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Deoxygenated and alkylated furanoses: Thorpe–Ingold effects on tautomeric equilibria and rates of anomerization

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ABSTRACT

2-Deoxy-D-*glycero*-tetrose, 3-deoxy-DL-*glycero*-tetrose, 3-deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose, 3-*C*-methyl-DL-erythrose, 3-*C*-methyl-DL-threose, 2-deoxy-5-*O*-methyl-D-*erythro*-pentose and 3-deoxy-5-*O*-methyl-D-*erythro*-pentose have been prepared, in some cases with ^{13}C-substitution at the anomeric carbon, and characterized by ^{1}H- (300 and 620 MHz) and ^{13}C-n.m.r. (75 MHz) spectroscopy. The proportions of cyclic (α and β furanoses) and acyclic (aldehyde and hydrate) forms were determined in aqueous ($^{2}H_2O$) solution, and ring-opening (k_{open}) and ring-closing (k_{close}) rate constants were measured by ^{1}H and ^{13}C saturation-transfer n.m.r. spectroscopy at p^{2}H 5.0 (acetate buffer) and 60°. The degree of furanose ring substitution was found to significantly affect both the thermodynamics and kinetics of furanose anomerization. Increased substitution enhances the proportion of cyclic forms in solution by stimulating furanose k_{close}. In contrast, furanose k_{open} was less affected by the degree of substitution; however, kinetic studies of 2-deoxyfuranose anomerization implicate furanose ring conformation as a potential determinant of k_{open}.

INTRODUCTION

The spontaneous ring-opening and ring-closing reactions that are characteristic of reducing sugars in solution[1] provide a unique biologically important system to study the mechanistic features of reversible intramolecular hemiacetal and hemiketal formation. Comparisons of intramolecular reactions to their intermolecular counterparts can be helpful in identifying and quantifying the factors that determine the efficiency of chemical processes. These comparisons serve as a means to better understand catalysis, the chemical basis of which lies partly on the proper juxtaposition of the reactive centers, either imposed internally (intramolecular reactions) or mediated by an external inorganic or organic agent (*e.g.*, a metal or an enzyme). This juxtaposition, which is embodied in the concept of "effective molarity"[2], minimizes the trial-and-error search time required in the uncatalyzed reaction and results in enhanced reaction rates.

In "neutral" furanoses (*i.e.*, furanoses that do not contain an ionizable substituent), rate constants of ring-opening (k_{open}) and -closing (k_{close}) depend highly on ring structure and configuration[3–7]. Within an anomeric pair, the anomer having O-1 and O-2 *cis* opens at a similar or greater rate than that having these atoms *trans*, and a mechanistic model[6] has been proposed to explain this behavior. In contrast, α anomers of the pentose 5-phosphates ring open more readily than β anomers at pH 4.2 (ref. 8),

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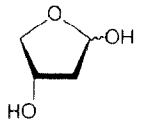
regardless of the relative configuration at C-1 and C-2, suggesting that a different ring-opening mechanism is involved with these compounds.

Recent studies have indicated that the percentage of acyclic aldehyde form found in aqueous solutions of the aldotetrofuranoses, D-erythrose and D-threose, is 5–10 fold greater than that found in solutions of the aldopentofuranoses (*e.g.*, 5-*O*-methylpentoses or 5-deoxypentoses[6]) and substituted aldotetrofuranoses (*e.g.*, apiofuranoses[5]). Furthermore, k_{open} for the aldotetrofuranoses and apiofuranoses were found to be similar[5]. Hence, these data suggest that k_{close} must be enhanced in alkyl-substituted aldofuranoses in order to account for the reduced amount of acyclic aldehyde form in aqueous solutions of these compounds. To examine these effects further, we synthesized several deoxygenated and alkylated furanoses (**2**, **5**, **7**, **10**, **11**, **15**, and **19**), and examined more quantitatively the effect of ring deoxygenation and alkylation on the kinetics and thermodynamics of furanose anomerization.



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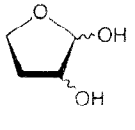

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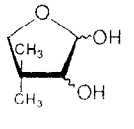

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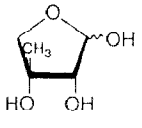

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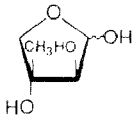

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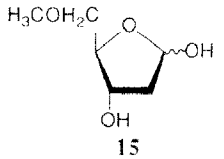

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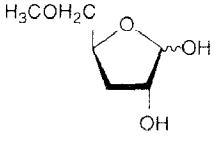

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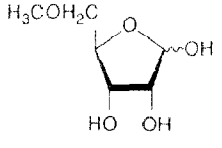

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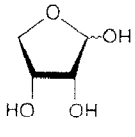

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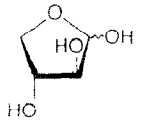

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EXPERIMENTAL

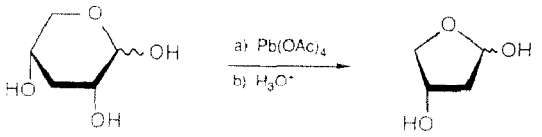
Materials. — Acrolein, acetol, 2,2-dimethyl-3-hydroxypropionaldehyde, 2-deoxy-D-*erythro*-pentose, and anhydrous sodium thiosulfate were purchased from Aldrich Chemical Co. D-Xylose and 5% palladium–barium sulfate ($Pd–BaSO_4$) were purchased from Sigma Chemical Co. Potassium (^{13}C)cyanide ($K^{13}CN$, 99 atom-% ^{13}C) was purchased from Cambridge Isotope Laboratories. Standard iodine solutions (0.1N) were purchased from Fisher Scientific Co.

Instrumentation. — ^1H- (300 MHz) and ^{13}C-n.m.r. (75 MHz) spectra were obtained on a Nicolet NT-300 Fourier-transform n.m.r. spectrometer equipped with a 293B pulse programmer and quadrature-phase detection. 2D ^1H–^1H COSY and ^{13}C–^1H chemical shift-correlation spectroscopy[9a] were conducted on the same spectrometer using software supplied by G. E. NMR Systems. F.t.-n.m.r. spectra (^1H) at 620 MHz were obtained at the NMR Facility for Biomedical Studies, Departement of Chemistry, Carnegie Mellon University.

^1H- and ^{13}C-saturation-transfer n.m.r. (s.t.-n.m.r.) spectroscopy was performed on the NT-300 300 MHz n.m.r. spectrometer as previously described[4]. S.t.-n.m.r. spectra were recorded with saturation times ranging from 0.1 to 20 s and relaxation delays of >20 s. At least ten (10) saturation times were employed in each experiment, and signal intensities were plotted semi-logarithmically as previously described[3] in order to obtain τ_1 from the slope. Using T_1 (spin-lattice relaxation times) and τ_1 values, ring-opening rate constants (k_{open}) in s^{-1} were determined from the relationship[3], $1/\tau_1 = k_{open} + 1/T_1$. ^{13}C-S.t.-n.m.r. was used to obtain k_{open} in **5**, **7**, **10** and **11**, while ^1H-s.t.-n.m.r. was used to measure k_{open} in **2**, **15** and **19**. Ring-closing rate constants (k_{close}) were determined from K_{eq} values and k_{open}.

