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Ring-opening kinetics of the D-pentofuranuronic acids

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ABSTRACT

The ring-opening reactions of the furanose forms of the penturonic acids D-arabinuronic acid (**1**), D-lyxuronic acid (**2**), D-riburonic acid (**3**), and D-xyluronic acid (**4**) in aqueous solution have been studied as a function of temperature and solution pH by ^{13}C saturation-transfer n.m.r. (s.t.-n.m.r.) spectroscopy using 1-^{13}C-substituted compounds. Unidirectional rate constants of ring-opening (k_{open}) have been determined for the cyclic forms of **1**–**4** in their protonated (pH 1.5) and ionized (pH 4.5) forms, and have been compared to the *k*-values measured previously for structurally related furanose sugars. At 50° and pH 1.5, k_{open} values decrease as follows: α-xyluronic acid (2.57 s^{-1}) > α-riburonic (1.65 s^{-1}) > β-arabinuronic (1.52 s^{-1})> β-xyluronic (1.09 s^{-1}) > β-riburonic (0.76 s^{-1}) > β-lyxuronic (0.55 s^{-1}) > α-arabinuronic (0.46 s^{-1}) > α-lyxuronic (0.40 s^{-1}). At 50° and pH 4.5, this order changes significantly (*e.g.*, β-arabinuronate is most reactive); in general k_{open} values for β anomers appear to be enhanced relative to those for corresponding α anomers, suggesting the involvement of intramolecular catalysis in which the carboxylate anion assists in abstracting the hydroxyl proton from O-1. Activation energies of ring-opening, determined for the α and β anomers of **1**–**4**, were found to depend on ring configuration and solution pH.

INTRODUCTION

The anomerization of reducing sugars in solution involves spontaneous ring-opening and ring-closing reactions that produce a dynamic, equilibrating mixture of cyclic and acyclic forms. The unidirectional rate constants of ring-opening of D-aldotetrofuranoses[1], 5-*O*-methyl-D-pentofuranoses[2], 5-deoxy-L-pentofuranoses[2], D-talofuranoses[3], D-idofuranoses[4], DL-apiofuranoses[5], D-2-pentulofuranoses[6], 6-*O*-methyl-D-fructofuranoses[7], and D-pentofuranose 5-phosphates[7] have been studied previously by saturation-transfer n.m.r. (s.t.-n.m.r.) spectroscopy. In neutral furanoses (*i.e.*, those that do not have an ionizable functional group) at pH 4.5, a dependence of k_{open} on anomeric configuration has been observed, namely, that anomers having the anomeric hydroxyl group and adjacent hydroxyl group *cis* (O-1,O-2 *cis* for aldofuranoses, O-2,O-3 *cis* for 2-ketofuranoses) open at rates similar to, or greater than, the rates for anomers having these groups *trans*. However, furanoses that carry an ionizable phosphate group, such as the D-pentofuranose 5-phosphates, exhibit different behavior[7]; in these compounds at pH 4.2, α anomers open at rates similar to, or greater than, those for the β anomers, regardless of the relative configurations of the hydroxyl groups near the anomeric carbon. Ring-opening is catalyzed by the phosphate monoanion[7], and this

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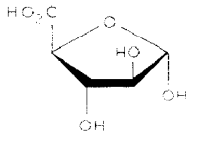
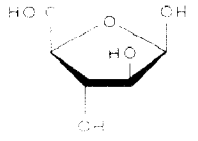
catalysis is apparently more potent in α anomers, where the anomeric hydroxyl group is *trans* to the phosphate moiety. Presumably the phosphate monoanion promotes the reaction by assisting in ring-oxygen protonation during ring-opening; steric factors may be responsible for the less efficient catalysis in β anomers.

