Conformational Studies on Pyranoid Sugar Derivatives. The Conformational Equilibria of the D-Aldopentopyranose Tetraacetates and Tetrabenzoates[1-3]

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Equilibria between chair conformers in solution have been measured in acetone-d_6 by the nmr method of averaging of spin couplings for the aldopentopyranose tetraacetates having the α-D-*ribo* (**1**), β-D-*ribo* (**2**), α-D-*arabino* (**3**), β-D-*arabino* (**4**), α-D-*xylo* (**5**), β-D-*xylo* (**6**), α-D-*lyxo* (**7**), and β-D-*lyxo* (**8**) configurations, and also for the corresponding tetrabenzoates (**9**–**16**). Conformational homogeneity was observed only for **4** (*1C*) and **5** (*C1*) and the corresponding benzoates; the other examples have substantial (>5%) contribution from the less favored chair conformer. In most examples the tetrabenzoates have more of that chair conformer having the 1 substituent axial than the corresponding tetraacetates. The effect of change of temperature on the position of the conformational equilibria in acetone-d_6 was examined in all 16 examples. The rate of conformational inversion at various temperatures was determined for compound **8** and compared with data for compound **2**. Changes in polarity of the solvent do not affect in any regular way the position of the conformational equilibria. The equilibrium data observed cannot be accommodated within the framework of existing interpretations based on additive contributions of steric and polar interactions for polysubstituted six-membered rings, except on a very broad, qualitative basis. Analogs of **2**, **3**, **6**, and **7** specifically deuterated in the 1-acetoxy group were synthesized and the effect of solvent on the position of the 1-OAc nmr signal was studied. Configurational equilibria for anomeric interconversion of the acetylated pentopyranoses were measured and found in good agreement with literature values except for the lyxose derivatives.

The use of high-resolution nmr spectroscopy for conformational analysis of substituted tetrahydropyran ring systems was initiated by Lemieux and coworkers.[13] They concluded that for six-membered compounds (1) axial protons usually resonate at higher field than equatorial protons in chemically similar environments, (2) the spin–spin coupling constant between vicinal, antiparallel protons is about 2–3 times larger than that between gauche-disposed protons, (3) axial acetyl methyl protons usually resonate at lower field than equatorial acetyl methyl protons. These considerations permitted the assignment of favored conformations to various aldopyranoses and their derivatives, including several of the peracylated aldopentopyranoses that form the subject of the present work.

The α anomer has been observed to be more stable than the β anomer in anomerically equilibrated mixtures of methyl D-glucopyranosides,[14] penta-*O*-acetyl-D-glucopyranoses,[15] and peracetylated D-glucopyranosyl halides,[16] even though the C-1 substituent is axial in the α anomer. This predisposition of a polar substituent at C-1 of a pyranose ring for the axial orientation, contrary to expectations based on steric considerations, has been termed[17] the "anomeric effect." The phenomenon has been attributed by Edward[18] to an unfavorable dipole–dipole interaction between the carbon–oxygen bonds of the ring and the bond from the anomeric carbon atom to the equatorial polar substituent. Lemieux and Chü[17] have interpreted the effect in terms of an electrostatic interaction between the C-1 substituent and C-5–O-5 bonds.

From data accumulated on the anomeric equilibria of certain peracetylated aldopyranoses in 1:1 acetic acid–acetic anhydride with perchloric acid as the catalyst, and an estimated value for the conformational equilibrium of β-L-arabinopyranose tetraacetate in chloroform solution, Lemieux and Chü proposed a quantitative magnitude of 1.3 kcal mol^{-1} for the anomeric effect of the acetoxy group in the pentoses and 1.5 kcal mol^{-1} in the hexoses.[17] A value of 1.35 kcal mol^{-1} was proposed by Anderson and Sepp[19] for the anomeric effect of the acetoxy group in 2-acetoxy-4-methyltetrahydropyran in acetic acid. From their equilibrium data Lemieux and Chü also estimated values for the various nonbonded interactions present in a pyranoid ring.

Advances in nmr instrumentation permitted Lemieux and Stevens to investigate in greater detail the spectra of pyranoid carbohydrate derivatives.[20] The favored conformations of six aldopentopyranose tetraacetates in chloroform solution near room temperature were determined from chemical-shift and spin-coupling data. The observed conformations were in satisfactory agreement with those predicted by summation of the estimated nonbonded interaction energies of the individual groups.[17] The aldopentopyranose tetraacetates were considered to exist almost entirely in the *C1*(D) conformation, except for the β-D-*ribo* derivative

(1) For previous papers in this series, see ref 4–10.
(2) For preliminary reports of parts of this work, see ref 5–7.
(3) Supported in part by Grant No. GP-9646 from the National Science Foundation.
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(11) NDEA Fellow, 1966–1969.
(12) To whom inquiries should be addressed.
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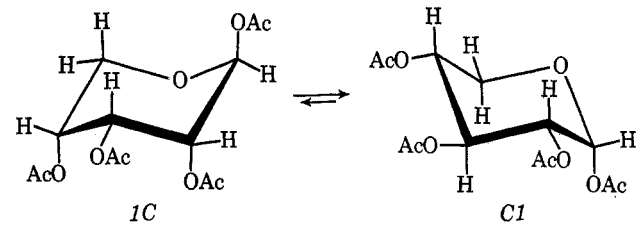

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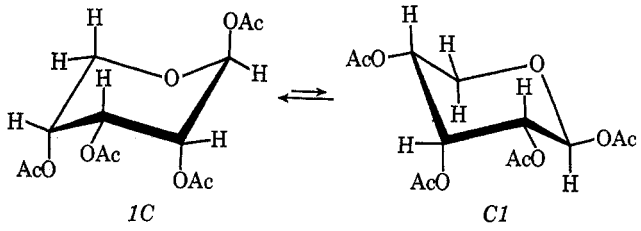
α-D-*ribo*