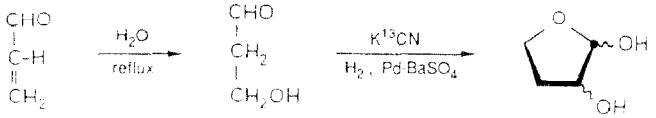
In addition to high-resolution ^1H- and ^{13}C-n.m.r. spectroscopy, gas-liquid chromatography–mass spectrometry (g.l.c.–m.s.) was used to characterize **2**, **5**, **7** and **15**. Mass spectra of their respective peracetylated alditol acetate derivatives were obtained on a Dupont DP-102 g.l.c.–m.s. instrument operated in the direct chemical-ionization mode with isobutane and a source temperature of 200°. The peracetylated alditol acetate derivatives were prepared as described by Blakeney *et al.*[9b] A gas–liquid chromatographic column (2 mm i.d. × 1.83 m) containing SP-2340 (3% on Chromosorb W-AW) was used with a temperature program of 190–230° at 2°/min. The quasi-molecular ion $(M + 1)^+$ was used to characterize each compound: **2**, *m/z* 233; (1-^{13}C)**5**, *m/z* 234; **7**, *m/z* 261; **15**, *m/z* 277. Spectra in all cases showed an intense signal at *m/z* (M − 59) corresponding to the loss of a single OAc group from the structure.

2-Deoxy-D-glycero-*tetrose* **2** *(Scheme 1).* — To a solution of 3-deoxy-D-*erythro*-pentose[10] **1** (2.2 g, 16.4 mmol in 1 mL of distilled H_2O) was added with stirring a solution of $Pb(OAc)_4$ (8.9 g, 20 mmol) in glacial acetic acid (225 mL). After 40 min at room temperature, solid oxalic acid (5 g, 40 mmol) was added with stirring. After 15 min, the suspension was filtered (vacuum) through Celite to remove lead oxalate, and the filtrate was evaporated at 30° *in vacuo* to ~5 mL and added to 100 mL of 0.1% (v/v) H_2SO_4. After 6 h at 37°, the acidic solution was neutralized with batchwise addition of Dowex-1



1 2

Scheme 1

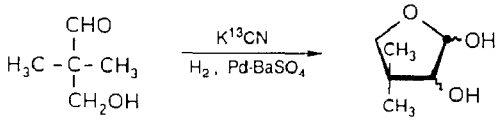


3 4 5

Scheme 2

× 8 (HCO_3^-) resin, and after concentration to ~10 mL at 30° *in vacuo*, it was chromatographed on a column (4.4 × 124 cm) containing Dowex-50 × 8 (200–400 mesh) (Ba^{2+}) ion-exchange resin, using distilled water as the eluent[11]. Fractions (10 mL) were collected at a flow rate of 1 mL/min and were assayed with phenol–sulfuric acid[12]. Fractions 45–56 were pooled and concentrated to ~10 mL at 30° *in vacuo*. The yield of **2** was 70% (1.2 g, 11.5 mmol) based on **1**.

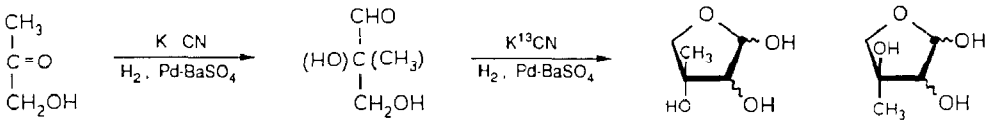
3-Deoxy-DL-glycero-*tetrose* **5** (*Scheme 2*). — To an aqueous solution of KCN (1.3 g, 20 mmol, in 60 mL of distilled H_2O) adjusted to pH 7.5 with glacial acetic acid was added a solution of distilled (Kugelrohr apparatus) 2-deoxyglyceraldehyde [(**4**, 3-hydroxypropionaldehyde, prepared from acrolein (**3**)][13] (1.11 g, 15 mmol, in 5 mL of distilled H_2O) with stirring. After 15 min, the reaction mixture was assayed by g.l.c.[14], and the solution was adjusted to pH 4.3 and aerated for 3 h with N_2 in a well-vented hood to remove excess HCN. The solution was readjusted to pH 4.3 with glacial acetic acid, and then further acidified to pH 1.7 with 18M H_2SO_4 and reduced with Pd-$BaSO_4$ and H_2 according to published procedures[15]. The mixture was vacuum-filtered through a glass-fiber filter to remove spent catalyst, and the filtrate was treated with $BaCO_3$ batchwise to remove SO_4^{2-}. After vacuum filtration through a Celite pad to remove the $BaSO_4$ precipitate (and excess $BaCO_3$), the filtrate was deionized by separate, batchwise treatment with excess Dowex-50 × 8 (H^+) and Dowex-1 × 8 (HCO_3^-) resins. The deionized solution was concentrated at 30° *in vacuo* to ~5 mL and chromatographed on a column (4.4 × 110 cm) containing Dowex-50 × 8 (200–400 mesh) (Ca^{2+}) ion-exchange resin[16], using distilled water as the eluent. Fractions (10 mL) were collected at a flow rate of 1 mL/min and assayed for aldose using phenol–sulfuric acid[12]. Fractions containing 3-deoxy-DL-*glycero*-tetrose **5** (fractions 64–72) were pooled and concentrated at 30° *in vacuo* (85% yield based on **4**). The (1-^{13}C)-substituted derivative of **5** was prepared and purified as described above for the unenriched compound by substituting $K^{13}CN$ for KCN in the protocol.



6 7

Scheme 3

3-Deoxy-3,3-di-C-*methyl*-DL-glycero-*tetrose* **7** *(Scheme 3).* — To an aqueous solution of KCN (2.0 g, 31 mmol, in 90 mL of distilled H_2O) adjusted to pH 7.7 was added with stirring an aqueous solution of 2,2-dimethyl-3-hydroxypropionaldehyde **6** (2.0 g, 20 mmol, in 5 mL of distilled H_2O) previously distilled on a Kugelrohr apparatus. After 15 min, the reaction mixture was assayed by g.l.c.[14], and the solution was readjusted to pH 4.3 and aerated as described above to remove excess HCN. The solution was reduced at pH 1.7 with Pd–$BaSO_4$ and H_2 according to published procedures[15], deionized, and chromatographed as described above. Fractions 70–75 were pooled and concentrated at 30° *in vacuo* (70% yield). 3-Deoxy-3,3-di-*C*-methyl-DL-(1-^{13}C)*glycero*-tetrose was prepared and chromatographed as described above for the preparation of **7** by substituting K^{13}CN for KCN in the reaction scheme.



