THE MUTAROTATION OF 2-DEOXY-β-D-*erythro*-PENTOSE ("2-DEOXY-β-D-RIBOSE"). CONFORMATIONS, KINETICS, AND EQUILIBRIA*

R. U. LEMIEUX,
Department of Chemistry, University of Alberta, Edmonton, Alberta (Canada)

LAURENS ANDERSON, AND ANTHONY H. CONNER
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin, Madison, Wisconsin 53706 (U. S. A.)

(Received January 4th, 1971; accepted March 27th, 1971)

ABSTRACT

In aqueous solution, 2-deoxy-β-D-*erythro*-pentopyranose retains the *1C* conformation of the solid. On mutarotation in water, the sugar rearranges, to give an equilibrium mixture containing the β-D-pyranose, α-D-pyranose (*1C* conformation), β-D-furanose, and α-D-furanose forms in the approximate ratios of 43:42:10:5 at 0° and 15:15:9:11 at 90°. The mutarotation is kinetically "complex", with a rate constant for the approach of the furanoses to their equilibrium level substantially greater than the constants for the pyranoses. The results, based on p.m.r. and optical rotatory measurements, are discussed in terms of conformational and isomer predisposition.

INTRODUCTION

Preliminary data on 2-deoxy-D-*erythro*-pentose ("2-deoxy-D-ribose"), a biologically important sugar, were included in a report by Lemieux and Stevens[1] on a p.m.r. spectroscopic study of the tautomeric equilibria of the common aldoses in deuterium oxide. The p.m.r. spectrum of 2-deoxy-D-*erythro*-pentose, like that of D-ribose, revealed the presence of four components in the equilibrium solution, and showed that the tautomerization process was amenable to further study by the p.m.r. technique. The results of our additional studies are detailed here. We also report new information gained by polarimetric study of the mutarotation.

RESULTS AND DISCUSSION

*The conformation of 2-deoxy-β-D-*erythro*-pentopyranose.* — Crystalline 2-deoxy-D-*erythro*-pentose, known to be the β-D-pyranose anomer, has been shown by X-ray diffraction studies to have the *1C* (D) conformation **1b** in the solid state[2]. That the β-D-pyranose form maintains this conformation in solution was evident from the

*Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.

p.m.r. spectrum recorded soon after dissolution in deuterium oxide at 0° (see Fig. 1). Spin-decoupling experiments showed that H-3 resonated at $\sim\tau$ 5.89, and when this proton was decoupled from H-2,2′, the signals for the latter collapsed to a pair of

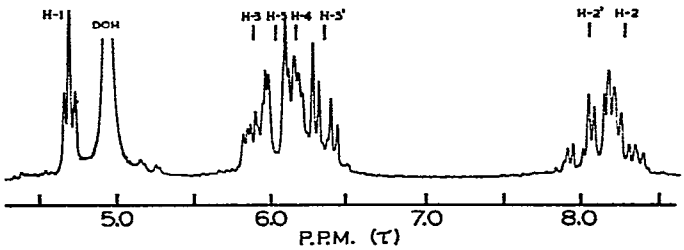
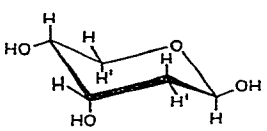
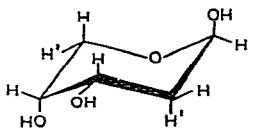


Fig. 1. The p.m.r. spectrum at 100 MHz of 2-deoxy-β-D-*erythro*-pentopyranose in deuterium oxide after 15 min at 0°.

quartets corresponding to the AB portion of the ABX system H-2,2′, H-1. Similarly, irradiation of H-1 at τ 4.69 gave the AB pattern for the overlapping ABX system H-2,2′, H-3. The coupling constants for these two systems were calculated, and are recorded in Table I. The small magnitudes and near equality of $J_{1,2}$ and $J_{1,2'}$ indicate torsional angles of about 60° for H-1 with both H-2 and H-2′. The value of 10.6 Hz for $J_{2',3}$ shows that both H-2′ and H-3 are in the axial orientation, as is required for the *1C* (D) conformation (**1b**). The presence of an appreciable proportion of the *C1* form (**1a**) seems precluded as, for this conformation, $J_{1,2}$ would increase to $\sim$10 Hz, and $J_{2',3}$ would decrease[3] to 2–4 Hz.