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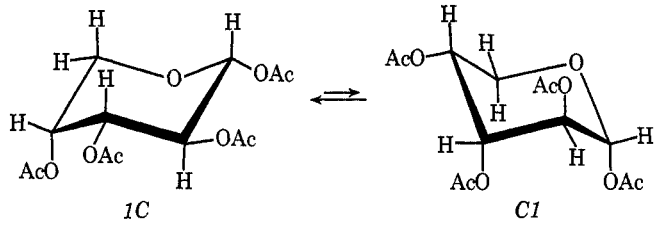

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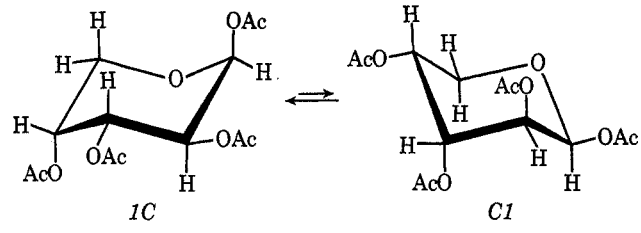
α-D-*arabino*



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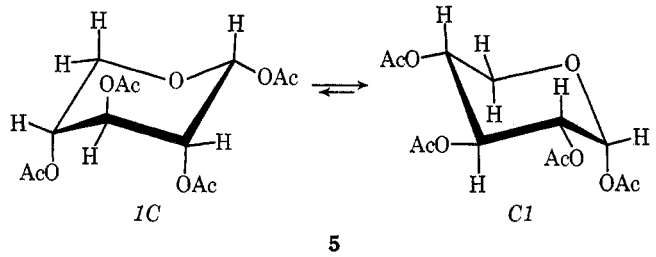
β-D-*arabino*



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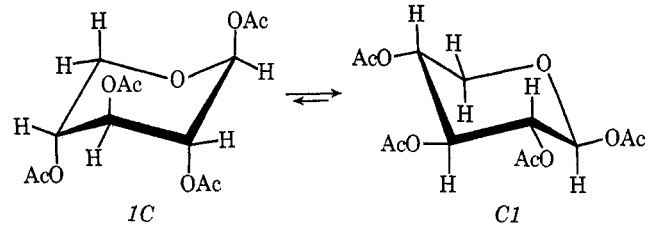

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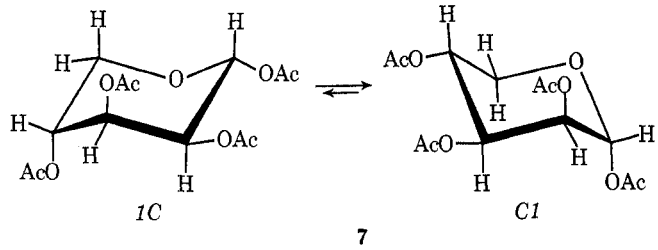

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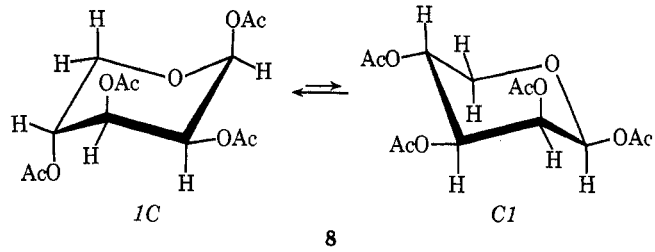

8
β-D-*lyxo*

which appeared to contain substantial proportions of each chair form and the β-L-*arabino* derivative[17] which contained about 80% of the *C1*(L) conformation. 2-Deoxy-β-D-*erythro*-pentopyranose triacetate was found to exist mainly in the *1C* conformation.

Conformational studies on various peracylated D-ribopyranoses were also made by Coxon.[21] β-D-Ribopyranose tetrabenzoate (**10**) in chloroform solution near room temperature was reported to exist in a 2:1 equilibrium of the *1C* and *C1* chair forms, whereas the α-D anomer (**9**) existed primarily in the *C1* conformation. The anomeric effect was invoked as the principal factor determining these differences in conformational distribution. Work done elsewhere showed that 2-deoxy-β-D-*erythro*-pentopyranose tribenzoate, whose *1C* conformation does not have the unfavorable syn-diaxial interaction between benzoyloxy groups at C-2 and C-4, exists almost exclusively in that conformation.[22]

That pyranoid sugar derivatives can indeed exist in rapid conformational equilibrium at room temperature (as do cyclohexane and some of its derivatives) was firmly established from the observation of the separate chair conformers of β-D-ribopyranose tetraacetate (**2**) in acetone-d_6 by low-temperature nmr spectroscopy.[8,10] The observed data indicate that **2** exists at room temperature as a mixture of conformers undergoing rapid interconversion and that at −84°, where the interconversion is slow on the nmr time scale, the *1C* and *C1* conformers are present in a 2:1 proportion. Nmr data for α-D-lyxopyranose tetraacetate (**7**) in acetone-d_6 indicate the *C1* form as the major chair conformer present at equilibrium near room temperature.[10]

A general program in this laboratory is concerned with determination of favored conformations, and conformational populations at equilibrium for polysubstituted tetrahydropyran ring systems, as provided by pyranoid sugar derivatives.[4-10,23] The determination of conformational equilibria for families of stereoisomeric, polysubstituted, cyclic compounds provides data useful for understanding and quantitatively interpreting the steric and electronic effects of multiple substituents on the conformations of ring systems. The

