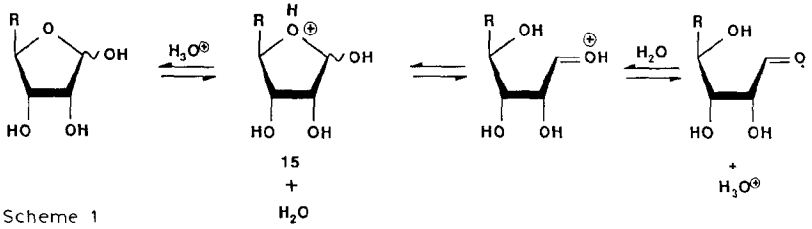
Compound	*Compound number*	$k_{\alpha o}$ (s^{-1})[c] ±10%	$k_{\beta o}$ (s^{-1})[c] ±10%	$k_{\alpha o}/k_{\beta o}$
5-Deoxy-L-arabinose	**1**	0.13 (1.3)[d]	0.23 (1.4)	0.6
5-Deoxy-L-lyxose	**2**	0.14 (1.1)	0.13 (0.9)	1.1
5-Deoxy-L-ribose	**3**	0.44 (1.3)	0.41 (1.3)	1.1
5-Deoxy-L-xylose	**4**	0.53 (1.4)	0.20 (1.3)	2.7
5-*O*-Methyl-D-arabinose	**5**	0.10	0.16	0.6
5-*O*-Methyl-D-lyxose	**6**	0.13	0.14	0.9
5-*O*-Methyl-D-ribose	**7**	0.35	0.31	1.1
5-*O*-Methyl-D-xylose	**8**	0.37	0.15	2.5
D-Erythrose	**9**	0.69	0.53	1.3
D-Threose	**10**	0.21	0.70	0.3
Arabinose 5-P	**11**	0.64	0.49	1.3
Lyxose 5-P	**12**	0.24	0.22	1.1
Ribose 5-P	**13**	0.86	0.44	2.0
Xylose 5-P	**14**	0.42	0.17	2.5

[a]Conditions: 0.25M aldose, 15% (v/v) ^2H_2O, 50mM acetate, pH 4.0, 60°. [b]Data taken from ref. 2; 0.15M sugar phosphate, 15% (v/v) ^2H_2O, pH 4.2, 40°. [c]The error in k_{open} values was estimated from uncertainties in the experimental values of τ_1 and T_1 used to compute k_{open} (see Experimental). [d]Values in parentheses are k_H/k_{OCH_3}, that is, the ratio of k_{open} for a given 5-deoxy anomer to that for the corresponding anomer in the 5-*O*-methyl series.

regardless of ring configuration[6] (see Table I). Under the same solution conditions, the ring-opening rate-constants of the tetrofuranoses, erythrose (**9**) and threose (**10**), exhibit a dependence on anomeric configuration similar to that observed for **1–8** (see Table I).

The difference in k_{open} between tetro- and pento-furanose anomers that have O-2 and O-3 *trans* (*e.g.*, **1, 4, 5, 8,** and **10**) is greater than for anomers that have O-2 and O-3 *cis* (*e.g.*, **2, 3, 6, 7,** and **9**). This effect of relative configuration at C-2 and C-3 on k_{open} is not found for the pentose 5-phosphates **11–14** (see Table I).

Although compounds **9** and **10** are structural homologs of pentofuranoses having the *ribo–lyxo* and *arabino–xylo* configurations, respectively, it appears that, with respect to k_{open}, compounds **9** and **10** resemble the pentofuranoses having *ribo* and *arabino* configurations, respectively. Considering the more-ring-destabilizing, *cis*-1,2 interactions only, **9** and **10** contain H–H and H–OH interactions between the C-3 and C-4 substituents. *arabino–ribo*-Pentofuranoses contain H–OH and CH_2OH–H interactions, whereas *xylo–lyxo*-pentofuranoses contain H–H and CH_2OH–OH interactions. The effect on furanose-ring conformation and dynamics upon substituting a CH_2OH–H interaction for an H–H interaction is probably smaller than that resulting on substituting CH_2OH–OH for H–OH, and may explain the observed correspondence in ring-opening behavior between tetrofuranoses and pentofuranoses.



Scheme 1

In general, 5-deoxypentoses open faster than 5-*O*-methylpentoses at pH 4.0 (k_H/k_{OCH_3} = ~1.3; see Table I), but the relative rates of ring-opening of anomers are conserved in each series (see Table I).