1a



1b

The adoption by 2-deoxy-β-D-*erythro*-pentopyranose of the *1C* conformation, in which the bonds to two of the three hydroxyl groups are axial, might at first sight seem surprising. The anomeric effect[4] favors the axial orientation for the 1-hydroxyl group[5], but, as evidenced by the mutarotational equilibria of such sugars as D-glucose D-galactose, and D-xylose, water appears to have a cancelling influence on the anomeric effect; this action by water has been attributed to its high dielectric constant[5]. On the other hand, because of its bifunctionality, water may give rise to solvation effects not present for other solvents. Indeed, Lemieux and co-workers[6] recently observed a specific solvation effect by water on the orientation of the methoxyl group of methyl 2-deoxyaldopyranosides, and concluded that the consequence of such solvation effects appears to be of greater importance than changes in the bulk dielectric constant of the solvent. 2-Deoxy-β-D-*erythro*-pentose was also expected to main-

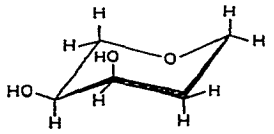
TABLE I

P.M.R. PARAMETERS FOR 2-DEOXY-D-*erythro*-PENTOSE AND ITS METHYL FURANOSIDES IN DEUTERIUM OXIDE

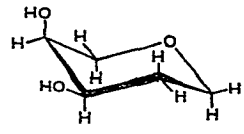
	Chemical shifts, τ values						*Spacings, Hz*								
	H-1	*H-2*	*H-2′*	*H-3*	*H-4*	*H-5,5′*	$J_{1,2}$	$J_{1,2'}$	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
β-Pyranose[a]	4.69	8.21	8.02	~5.9	~6.1	6.00 6.33	3.3[b]	3.1[b]	~−13.8[b]	4.2[b]	10.6[b]		2	4	−12.5
α-Pyranose[a]	5.18						2.8	8.7							
β-Furanose[a]	4.35	~7.9	~7.9				4.5	4.5							
α-Furanose[a]	4.41	7.6	8.1				2.4	5.5							
Methyl β-furanoside[c]	4.77	7.76	7.83	5.64	6.00	6.28 6.40	2.7	5.3	−12.0	6.2	6.2	4.1	7.2	4.3	−14.5
Methyl α-furanoside[d]	4.83	7.7	8.1				2.0	5.0							

[a]At 100 MHz. [b]Calculated as ABX patterns [H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can J. Chem.*, 35 (1957) 65] from the spectrum at 0°. For the furanoid structures, H-2 and H-2′ and H-5 and H-5′ are not defined. [c]At 220 MHz. The spectrum was reproduced to provide the coupling constants within ±0.2 Hz by calculations that employed a Newmar program for spectrum simulation, involving 7 spins, provided by Allan R. Quirt, Department of Chemistry, University of Alberta. [d]At 60 MHz.

tain the *1C* conformation on dissolution in water, because the *syn*-axial interactions*, O-3//H-1+O-3//H-5′, in the *C1* conformation **1a** are more strongly destabilizing than the nonbonded interactions O-4/O-5+O-4//H-2′ in the other chair form (**1b**). This is required by the fact that, for 1,5-anhydro-2-deoxy-L-*erythro*-pentitol in aqueous solution, the conformation **2b** preponderates extensively, as judged by the



2a



2b

optical rotation[7]. Evidently, the O-4/O-5 interaction, which probably involves only dipole interactions, is much less than an O//H interaction[8], which probably arises mainly for steric reasons. The polar grouping consisting of the hydroxyl group and the ring-oxygen atom in gauche relationship can be expected to be effectively stabilized by the highly polar solvent.

Composition of the equilibrium solution. Conformations of the other anomers. — On standing of a solution in deuterium oxide, 2-deoxy-D-*erythro*-pentose tautomerizes to a mixture that gives the p.m.r. spectrum shown in Fig. 2. The region of the spectrum characteristic of anomeric protons (τ 4.3–5.4) exhibits, in addition to the H-1 triplet

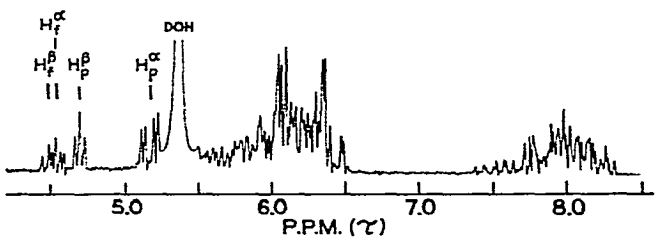
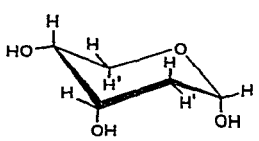


Fig. 2. The p.m.r. spectrum at 100 MHz of the equilibrium mixture of pyranose and furanose forms of 2-deoxy-D-*erythro*-pentose in deuterium oxide at 40°.

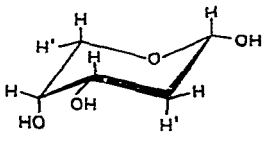
at τ 4.69 of the original β-pyranose (now diminished in relative intensity), a quartet at τ 5.18 and a group of lines at τ 4.30–4.46. Comparison of the 60- and 100-MHz spectra, and of 100-MHz spectra recorded at different temperatures, leaves no doubt that the latter group of lines comprises a triplet, centered at τ 4.35, overlapping a quartet centered at τ 4.41. There are thus at least four components in the equilibrium mixture. Particularly at the higher temperatures, the lines of the anomeric multiplets were sharp and narrow. There was no evidence of a "hidden", fifth component.