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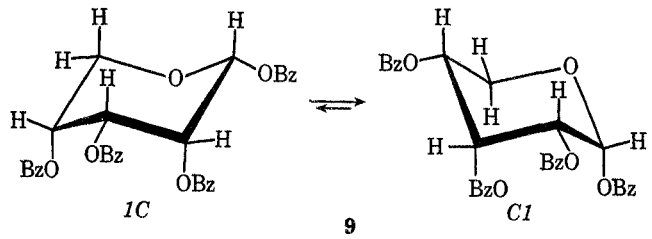
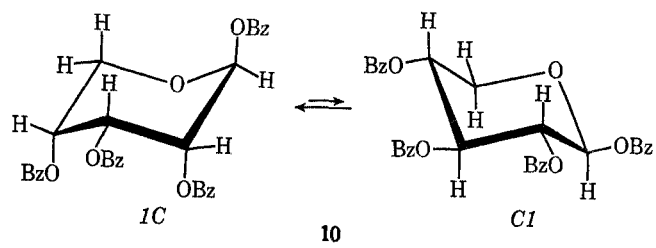
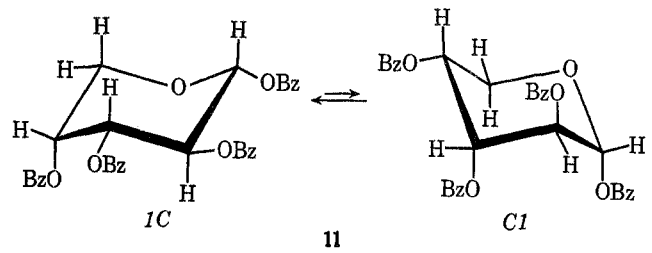
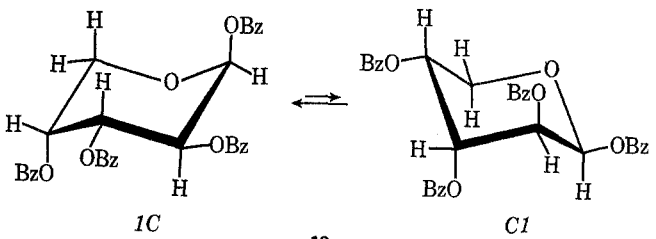
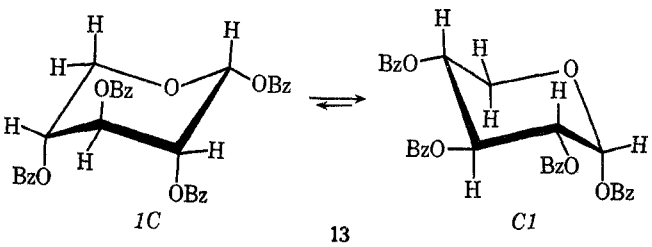
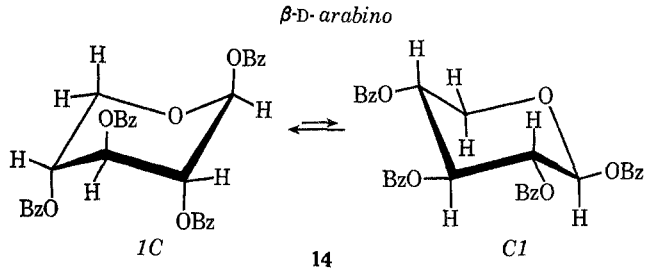


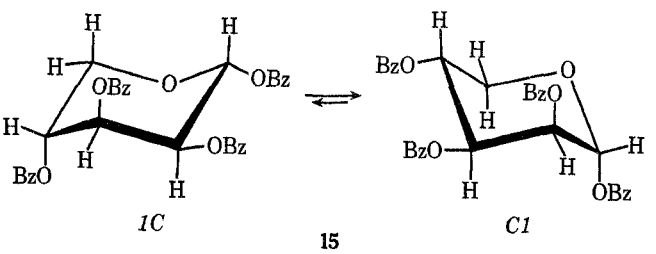


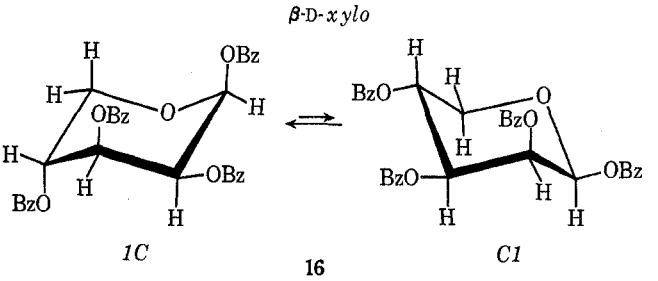






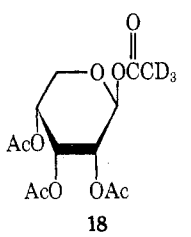


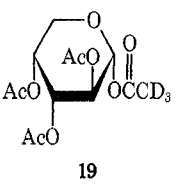


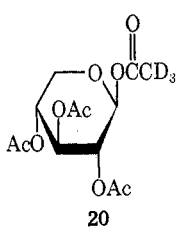


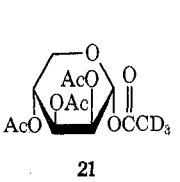
present work reports the measurement of the conformational equilibria in solution of the eight peracetylated D-aldopentopyranose sugars (**1**–**8**)[24] and the eight perbenzoylated D-aldopentopyranose sugars (**9**–**16**);[24] these represent all of the different stereochemical arrangements possible for a 2,3,4,5-tetraacetoxytetrahydropyran and a 2,3,4,5-tetrabenzoyloxytetrahydropyran (the L enantiomorphs would give identical equilibrium data).