Catalysis by hydronium ion. — It is well known that monosaccharide anomerization is catalyzed by hydronium ion. It is generally considered that H^+-catalyzed ring-opening proceeds[10] by initial protonation of the ring-oxygen atom, as shown in Scheme 1. The response of k_{obs} for ring-opening of **2** and **6** to solution pH (see Tables I and II) shows that H^+-catalysis is not equally potent for both anomers of a furanose sugar, although H^+ does stimulate ring-opening as expected. At pH 4.0 in acetate buffer at 60°, k_{open} for 5-deoxy-α-L-lyxose is 0.14 s^{-1}, whereas, in HCl at pH 2.5 at 37°, k_{open} = 0.27 s^{-1}. Despite the temperature difference of 23°, the observed rate-constant increases two-fold as the pH is decreased by 1.5 units. The response of 5-deoxy-L-lyxose (**2**) and 5-*O*-methyl-D-lyxose (**6**) to pH differs (see Table II), with the latter compound less sensitive to catalysis by H^+.

The observed rate-constant, k_{obs}, for ring-opening is composed of H_2O-catalyzed (k_{H_2O}) and H_3O^+-catalyzed ($k_{H_3O^+}$) contributions[10] according to the following equation:

$$k_{obs} = k_{H_2O} + k_{H_3O^+}[H_3O^+]. \qquad (1)$$

The value of $k_{H_3O^+}$ is calculated from Eq. *1* by plotting k_{obs} (see Table II) against hydronium ion concentration (pH), and estimating the slope. Plots were obtained for 5-deoxy-L-lyxose (**2**) and 5-*O*-methyl-D-lyxose (**6**) in order to compare the H_3O^+-catalyzed ring-opening rate-constants for one configuration in each series. A linear relationship was found (see Fig. 1) between $[H^+]$ and the ring-opening rate-constant for both compounds. Values of $k_{H_3O^+}$ for 5-deoxy-L-lyxose (**2**) anomers were greater (α, 78 $s^{-1}.M^{-1}$; β, 190 $s^{-1}.M^{-1}$) than for corresponding 5-*O*-methyl-D-lyxose (**6**) anomers (α, 24 $s^{-1}.M^{-1}$; 65 $s^{-}.M^{-1}$). These results are consistent with those obtained previously for the hydronium-ion-catalyzed mutarotation of 6-deoxy-D-glucose and 6-*O*-methyl-D-glucose, the former being faster than the latter[11], although these studies measured the effect on k_{mut}, not on k_{open}. Apparently, the more electron-donating character of the exocyclic methyl group increases electron density at the ring-oxygen atom, and facilitates ring-oxygen protonation of **2**, generating a greater steady-state concentration of **15** (see Scheme 1) and increasing the reaction rate.

TABLE II

RING-OPENING RATE-CONSTANTS FOR 5-DEOXY-L-LYXOSE (**2**) AND 5-*O*-METHYL-D-LYXOSE (**6**) AS A FUNCTION OF SOLUTION pH

Compound	*Compound number*	*pH*[a]	k^{α}_{obs} (s^{-1})[b] ±10%	k^{β}_{obs} (s^{-1})[b] ±10%	k_{β}/k_{α}
5-Deoxy-L-lyxose	**2**	2.50	0.27	0.57	2.1
		2.26	0.48	1.03	2.1
		2.06	0.59	1.41	2.4
		1.95	0.91	2.14	2.4
		1.83	1.19	2.79	2.3
5-*O*-Methyl-D-lyxose	**6**	2.47	0.11	0.22	2.0
		2.10	0.23	0.57	2.5
		1.84	0.39	1.02	2.6
		1.70	0.70	1.71	2.4
		1.43	0.90	2.39	2.7

[a]Conditions: 0.25M sugar, 50mM KCl, 37°, adjusted to the indicated pH with HCl, 15% (v/v) ^2H_2O. [b]The error in k_{open} values was estimated from uncertainties in the experimental values of τ_1 and T_1 used to compute k_{open} (see Experimental).