The chemical shift and spacings[1] of the quartet at τ 5.18 warrant the assignment of this signal to the anomeric proton of the α-pyranose form, largely in the *1C* (D) conformation **3b**. This conformation, but not the *C1* (D) form **3a**, explains the large

*For symbolism, see Ref. 4.



3a



3b

value (8.7 Hz) of $J_{1,2}$. The *1C* conformation for 2-deoxy-α-D-*erythro*-pentopyranose is opposed by the anomeric effect, but is, perhaps, to be expected by analogy with methyl 2-deoxy-α-D-*erythro*-pentopyranoside and methyl 3-deoxy-β-L-*erythro*-pentopyranoside, both of which, in water, adopt the conformation wherein two of their three exocyclic oxygen atoms are equatorially attached[9,10]. On the other hand, in such weakly basic solvents as chloroform, acetone, and acetonitrile, both of these methyl glycosides pass over to the form in which *syn*-axially opposed functions are stabilized by internal hydrogen-bonding[10]. The prediposition for the *1C* (D) conformation in water can be attributed to the tendency of this solvent to form strong hydrogen bonds with hydroxyl groups, with resultant destabilization of the conformers [*C1* (D)] that have *syn*-axial, exocyclic oxygen atoms.

The spacings in the low-field triplet and quartet of the spectrum at equilibrium give no definitive clues for the labeling of these signals, which *a priori* could be due to the two furanose forms of the sugar, or to one furanose form and the acyclic aldehydrol. However, comparison of the spectrum with the spectra of the two methyl 2-deoxy-D-*erythro*-pentofuranosides leads to assignment of the triplet at τ 4.35 to H-1 of the β-furanose anomer of the sugar, and of the quartet at τ 4.41 to H-1 of the α-furanose anomer. Additional evidence for these assignments was provided by a correlation of equilibrium rotations with the composition of the solution at different temperatures, as discussed later.

The methyl 2-deoxy-D-*erythro*-pentofuranosides used as standards were obtained by catalytic de-esterification of samples of the corresponding crystalline 3,5-bis(*p*-toluates)[11,12]. From Hudson's rule that $[\alpha]_D$ (α-anomer) > $[\alpha]_D$ (β-anomer) in the D series, the syrupy methyl furanoside having $[\alpha]_D$ +155°, derived from the dextrorotatory *p*-toluate, is taken to be the α anomer. The methyl furanoside (also a syrup) having $[\alpha]_D$ −70° from the levorotatory *p*-toluate is, therefore, the β anomer. These assignments conform to those given the parent *p*-toluates by MacDonald and Fletcher[12], apparently by the same criterion. Although the specific rotations of some nucleosides of 2-deoxy-D-*erythro*-pentofuranose[13] do not obey Hudson's rule, the rule has been shown to hold for the methyl furanosides of D-ribose, and, so far as we are aware, for all simple alkyl glycosides that have been critically checked. Furthermore, Leonard and co-workers[14] have proved by chemical means that the rules hold for the methyl 2-deoxy-5-*O*-trityl-D-*erythro*-pentofuranosides. There can thus be no doubt as to the identities of the anomeric methyl furanosides.

Key features of the spectra of the methyl furanosides are the triplet for H-1 of the β-furanoside at τ 4.77 and the quartet for H-1 of the α-furanoside at slightly higher field (τ 4.83). A similar relationship has been found for the thymidines[15]; the

β anomer provides a triplet at τ 3.67, and the α anomer, a quartet at τ 3.70. In addition, the methylene protons (H-2, H-2′) of the methyl β-furanoside give a single, narrow multiplet centered at τ 7.79, whereas the methyl α-furanoside shows two broader, well separated, H-2 signals. Analogous groups of lines on the low-field side of the methylene envelope are present in the spectrum of the sugar (see Fig. 2), at τ 7.87–7.92 and 7.40–7.70; the latter group presumably corresponds to *one* H-2 proton. These groups of lines were shown, by decoupling, to be related to the low-field, anomeric signals. These correlations of chemical shift and signal multiplicity, as well as the similarity of the spacings in the H-1 signals of the methyl furanosides, the thymidines, and the sugar (at low field) strongly indicate that the third and fourth components of an equilibrium solution of 2-deoxy-D-*erythro*-pentose in water are the two furanose anomers.

Although the anomeric proton of methyl 2-deoxy-β-D-*erythro*-pentofuranoside gives rise to a triplet when observed at 100 MHz, this signal becomes a quartet having couplings of 2.7 and 5.3 Hz when the spectrum is recorded at 220 MHz. The triplet observed at the lower magnetic field is not surprising, as, even at 220 MHz, H-2 and H-2′ are still only weakly shifted as compared to the coupling constant expected for geminal protons. Because, almost certainly, the spectra of solutions of furanosides are time-averaged spectra of two or more conformers, it is not possible to interpret the n.m.r. parameters in the absence of knowledge regarding the conformational equilibria. This is especially evident for the α-furanose form of the sugar, for which the spacings observed for the signal of the anomeric proton were appreciably temperature-dependent.