The D-penturonic acids, *viz.* D-arabinuronic acid (**1**), D-lyxuronic acid (**2**), D-riburonic acid (**3**), and D-xyluronic acid (**4**), like the pentose 5-phosphates, have an ionizable carboxyl group as their C-5 function, and thus serve as useful model compounds for further investigation of the effect of an ionizable ring substituent on the kinetics of furanose anomerization. In a previous study[8], we described chemical methods for the preparation of the four D-penturonic acids with ^{13}C substitution at the anomeric carbon, and studied their fundamental solution properties by ^{1}H- and ^{13}C-n.m.r. spectroscopy. In this report, we have examined the ring-opening kinetics of **1**–**4** by ^{13}C-s.t.-n.m.r. spectroscopy in order to explore further the effect of furanose structure on the kinetics of this important reaction.



1a



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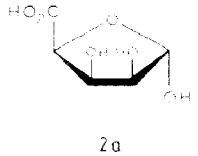

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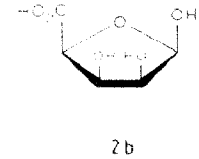

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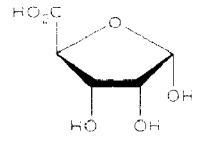
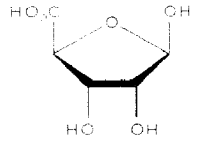
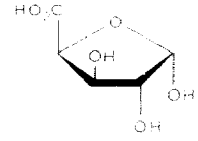


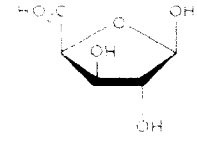
3a



3b



4a



4b

EXPERIMENTAL

Materials. — D-Glucuronic acid was purchased from Sigma Chemical Company. D-(1-^{13}C)Arabinuronic acid, D-(1-^{13}C)lyxuronic acid, D-(1-^{13}C)riburonic acid, and D-(1-^{13}C)xyluronic acid were synthesized as described previously[8]. Deuterium oxide ($^{2}H_2O$, 98 atom-% ^{2}H) was purchased from Cambridge Isotope Laboratories.

Instrumentation. — ^{13}C-Saturation-transfer n.m.r. (s.t.-n.m.r.) spectra were obtained on a Nicolet NT-300 300 MHz superconducting F.t.-n.m.r. spectrometer operating at 75 MHz for ^{13}C and equipped with a variable temperature accessory, quadrature phase detection, a 293B pulse programmer, and a broadband F_2 decoupler to supply the saturating ^{13}C r.f. at the C-1 resonance of the acyclic aldehyde form. All experiments were conducted with 10 mm n.m.r. tubes (Wilmad) containing 1.5–2.0 mL of sample solution; vortex formation was eliminated with Teflon vortex suppressors (Wilmad).

Solution-pH measurements were made at 23° with a microelectrode purchased from Microelectrodes, Inc., and a Corning Model 125 pH meter.

Sample temperature in the n.m.r. spectrometer was measured with a Fluke Model 2160A digital thermometer equipped with a copper–constantan thermocouple. The thermocouple was inserted into a 10 mm n.m.r. tube containing a duplicate unenriched sample solution and secured with a plastic cap, the assembly was lowered into the n.m.r. probe, and the solution temperature was recorded after it had stabilized (> 20 min). The assembly was then removed and replaced by an idential ^{13}C-substituted sample solution, which was allowed to equilibrate in the probe for 0.5 h before measurements were initiated. This indirect method of temperature measurement was adopted in order to avoid potential metal contamination of the experimental sample by exposure to the thermocouple.

Preparation and quantitation of sample solutions. — Aqueous solutions of known concentrations (determined colorimetrically by the phenol–sulfuric assay[9] using D-glucuronic acid as the standard) of D-(1-^{13}C)penturonic acids were treated batchwise with excess Dowex HCR-W2 (H^+) resin to generate the free acid, the resin was removed by vacuum filtration, and the resulting solutions were concentrated to ~0.5 mL at 30° *in vacuo*. The solutions were transferred to 2 mL glass vials, ^2H_2O (0.6 mL) was added, and the solution pH was adjusted to pH 4.5 with M NaOH [no correction[10] was applied to the meter reading to account for isotope effects since ^2H_2O concentration (30% v/v) was low]. Sample volumes were adjusted to 2 mL with distilled water and the solutions were transferred to 10 mm n.m.r. tubes. Teflon vortex plugs were inserted and the tubes were sealed with plastic caps.