The *difference* in k_{open} between anomers in the 5-deoxy and 5-*O*-methyl series increases significantly under conditions of H^+-catalysis (for **2** in acetate buffer at pH 4.0, $k_{\beta}/k_{\alpha} = 1.0$, whereas, in HCl at pH 1.8, $k_{\beta}/k_{\alpha} = 2.3$; see Tables I and II) and probably reflects the different mechanisms of catalysis by H_2O and H_3O^+. The latter observation points to the importance of solution conditions in the interpretation of anomerization structure–reactivity data.

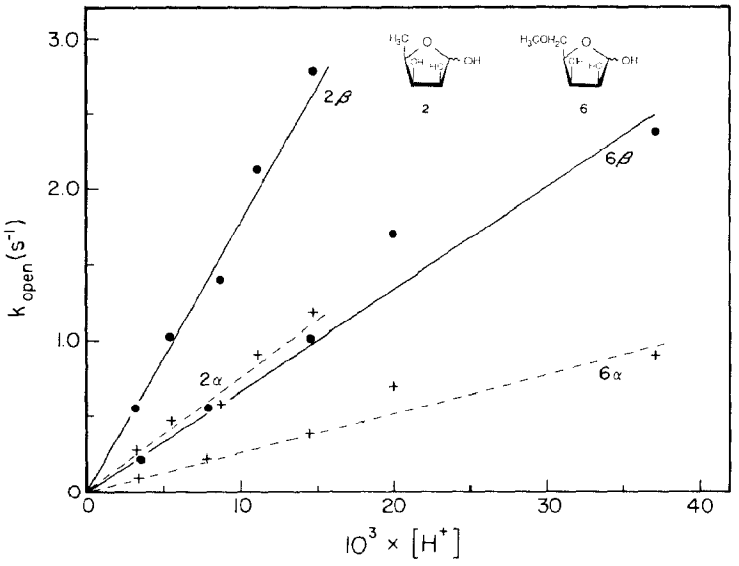


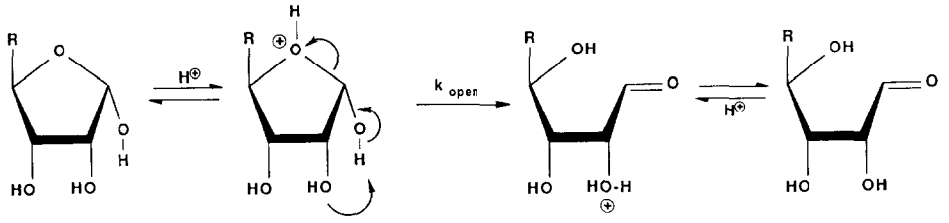
Fig. 1. Effect of hydrogen-ion concentration on k_{open} for the α- and β-furanose forms of 5-deoxy-L-(1-^{13}C)lyxose (**2**) and 5-*O*-methyl-D-(1-^{13}C)lyxose (**6**). Slopes obtained from these plots were used to calculate acid-catalyzed ring-opening rate-constants ($k_{H_3O^+}$) for each form (see text).

DISCUSSION

The spontaneous and reversible formation of hemiacetals is a characteristic reaction of aldoses in solution. In one direction, the process involves ring formation through intramolecular attack by a lone electron pair of an oxygen atom on a carbonyl carbon atom. In general, rates of ring-closure of such bifunctional molecules as aldoses are determined by the difference in the free energies of the acyclic and transition-state structures in their most stable conformations, assuming that ring closure is rate-determining, that is, that a preprotonation step is not rate-limiting. Reactivity in cyclization reactions is generally interpreted[12] in terms of activation energy (enthalpic factors) and the probability of end-to-end encounters (entropic factors). On the other hand, ring-opening rates will be relatively unaffected by the enthalpic differences between the cyclic and transition-state structures, because similar destabilizing forces (*e.g.*, steric factors) should be present in each. In general, the factors influencing reaction rates are less understood for ring-opening than for ring-forming reactions.

Furanose structure and ring-opening rate-constants. — A potential mechanism that explains the dependence of k_{open} on pentofuranose anomeric configuration is shown in Scheme 2. The enhanced value of k_{open} for anomers having *cis*-O-1–O-2 suggests that O-2 may assist in the abstraction of the proton on O-1 during ring opening. Anchimeric assistance is not feasible in *trans*-O-1–O-2 anomers, because of structural constraints. The fact that compounds having *cis*-O-2–O-3-atoms show a smaller difference in k_{open} between anomers, at least at pH 4.0–5.0, may suggest the existence of intramolecular hydrogen-bonding between these substituents, thereby eliminating (or minimizing) potential assistance by O-2. Caution must be exercised, however, in invoking this explanation, as the solution conditions can drastically affect the ratio of $k^{\beta}_{open}/k^{\alpha}_{open}$, as demonstrated for **2** and **6**. Under solution conditions where acid catalysis becomes important, even compounds having O-2 and O-3 *cis* exhibit marked differences in k_{open} between anomers that were not observed under conditions of H_2O-catalysis (pH 4–5).