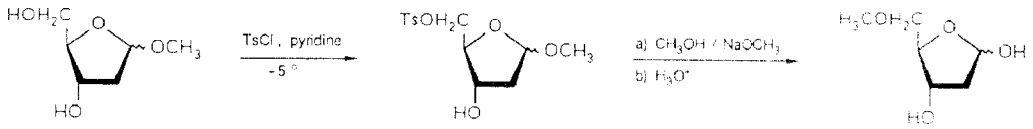
8 9 10 11

Scheme 4

3-C-Methyl-DL-*erythrose* **10** *and 3-C-methyl*-DL-*threose* **11** *(Scheme 4).* — To an aqueous solution of KCN (32.5 g, 500 mmol, in 100 mL of distilled H_2O) adjusted to pH 7.5 with glacial acetic acid was added acetol **8** (6.85 mL, 100 mmol, glass-distilled twice). The pH was maintained at pH 7.5–7.6 with additions of dilute acetic acid. After 20 min, the solution was adjusted to pH 5.5, and an aliquot was removed for g.l.c. analysis[14]. The solution was readjusted to pH 4.3 and aerated for 6 h with N_2 in a well-vented hood, trapping the excess HCN as previously described[15b,17]. The nitriles were hydrogenated over Pd–$BaSO_4$ at pH 1.7 as described above. After reduction was complete (~ 6 h), the solution was filtered through a glass fiber filter to remove spent catalyst, and the filtrate was treated batchwise with $BaCO_3$ to remove SO_4^{2-}. The white suspension was filtered through a Celite pad, the filtrate was deionized by batchwise and separate treatment with Dowex-50 × 8 (20–50 mesh) (H^+) and Dowex-1 × 8 (20–50 mesh) (HCO_3^-) ion-exchange resins, and the solution was evaporated to ~ 30 mL at 30° *in vacuo*, giving 2-*C*-methyl-DL-glyceraldehyde **9** in 90% yield.

To an aqueous solution of **9** (2.8 g, 27 mmol, 30 mL H_2O) was added a solution of

KCN (2 g, 31 mmol, 15 mL H_2O) adjusted to pH 7.5. After 20 min, the solution was adjusted to pH 5.5, and an aliquot was removed for g.l.c. analysis[14]. The solution was reduced at pH 1.7, deionized, and chromatographed as described above for the preparation of **5**. Fractions were assayed with phenol–sulfuric acid[12], and those containing 3-*C*-methyl-DL-threose **11** (39–42) and 3-*C*-methyl-DL-erythrose **10** (68–73) were pooled and concentrated *in vacuo* at 30° to ~10 mL. The yield (**10** + **11**) was 45% from **9**. 3-*C*-Methyl-DL-(1-^{13}C)threose and 3-*C*-methyl-DL-(1-^{13}C)erythrose were prepared as described for the unenriched compounds by substituting K^{13}CN for KCN in the reaction scheme.



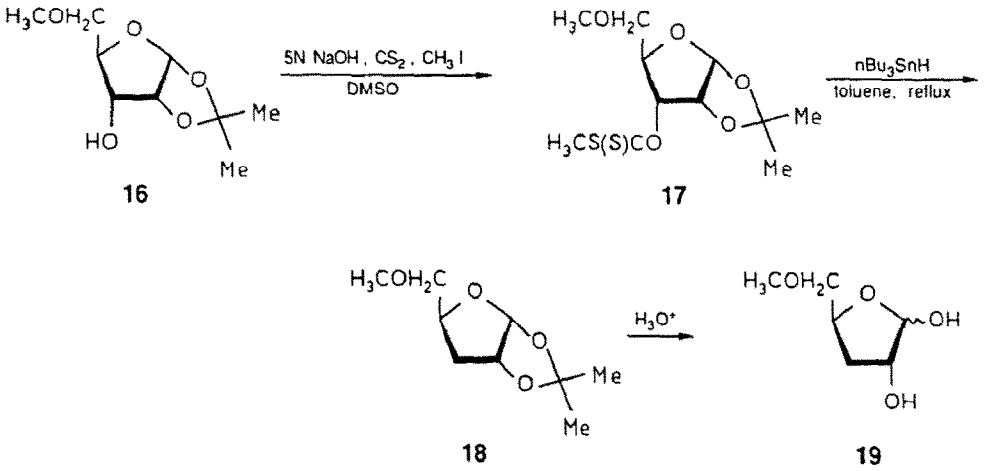
13 14 15

Scheme 5

2-Deoxy-5-O-methyl-D-erythro-*pentose* **15** (*Scheme 5*). – To a solution of 0.5% (v/v) HCl in methanol (340 mL) was added 2-deoxy-D-*erythro*-pentose **12** (5.0 g, 37.3 mmol). After 6 min at 25°, the acidic solution was neutralized with batchwise addition of Amberlite IRA-68 resin (OH^-, 80 g). The neutral solution was concentrated to a syrup at 30° *in vacuo*, and the mixture of glycosides was separated on a Dowex-1 × 2 (200–400 mesh) (OH^-) column, using distilled water as the eluent[15]. Fractions (10 mL) were collected at a flow rate of 1 mL/min and assayed with phenol–sulfuric acid[12]. The α furanoside eluted first (fractions 33–43), followed by the β furanoside (fractions 46–58) (yield, 94%).

Either glycoside **13** (3.1 g, 19 mmol) was dissolved in anhydrous pyridine (80 mL) in a three-neck flask equipped with a drying tube, thermometer, and equalizing dropping funnel, and *p*-toluenesulfonyl chloride (3.9 g, 20.6 mmol) dissolved in h.p.l.c.-grade CH_2Cl_2 (32 mL) was added slowly at −5°, maintaining the reaction mixture between −5 and 0° during the addition. The temperature was maintained for 1 h at 0°, after which time the solution was allowed to warm to room temperature. After stirring overnight, ice-cold water (200 mL) was added, the mixture was extracted with $CHCl_3$ (3 × 40 mL), and the organic extracts were pooled and dried over anhydrous $MgSO_4$. After evaporation, 4.3 g (yield, 71%) of **14** was obtained.

A solution of **14** (8 g, 25.2 mmol) in dry methanol (10 mL) was mixed with 4.6M $NaOCH_3$ (35 mL, 161 mmol) in a Pyrex screw-capped (Teflon-lined) test tube, and the red reaction mixture was heated for 0.5 h in an oil bath at 100°. After cooling, water (5 mL) was added to dissolve the precipitate, and the aqueous solution was extracted with $CHCl_3$ (3 × 20 mL). The organic extracts were pooled and dried over anhydrous $MgSO_4$ and evaporated at 30° *in vacuo* (yield, 3.1 g, 84%).



Scheme 6

The glycoside was hydrolyzed with Dowex-50 × 8 (H^+) (3 g, 20–50 mesh) ion-exchange resin for 1 h at 37° in $CHCl_3$–H_2O (15 mL) to generate **15** (yield, 50%, based on **12**).

*3-Deoxy-5-*O*-methyl-*D*-erythro-pentose* **19** *(Scheme 6).*—To a solution of 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-xylofuranose (**16**) (5.4 g, 26.5 mmol)[19] in methyl sulfoxide (53 mL) was added 5M aqueous sodium hydroxide (9 mL, 39.8 mmol) and carbon disulfide (2.1 mL, 34.5 mmol). The resulting burgundy solution was stirred for 30 min, and methyl iodide (2 mL, 32.3 mmol) was added. The yellow solution was stirred for an additional 30 min and poured into 100 mL of H_2O. The mixture was extracted with hexane (3 × 30 mL), and the organic extracts were pooled and dried over anhydrous $MgSO_4$, giving 3.4 g of **17**.