Measurement of ring-opening rate constants. — ^{13}C-S.t.-n.m.r. spectra were recorded with saturation times varying from 5 μs to 15 s and relaxation delays > 15 s. At least ten (10) saturation times were employed in each experiment (four transients per spectrum), and signal intensities were treated graphically (Fig. 1C) as described previously[1] in order to obtain τ_1 from the slope. Using T_1 (spin-lattice relaxation time) and τ_1 values, ring-opening rate constants (k_{open}) in s^{-1} were determined[1] from the relationship, $1/\tau_1 = k_{open} + 1/T_1$.

RESULTS AND DISCUSSION

Unidirectional rate constants of ring-opening (k_{open}) in **1–4**. — ^{13}C-N.m.r. spectra of **1–4** substituted with ^{13}C at C-1 show the presence of several equilibrating forms in aqueous solution[8]: α-furanose, β-furanose, acyclic hydrate (1,1-*gem*-diol), acyclic aldehyde, and/or 2,5-lactone hydrate (Fig. 1A, Scheme 1). The acyclic aldehyde **3c** (Scheme 1) is the presumed intermediate[1,7] in the interconversion of the α- and β-furanose forms **3a** and **3b**; thus, the transfer of saturation from the C-1 signal of the acyclic aldehyde form ($\delta_{C\text{-}1}$ ~206 p.p.m.) to the C-1 signals of the cyclic forms ($\delta_{C\text{-}1}$ ~98–104 p.p.m.) may be treated quantitatively by considering **3a** ⇌ **3c** and **3b** ⇌ **3c** as separate two-site exchange reactions in order to obtain the ring-opening rate constant (k_{open}) of each furanose form (Fig. 1A–C). The transfer of saturation to C-1 of the acyclic hydrate form

3d may, in principle, be used to determine the rate constant of dehydration (k_{H_2O}); however, the presence of a cyclic pathway involving **3c**, **3d**, **3e**, and **3f** (Scheme 1) complicates the interpretation of data, as discussed below.

The acyclic aldehyde form accounts for <0.2 mol % of the total forms present[8] in aqueous solutions of **1**–**4** at 23°. This low abundance, and the significant line-broadening of the aldehyde C-1 resonance caused by chemical exchange, made it difficult to achieve spectral signal-to-noise ratios at 75 MHz that were sufficient for a reliable integration of the signal. Therefore, the equilibrium constants for the component reactions (Scheme 1), and therefore k_{close} values derived from them and k_{open}, were subject to large errors. Consequently, ring-closing rate constants (k_{close}) were not examined in this study.

The D-penturonic acids **1**–**4** have an ionizable carboxyl group (C-5) whose pK_a is expected to be similar to that of the carboxyl group in D-glucuronic acid (pK_a 2.7) (ref. 11); recently a pK_a of ~2.9 was determined for **3** based on ^{13}C chemical-shift titration curves[8]. Thus, at pH 1.5, this group exists primarily in the protonated (*i.e.*, uncharged) state, whereas at pH 4.5, it exists primarily in the ionized (*i.e.*, negatively charged) state.