Materials and Methods.—The eight D-aldopentopyranose tetraacetates (**1**–**8**) were prepared by previously established procedures and had physical constants in good agreement with the literature values (see Experimental Section). Seven of the eight D-aldopentopyranose tetrabenzoates (**9**–**16**) were also prepared by known methods and again their physical constants were in good agreement with literature values. α-D-Ribopyranose tetrabenzoate[25] (**9**) was obtained anomerically pure for the first time as an amorphous glass by column chromatography on silica gel of an α,β mixture obtained from the preparation of β-D-ribopyranose tetrabenzoate (**10**). The pure α-D anomer gave a satisfactory elemental analysis and its 100-









MHz spectrum in chloroform was identical with that obtained by Coxon by electronic subtraction of the spectrum of **10** from that of the mixture of α and β anomers by use of computer of average transients.[21] β-D-Ribopyranose tetra-*p*-toluate (**17**) was prepared by the procedure of Zinner and Belau[26] and had physical constants in good agreement with the reported values. The tetraacetates, specifically deuterated in the 1-acetyl methyl group, having the β-D-*ribo* (**18**), α-D-

(24) The results reported here for these two configurational series represent a refinement of the data given in ref 7 and 6, respectively.

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TABLE I

CHEMICAL SHIFT DATA FOR PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°[a]

Compd	Configuration	Chemical shifts,[b] H-1	H-2	H-3	H-4	H-5[c]	H-5'[c]	Acetyl methyl
1	α-D-*ribo*	3.92 d	4.85 t	4.42 t	4.92 m	5.99 q	6.26 o	7.88, 7.90, 8.00, 8.01
2	β-D-*ribo*	4.04 d	5.00 sp	4.54 t	4.86 m	5.90 q	6.16 q	7.89, 7.94, 7.95, 7.97
2	β-D-*ribo*[d,e]	3.75 d	4.81 o	4.43 t	4.97 m	6.30 d[f]		8.25, 8.27, 8.30, 8.37
2	β-D-*ribo*[g]	3.96 d	4.96 o	4.50 t	4.85 m	5.95 q	6.13 q	7.876, 7.907, 7.916, 7.923[h]
3	α-D-*arabino*	4.27 m		4.72–4.83 m		6.04 m		7.91, 7.93, 7.98, 8.02
3	α-D-*arabino*[d]	4.19 d	4.45 m	4.74–4.86 m		6.26 qn	6.70 qn	8.24, 8.27, 8.31, 8.32
3	α-D-*arabino*[g]	4.32 d	4.72 q	4.89 q	4.71 m	5.96 q	6.23 q	7.87, 7.89, 7.94, 7.97
4	β-D-*arabino*	3.73 d	4.79 o	4.68 m	4.65 m	5.82 q	6.21 q	7.85, 7.89, 8.01, 8.04
5	α-D-*xylo*	4.29 d	5.01 q	4.56 t	4.99 o	6.10 q	6.30 t	7.83, 7.99, 8.00, 8.02
6	β-D-*xylo*	4.22 d	5.04 q	4.74 t	5.07 m	5.89 q	6.38 q	7.936, 7.985, 7.992, 8.000[h]
6	β-D-*xylo*[d,i]	4.16 m	4.77 m	4.66 t	5.01 m	6.15 q	6.90 q	8.29, 8.31, 8.37, 8.39
6	β-D-*xylo*[g]	4.26 d	4.98 m	4.78 t	5.04 m	5.86 q	6.48 q	7.903, 7.947, 7.959[h,j]
7	α-D-*lyxo*	4.05 d	4.81 t	4.69 q	4.88 sx	6.04 q	6.29 q	7.85, 7.90, 7.96, 8.00
7	α-D-*lyxo*[d]	3.82 d	4.56 t	4.45 q	4.67 sx	6.09 q	6.38 q	8.25, 8.29, 8.33, 8.36
7	α-D-*lyxo*[g]	4.00 d	4.75 t	4.62 q	4.81 sx	5.99 q	6.31 q	7.85, 7.88, 7.94, 7.96
8	β-D-*lyxo*	3.94 t	3.68–3.78 m		5.01 m	5.82 q	6.38 sx	7.91, 7.93, 7.94, 7.97

[a] Data taken from spectra measured at 100 MHz at a sweep width of 500 Hz. [b] Observed multiplicities: d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; sp, septet; o, octet; m, complex multiplet. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] In benzene-d_6. [e] Measured at 15% (w/v) concentration. [f] AB portion of a deceptively simple ABX system. [g] In chloroform-*d*. [h] Measured at 50-Hz sweep width. [i] Measured at 10% (w/v) concentration. [j] Six-proton singlet.

TABLE II

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Coupling constants,[a] Hz $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$[b,c]	$J_{4,5'}$[b,c]	$J_{5,5'}$
1	α-D-*ribo*[d]	3.6	3.3	3.2	9.3	4.7	−11.2
2	β-D-*ribo*[e]	4.6	3.5	3.4	3.4	5.8	−12.4
2	β-D-*ribo*[e–g]	5.0	3.3	3.3	*h*, *i*	*h*, *i*	*h*, *i*
2	β-D-*ribo*[e,i]	4.7	3.4	3.3	3.4	5.9	−12.5
3	α-D-*arabino*	*h*	*h*	*h*	*h*	*h*	*h*
3	α-D-*arabino*[f]	7.0	*h*	*h*	3.0	1.7	−13.0
3	α-D-*arabino*[i]	6.4	9.0	3.2	3.6	2.0	−13.0
4	β-D-*arabino*	2.9	11.8	3.0	1.0	1.9	−13.2
5	α-D-*xylo*	3.5	9.8	9.6	5.5	11.6	−11.2
6	β-D-*xylo*	6.7	8.1	8.1	4.9	8.8	−11.8
6	β-D-*xylo*[f,k]	7.0	8.2	8.1	5.1	8.4	−11.8
6	β-D-*xylo*[i]	6.6	8.1	7.9	4.5	8.5	−12.0
7	α-D-*lyxo*	3.0	3.4	9.0	4.4	8.7	−11.6
7	α-D-*lyxo*[f]	3.2	3.3	8.8	4.5	8.5	−11.5
7	α-D-*lyxo*[i]	3.1	3.4	9.0	4.5	8.6	−11.5
8	β-D-*lyxo*[l]	2.5	*h*	*h*	3.3	5.4	−12.4

[a] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b] Coupling constants calculated by ABX analysis. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] $J_{3,5}$ = 0.8 Hz. [e] $J_{2,4}$ = 0.7 Hz. [f] In benzene-d_6. [g] Measured at 15% (w/v) concentration. [h] First-order couplings not observed. [i] Deceptively simple ABX system. [j] In chloroform-*d*. [k] Measured at 10% (w/v) concentration. [l] $J_{3,5}$ = 0.6 Hz.

arabino (**19**), β-D-*xylo* (**20**), and α-D-*lyxo* (**21**) configurations, were prepared by treating a solution of the appropriate aldopentopyranosyl chloride or bromide in acetonitrile with deuterated silver acetate.