To a solution of **17** (1.4 g, 5 mmol) under reflux in dry toluene (10 mL) was added *via* a dropping funnel, over a period of 30 min, a solution of tri-n-butyl stannane (2.08 g, 7.1 mmol) in dry toluene (71 mL). Refluxing was continued under N_2 for 60 h, and the reaction was monitored periodically by t.l.c. (silica gel; 3:2 ether–hexane solvent; R_f **17**, 0.93; R_f **18**, 0.71). The toluene was removed *in vacuo* to give a crude, white product, which was dissolved in 150 mL of hot acetonitrile and extracted with hexane (3 × 50 mL) to remove tin-containing products. The acetonitrile phase was evaporated to a syrup, giving 0.6 g (68% yield) of **18**.

Hydrolysis of the isopropylidene ketal moiety in **18** to yield **19** was achieved by reflux in 0.1 % H_2SO_4 (~60% yield based on **18**).

RESULTS

^1H- and ^{13}C-N.m.r. chemical shifts. — The ^1H chemical shifts of the deoxy- and alkyl-substituted furanoses in ^2H_2O at 25° are given in Table I. The α- and β-anomeric proton signals of **5**, **7**, **10**, **11**, and **19** were assigned *via* their correlation with anomeric

TABLE I

^{1}H-N.m.r. chemical shifts[a] of deoxyfuranoses and alkyl-substituted furanoses in ^2H_2O at 25°

Compound	*Chemical shift (p.p.m.)*										
	H-1	*H-2*	*H-2'*	*H-3*	*H-3'*	*H-4*	*H-4'*	*H-5*	*H-5'*	CH_3	CH_3'
2-Deoxy-α-D-*glycero*-tetrose **2a**	5.49	2.25	1.87	4.46		~3.92	~3.92				
2-Deoxy-β-D-*glycero*-tetrose **2b**	5.65	2.18	2.02	4.54		4.01	3.77				
2-Deoxy-D-*glycero*-tetrose hydrate **2c**	5.18	1.71	1.71	obs[b]		3.45	3.57				
3-Deoxy-α-DL-*glycero*-tetrose **5a**	5.20										
3-Deoxy-β-DL-*glycero*-tetrose **5b**	5.22	4.19		2.24	1.89	4.07	4.02				
3-Deoxy-DL-*glycero*-tetrose hydrate **5c**	4.83										
3-Deoxy-3,3-di-*C*-methyl-α-DL-*glycero*-tetrose **7a**	5.44	3.73				3.75	3.50			1.03[c]	1.03[c]
3-Deoxy-3,3-di-*C*-methyl-β-DL-*glycero*-tetrose **7b**	5.18	3.70				3.81	3.67			1.05[c]	0.99[c]
3-*C*-Methyl-α-DL-erythrose **10a**	5.25	3.81				3.91	3.70			1.27	
3-*C*-Methyl-β-DL-erythrose **10b**	5.19	3.71				3.95	3.78			1.25	
3-*C*-Methyl-α-DL-threose **11a**	5.18	3.87				3.99	3.80[c]			1.32[d]	
3-*C*-Methyl-β-DL-threose **11b**	5.56	3.83				3.86[c]	3.67			1.31[d]	
2-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **15a**	5.50	2.37	1.83	4.17		4.15		3.56	3.44	3.37	
2-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **15b**	5.55	2.12	2.09	4.29		3.94		3.58	3.49	3.34	
3-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **19a**	5.26	4.23								3.34	
3-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **19b**	5.21	4.18		1.98	1.88	4.43		3.57	3.44	3.36	

[a] Values are reported in p.p.m. and are accurate to ±0.01 p.p.m. Spectra are referenced internally to 3-(trimethylsilyl)-1-propanesulfonate. [b] "Obs" denotes obscured signals. [c] These assignments are tentative. [d] Assignments may be reversed.

TABLE II

^1H–^1H Spin coupling constants[a] for deoxyfuranoses and alkyl-substituted furanoses in ^2H_2O at 25°.

Compound	*Coupling constant (Hz)*													
	1,2	*1,2′*	*2,2′*	*2,3*	*2′,3*	*2,3′*	*3,3′*	*3,4*	*3,4′*	*3′,4*	*3′,4′*	*4,4′*	*4,5*	*4,5′*	*5,5′*
2-Deoxy-α-D-*glycero*-tetrose **2a**	5.7	1.8	−14.4	~5.9	>1.9										
2-Deoxy-β-D-*glycero*-tetrose **2b**	5.7	4.2	−14.7	1.8	5.9										
2-Deoxy-D-*glycero*-tetrose hydrate **2c**	5.6	5.9										−11.8			
3-Deoxy-α-DL-*glycero*-tetrose **5a**	4.2														
3-Deoxy-β-DL-*glycero*-tetrose **5b**	<0.5			5.2		1.6	~−14.2	9.3	8.6	3.7	7.4	~−8.4			
3-Deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose **7a**	4.4											−8.3			
3-Deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose **7b**	4.1											−8.7			
3-*C*-Methyl-α-DL-erythrose **10a**	4.8														
3-*C*-Methyl-β-DL-erythrose **10b**	5.0											−10.0			
3-*C*-Methyl-α-DL-threose **11a**	1.9											nd			
3-*C*-Methyl-β-DL-threose **11b**	4.0											nd			
2-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **15a**	5.5	2.4	−14.2	7.1	3.7			4.5					3.2	6.0	−11.0
2-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **15b**	5.1	4.0	−14.0	5.7	6.5			4.4					4.1	7.2	−10.9
3-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **19a**	4.0														
3-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **19b**	0.5			1.1		4.8	−13.9	6.6		9.5			3.2	7.8	−10.8

[a] Values are reported in hertz (Hz) and are accurate to ±0.1 Hz. "Nd" denotes values which were not determined.

carbon signals in 2D ^{13}C–^{1}H chemical shift-correlation spectra. The anomeric carbon signals were assigned by noting that, in all aldofuranose rings studied to date[19–21], the C-1 signal of the anomer having O-1 and O-2 *trans* resonates downfield of the C-1 signal of its anomeric partner having O-1 and O-2 *cis*.

Since the above method could not be applied to assign the anomeric protons of the 2-deoxyfuranoses **2** and **15**, the "*syn*-upfield rule"[20,22] was used to initially assign the C-2 methylene protons in these structures. This rule predicts that the *difference* in the chemical shifts of H-2*R* and H-2*S* ($|\delta_{H\text{-}2R} - \delta_{H\text{-}2S}|$) in α anomers will be greater than that in β anomers. In the former, H-2*R* is *cis* to O-1 and O-3, and H-2*S* is *trans* to O-1 and O-3, and the "*syn*-upfield rule"[20,22] predicts that H-2*R* will be more shielded than H-2*S*. In contrast, H-2*R* and H-2*S* in β anomers each experience one *cis* and one *trans* interaction with vicinal oxygens, and the rule predicts their chemical shifts to be similar. Therefore, ^{1}H–^{1}H COSY data were used to establish correlations between pairs of H-2/H-2′ signals and the H-1 signals; the H-1 signal correlating with H-2 and H-2′ signals having the larger $|\delta_{H\text{-}2R} - \delta_{H\text{-}2S}|$ was assigned to the α furanose (Table I).

The remaining ^{1}H signals for **2**, **5**, **7**, **10**, **11**, **15** and **19** were assigned through an analysis of coupling patterns in 1D ^{1}H-n.m.r. spectra (Table II), assisted in some cases by homonuclear spin-decoupling and ^{1}H–^{1}H COSY spectra.