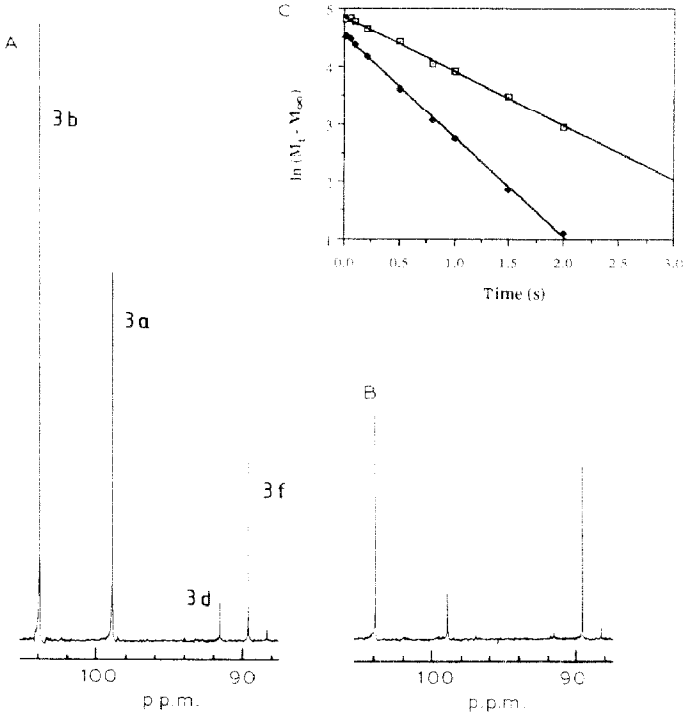


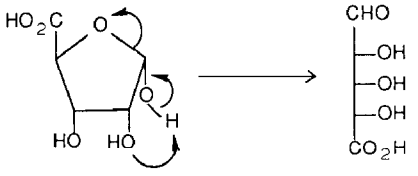
Fig. 1. A and B, ^{13}C saturation-transfer (s.t.) n.m.r. spectra of 0.3M D-(1-^{13}C)riburonic acid (**3**) at pH 1.5, 50°, in 30% (v/v) ^2H_2O, showing only the resonances of the enriched carbons (assignments on figure). The spectrum in A shows the C-1 resonance intensities of each anomer in the absence of aldehyde saturation [$M_z(0)$]. The spectrum in B is the $M_z(\infty)$ spectrum obtained by saturation of C-1 of **3c**, showing the significant loss of intensity of the signals for C-1 of **3a**, **3b**, and **3d**, whereas that of **3f** remained unchanged. C, semi-log plot of M_z for **3a** (■) and **3b** (□) as a function of saturation time in a ^{13}C-s.t.-n.m.r. experiment with 0.3M D-(1-^{13}C)riburonic acid, pH 1.5, 45°.

Therefore, k_{open} values were determined at pH 1.5 and pH 4.5 (Tables I and II) to assess the effect of the carboxyl ionization state on the ring-opening kinetics of **1**–**4**. Rate constants were also determined over a 40° temperature range at both pH values (Tables I and II) to evaluate ring-opening activation energies (Table III).

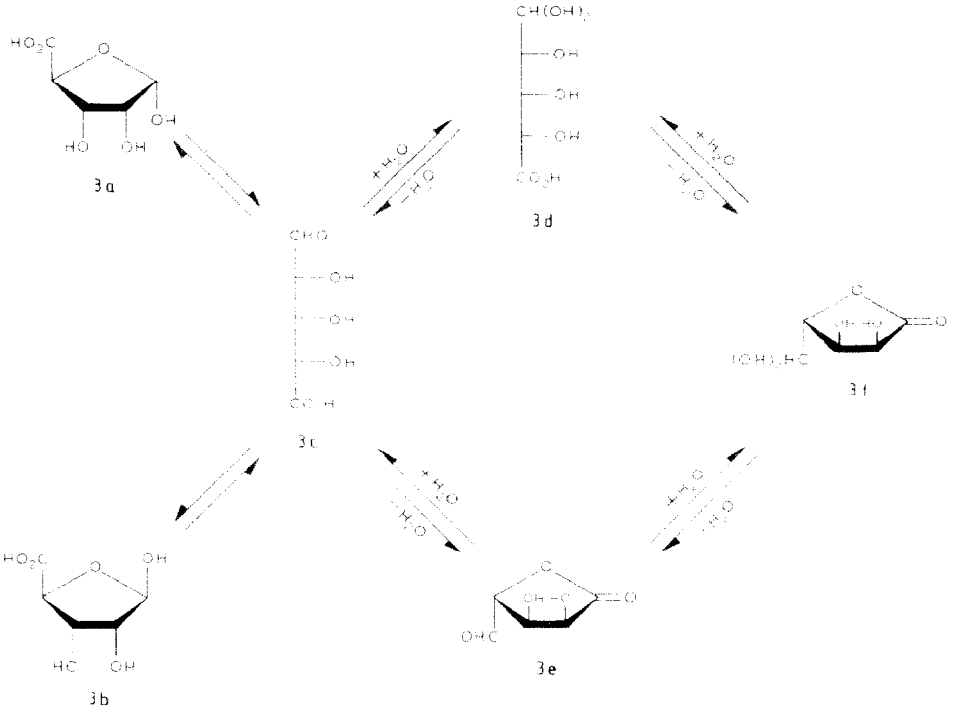
Data in Table I show that, within each anomeric pair at pH 1.5 and at all temperatures studied, anomers having O-1 and O-2 *cis, viz.* β-*arabino* (**1b**), β-*lyxo* (**2b**), α-*ribo* (**3a**), and α-*xylo* (**4a**), undergo ring-opening at rates greater than or equal to the rates for the corresponding anomers having O-1 and O-2 *trans, viz.* α-*arabino* (**1a**), α-*lyxo* (**2a**), β-*ribo* (**3b**), and β-*xylo* (**4b**). Thus, in their uncharged (protonated) forms, the D-penturonic acids behave like the electrically neutral 5-deoxy- and 5-*O*-methylpentoses[2]. A mechanism[2] that may be responsible for enhancing k_{open} of O-1,O-2-*cis* furanose anomers involves the anchimeric assistance of O-2 in abstracting, either directly or *via* an intervening solvent water molecule, the hydroxyl proton from O-1 (Eq. *1*).