The nature of the solvent does not appear to play a major role in determining the relative effect of anomeric configuration on k_{open} of furanoses. For example, in the nonhydroxylic solvent, acetonitrile, containing acetic acid as a catalyst, the β-furanose of **10** opened 4 to 5 times as fast as the α-furanose, behavior which is



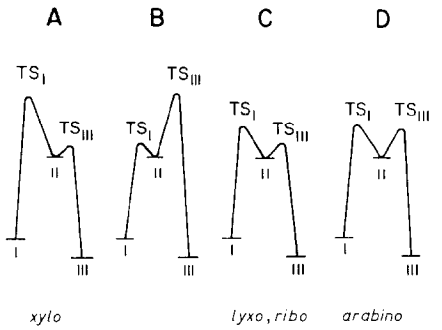
Scheme 2

similar to that observed in water (see Table I). This fact suggests that the intrinsic structure of the furanose ring is the primary determinant of ring-opening reactivity.

Relative rates of ring opening in the 5-deoxypentoses decrease in the order *α-xylo* > *α-ribo* ≈ *β-ribo* > *β-arabino* ≈ *β-xylo* > *α-lyxo* ≈ *α-arabino* ≈ *β-lyxo*. A similar, but not identical, trend is found for the 5-*O*-methylpentoses. These relative rates show clearly that the thermodynamic stability of the furanose does not affect the rate of ring opening: the *β-lyxo* configuration is presumably the least stable of the furanoses, and yet it opens most slowly. The *α-xylo* configuration appears to confer the greatest kinetic instability towards ring opening, probably because of the presence of three structural features that enhance reactivity: a *cis*-O-1–O-2 configuration required for anchimeric assistance, a *trans*-O-2–O-3 configuration which prevents potential intramolecular H-bonding between these hydroxyl substituents, and a *cis*-O-3–C-5 configuration that destabilizes the ring. Of course, ring conformation and dynamics, and stereoelectronic effects in the transition state, probably play important roles in ring opening and may dominate the aforementioned features.

Furanose structure and ring-closing rate-constants. — The relative rates of ring closing in the 5-deoxypentoses and 5-*O*-methylpentoses differ markedly from those of ring opening, and decrease in the deoxy series in the order *β-ribo* > *α-ribo* > *α-xylo* > *α-arabino* ≈ *β-arabino* > *α-lyxo* ≈ *β-xylo* > *β-lyxo*. This difference is expected, as rates of ring opening and closing are distinct kinetic events affected by different structural parameters (see earlier). Apparently, the acyclic conformation of 5-deoxy-*β*-L-ribose in solution must more closely resemble the transition-state structure during ring closure than does the acyclic conformation of 5-deoxy-*β*-L-lyxose. The acyclic aldehyde having the *ribo* configuration is expected to assume a pseudocyclic conformation in solution, predisposing itself to efficient ring-closure (*i.e.*, the entropic factor is more favorable). On the other hand, the acyclic *lyxo* configuration appears less able to undergo closure, especially to afford the *β* anomer, suggesting that the structures of the acyclic carbonyl form and transition-state are significantly different. These conclusions are consistent with observations made by Horton and Wander[13] on the conformations of *aldehydo*-pentose peracetates in C^2HCl_3. Structures having the *ribo* and *xylo* configurations were found to favor sickle or pseudocyclic conformations in solution in order to alleviate destabilizing 1,3-interactions that occur in the alternative, extended zigzag conformers. Structures having the *arabino* and *lyxo* configurations assume an extended zigzag conformation, because destabilizing 1,3-interactions are absent in these forms. There appears, then, to be a correlation, albeit fortuitous, between the favored *aldehydo* conformation and the rates of ring closure. This correlation must, however, be viewed with caution, as the conformational studies were conducted on aldehyde peracetates in organic solvents; it is possible that unsubstituted, hydroxy aldehydes have different conformational and dynamic properties in aqueous solution.