The nmr spectra were measured at 100 MHz on 20% (w/v) solutions (unless otherwise indicated) of the freshly prepared compounds in the appropriate deuterated solvent containing 5% of tetramethylsilane. The chemical shifts recorded are given on the τ scale and were obtained by analysis of the spectra on a first-order basis and are considered accurate to within ±0.005 ppm. The time-averaged $J_{4,5}$ and $J_{4,5'}$ spin couplings employed in the calculation of conformational populations were obtained by ABX analysis[27] of spectra measured at 100-Hz sweep width. The values reported are considered accurate to within ± 0.1 Hz. All other coupling constants recorded were obtained on a first-order basis as direct peak spacings from spectra measured at a sweep width of 100 Hz, and are considered precise to within ± 0.1 Hz. The values reported are considered accurate to ±0.1 Hz. Spectral data for the 21 compounds are tabulated in Tables I–IX. Nmr spectra for compounds **13**, **14**, **15**, and **17** are given in Figures 1–4, respectively.

For each of the sugar acetates (**1**–**8**) and benzoates (**9**–**16**) in acetone-d_6 at 31°, the nmr spectral method of averaging of spin coupling[28] was used, by procedures already detailed,[6–8] to determine the proportions of the *1C*(D) and *C1*(D) conformers present at equilibrium.

(27) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 105–113.

(28) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962); H. Feltkamp and N. C. Franklin, *ibid.*, **87**, 1616 (1965); see also G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, **31**, 544 (1966); Y. Pan and J. B. Stothers, *Can. J. Chem.*, **45**, 2943 (1967); G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **33**, 2572 (1968).

TABLE III
CHEMICAL SHIFT DATA FOR PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°[a]

Compd	Configuration	Chemical shifts,[b] H-1	H-2	H-3	H-4	H-5[c]	H-5'[c]	Benzoyl
9	α-D-*ribo*	3.28 d	4.13 t	3.67 t	4.29 o	5.39 q	5.77 o	1.84–2.76
10	β-D-*ribo*	3.30 d	4.17 t	3.82 t	4.18 m	5.35 q	5.66 q	1.75–2.73
11	α-D-*arabino*[d]	3.70 d		3.94–4.25 m		5.55 q	5.85 q	1.90–2.78
12	β-D-*arabino*	3.04 d	3.87 q	3.74 q	3.98 m	5.27 q	5.73 q	1.71–2.78
13	α-D-*xylo*	3.13 d	4.22 q	3.63 t	4.28 sx	5.59 q	5.73 t	1.75–2.77
14	β-D-*xylo*[e]	3.54 d	4.31 q	4.02 t	4.48 sx	5.36 q	5.86 q	1.91–2.72
15	α-D-*lyxo*	3.36 d	4.00 t	3.83 q	4.12 sx	5.52 q	5.72 q	1.74–2.72
16	β-D-*lyxo*	3.25 q	4.01 t	3.93 m	4.36 m	5.23 q	5.86 o	1.81–2.73
17	β-D-*ribo* tetra-*p*-toluate[f]	3.35 d	4.24 t	3.85 t	4.25 m	5.42 q	5.71 q	1.90–2.89

[a] Data taken from spectra measured at 100 MHz. [b] Observed multiplicities: d, doublet; t, triplet; q, quartet; sx, sextet; o, octet; m, complex multiplet. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] In chloroform-*d*. [e] Measured at 10% (w/v) concentration. [f] *p*-Me: 7.61, 7.64 (6-proton singlet), 7.68.

TABLE IV
COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Coupling constants,[a] Hz $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$[b,c]	$J_{4,5'}$[b,c]	$J_{5,5'}$
9	α-D-*ribo*[d]	3.6	3.3	3.2	9.0	4.6	−11.4
10	β-D-*ribo*	3.1	3.8	3.7	2.3	3.9	−12.9
11	α-D-*arabino*[e]	5.1	*f*	*f*	4.6	2.1	−12.7
12	β-D-*arabino*	3.3	10.7	3.4	0.8	2.0	−13.3
13	α-D-*xylo*	3.6	9.9	9.7	5.9	11.8	−11.0
14	β-D-*xylo*[g]	5.1	6.7	6.6	4.0	6.6	−12.3
15	α-D-*lyxo*	3.1	3.3	9.0	4.6	9.1	−11.7
16	β-D-*lyxo*[h]	3.0	3.6	*e*	2.4	3.8	−12.9
17	β-D-*ribo* tetra-*p*-toluate	3.6	3.9	3.8	2.7	4.4	−12.9

[a] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b] Coupling constants calculated by ABX analysis. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] $J_{3,5}$ = 0.6 Hz. [e] In chloroform-*d*. [f] First-order couplings not observed. [g] Measured at 10% (w/v) concentration. [h] $J_{1,3}$ = 0.7 Hz; $J_{3,5}$ = 0.6 Hz.