Kinetics of tautomerization at 0°. — The proportions of the components of tautomerizing solutions of 2-deoxy-β-D-*erythro*-pentopyranose in deuterium oxide, determined by integration of spectra recorded at suitable intervals, are plotted *versus* time in Fig. 3. Data were collected at 0° only, because the tautomerization, even in

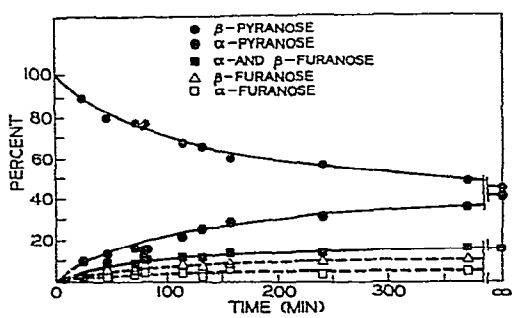


Fig. 3. The composition of mutarotating solutions of 2-deoxy-β-D-*erythro*-pentose in deuterium oxide at 0° after various times, as determined by p.m.r. spectroscopy at 100 MHz.

deuterium oxide[16], is too rapid at higher temperatures to be quantitatively monitored by p.m.r. spectroscopy without resort to elaborate procedures. It is readily apparent

that the plots give no obvious indication of maxima, minima, or lag phases in the progress of any component to its equilibrium level.

The data for the β-pyranose, the α-pyranose, and total furanose were fitted to exponential equations by a computer-programmed, least-squares procedure*. For each tautomer, plots were then prepared of $\ln(N_{eq}-N_t)/(N_{eq}-N_0)$ *vs.* time, where N_{eq} is the mole fraction of the given tautomer at equilibrium, and N_t and N_0 are the mole fractions at times t and zero, respectively. From these plots, it may be seen that the approach of each component to its equilibrium level is, *to a first approximation*, a first-order process. The slopes of the plots gave rate constants, in min^{-1} ±the standard deviation, as follows (half-times in parentheses): β-pyranose (disappearance), 0.0090 ±0.0008 (77 min); α-pyranose (appearance), 0.0076 ±0.0010 (91 min); total furanose (appearance), 0.013 ±0.002 (54 min). The kinetic data for the individual furanoses, which had to be obtained by somewhat arbitrary partitioning of the area of the furanose multiplet, are too imprecise for highly meaningful treatment. There are, however, indications (see Fig. 3) that the rates of appearance of the two furanoses are proportional to their respective equilibrium levels, *i.e.*, no evidence was obtained that, early in the mutarotation, either furanose is kinetically favored over the other.

It is commonly held that, in systems in which more than two tautomeric forms of a sugar are present in significant proportions, the initial phase of mutarotation mainly involves pyranose–furanose interconversion, and the later phase, apparent pyranose–pyranose interconversion[17], because, normally, the furanose forms more rapidly achieve concentration levels that are less than, but near to, their equilibrium values; this is illustrated by the data presented in Fig. 3. Mechanistic considerations support this point of view for mutarotation of those sugars for which the crystalline form used for dissolution remains a major component of the equilibrium mixture. It is widely accepted[17] that the acyclic, aldehydo form is the common intermediate in all conversions of one ring form or anomeric form of an aldose to another. The aldehydo form is, presumably, also in equilibrium with the aldehydrol form. The concentrations of these compounds are normally too low to be detected by p.m.r. spectroscopy, but have been estimated by polarography[17]. In view of the generally low energy-barriers to conformational change, the aldehydo form should undergo the conformational interconversions that precede ring-closure at rates much higher than the rates of the actual ring-closure reactions. Because of the more favorable entropy requirement, the closure of a five-membered, saturated, oxygen-containing ring is an inherently faster process than the closure of a six-membered ring[18,19]. Ample experimental verification of this principle has been supplied by studies on the formation of methyl glycosides[20] and anhydroalditols[21,22]. Consequently, the formation of the furanose anomers of 2-deoxy-D-*erythro*-pentose from the aldehydo intermediate must be expected to be faster than the formation of the pyranoses.