Unidirectional rate-constants and reaction coordinate diagrams. — The differences in k_{open} between anomers of neutral furanoses have been explained here by



Scheme 3

proposing that anomers having O-1–O-2 in the *cis* orientation experience intramolecular catalysis *via* anchimeric assistance (see Scheme 2). It should be noted, however, that whereas α-furanoses open more rapidly than β-furanoses for compounds having the *xylo* configuration (**4** and **8**, Table I), the α-xylofuranoses are thermodynamically more stable than the β-xylofuranoses ($[\alpha]_{eq}/[\beta]_{eq}$ = 1.3; see Table III)[2,9]. In other words, a correlation does not exist between thermodynamic and kinetic stability. The thermodynamics and kinetics of anomerization can be viewed more carefully by using reaction coordinate diagrams that describe the interconversion of two cyclic compounds I and III *via* a common intermediate II, with III more thermodynamically stable than I (Scheme 3). Implicit in the following discussion are the assumptions that the *relative energies* of the putative, protonated cyclic intermediates and the unprotonated cyclic forms are the same, and that the ring-opening reaction is rate-limiting in the overall conversion of I into III and of III into I. The latter assumption has been validated by experiment, and can be invoked with confidence. The former assumption, however, remains to be tested by calculational approaches. With these caveats, four diagrams can be constructed that differ with respect to the relative energies of the transition states, TS_I and TS_{III}. An inspection of these diagrams permits some predictions about permissible relative ring-opening and -closing rates for I and III: (*a*) I may open and close more slowly than III (curve A); (*b*) I may open and close more rapidly than III (curve B); (*c*) I may open at the same rate as, but close more slowly than, III (curve C); (*d*) I may open more rapidly than, but close at the same rate as, III (curve D); (*e*) I may never open at the same rate as, but close more rapidly than, III; and (*f*) I may never open more slowly than, but close at the same rate as, III.

Using k_{open} and k_{close} values in Tables I and III, it is possible to evaluate the relationship between these reaction-coordinate profiles and furanose ring configuration in compounds **1–10**. Only curve A is appropriate for *xylo* compounds (**4** and **8**), that is, the transition-state energy for α-*xylo* must be lower than for β-*xylo*, and the energy difference between transition-state structures must *exceed* the energy difference between α- and β-*xylo* cyclic forms. Curve A is also consistent with the greater thermodynamic stability of the α-*xylo* configuration (see Table III), and the greater kinetic instability of α-*xylo* towards both ring opening and closing (see

TABLE III

TAUTOMERIC EQUILIBRIUM DATA FOR THE C-5-SUBSTITUTED PENTOSES AND CALCULATED RING-CLOSING RATE-CONSTANTS

Compound	*Compound number*	*Solution percentages*[a]			*Equilibrium constants*		*Ring-closing rate-constants*[b]	
		α	β	o	α/o	β/o	$k_{o\alpha}$	$k_{o\beta}$
5-Deoxy-L-arabinose	**1**	62.3	36.3	0.3	208	121	27	28
5-Deoxy-L-lyxose	**2**	73.4	24.9	0.6	122	42	17	5
5-Deoxy-L-ribose	**3**	36.3	63.0	0.2	182	315	80	129
5-Deoxy-L-xylose	**4**	51.2	45.0	0.6	85	75	45	15
5-*O*-Methyl-D-arabinose	**5**	60.9	39.0	0.2	305	195	31	31
5-*O*-Methyl-D-lyxose	**6**	69.1	27.4	0.6	115	46	15	6
5-*O*-Methyl-D-ribose	**7**	37.4	62.3	0.3	125	208	44	64
5-*O*-Methyl-D-xylose	**8**	52.5	44.1	0.4	131	110	48	17
D-Erythrose	**9**				13.2	27.2	9	14
D-Threose	**10**				22.8	17.4	5	12

[a]Solution conditions were the same as those given in Table I. The symbols α, β, and o denote α-furanose, β-furanose, and aldehyde forms. Hydrate forms have been detected[9], but were not quantified under these conditions. [b]In s^{-1} ($\pm 20\%$). These values were calculated from the accompanying equilibrium constants and ring-opening rate-constants given in Table I; the error in k_{close} ($\pm 20\%$) is greater than that for k_{open} ($\pm 10\%$; see Tables I and II), because of the added uncertainty in K_{eq} used to compute k_{close}.