^{13}C-N.m.r. chemical shifts for the deoxy- and alkyl-substituted furanoses are listed in Table III. The C-1 signals of anomers of **5**, **7**, **10**, **11**, and **19** were assigned as described above. In **2** and **15**, ^{1}H–^{1}H COSY spectra and the "*syn*-upfield rule"[20,22] were used to assign H-1, and 2D ^{13}C–^{1}H shift correlation spectra were used to correlate H-1 with C-1. The remaining ring carbons were assigned with assistance from 2D ^{13}C–^{1}H shift correlation spectra and/or relative signal intensities. C-2 Assignments in **5**, **7**, **10** and **11** were confirmed by observing $^{1}J_{C\text{-}1,C\text{-}2}$ in (1-^{13}C)-substituted compounds (Table IV). $^{1}J_{C\text{-}1,C\text{-}2}$ values also served to confirm the assignment of anomers, as larger couplings are expected in aldofuranose anomers having O-1 and O-2 *trans*[20,21,23]; in the available data, $^{1}J_{C\text{-}1,C\text{-}2}$ (*cis*) = 42.6 ± 0.6 Hz, and $^{1}J_{C\text{-}1,C\text{-}2}$ (*trans*) = 46.6 ± 1.0 Hz.

Solution composition. — The tautomeric forms (α and β furanoses, acyclic hydrate, and acyclic aldehyde) present in aqueous ($^{2}H_2O$) solutions of the deoxy- and alkyl-substituted furanoses were determined from ^{13}C-n.m.r. spectra of 1-^{13}C-substituted derivatives or ^{1}H-n.m.r. spectra of the natural compounds (Table V). In furanoses containing an oxygen substituent at C-2 (**5**, **7**, **10**, **11**, **19**, **20**, **21**, and **22**), the more stable anomer has O-1 and O-2 *trans*. In the 2-deoxyaldotetrofuranose **2**, the β anomer **2b** predominates, whereas in its 2-deoxyaldopentofuranose homolog **15**, the α furanose **15a** is more stable. Apparently **15b** is destabilized by the 1,3-interaction between O-1 and the exocyclic $-CH_2OCH_3$ substituent at C-4. Alternatively, the exocyclic $-CH_2OCH_3$ substituent, which prefers a quasi-equatorial orientation, may limit the conformations of **15b** to those of lesser stability than those available to **15a**. In all compounds studied, the α:β ratio is not affected significantly by temperature (Table V).

In general, deoxygenation at C-2 of aldofuranoses increases the amount of acyclic aldehyde form in aqueous solution (Table V). For example, in aldotetrofuranose rings, the deoxygenation of **21** to give **2** causes a 1.6-fold increase in the percentage of acyclic

TABLE III

^{13}C-N.m.r. chemical shifts[a] of deoxyfuranoses and alkyl-substituted furanoses in $^{2}H_2O$ at 25°.

Compound	*Chemical Shift (p.p.m.)*							
	C-1	*C-2*	*C-3*	*C-3′*	*C-3″*	*C-4*	*C-5*	*CH$_3$*
2-Deoxy-α-D-*glycero*-tetrose **2a**	99.73	42.6	71.5			75.7		
2-Deoxy-β-D-*glycero*-tetrose **2b**	99.67	43.5	72.6			74.9		
2-Deoxy-D-*glycero*-tetrose hydrate **2c**	90.4	42.0	70.3			67.1		
3-Deoxy-α-DL-*glycero*-tetrose **5a**	97.2	72.4	31.4			66.4		
3-Deoxy-β-DL-*glycero*-tetrose **5b**	103.2	76.9	32.1			68.1		
3-Deoxy-DL-*glycero*-tetrose hydrate **5c**	93.4	72.5	35.0			60.0		
3-Deoxy-3,3-di-*C*-methyl-α-DL-*glycero*-tetrose **7a**	99.2	79.3	42.5	26.1	obs[b]	78.6		
3-Deoxy-3,3-di-*C*-methyl-β-DL-*glycero*-tetrose **7b**	104.2	85.7	42.8	24.2	20.6	79.7		
3-Deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose hydrate **7c**	91.1							
3-*C*-Methyl-α-DL-erythrose **10a**	97.9	76.3	76.8	23.0		77.2		
3-*C*-Methyl-β-DL-erythrose **10b**	103.1	82.7	77.9	21.9		77.4		
3-*C*-Methyl-DL-erythrose hydrate **10c**	91.2							
3-*C*-Methyl-α-DL-threose **11a**	104.9	83.6	79.9	20.1		78.6		
3-*C*-Methyl-β-DL-threose **11b**	99.6	78.7	80.9	20.2		76.9		
3-*C*-Methyl-DL-threose hydrate **11c**	90.9							
2-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **15a**	99.5	42.5	72.5			84.8	73.7	60.1
2-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **15b**	99.7	42.4	72.8			85.2	75.1	60.1
3-Deoxy-5-*O*-methyl-α-D-*erythro*-pentose **19a**	98.3	72.2	33.7			76.7	76.1	60.03
3-Deoxy-5-*O*-methyl-β-D-*erythro*-pentose **19b**	103.7	77.1	34.4			79.4	77.6	59.96

[a] Values are reported in p.p.m. and are accurate to ±0.1 p.p.m. Spectra are referenced externally to the C-1 signal of β-D-(1-^{13}C)glucopyranose (97.4 p.p.m.).
[b] "Obs" denotes obscured resonance.

TABLE IV

^{13}C–^{13}C and ^{13}C–^{1}H Coupling constants[a] for deoxyfuranoses and alkyl-substituted furanoses

Compound	*Coupled nuclei*				
	C-1, C-2	*C-1, C-3*	*C-1, C-3'*	*C-1, C-4*	*C-1, H-1*
3-Deoxy-α-DL-*glycero*-tetrose **5a**	42.5	nc			171.9
3-Deoxy-β-DL-*glycero*-tetrose **5b**	45.2	nc			172.4
3-Deoxy-DL-*glycero*-tetrose hydrate **5c**	48.3				162.4
3-Deoxy-3,3-di-*C*-methyl-α-DL-*glycero*-tetrose **7a**	42.1	1.5	nc	nc	171.1
3-Deoxy-3,3-di-*C*-methyl-β-DL-*glycero*-tetrose **7b**	47.1	3.1	1.6[b]	nc	169.1
3-*C*-Methyl-α-DL-erythrose **10a**	43.4	1.5	2.2	nc	174.0
3-*C*-Methyl-β-DL-erythrose **10b**	47.6	3.3	2.5	nc	170.3
3-*C*-Methyl-α-DL-threose **11a**	46.5	3.5	br	nc	171.6
3-*C*-Methyl-β-DL-threose **11b**	42.2	2.4	1.7	nc	172.6

[a] Values are reported in hertz (Hz) and are accurate to ±0.1 Hz. "Nc" denotes no observed coupling. [b] No coupling was observed to C-3" of this compound.