At pH 1.5 and 50°, k_{open} values decrease as follows: α-xyluronic acid (2.57 s^{-1}) > α-riburonic (1.65 s^{-1}) > β-arabinuronic (1.52 s^{-1}) > β-xyluronic (1.09 s^{-1}) > β-riburonic (0.76 s^{-1}) > β-lyxuronic (0.55 s^{-1}) > α-arabinuronic (0.46 s^{-1}) > α-lyxuronic acid (0.40 s^{-1}). As observed[2] for the 5-deoxypentoses and 5-*O*-methylpentoses at pH 4.0 and 60°, the α-*xylo* configuration is most reactive towards ring-opening, whereas the α-*arabino*, α-*lyxo* and β-*lyxo* configurations are least reactive. Thus, the protonated (uncharged) forms of **1**–**4** behave like the electrically neutral pentofuranoses with respect to the effect of ring configuration on k_{open}.

The behavior of **1**–**4** at pH 4.5 and 50° differs notably from that observed at pH 1.5 and 50° (Table II), indicating that the ionization state of the carboxyl group influences furanose ring-opening reactivity. The O-1,O-2 *cis* effect is not observed throughout the series; for example, at all temperatures studied, k_{open} for β-riburonate (**3b**) is greater than k_{open} for α-riburonate (**3a**). At 50°, it appears that, upon increasing the solution pH from 1.5 to 4.5, k_{open} for β anomers ($k_{\beta o}$) is enhanced relative to that of corresponding α anomers ($k_{\alpha o}$) in all four compounds. For example, in **1**, $k_{\beta o}$ is 3.3-fold greater than $k_{\alpha o}$ at pH 1.5, whereas it is 4.8-fold greater at pH 4.5. The relative enhancement of $k_{\beta o}$ at pH 4.5 implicates the C-5 carboxylate anion in catalysis; when *cis* to O-1, as it is in β anomers, this anionic group may assist, either directly or indirectly *via* solvent-water molecules, in abstracting the hydroxyl proton from O-1 (Eq. *2*). Thus, at pH 1.5, both hydronium ion[2] and the protonated carboxyl group are expected to catalyze ring-opening, but neither mechanism should favor one anomer over the other if it is assumed that the affinity of the ring oxygen for protons, that is, its basicity, is not



(1)



Scheme 1

TABLE I

Ring-opening rate constants for D-penturonic acids (free-acid form) at different temperatures