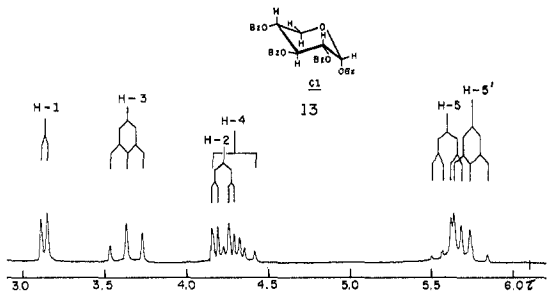


Figure 1.—Partial nmr spectrum of α-D-xylopyranose tetrabenzoate (**13**) at 100 MHz in acetone-d_6.

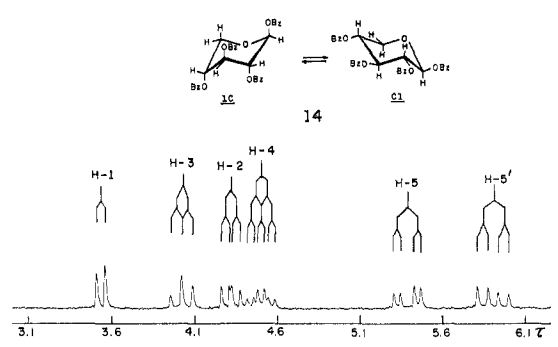


Figure 2.—Partial nmr spectrum of β-D-xylopyranose tetrabenzoate (**14**) at 100 MHz in acetone-d_6.

Chloroform-*d* was used as solvent with compounds **3** and **11** in order to obtain easily interpreted spectra.

Analysis of the signals of H-4 and the two protons at C-5 as ABX spin systems[27] gave $J_{4,5}$ and $J_{4,5'}$ values for the peracetylated (**1–8**) and perbenzoylated (**9–16**) aldopentopyranose sugars that are weighted time

TABLE V
RATE OF CONFORMATIONAL INVERSION FOR β-D-RIBOPYRANOSE TETRAACETATE (**2**) AND β-D-LYXOPYRANOSE TETRAACETATE (**8**) IN ACETONE-d_6 AT VARIOUS TEMPERATURES

Compd	Spectrometer frequency, MHz	Coalescence temp (T_c), °C	Rate of conformational inversion (k), sec^{-1} at T_c $1C \rightarrow C1$	$C1 \rightarrow 1C$
2	220	−60	57	117
	100	−68	25	51
	60	−73	14	29
8	100	−82	38	25

TABLE VI
TEMPERATURE DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-RIBOPYRANOSE TETRABENZOATE (**10**) AND β-D-XYLOPYRANOSE TETRABENZOATE (**14**) IN CHLOROFORM-*d*

Compd	Temp,[a] °C	$J_{1,2}$,[b] Hz
10	+59	3.5
	+42	3.4
	+6	3.0
	−23	2.7
	−46	2.3
14	+67	4.5
	+36	4.2
	−5	3.9
	−29	3.4
	−48	3.0

[a] ±2°. [b] A decrease in the coupling indicates a shift in the equilibrium position toward the $1C$(D) conformation.

TABLE VII

SOLVENT DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-RIBOPYRANOSE TETRAACETATE (2) AT 31°

Solvent	ϵ[a]	$J_{1,2}$,[b] Hz
CCl_4	2.2	5.5
C_6D_6	2.3	5.0
$C_6D_5CD_3$	2.4	5.3
$CDCl_3$	4.8	4.7
C_5D_5N	12.3	4.5
$(CD_3)_2CO$	20.7	4.6
CD_3CN	37.5	4.5
$(CCl_3)_2CO$		5.2

[a] Values taken from A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951. [b] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz.

TABLE VIII

SOLVENT DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-XYLOPYRANOSE TETRABENZOATE (14) AT 29°

		Coupling constants,[a] Hz	
Solvent	ϵ[b]	$J_{1,2}$	$J_{2,3}$
C_6D_6	2.3	5.0	6.7
$C_6D_5CD_3$	2.4	5.2	6.9
$CDCl_3$	4.8	4.3	5.9
C_5D_5N	12.3	4.3	5.9
$(CD_3)_2CO$	20.7	5.1	6.7
$(CD_3)_2SO$	48.9	5.3	6.9
$(CCl_3)_2CO$		4.1	5.7

[a] Values taken from A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951. [b] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz.

TABLE IX

CHEMICAL SHIFTS OF 1-ACETYL METHYL GROUPS IN β-D-RIBOPYRANOSE (2), α-D-ARABINOPYRANOSE (3), β-D-XYLOPYRANOSE (6), AND α-D-LYXOPYRANOSE (7) TETRAACETATES, AS ASSIGNED BY SYNTHESIS OF SPECIFICALLY DEUTERATED DERIVATIVES

	Chemical shifts (τ) of 1-acetyl group signals			
Solvent	2	3	6	7
Chloroform-*d*	7.876[a]	7.89	7.903[a]	7.85
Acetone-d_6	7.89	7.93	7.936[a]	7.85
Benzene-d_6	8.37	8.31	8.37	8.36

[a] Measured at 50-Hz sweep width.

averages for the two chair confromers in rapid equilibrium. Conformational populations at 31° were determined from the observed coupling of H-4 with the trans-disposed proton at C-5, taken in conjunction with values for $J_{4e,5e}$ and $J_{4a,5a}$ that had been obtained from model compounds. The model compounds chosen for $J_{4a,5a}$ were α-D-xylopyranose tetraacetate (**5**) and tetrabenzoate (**13**). The vicinal spin couplings for these two derivatives remained unchanged as the temperature was lowered to −50°, and it was thus concluded that both **5** and **13** were essentially all in the *C1*(D) conformation at 31°. Accordingly, the $J_{4,5a}$ value of 11.6 Hz measured for **5** was taken as the magnitude of $J_{4a,5a}$ for each sugar acetate and the $J_{4,5a}$ of 11.8 Hz for **13** as the magnitude of $J_{4a,5a}$ for each benzoate. The model compounds chosen for $J_{4e,5e}$ were β-D-arabinopyranose tetraacetate (**4**) and tetrabenzoate (**12**). The $J_{4,5'}$ values for both compounds decreased to a limit of 1.5 Hz at low temperatures, and this value was used throughout as the magnitude of $J_{4e,5e}$ for each sugar