TABLE V

Tautomeric forms of deoxyfuranoses and alkyl-substituted furanoses in aqueous ($^{2}H_2O$) solution

Compound	*Percent in solution*					
	α-furanose	*β-furanose*	*α/β*	*hydrate*	*aldehyde*	*h a*
2-Deoxy-D-*glycero*-tetrose **2**[a]	25.3	59.2	0.43	12.4	3.1	4.0
	(27.4)	(54.7)	0.50	(9.4)	(8.5)	1.1
3-Deoxy-DL-*glycero*-tetrose **5**[a]	21.3	70.1	0.30	7.8	0.7	11.1
	(19.4)	(69.5)	0.28	(9.6)	(1.5)	6.4
3-Deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose **7**[b]	29.0	71.0	0.41	0.04	0.1	0.4
	(31.0)	(68.3)	0.45	(0.1)	(0.6)	0.2
3-*C*-Methyl-DL-erythrose **10**[c]	30.1	69.4	0.43	0.3	0.2	1.5
	(35.8)	(62.9)	0.57	(0.6)	(0.8)	0.8
3-*C*-Methyl-DL-threose **11**[c]	55.0	44.3	1.24	0.5	0.3	1.7
	(56.2)	(42.4)	1.33	(0.6)	(0.8)	0.8
2-Deoxy-5-*O*-methyl-D-*erythro*-pentose **15**[a]	52.0	44.6	1.17	2.3	~1.1	~2.1
	(52.2)	(46.2)	1.13	(nd)	(~1.6)	
5-*O*-Methyl-D-ribose **20**[a]	34.5	64.6	0.53	0.8	0.1	8.0
D-Erythrose **21**[c]	25	63	0.40	10	2	5.0
	(28.2)	(57.7)	0.49	(11.1)	(2.9)	3.8
D-Threose **22**[a]	51.8	37.6	1.38	9.6	0.96	10.0
	(48.5)	(37.4)	1.30	(11.2)	(2.8)	4.0
3-Deoxy-5-*O*-methyl-D-*erythro*-pentose **19**	23.2	76.8	0.30	nd	nd	

[a] Values determined by ^{1}H-n.m.r. spectroscopy. Solution conditions: 0.1M aldose in $^{2}H_2O$ at 30°. Nd = not determined. Values in parentheses were determined at 60°; solution conditions are given in Table VI. [b] Values determined by ^{13}C-n.m.r. spectroscopy using (1-^{13}C) aldoses, 0.25M in $^{2}H_2O$ at 25°. [c] From ref. 8. [d] From ref. 3.

aldehyde at 30° and a 2.9-fold increase at 60°. Comparison of **20** and **15** shows an 11-fold increase in aldehyde content upon C-2 deoxygenation of aldopentofuranose rings. This increase in aldehyde content may result, in part, from the more electrophilic carbonyl in **20** and **21** (compared to that in **2** and **15**) caused by the presence of an oxygen substituent at C-2 of the former. Increasing temperature enhances the amount of acyclic aldehyde form in aqueous solutions of all compounds studied (Table V). Increasing temperature has a smaller effect on the amount of hydrate in solution; however, the [hydrate]:[carbonyl] ratio consistently decreases with increasing temperature due to increasing [carbonyl] (Table V).

Increasing alkyl substitution of the aldofuranose ring decreases the total percent of acyclic forms in solution. Thus, at 30° the percentage of acyclic forms (aldehyde + hydrate) decreases in the series aldotetrofuranoses **21**:**22** (~11%) → 3-*C*-methyl-aldotetrofuranoses **10**:**11** (~0.7%) → 3-dimethyl-*glycero*-tetroses **7** (~0.1%).

The quantity of acyclic hydrate seems to be more affected by furanose ring alkylation than that of the acyclic aldehyde. For example, at 30° aqueous solutions of D-erythrose **21** contain 250-fold more acyclic hydrate than those of **7**, but only 20-fold more acyclic aldehyde. The hydrate of **7** contains unfavorable 1,3-interactions between the *gem*-diol oxygens at C-1 and the *gem*-dimethyl groups at C-3; these interactions are absent in the acyclic aldehyde of **7**. Thus, the [hydrate]:[carbonyl] ratio in aldofuranoses will depend, among other factors, on the state of alkylation of the ring.

As previously noted[24], alkyl substitution at C-4 of the furanose ring significantly reduces the percentage of acyclic forms in solution. This effect may be observed by comparing the amounts of acyclic forms in solutions of the homologs **2**:**15**, and **20**:**21**.

Ring-opening and ring-closing rate constants. — The ring-opening (k_{open}) and ring-closing (k_{close}) rate constants for the deoxyfuranoses and alkyl-substituted furanoses (p^2H 5.0 in 50mM acetate buffer, 60°) are given in Table VI. In compounds containing an oxygen substituent at C-2 (**5**, **7**, **10**, **11**, and **22**), anomers having O-1 and O-2 *cis* open at rates greater than, or approximately equal to, corresponding anomers having O-1 and O-2 *trans*. This behavior is consistent with that observed previously in the aldotetrofuranoses,[3] 5-deoxy- and 5-*O*-methylpentoses[6], and the D-pentuloses[24].

The 3-*C*-methyl-tetroses **10** and **11** are the deoxy analogs of the apiofuranoses previously studied[5]. A comparison of k_{open} of corresponding configurations in both series shows that k_{open} is greatest for the *β-threo* configuration and smallest for the *β-erythro* configuration, with k_{open} of the *α-erythro* and *α-threo* configurations intermediate in magnitude. Thus, the conversion of a $-CH_2OH$ substituent at C-3 of the apiofuranose ring to $-CH_3$ found in 3-*C*-methyl-tetroses does not affect the relative ring-opening reactivities of the four isomers.

A comparison of k_{open} (Table VI) for **2** and **15** suggests that alkylation (in this case at C-4) reduces ring-opening reactivity. Likewise, a comparison of **21** and **7** leads to the same conclusion. However, the effect is small and not uniform (for example, compare **22** and **11**) and further studies will be required to examine this effect in more detail.

In contrast, k_{close} is enhanced when the furanose ring is alkylated. For example, the alkylation of **2** to give **15** causes a ~3-fold enhancement in k_{close}. Likewise,

TABLE VI

Ring-opening[a] and -closing[b] rate constants for deoxyfuranoses and alkyl-substituted furanoses.

Compound	*Rate constant* (s^{-1})			
	$k_{\alpha o}$	$k_{\beta o}$	k_{co}	k_{oc}
2-Deoxy-D-*glycero*-tetrose **2**	0.43	0.30	1.4	1.9
D-Erythrose **21**	0.49	0.31	4.8	6.2
D-Threose **22**	0.090	0.45	1.6	6.0
3-*C*-Methyl-DL-erythrose **10**	0.27	0.12	12.1	9.4
3-*C*-Methyl-DL-threose **11**	0.18	0.74	12.6	39.2
3-Deoxy-3,3-di-*C*-methyl-DL-tetrose **7**	0.38	0.075	19.6	8.5
3-Deoxy-DL-tetrose **5**	0.23	0.15	3.0	7.0
2-Deoxy-5-*O*-methyl-D-*erythro*-pentose **15**	0.15	0.16	5.2	4.6

[a] Determined by ^{1}H-(**2** and **15**) or ^{13}C-(**21**, **22**, **10**, **11**, **7**, and **5**) saturation-transfer n.m.r. spectroscopy. Solution conditions, ^{1}H: 0.1M aldose, p^{2}H 5.0, 50mM acetate, 60°. Solution conditions, ^{13}C: 0.25M aldose, p^{2}H 5.0, 50mM acetate, 60°. [b] Determined from k_{open} and K_{eq} at 60°.

ring-closing reactivity is greater for the 3-*C*-methyl-tetroses **10** and **11** than for the aldotetroses **21** and **22**. The reduced ring-closing reactivity caused by ring deoxygenation (*e.g.*, compare **2** with **21** and **22**) is probably due to the loss of a ring substituent and/or a reduction in the electrophilicity of the carbonyl carbon.