Compound, formula no.[a]	k_{ring} (s^{-1})[b]						
	23°	*30*	*35*	*40*	*45*	*50*	*59*
α-D-Arabinuronic acid, **1a**	0.17	0.21	0.27[c]	0.30	0.39	0.46	0.68
β-D-Arabinuronic acid, **1b**	0.99	1.00	1.23[c]	1.35	1.53	1.52	1.80
α-D-Lyxuronic acid, **2a**	0.13	0.18[c]	0.21	0.29	0.33[c]	0.40	
β-D-Lyxuronic acid, **2b**	0.13[c]	0.20	0.26	0.36	0.44	0.55	
α-D-Riburonic acid, **3a**	0.47	0.75	0.88[c]	1.13	1.51	1.65[c]	2.28
β-D-Riburonic acid, **3b**	0.098	0.18[c]	0.26[c]	0.39	0.60	0.76	1.24
D-Riburonic acid hydrate, **3d**[d]	0.24	0.40	0.49[c]	0.65	0.84	1.22	1.79
α-D-Xyluronic acid, **4a**	1.39	1.65	1.85[c]	2.06	2.30[c]	2.57	
β-D-Xyluronic acid, **4b**	0.27	0.41[c]	0.51	0.75	0.97	1.09	

[a] Solution conditions: 0.3M penturonic acid, pH 1.5, 30% (v/v) ^2H_2O. [b] These values were obtained by interpolation on Arrhenius plots. [c] k_{H_2O}.

TABLE II

Ring-opening rate constants for D-penturonates (pH 4.5) at different temperatures

Compound, formula no.[a]	k_{open} (s^{-1})						
	23°	*30°*	*35°*	*40°*	*45°*	*50°*	*59°*
α-D-Arabinuronate, **1a**	0.23[b]	0.31	0.36	0.45[b]	0.54[b]	0.67	
β-D-Arabinuronate, **1b**	0.36	0.80	1.26	1.46	2.17	3.22	
α-D-Lyxuronate, **2a**	0.061	0.12	0.16[b]	0.17	0.34	0.59	
β-D-Lyxuronate, **2b**	0.13	0.32	0.45	0.71	0.77	1.12	
α-D-Riburonate, **3a**	0.15	0.22	0.36[b]	0.53[b]	0.76	1.03	2.12
β-D-Riburonate, **3b**	0.20[b]	0.30	0.50[b]	0.85	1.20	1.27	2.57
α-D-Xyluronate, **4a**	0.24	0.32	0.56	0.79	1.14	1.58	
β-D-Xyluronate, **4b**	0.14	0.33	0.47	0.71	1.24	1.55	

[a] Solution conditions: 0.3M penturonate, pH 4.5, 30% (v/v) ^2H_2O. [b] These values were obtained from Arrhenius plots by interpolation or extrapolation.

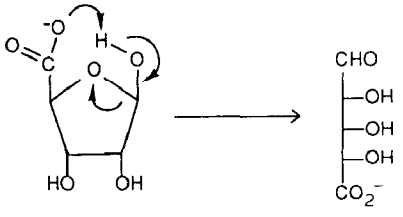
TABLE III

Activation energies for ring-opening of the D-penturonic acids.

pH	E_{act} (*kcal/mol*)[a]							
	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**
1.5	7	3	8	10	8	14	4	10
4.5	7	14	15	14	14	14	14	17

[a] Values were obtained from Arrhenius plots of the data in Tables I and II and are accurate to within ±2 kcal/mol.

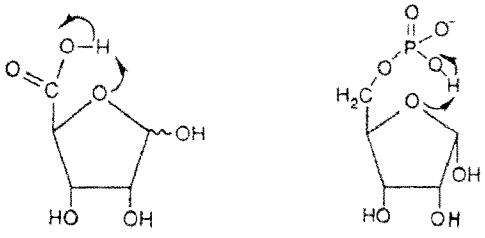
significantly affected by furanose anomeric configuration. At pH 1.5, the O-1,O-2 *cis* effect is the primary determinant of the relative reactivities of anomers. In contrast, at pH 4.5, the water-catalyzed and carboxylate anion-catalyzed reactions occur, with the former favoring O-1,O-2 *cis* anomers (a conclusion supported by previous studies[1] of neutral furanoses at this pH) and the latter favoring β anomers, and with the overall effect of enhancing the reactivity of β anomers relative to α anomers.