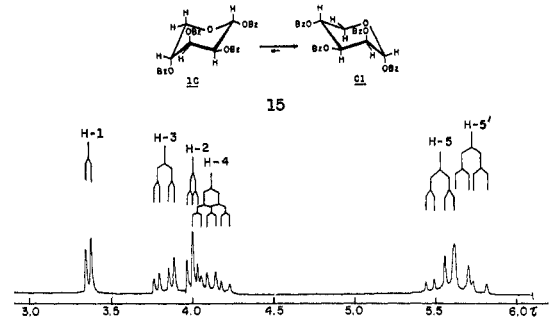


Figure 3.—Partial nmr spectrum of α-D-lyxopyranose tetrabenzoate (**15**) at 100 MHz in acetone-d_6.

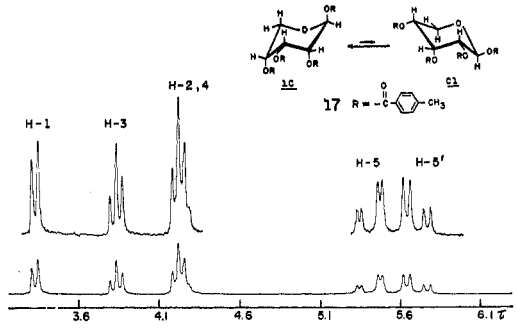


Figure 4.—Partial nmr spectrum of β-D-ribopyranose tetra-*p*-toluate (**17**) at 100 MHz in acetone-d_6.

acetate and benzoate. The limits of accuracy for the calculations were determined from the uncertainty of ±0.1 Hz in the experimental values of the time-averaged couplings, in conjunction with a conservative estimate (±0.5 Hz) of the extent to which the "model" coupling values actually vary from the true couplings for the separate conformers of each compound. From the conformational populations determined from the spin-coupling data, the equilibrium constants (K) and free-energy differences ($\Delta G°$) for the *1C*(D) ⇄ *C1*(D) equilibria given in Tables X and XI were calculated.

Results and Discussion

Conformational Equilibrium near Room Temperature.—For the aldopentopyranose tetraacetates and tetrabenzoates in solution, a conformational equilibrium between the two chair forms, with an appreciable (10% or more) proportion of the less favored chair form, is the rule rather than the exception. Of the seventeen examples in Tables X and XI, only for the *α-xylo* configuration is the *C1*(D) conformer favored overwhelmingly, and only for the *β-arabino* configuration is the *1C*(D) conformer favored very strongly.

Inspection of the equilibrium constants listed in Tables X and XI reveals that, except for the *α-ribo* derivatives, the tetrabenzoates have a greater proportion of that chair conformer having the 1 substituent axial than the corresponding tetraacetates. Thus, β-D-xylopyranose tetraacetate (**6**) has approximately 72% of the *C1* form, whereas β-D-xylopyranose tetrabenzoate (**14**) has about an equal amount of each conformer ($\Delta\Delta G°$ = −0.59 kcal mol^{-1}). Also, α-D-arabinopyranose tetraacetate (**3**) has about 10% less of the *C1*(D) conformation at equilibrium than does the tetrabenzoate (**11**) ($\Delta\Delta G°$ = 0.30 kcal mol^{-1}). Furthermore, β-D-lyxopyranose tetraacetate (**8**) has 39% of the *C1*-

TABLE X

CONFORMATIONAL EQUILIBRIA OF PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Equilibrium data: % *C1*	% *1C*	$K = C1/1C$	$\Delta G°_{31}$, kcal mol^{-1} for *1C*(D) ⇄ *C1*(D)
1	α-D-*ribo*	77	23	3.4	−0.74 ± 0.33
2	β-D-*ribo*	43	57	0.74	+0.18 ± 0.26
3	α-D-*arabino*[a]	79	21	0.26	+0.81 ± 0.34
4	β-D-*arabino*	96	4	0.04	+1.9 ± 1.0
5	α-D-*xylo*	>98	<2	>50[b]	<−2.4
6	β-D-*xylo*	72	28	2.6	−0.58 ± 0.30
7	α-D-*lyxo*	71	29	2.5	−0.55 ± 0.30
8	β-D-*lyxo*	39	61	0.63	+0.28 ± 0.27

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°.

TABLE XI

CONFORMATIONAL EQUILIBRIA OF PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Equilibrium data: % *C1*	% *1C*	$K = C1/1C$	$\Delta G°_{31}$, kcal mol^{-1} for *1C*(D) ⇄ *C1*(D)
9	α-D-*ribo*	73	27	2.7	−0.60 ± 0.29
10	β-D-*ribo*	23	77	0.30	+0.72 ± 0.31
11	α-D-*arabino*[a]	30	70	0.43	+0.51 ± 0.28
12	β-D-*arabino*	5	95	0.05	+1.8 + 0.9
13	α-D-*xylo*	>98	<2	>50[b]	<−2.4
14	β-D-*xylo*[c]	49	51	0.98	+0.01 ± 0.21
15	α-D-*lyxo*	74	26	2.8	−0.63 ± 0.30
16	β-D-*lyxo*	22	78	0.29	+0.76 ± 0.32
17	β-D-*ribo* tetra-*p*-toluate	28	72	0.39	+0.57 ± 0.29

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°. [c] Measured at 10% (w/v) concentration.