As the aldehydo form may be postulated as being the ground state for the four ring-closing processes, and as, normally, the furanose forms are thermodyna-

*Devised by Prof. W. W. Cleland.

mically less stable than the pyranose forms, it follows that both formation and ring-opening of furanoses are faster than those processes for the pyranose forms. The higher rate for conversion of the furanose to the aldehydo form as compared with conversion of the pyranose to the aldehydo form is undoubtedly related to the greater ring-strain present in the furanose form. Thus, it is reasonable to expect that the ring-oxygen atom will be somewhat more basic and the anomeric hydroxyl group somewhat more acidic for the furanose than for the pyranose forms. As a result, and in accordance with a widely accepted mechanism for mutarotation[23], protonation of the ring-oxygen atom should be more extensive for the furanoses; moreover, the rate-controlling abstraction of the proton from the anomeric hydroxyl group should be more facile for the furanose forms. In view of these considerations, it is to be expected that (*a*) the first stage for the mutarotation of a single pyranose form will be a more rapid accumulation of the furanose forms than of its anomeric pyranose form, and (*b*) the equilibration of the furanose forms will be a relatively fast process as compared with the equilibration of the pyranose forms. In this regard, it is of interest that, during formation of methyl glycosides, the rate of equilibration of the two furanosides is much higher than that of their conversion into pyranosides[20].

Mutarotation. — Polarimetric studies of the mutarotation of 2-deoxy-D-*erythro*-pentose in water[24] had shown that the process is very rapid at ordinary temperatures, but had given no indication that it is "complex" (*i.e.*, that it gives a nonlinear plot of log $|r_t - r_\infty|$, or similar function, *vs.* time). Complex mutarotation had, however, been observed for 2-deoxy-D-*erythro*-pentose in pyridine[25]. Such nonlinear (log) behavior is commonly associated with the presence of more than two tautomers during the mutarotation process[17]. In the present work, the use of an automatic recording polarimeter and a flow system for filling the cell permitted close examination of the early period of the mutarotation. As may be seen in Fig. 4, the change in the optical rotation of 2-deoxy-β-D-*erythro*-pentopyranose in water at 25° is markedly faster in the first four minutes than during the subsequent period. The ratio of the slopes of the two portions of the plot (best straight lines, estimated visually) is 1.16:1.00. At 0°, where the overall rate of mutarotation is about 0.13 that at 25°, a

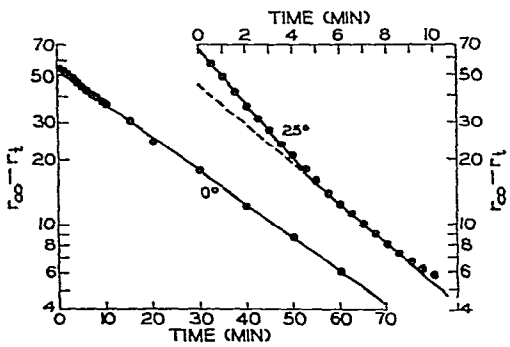


Fig. 4. Logarithmic plots of the changes in observed rotation with time for solutions of 2-deoxy-β-D-*erythro*-pentopyranose in water; r_∞ = specific rotation at equilibrium, and r_t = specific rotation at time *t*.

biphasic plot was also obtained. The difference between the initial and later slopes is less readily perceived in this plot, because the slopes are numerically much smaller than at 25°, but the ratio is about the same. Extrapolation of the early portions of these plots, and allowance for the equilibrium rotations, gave values for the specific rotation of 2-deoxy-β-D-*erythro*-pentopyranose of $[\alpha]_D^0$ −121° and $[\alpha]_D^{25}$ −122°. These values are some 30° more negative than the one previously recorded[24], and are in much better agreement with the figures predicted by the empirical calculations described later.

It is pertinent to consider whether the mutarotatory behavior of 2-deoxy-D-*erythro*-pentose is satisfactorily explained by the data obtained by p.m.r. spectral analysis regarding changes in the composition of the tautomeric mixture in solution. Any attempt to answer this question requires knowledge of the specific rotation of each of the tautomeric forms, but, owing to the complexity of the equilibrium mixture, this information can be obtained experimentally only for the crystalline β-pyranose form. Nevertheless, the success achieved in relating structure to rotation by the application of empirical rules[26–28] suggests that useful values for the other forms can be derived by subtracting the contribution of the asymmetric conformational unit defined[28] by the methyl group, namely, ±115°, from the molecular rotations of the corresponding methyl glycosides. The rotations thus arrived at for the four forms of 2-deoxy-D-*erythro*-pentose that had been indicated by p.m.r. spectroscopy are given in Table II. For the pyranose forms, optical rotations can also be estimated by summa-

TABLE II

ROTATIONS CALCULATED FOR THE VARIOUS FORMS OF 2-DEOXY-D-*erythro*-PENTOSE IN WATER AT 25°

	Observed rotations (degrees) for methyl glycoside		*Calculated rotations (degrees) for the sugar*	
	$[\alpha]_D$	$[M]_D$	$[M]_D$	$[\alpha]_D$
β-Pyranose	−202.3	−300	−185	−138
α-Pyranose	+43.4	+64	−51	−38
β-Furanose	−70	−104	+11	+8.4
α-Furanose	+155	+230	+115	+85