(2)

Under similar reaction conditions, k_{open} values for **1**–**4** are significantly greater than k_{open} for 5-deoxy- and 5-*O*-methylpentoses[2], and are similar in magnitude to those

of the pentose 5-phosphates[7], further implicating the carboxyl group in stimulating ring-opening in these compounds. In the protonated state, the carboxyl group may enhance the reaction by assisting in ring oxygen protonation (A, Chart 1), while the electron-withdrawing properties of the COOH group may, to an unknown extent, mitigate this effect by reducing electron density around the ring oxygen and thus reduce its affinity for protons. The ionized carboxyl group, on the other hand, may enhance the ring-opening of β anomers by assisting in proton abstraction at O-1 (Eq. 2). Similar catalytic mechanisms have been proposed for the anomerization of 6-deoxy-D-*gluco*-hepturonic acid[12].



A B

Chart 1

The modes of catalysis by phosphate monoanion and carboxylate anion differ, with the former favoring α anomers, and the latter favoring β anomers. In contrast to the carboxylate anion, the phosphate monoanion is believed to act by facilitating the protonation of the ring-oxygen (B, Chart 1). Presumably the steric hindrance generated by O-1 when it is *cis* to C-5 interferes with the proper orientation of the phosphate group and thus inhibits the catalytic effect in β anomers.

The effect of carboxyl ionization on ring-opening rate is also reflected in an altered decreasing order of k_{open} values for **1**–**4** at pH 4.5 and 50°: β-arabinuronate (3.22 s^{-1}) > α-xyluronate (1.58 s^{-1}) > β-xyluronate (1.55 s^{-1}) > β-riburonate (1.27 s^{-1}) > β-lyxuronate (1.12 s^{-1}) > α-riburonate (1.03 s^{-1}) > α-arabinuronate (0.67 s^{-1}) > α-lyxuronate (0.59 s^{-1}). In contrast to results obtained at pH 1.5 where the α-*xylo* isomer is most reactive, β-arabinuronate shows the highest rate at pH 4.5, presumably because two catalytic mechanisms are available to stimulate ring-opening: carboxylate-assisted and O-2-assisted abstraction of the hydroxyl proton from O-1.

The mechanisms proposed for the catalysis of ring-opening in **1**–**4** will certainly be modulated by furanose-ring conformation and dynamics. The carboxylate mechanism (Eq. 2) may not be as potent in β-furanoses that prefer an E_1 conformation in which the C-1–O-1 bond is quasi-equatorial and thus not oriented properly for proton abstraction by the carboxylate anion. Likewise, the efficiency of the O-2-assisted mechanism (Eq. 1) will be affected by ring conformation and dynamics, although this mechanism may be less sensitive to torsional factors than the carboxylate anion-assisted process.

Unidirectional rate constants of dehydration (k_{H_2O}) *of* D-*riburonic acid hydrate.* — In previous saturation-transfer studies of aldoses[1-7] k_{H_2O} could not be measured, since

only a small percent decrease in the signal intensity of C-1 of the acyclic hydrate was observed when C-1 of the *aldehydo* form was irradiated. Although k_{-H_2O} could not be measured quantitatively, the lack of saturation transfer indicated that k_{-H_2O} was significantly smaller than k_{open} of both furanose anomers. In contrast to these previous studies, k_{-H_2O} could be measured at pH 1.5 for D-riburonic acid hydrate (Table I). Interestingly, at each temperature studied, $k_{\alpha o} > k_{-H_2O} > k_{\beta o}$. The value of k_{-H_2O} for D-riburonic acid hydrate at pH 1.5 and 50° (1.22 s^{-1}) is significantly larger than the estimated k_{-H_2O} for D-threose hydrate[1] at p^{2}H 5.0 and 55° (< 0.05 s^{-1}), indicating that hydronium ion is a potent catalyst of the dehydration reaction. However, this rate enhancement may not be solely attributed to catalysis by H^+ ion in solution. Intramolecular catalysis by the protonated carboxyl group may also play a role in enhancing k_{-H_2O} in D-riburonic acid hydrate, as the expected sickle conformation[13] of this acyclic compound would orient this group near C-1 to promote intramolecular proton transfer.