Interestingly, the ring-closing reactivities of the 3-*C*-methyl-tetroses **10** and **11** are similar to those of the 3-deoxy-3,3-di-*C*-methyltetroses **7**; this is not unexpected, as the substitution of $-CH_3$ for $-OH$ at C-3 of **10** and **11** constitutes a relatively small change in the state of substitution of the ring.

The enhanced ring-opening reactivity of furanose anomers having O-1 and O-2 *cis* was previously explained[6,24] by invoking anchimeric assistance by O-2 in abstracting, either directly or *via* intervening water molecules, the hydroxyl proton on O-1 during ring-opening. However, although **2** lacks a hydroxyl substituent at C-2, its α anomer **2a** nevertheless ring-opens slightly faster than **2b**, and thus seemingly challenges the validity of the anchimeric mechanism. ^{1}H–^{1}H Coupling constants (Table II) show that, in **2a**, $^3J_{H\text{-}1,H\text{-}2S} > {}^3J_{H\text{-}1,H\text{-}2R}$, and $^3J_{H\text{-}2S,H\text{-}3} > {}^3J_{H\text{-}2S,H\text{-}3}$. This pattern is consistent with the ^2E, E_1, ^0E, and E_4 conformations determined to be preferred by **2a** in the gas phase from *ab initio* molecular orbital calculations with the 3-21G basis set[25]. In these conformers, the dihedral angles made by H-2*S* to H-1 and H-3 are 0–30°, while those made by H-2*R* to H-1 and H-3 are 80–120° and 90–150°, respectively, and thus larger couplings are expected for the former. More importantly, the preferred conformers of **2a** orient O-1 and O-3 quasi-axial, or near quasi-axial, allowing O-3 to substitute for O-2 in abstracting the hydroxyl proton on O-1.

In contrast, the 2-deoxypentofuranose anomers, **15a** and **15b**, ring-open at similar rates (Table VI). ^{1}H–^{1}H spin-couplings in **15a** (Table II) differ from corresponding values in **2a** and suggest a greater contribution of "north" conformers (*e.g.*, ^3E) in which O-3 is quasi-equatorial or near quasi-equatorial and thus unable to participate in

TABLE VII

Thermodynamic parameters for the ring-closing reactions of **21**, **10**, and **7** at 30°

Compound	$\Delta G_{\alpha}^{\circ a}$	$\Delta G_{\beta}^{\circ a}$	$\Delta H_{\alpha}^{\circ b}$	$\Delta H_{\beta}^{\circ b}$	$\Delta S_{\alpha}^{\circ c}$	$\Delta S_{\beta}^{\circ c}$
D-Erythrose **21**	−1.6	−2.1	−4.0	−5.1	−7.8	−9.8
3-*C*-Methyl-DL-erythrose **10**	−2.6	−3.0	−4.3	−5.8	−5.8	−9.2
3-Deoxy-3,3-di-*C*-methyl-DL-*glycero*-tetrose **7**	−2.8	−3.3	−5.2	−6.2	−8.0	−9.6

[a] In kcal/mol. [b] In kcal/mol ±1.5. [c] In cal/K/mol ±3.

proton abstraction at O-1. Thus, this limited set of data suggests that furanose ring conformation may influence the relative ring-opening reactivities of some furanose anomers.

A conformational effect may also be operating in **21** and **22**, and **10**, and **11**. Within these pairs, the *threo* isomers show a greater *difference* in k_{open} between anomers than is shown between *erythro* isomers. This effect was observed previously in the 5-deoxy- and 5-*O*-methyl pentoses[6], where the smaller difference in *erythro* isomers was attributed to the lower reactivity of *erythro* isomers having O-1 and O-2 *cis*. This reduced reactivity may be caused by intramolecular hydrogen bonding between the *cis* O-2 and O-3 which limits the ability of O-2 to participate in proton abstraction[6]. It is possible, however, that conformational properties of O-1, O-2-*cis erythro* isomers do not allow, on average, O-1 and O-2 to orient as well at those of O-1, O-2-*cis threo* isomers.

Ring alkylation and thermodynamic parameters. — Free-energies of conversion (ΔG°) for the ring closure reactions of **7**, **10** and **21** at 30° are given in Table VII. These values are expected to become more negative as ring alkylation increases, since the [cyclic]:[carbonyl] ratio increases with increased alkylation (see above).

By determining equilibrium constants as a function of temperature, enthalpies of conversion (ΔH°) were determined, thus allowing ΔG° values to be divided into their two components, ΔH° and entropies of conversion, ΔS° (Table VII). While the data set is limited and subject to inherently large errors due to the experimental methodology, these results suggest that changes in ring alkylation have only a small and random effect on ΔS° as ring alkylation increases. In contrast, a small but consistent decrease is observed in ΔH°. Thus, it appears that enthalpic factors are primarily responsible for the observed effect of ring alkylation on the free-energies of conversion for furanose ring-closure.

DISCUSSION

The anomerization reaction of reducing sugars in solution has been known for over a century[1], yet the effects of carbohydrate structure on the kinetics of this

important reaction remain to be fully elucidated. The reaction is catalyzed by H^+, OH^-, and H_2O in aqueous solution[1]. In non-aqueous environments, bifunctional catalysts such as 2-pyridone (2-hydroxypyridine) and various carboxylic acids promote the reaction[26]. Recent studies have revealed some important structural features that control furanose ring-opening and ring-closing rate constants[3,6,8,24,27]. This study has examined the effect of ring substitution—at sites other than the anomeric carbon—on the thermodynamics and kinetics of furanose anomerization.

Alkyl substitution has been known to enhance ring stability for over seventy years, and this observation is embodied in the "*gem*-dialkyl effect" or "Thorpe–Ingold effect". Beesley *et al.*[28] first explained this effect by proposing that alkyl substitution decreases the endocyclic bond angle and increases the exocyclic bond angle at the substituted carbon, with both effects conferring greater stability to the cyclic structure. Allinger and Zalkow[29] found that alkyl substitution in cyclohexane systems shifts equilibria towards the cyclic compound, an effect attributed to both enthalpic and entropic factors. In a more substituted compound, ring formation involves a smaller increase in gauche interactions over the acyclic compound than occurs in a less substituted compound. This smaller change in gauche interactions gives a more negative ΔH of ring-closure. In addition, the difference in the degrees of freedom between the acyclic and cyclic compound is smaller for more substituted molecules, resulting in a smaller overall loss in entropy upon ring-closure. Both effects enhance the stability of the cyclic form relative to the acyclic form.