tion of the contributions of the individual conformational units of the respective ring structures, as described by Lemieux and Martin[28]; this method gives an estimate of −80° for the molecular rotation of the α-pyranose form, and of −185° for the β-pyranose form, when both are assumed to be present in the *1C* (D) conformation. The corresponding figures for the specific rotations are −60° and −138°, which agree satisfactorily with the respective values of −38° and −138° (see Table II) derived from the rotations of the methyl glycosides. It may be seen from Table II that the β-pyranose form has the most negative specific rotation of the series, and the furanose forms, the most positive. Thus, any conversion of 2-deoxy-β-D-*erythro*-

pentopyranose into other tautomers results in a shift of the rotation toward more positive values. It also follows that, during the early stages of the tautomerization, when, *relative to their respective equilibrium levels*, the concentration of furanoses is rising faster than that of the α-pyranose, the rate constant for the rotation change should be greater than in the later stages of the process. This is, in fact, what is revealed by the nonlinear, log plots in Fig. 4. However, it must be noted that, in order to decide whether there is a quantitative correlation between these curves and those for composition, more accurate data would be required.

Equilibrium compositions versus *temperature.* — Integration of the n.m.r. spectra of solutions of 2-deoxy-D-*erythro*-pentose brought to equilibrium at various temperatures from 0 to 90° gave the data plotted in Fig. 5. It may be seen that the ratio of

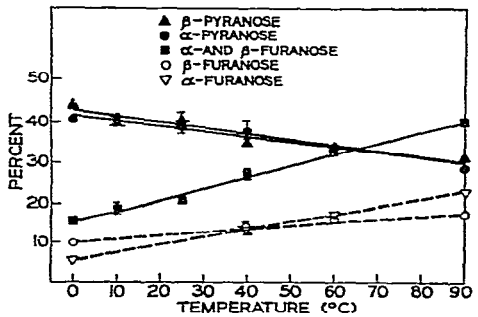


Fig. 5. The equilibrium compositions of ~1.8M solutions of 2-deoxy-D-*erythro*-pentose in deuterium oxide in the temperature range of 0–90°, as measured by p.m.r. spectroscopy at 100 MHz.

the α-pyranose to the β-pyranose form remains essentially constant over the temperature range studied, but that the proportion of furanose forms increases with higher temperature (at the expense of the pyranose forms). Although the estimates of the proportions of the individual furanose forms are less reliable than the estimates of total furanose forms, it is clear that the ratio of the furanose anomers to each other changes markedly as the temperature is raised. At 0°, the concentration of β-furanose is approximately twice that of the α-furanose, whereas, at 90°, the α-anomer preponderates by a factor of about 1.3:1.0.

These data on the changes in the composition of solutions of 2-deoxy-D-*erythro*-pentose with change in temperature can be correlated with change in the equilibrium specific rotation, which was found by Zinner and co-workers[25] to change linearly from −66.3° at 0° to −21.8° at 90°. We have verified these results for the temperatures of 0 and 25°. Equilibrium specific rotations were calculated for the various forms of 2-deoxy-D-*erythro*-pentose from the values given in Table II and the compositional data of Fig. 5, on the assumption that the low-field triplet and quartet signals in the p.m.r. spectrum arise from the β-furanose and α-furanose forms, respectively, as such calculations gave results of $[\alpha]_D^0$ −72° (equil.) and $[\alpha]_D^{90}$ − 34° (equil.), in better agreement with the experimental values than those made on the reverse assumption. Thus, the assignments of anomeric configuration to the two furanose forms made on

the basis of the p.m.r. spectra of the methyl furanosides are further substantiated. Particularly in view of the fact that the calculations neglect possible variations in the specific rotations of individual tautomers with change in temperature, the agreement with the experimental values is adequate to confirm the utility of the procedure used for estimating the specific rotations of the several forms of the sugar from the rotations of the corresponding methyl glycosides.

Thermodynamic properties. — The mole fractions, N, found for the various forms at equilibrium (plotted in Fig. 5) suggest the following linear relationships between mole fraction and temperature. These equations were used to obtain the

$$N_\beta^p = 0.430 - 0.0015\ (T-273)$$
$$N_\alpha^p = 0.420 - 0.0014\ (T-273)$$
$$N_\beta^f = 0.100 + 0.00084\ (T-273)$$
$$N_\alpha^f = 0.54\ + 0.0019\ (T-273)$$

equilibrium constants for the relationships, at successive, 10° increments in temperature, of the β-pyranose form to each of the other tautomers, and of the two furanose anomers to each other. The thermodynamic parameters derived from the equilibrium constants are listed in Table III, with ΔH values based on temperature ranges of 20°. No entries are made for the β-pyranose–α-pyranose pair, because the equilibrium constant for their interconversion does not change appreciably over the range of temperature studied. The observed free-energy difference between the two pyranose forms corresponds, within experimental error, to that reported by Angyal[5] for the anomeric forms of 2-deoxy-D-*arabino*-hexopyranose, namely, 0.05 kcal.mol^{-1} (47.5% of α anomer). This correspondence, which is expected only when both anomers are present in the same chair form, with no O/O interactions in either anomer, substantiates our assignment of the *1C* (D) conformation to both anomers of 2-deoxy-D-*erythro*-pentopyranose in aqueous solution.