The acyclic hydrate forms of D-penturonic acids may be generated in aqueous solution either by the direct hydration of the acyclic *aldehydo* form, or indirectly *via* the unhydrated and hydrated 2,5-lactones (Scheme 1). Hence, the observed transfer of saturation to the hydrate C-1 signal could be caused by contributions from both reaction pathways. Saturation-transfer experiments showed no change in the signal intensity of the 2,5-lactone hydrate (**3f**) when the signal at 206 p.p.m. (presumably due to both **3c** and **3e**) was irradiated for 15 s (Fig. 1B). This result suggests that the contribution made to the loss of intensity of the acyclic hydrate signal by the indirect lactone pathway is small. However, until the kinetics of both contributing processes can be established, k_{-H_2O} values determined by treating the hydrate $\rightleftharpoons$ aldehyde equilibrium as an isolated two-site exchange system must be considered approximate.

Activation energies (E_{act}) of ring-opening and dehydration in **1–4** — Activation energies (E_{act}) of ring-opening for the D-penturonic acids **1–4** were determined from Arrhenius plots of k_{open} as a function of temperature (Fig. 2). While significant errors are associated with these values due to the limited temperature range studied, values range

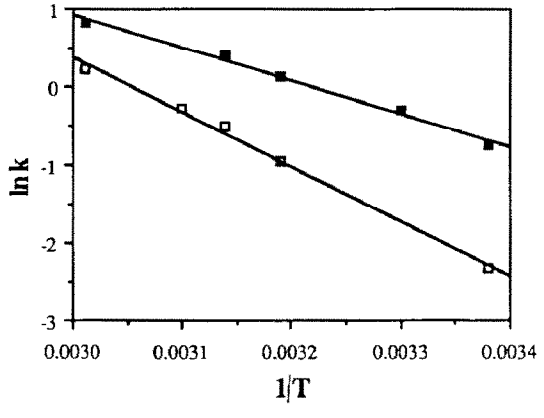


Fig. 2. The temperature dependence of k_{open} for the α- (■) and β- (□) furanose forms of D-(1-^{13}C)riburonic acid (**3**), 0.3M, pH 1.5, 30% (v/v) ^2H_2O. Rate constants were determined by ^{13}C-s.t.-n.m.r. spectroscopy.

from ~3 kcal/mol (*β-arabino*, pH 1.5) to ~17 kcal/mol (*β-xylo*, pH 4.5); by comparison, E_{act} for the dehydration of D-riburonic acid hydrate was found to be ~11 kcal/mol. Energies of activation determined for each isomer at pH 1.5 were found to be equal to or less than those measured at pH 4.5. In most cases, *viz. β-arabino* (**1b**), *α-lyxo* (**2a**), *α-ribo*(**3a**), *α-xylo* (**4a**), and *β-xylo* (**4b**), the difference is substantial (6–11 kcal/mol).

SUMMARY

The state of ionization of the carboxyl group of the D-penturonic acids significantly affects the ring-opening reactivity of these compounds. The *relative* rates of ring-opening of the protonated, electrically neutral anomers of **1**–**4** resemble those of other neutral furanoses such as the 5-*O*-methyl- and 5-deoxy-pentofuranoses[2]; however, at pH 1.5, both intramolecular catalysis by the COOH group and intermolecular catalysis by H^+ enhance these rates relative to those found for the C-5-modified, neutral pentofuranoses. At pH 4.5, where the carboxyl group is mostly ionized, the relative rates of ring-opening of the anomers of **1**–**4** are notably altered, apparently due to selective intramolecular catalysis by the carboxylate anion in the *β* anomers. This change in ring-opening reactivity with solution pH is reflected in different ring-opening activation energies at pH 1.5 and 4.5.

This study has shown that, while both the pentose 5-phosphates and penturonic acids are subject to intramolecular ring-opening catalysis, the nature of this catalysis differs. At solution pH values between 1 and 5, the phosphate group functions as a proton donor to facilitate ring-opening. In contrast, over the same pH range, the function of the carboxyl group changes from that of proton donor to proton acceptor, and this change is accompanied by an altered relative reactivity of the anomers of the penturonic acid.

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