In addition to the effect on chemical equilibria, alkylation also promotes the rate of ring formation. A classic example of this effect was provided by Bruice and Pandit[30] in their study of the rates of anhydride formation from mono-*p*-bromophenyl esters of dicarboxylic acids. In this case, *gem*-dimethyl alkylation apparently limits the degrees of freedom of the dicarboxylic acid, thus increasing the probability of correct alignment of the reaction centers for anhydride formation. A 20-fold rate enhancement was observed over that of the unsubstituted molecule. In sugars, deoxygenation at C-2 of D-glucose increased the mutarotation rate four-fold compared to D-glucose under H_2O-catalyzed conditions[31]. The enhanced rate was attributed to a combination of steric and electronic factors.

This study has shown that carbohydrate systems respond to the effects of alkylation in a manner consistent with expectations based on the above considerations. In aldofuranose systems, alkylation enhances the amount of cyclic forms and reduces the amount of acyclic forms in aqueous solution. From a kinetic standpoint, alkylation does not appear to affect ring-opening significantly; ring-opening rates of alkylated aldofuranose anomers were found to be influenced by the O-1, O-2-*cis* effect observed earlier in simple aldofuranoses[3,6]. In contrast, ring-closing is clearly stimulated in alkylated furanoses, although this stimulation was modest in the compounds studied; the largest rate enhancement in k_{close} (28-fold) was observed between **2a** and **11b**. Previous studies have suggested that the conformation of the acyclic carbonyl form plays a role in determining the rates of furanose ring-closure[6,24]. The effect of alkylation on k_{close} may be another manifestation of this conformational factor, as added sub-

stituents may act to stabilize pseudocyclic conformations of the open-chain forms.

Alkylation at various sites in the furanose ring does not have an equal effect on the kinetics of furanose ring-closing. For example, while **2** and **5** have the same degree of substitution, their k_{close} values differ (Table VI). The most extreme comparison involves the hydroxymethylation of the anomeric carbon of aldotetrofuranoses, generating 2-ketopentofuranoses. This kind of alkylation results in a significant *reduction* of k_{close}[24]. The present study shows that alkylation at non-anomeric furanose ring carbons *enhances* ring-closure, but the magnitude of this enhancement will probably depend on the specific site involved. For example, while *gem*-dialkyl effects may be invoked to explain the enhanced k_{close} upon substitution at C-4 of aldofuranoses, substitution at this site is also likely to affect ring-closing rates by altering the electronic character of O-4.

The observed difference in the ring-opening behavior of the anomers of **2** and **15** points to the potential importance of furanose conformation and dynamics in governing k_{open}. From the limited data available, it appears that O-3 may play a role in catalyzing the opening of aldofuranoses rings under the proper conformational circumstances. This effect, which deserves further scrutiny, serves to emphasize that numerous, competing structural factors influence the kinetics of furanose anomerization.

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REFERENCES

1 (a) H. S. Isbell and W. Pigman, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 13–65. (b) W. Pigman and H. S. Isbell, *Adv. Carbohydr. Chem.*, 23 (1968) 11–55.
2 (a) W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, Inc., 1969, 7–41. (b) M. L. Bender, R. J. Bergeron, and M. Komiyama, *The Bioorganic Chemistry of Enzymatic Catalysis*, John Wiley and Sons, New York, 1984, pp. 216–247.
3 A. S. Serianni, J. Pierce, S.-G. Huang, and R. Barker, *J. Am. Chem. Soc.*, 104 (1982) 4037–4044.
4 J. R. Snyder and A. S. Serianni, *J. Org. Chem.*, 51 (1986) 2694–2702.
5 J. R. Snyder and A. S. Serianni, *Carbohydr. Res.*, 166 (1987) 85–99.
6 J. R. Snyder and A. S. Serianni, *Carbohydr. Res.*, 184 (1988) 13–25.
7 J. R. Snyder and A. S. Serianni, *J. Am. Chem. Soc.*, 111 (1989) 2681–2687.
8 J. Pierce, A. S. Serianni and R. Barker, *J. Am. Chem. Soc.*, 107 (1985) 2448–2456.
9 (a) G. A. Morris and L. D. Hall, *J. Am. Chem. Soc.*, 103 (1981) 4703–4711. (b) A. B. Blakeney, P. J. Harris, R. H. Henry, and B. A. Stone, *Carbohydr. Res.*, 113 (1983) 291–299.
10 Z. J. Witczak and R. L. Whistler, *Carbohydr. Res.*, 110 (1982) 326–329.
11 J. K. N. Jones and R. A. Wall, *Can. J. Chem.*, 38 (1960) 2290–2294.
12 J. E. Hodge and B. T. Hofreiter, *Methods Carbohydr. Chem.*, 1 (1962) 380–394.
13 A. R. Gallopo and W. W. Cleland, *Arch. Biochem. Biophys.*, 195 (1979) 152–154.
14 A. S. Serianni and R. Barker, *J. Org. Chem.*, 45 (1980) 3329–3341.
15 (a) A. S. Serianni, E. L. Clark, and R. Barker, *Carbohydr. Res.*, 72 (1979) 79–91. (b) A. S. Serianni and R. Barker, in E. Buncel and J. Jones (Eds.), *Isotopes in the Physical and Biomedical Sciences*, Elsevier, New York, 1987, pp. 211–236.

16 S. J. Angyal, G. S. Bethell, and R. J. Beveridge, *Carbohydr. Res.*, 73 (1979) 9–18.
17 A. S. Serianni, H. A. Nunez, M. L. Hayes, and R. Barker, *Methods Enzymol.*, 89 (1982) 73–92.
18 P. W. Austin, F. E. Hardy, J. C. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1963, 5350–5353.
19 R. G. S. Ritchie, N. Cyr, B. Korsch, H. J. Koch, and A. S. Perlin, *Can. J. Chem.*, 53 (1975) 1424–1433.
20 A. S. Serianni and R. Barker, *J. Org. Chem.*, 49 (1984) 3292–3300.
21 J. R. Snyder and A. S. Serianni, *Carbohydr. Res.*, 163 (1987) 169–188.
22 M. Anteunis and D. Danneels, *Org. Magn. Reson.*, 7 (1975) 345–348.
23 A. S. Serianni, J. Pierce, and R. Barker, *Biochemistry*, 18 (1979) 1192–1199.
24 T. Vuorinen and A. S. Serianni, *Carbohydr. Res.*, 207 (1990) 185–210.
25 E. C. Garrett and A. S. Serianni, in J. Brady and A. French (Eds.), *Computer Modeling of Carbohydrate Molecules*, ACS Symposium Series No. 430, Washington, DC, 1990, pp. 91–119.
26 M. L. Bender, R. J. Bergeron, and M. Komiyama, *The Bioorganic Chemistry of Enzymatic Catalysis*, John Wiley and Sons, New York, 1984, pp. 255–256.
27 W. Goux, *J. Am. Chem. Soc.*, 107 (1985) 4320–4327.
28 R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, 107 (1915) 1080–1106.
29 N. L. Allinger and V. Zalkow, *J. Org. Chem.*, 25 (1960) 701–704.
30 T. C. Bruice and U. K. Pandit, *Proc. Natl. Acad. Sci. USA*, 46 (1960) 402–404.
31 D. M. Morgan and A. Neuberger, *Proc. Roy. Soc. London, A*, 337 (1974) 317–332.