TABLE III

APPROXIMATE THERMODYNAMIC CONSTANTS[a] FOR THE EQUILIBRATION OF THE PYRANOSE AND FURANOSE FORMS OF 2-DEOXY-D-*erythro*-PENTOSE IN DEUTERIUM OXIDE[b]

Temperature (degrees)	*Equilibrium*								
	β-Furanose⇄ β-pyranose			*α-Furanose⇄ β-pyranose*			*α-Furanose⇄ β-furanose*		
	−ΔG°	−ΔH	−ΔS	−ΔG°	−ΔH	−ΔS	−ΔG°	−ΔH	−ΔS
10	0.76	1.81	3.6	0.98	4.8	13.5	0.22	3.0	10
20	0.73	1.87	3.9	0.86	4.3	11.7	0.13	2.3	8
30	0.68	1.93	4.1	0.76	3.9	10.5	0.08	1.9	6
40	0.64	2.01	4.3	0.65	3.7	9.7	0.01	1.7	5
50	0.60	2.10	4.5	0.56	3.6	9.3	−0.04	1.5	5
60	0.55	2.21	5.0	0.47	3.5	9.0	−0.08	1.3	4
70	0.50	2.33	5.4	0.38	3.5	9.1	−0.12	1.2	4
80	0.44	2.44	5.7	0.29	3.6	9.3	−0.15	1.1	4

[a] $\Delta G°$ and ΔH, in kcal.mol^{-1}; ΔS in e.u. [b] Approximately 1.8 M solution.

In contrast to the pyranose ⇄ pyranose equilibrium, the furanose ⇄ pyranose and furanose ⇄ furanose equilibria are highly temperature-dependent. The associated changes in enthalpy are in accord with the general expectation that the pyranose forms are inherently less strained than the furanose forms. Also, the higher entropy contents of the furanose forms are expected, in view of the greater flexibility of the furanose ring, together with the possibility of freedom of rotation about the C-4–C-5 bond in the furanoses. The high entropies of the furanose forms relative to those of the pyranose forms cannot, however, be explained in terms of entropies of mixing for the conformers of the sugar molecules alone. The magnitude of the entropy differences, and the fact that both the enthalpy and the entropy differences change substantially with change in temperature, are indicative of large differences in the hydration of the several tautomers and, in the case of the furanoses, their various conformers. Considering the furanose ⇄ furanose equilibrium (see Table III), the enthalpy difference is greatest when the entropy difference to provide an opposing driving-force is greatest. This situation is compatible with stronger solvation of the β-furanose form at the lower temperatures, concomitant with a much higher entropy for the α-form. As the temperature is increased, the stabilization of both of these forms by hydration would, presumably, become more equal and the entropy difference would decrease. Whatever the precise explanation of these data may be, they show that, despite its success in dealing with the pyranose forms, there are important limitations to quantitative conformational analysis based on interactions within the solute only.

In conclusion, in addition to providing a deepened insight into the properties of 2-deoxy-D-*erythro*-pentose in aqueous solution, the present study further illustrates[6,28,29] the value of combining structural information based on nuclear magnetic resonance spectroscopy with that derived from optical rotation measurements and empirical rules for calculating the rotations of saturated carbohydrate structures.

EXPERIMENTAL

The p.m.r. experiments were conducted by use of Varian Associates instruments operating at the radiofrequencies indicated, with variable-temperature probes. All chemical shifts reported are from 5% tetramethylsilane in $CDCl_3$ as the external reference. In certain experiments, sodium 3-(trimethylsilyl)-1-propanesulfonate was used as the internal standard, and the shifts obtained were corrected to those based on 5% Me_4Si in $CDCl_3$ as the external standard (in an A-60 instrument) by subtracting 0.02 p.p.m. The shifts obtained with pure Me_4Si in a capillary at 220 MHz were empirically corrected to those obtained with the A60 spectrometer using 5% Me_4Si in $CDCl_3$ by subtracting τ 0.66.

The relative amounts of the tautomeric forms of 2-deoxy-D-*erythro*-pentose at various times and temperatures were determined from the relative intensities of the signals for the anomeric protons. Except at 0°, the spectra for the solutions at equilibrium were recorded after equilibrium had been attained from both directions.

The optical rotations were measured with a Perkin–Elmer Model 141 automatic, recording polarimeter by use of 1-dm tubes.

Dissolution of the 2-deoxy-β-D-*erythro*-pentopyranose for measurement of the rates of mutarotation was conducted under magnetic stirring in an apparatus that allowed the water (25 ml) to dissolve the sugar (0.2 g) weighed onto a sintered-glass plate. After momentary stirring, the solution was sucked into the polarimeter tube. The whole operation was performed under thermostatted conditions. This procedure permitted readings to be taken within 30 sec after dissolution.