Tables I and III). On the other hand, curve C, in which the energy differences between ground-state and transition-state structures are the same, appears consistent with the thermodynamic and kinetic behavior of the *ribo* (**3** and **7**) and *lyxo* (**2** and **6**) compounds. The *arabino* compounds (**1** and **5**) behave in a manner consistent with curve D, in which both transition-state structures have similar energies. Curve B does not fit data for any of the pentofuranoses; in this diagram TS_I is considerably more stable than TS_{III}, a situation somewhat less likely, because, in the ground state, I is less stable than III. Curve B does, however, appear appropriate for threofuranoses **10**, in which the less thermodynamically stable anomer (β-threofuranose) is also less kinetically stable towards ring opening and closing than α-threofuranose. Erythrofuranoses **9** appear consistent with a modified form of curve A in which the energies of the transition-state species are more similar, allowing for more similar rates of ring-opening between anomers. Interestingly, as already discussed, compounds **9** and **10** resemble *ribo* (**3** and **7**) and *arabino* (**1** and **5**) pentofuranoses with respect to the dependence of anomeric configuration on ring-opening kinetics. In contrast, **9** behaves the same as *lyxo, ribo,* and *xylo* pentofuranoses with respect to ring closing, whereas **10** is unique. This is not surprising, as the conformation and dynamics of the acyclic form play key roles in affecting ring-closure rates, and may differ in configurationally related tetrofuranoses and pentofuranoses.

The reaction-coordinate diagrams depicted in Scheme 3 are very simplistic; more realistic diagrams would include discrete, protonated intermediates that have been implicated previously in H^+-catalyzed anomerization. This representation assumes that ring-opening/ring-closing events are rate-limiting, and not individual protonation–deprotonation steps that presumably occur during the reaction.

Other considerations in anomerization structure–reactivity studies. — Future refinements of structure–reactivity data on anomerization will depend on an improved understanding of several more-subtle features of this reaction. Theoretical calculations[14–16] have been conducted to evaluate potential attack trajectories by nucleophiles on a carbonyl center. The reaction studied in the most detail was the reduction of formaldehyde by hydride ion[14,15]. Gas-phase calculations show that, at distances <2Å, H^- approaches the formaldehyde molecule on a lowest-energy pathway which makes an angle of ~60° with respect to the molecular plane, and bisects the H–C–H bond-angle[14,15]. Furthermore, a recent study[16] of the reaction of hydroxide ion with formaldehyde revealed a similar favored trajectory. The importance of attack trajectory in determining ring-closure rates in aldose anomerization remains to be quantitatively evaluated. However, an empirical approach to this problem points to some potential differences between pyranoses and furanoses. Inspection of models shows that, in pyranose-ring formation, O-5 approaches C-1 favorably when a pseudo-chair conformation is assumed by the acyclic aldehyde in which O-1 (the carbonyl oxygen atom) and C-3 are nearly antiperiplanar, and H-1 and C-3 are nearly eclipsed, generating a β-pyranose. Now, at a minimum, C-1–C-2 bond-rotation must occur in order to expose the opposite carbonyl face to attack,

forming the α-pyranose. Rotation of the C-1–C-2 bond by ~120° generates an O-5–C-1 trajectory comparable to that available to the alternative face, making C-1–C-2 bond rotation necessary and sufficient for pyranose anomerization. However, these trajectories are not structurally equivalent; for example, in one pseudo-chair conformer, C-5 and O-1 are antiperiplanar in the transition state, whereas, in the other, they are *gauche*. Therefore, although comparable reaction-trajectories for ring-closure to both pyranoses are available, the intermediates are not identical with respect to potential steric and stereoelectronic effects. Only ring inversion (or conversion into a boat-like form) orients the opposite face of the carbonyl in an identical fashion for attack with respect to the relative orientation of "ring" atoms near the reaction center. Ring inversion, however, will generate a different set of substituent interactions farther removed from the reaction center.