The 2-deoxy-β-D-*erythro*-pentopyranose used had m.p. 89–90° (lit.[30] 95–97°) and $[\alpha]_D^{25}$ −54.1° (equilibrium) (lit.[25] $[\alpha]_D^{25}$ −54.1°).

ACKNOWLEDGMENTS

This work was supported by NRC-T172, Grant in Aid of Research, to R. U. L.; by Research Grant AM-10588 from the U. S. National Institutes of Health to L. A.; and by Training Grant No. GM00236 BCH from the U. S. National Institute of General Medical Sciences (traineeship for A. H. C.).

We thank Dr. H. G. Fletcher, Jr., for providing generous quantities of 2-deoxy-D-*erythro*-pentose, Dr. D. L. MacDonald for samples of the methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosides, and Mr. G. Bigam (University of Alberta) for spectral services.

REFERENCES

1 R. U. LEMIEUX AND J. D. STEVENS, *Can. J. Chem.*, 44 (1966) 249.
2 S. FURBERG, *Acta Chem. Scand.*, 14 (1960) 1357.
3 R. U. LEMIEUX, R. K. KULLNIG, AND R. Y. MOIR, *J. Amer. Chem. Soc.*, 80 (1958) 2237.
4 R. U. LEMIEUX, in P. DE MAYO (Ed.), *Molecular Rearrangements*, Interscience, New York, 1964, Part 2, pp. 735 and 737.
5 S. J. ANGYAL, *Aust. J. Chem.*, 21 (1968) 2737.
6 R. U. LEMIEUX, A. A. PAVIA, J. C. MARTIN, AND K. A. WATANABE, *Can. J. Chem.*, 47 (1969) 4427.
7 J. S. BRIMACOMBE, A. B. FOSTER, M. STACEY, AND D. H. WHIFFEN, *Tetrahedron*, 4 (1958) 351.
8 F. A. L. ANET, *J. Amer. Chem. Soc.*, 84 (1962) 1053.
9 R. U. LEMIEUX AND S. LEVINE, *Can. J. Chem.*, 42 (1964) 1473.
10 R. U. LEMIEUX AND A. A. PAVIA, *Can. J. Chem.*, 46 (1968) 1453.
11 M. HOFFER, *Chem. Ber.*, 93 (1960) 2777.
12 D. L. MACDONALD AND H. G. FLETCHER, JR., *J. Amer. Chem. Soc.*, 84 (1962) 1262.
13 R. U. LEMIEUX AND M. HOFFER, *Can. J. Chem.*, 39 (1961) 110.
14 N. J. LEONARD, F. C. SCIAVOLINO, AND V. NAIR, *J. Org. Chem.*, 33 (1968) 3169.
15 R. U. LEMIEUX, *Can. J. Chem.*, 39 (1961) 116.
16 H. S. ISBELL AND C. W. R. WADE, *J. Res. Nat. Bur. Stand., A*, 71 (1967) 137.
17 W. PIGMAN, in W. PIGMAN (Ed.), *The Carbohydrates — Chemistry, Biochemistry, Physiology*, Academic Press, New York, 1957, pp. 49–57; W. PIGMAN AND H. S. ISBELL, *Advan. Carbohyd. Chem.*, 23 (1968) 11; H. S. ISBELL AND W. PIGMAN, *Advan. Carbohyd. Chem. Biochem.*, 24 (1969) 13.
18 B. CAPON, *Quart. Rev.* (London), 18 (1964) 45.
19 E. L. ELIEL, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, p. 198.
20 C. T. BISHOP AND F. P. COOPER, *Can. J. Chem.*, 41 (1963) 2743.
21 R. BARKER, *J. Org. Chem.*, 35 (1970) 461.
22 D. D. HEARD, B. G. HUDSON, AND R. BARKER, *J. Org. Chem.*, 35 (1970) 464.

23 B. C. CHALLIS, F. A. LONG, AND Y. POCKER, *J. Chem. Soc.*, (1957) 4679.
24 R. E. DERIAZ, W. G. OVEREND, M. STACEY, E. G. TEECE, AND L. F. WIGGINS, *J. Chem. Soc.*, (1949) 1879.
25 H. ZINNER, H. NIMZ, AND E. WITTENBURG, *Chem. Ber.*, 93 (1960) 340.
26 D. H. WHIFFEN, *Chem. Ind.* (London), (1956) 964.
27 J. H. BREWSTER, *J. Amer. Chem. Soc.*, 81 (1959) 5483.
28 R. U. LEMIEUX AND J. C. MARTIN, *Carbohyd. Res.*, 13 (1970) 139.
29 R. U. LEMIEUX AND A. A. PAVIA, *Can. J. Chem.*, 47 (1969) 4441.
30 H. W. DIEHL AND H. G. FLETCHER, JR., *Arch. Biochem. Biophys.*, 78 (1958) 386.