In certain circumstances, non-chair-like, acyclic conformations could be involved in the transition state. Certainly, there is destabilization of chair-like acyclic forms having axial hydroxyl groups at C-2, C-3 and/or C-4. Destabilizing 1,3-interactions between an axial O-2 and an axial O-4 will occur in the formation of both anomers, whereas an axial O-3 may preferentially hinder α-anomer formation. These effects are lessened in boat-like, acyclic conformations formed by C-1–C-2, C-2–C-3, and C-5–O-5 bond rotations that also allow for a favorable O-5–C-1 trajectory. The question is one of opposing effects, that is, is the eclipsing of groups at C-2 and C-3 in "boat" forms less destabilizing than the O–O interactions found in "chair" forms?

Ring closure to form aldofuranoses involves attack by O-4 on C-1, the carbonyl carbon atom. From inspection of models, the most ideal trajectory appears to occur in "envelope" conformations with C-1 out-of-plane. For example, to form β-D-furanoses, a *pseudo*-E_1 conformation in the transition state may be required. However, C-1–C-2 bond-rotation to generate the α-furanose does not provide a comparable O-4–C-1 trajectory; that is, C-1–C-2 bond-rotation may not be sufficient for furanose anomerization. An identical trajectory is obtained, however, by rotating the C-1–C-2, C-2–C-3, and O-4–O-5 bonds to form a *pseudo*-^1E conformer. If *pseudo*-^1E and -E_1 forms are involved in forming α- and β-furanoses, respectively, the initial furanose conformers produced upon ring closure (^1E and E_1, respectively) have C-1–O-1 bonds oriented *quasi*-equatorially. The C-1–O-1 bond of furanoses favours a *quasi*-axial orientation[17], because of the "anomeric effect"[18]. "Higher-energy" furanoses would, therefore, be the initial products of ring closure. By microscopic reversibility, then, "higher-energy" (and therefore less-abundant) conformers could be involved in ring opening, making pseudorotation rates a potential determinant of ring-opening rates.

The foregoing discussion serves to emphasize that the structural and dynamic characteristics of furanose ring-opening and -closing are different from those of pyranoses.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (GM 33791) and the Research Corporation (10028). We thank Rosemary Patti for typing the manuscript.

REFERENCES

1 A. S. SERIANNI, J. PIERCE, S.-G. HUANG, AND R. BARKER, *J. Am. Chem. Soc.*, 104 (1982) 4037–4044.
2 J. R. SNYDER AND A. S. SERIANNI, *J. Org. Chem.*, 51 (1986) 2694–2702.
3 W. GOUX, *J. Am. Chem. Soc.*, 107 (1985) 4320–4327.
4 J. R. SNYDER AND A. S. SERIANNI, *Carbohydr. Res.*, 166 (1987) 85–99.
5 J. R. SNYDER, E. R. JOHNSTON, AND A. S. SERIANNI, *J. Am. Chem. Soc.*, in press.
6 J. PIERCE, A. S. SERIANNI, AND R. BARKER, *J. Am. Chem. Soc.*, 107 (1985) 2448–2456.
7 A. S. SERIANNI, H. A. NUNEZ, AND R. BARKER, *Carbohydr. Res.*, 72 (1979) 71–78.
8 A. S. SERIANNI, H. A. NUNEZ, M. L. HAYES, AND R. BARKER, *Methods Enzymol.*, 89 (1982) 64–73.
9 J. R. SNYDER AND A. S. SERIANNI, *Carbohydr. Res.*, 163 (1987) 169–188.
10 H. S. ISBELL AND W. PIGMAN, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 13–65.
11 B. CAPON AND R. B. WALKER, *J. Chem. Soc., Perkin Trans. 2*, (1974) 1600–1610.
12 G. ILLUMINATI AND L. MANDOLINI, *Acc. Chem. Res.*, 14 (1981) 95–102.
13 D. HORTON AND J. D. WANDER, *Carbohydr. Res.*, 15 (1970) 271–284.
14 H. B. BURGI, J. M. LEHN, AND G. WIPFF, *J. Am. Chem. Soc.*, 96 (1974) 1956–1957.
15 H. B. BURGI, J. D. DUNITZ, J. M. LEHN, AND G. WIPFF, *Tetrahedron*, 30 (1974) 1563–1572.
16 J. D. MADURA AND W. L. JORGENSEN, *J. Am. Chem. Soc.*, 108 (1986) 2517–2527.
17 A. S. SERIANNI AND R. BARKER, *J. Org. Chem.*, 49 (1984) 3292–3300.
18 R. U. LEMIEUX, in P. DEMAYO (Ed.), *Molecular Rearrangements*, Wiley–Interscience, New York, 1963, p. 173.