(D) conformation, whereas the tetrabenzoate (**16**) has only 22% at equilibrium ($\Delta\Delta G°$ = −0.48 kcal mol^{-1}). Similar shifts of the equilibrium position, toward the chair conformation having the anomeric polar substituent axially disposed, in going from the tetraacetates to the tetrabenzoates were observed for the β-D-*ribo* ($\Delta\Delta G°$ = −0.54 kcal mol^{-1}) and α-D-*lyxo* ($\Delta\Delta G°$ = 0.08 kcal mol^{-1}) derivatives. The *α-xylo* and *β-arabino* derivatives are observed to have, within experimental error, the same conformational populations. It is evident from the $\Delta\Delta G°$ values that the changes in the conformational populations are dependent on the total stereochemistry of the derivative. These results accord with earlier observations[4] that the all-axial form of the tri-*O*-acyl-β-D-xylopyranosyl chlorides in chloroform-*d* is favored to the extent of ~80% with the acetate, but to >95% with the benzoate (see also ref 21, cited in ref 4). Similar results are evident from studies with alkyl tri-*O*-acylpentopyranosides[29a] and various other pentopyranose esters.[29a]

Shifts in the position of the conformational equilibria in comparing the tetraacetates with the tetrabenzoates evidently result from differences in the nonbonded syn-diaxial and gauche-vicinal interactions and/or electronic interactions in the two groups of derivatives. Differences in steric interactions should, however, not be significant since the conformational free energies ("*A*" values)[29b] at room temperature of the acetoxy and benzoyloxy groups are very similar, that of the benzoyloxy substituent being only 0.02 kcal mol^{-1} smaller. From an inspection of molecular models, differences in nonbonded gauche interactions are also anticipated to be minor. The observed differences in conformational populations must, therefore, be controlled mainly by the changes in the electronic forces that occur upon replacement of acetoxy by benzoyloxy groups. The magnitude of the anomeric effect of the benzoyloxy substituent should be slightly larger than that of the acetoxy group because of the greater electron-withdrawing ability of the benzoyl group, and replacement of the acetoxy groups at C-2, C-3, and C-4 with the more electronegative benzoyloxy substituents should result in an enhancement of the magnitude of the axial-directing effect exhibited by the polar group at C-1, as predicted from Lemieux's interpretation of the anomeric effect.[17,18] Such augmentation of the anomeric effect has been also observed in other pyranoid ring systems.[17,30] Enhancement[4,31] of polar contributions from substituents other than that at C-1 may also be a factor. The net effect of these changes in the electronic interactions would be to increase the equilibrium proportion for the perbenzoates of the chair conformation having the anomeric substituent in axial orientation, in accord with the observed shifts in the conformational equilibria for most of the examples, when the tetrabenzoates are compared with the tetraacetates.

The larger proportion of the *1C*(D) conformation at equilibrium for α-D-ribopyranose tetrabenzoate (**9**) than for the corresponding tetraacetate (**1**) ($\Delta\Delta G°$ = −0.14 kcal mol^{-1}), in the direction opposite to the shifts found for the other configurations, may be due in part to an attractive interaction between the syn-diaxial benzoyloxy groups at C-2 and C-4. That such attractive forces may actually be a factor is seen from the fact that the $\Delta\Delta G°$ values for the *β-xylo* and *β-ribo* derivatives, where substituents on O-2 and O-4 are syn

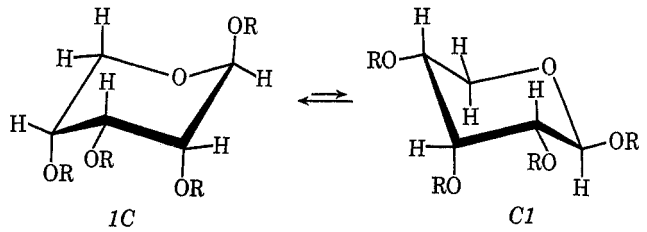
(29) (a) P. L. Durette and D. Horton, *Carbohyd. Res.*, **18**, 289, 389, 403, 419(1971); (b) F. A. L. Anet and P. M. Henrichs, *Tetrahedron Lett.*, 741 (1969).

(30) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1543 (1968).

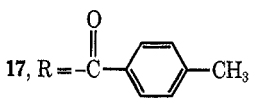
(31) G. Wood, E. P. Woo, and M. H. Miskow, *ibid.*, **47**, 429 (1969); C. B. Anderson, D. T. Sepp, M. P. Geis, and A. A. Roberts, *Chem. Ind. (London)*, 1805 (1968); R. D. Stolow, T. Groom, and P. D. McMaster, *Tetrahedron Lett.*, 5781 (1968); R. D. Stolow, T. W. Giants, and J. D. Roberts, *ibid.*, 5777 (1968).

diaxial in the *1C*(D) conformation, are larger than the values for the *α-arabino*, *α-lyxo*, and *β-lyxo* derivatives, where no such interactions are present in either conformer.

The conformational equilibrium at room temperature of β-D-ribopyranose tetra-*p*-toluate (**17**) in acetone-d_6 was also examined. The proportion of the *1C*(D) form



1C *C1*



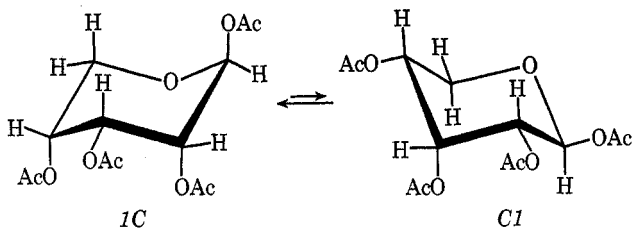
17, R = –C(=O)–C$_6$H$_4$–CH$_3$

$K = 0.39$

present at equilibrium was found to be intermediate between that for the corresponding tetraacetate (**2**) and tetrabenzoate (**10**), but, as expected, it was closer to the value for the tetrabenzoate. The observed shift in the equilibrium toward the *C1*(D) conformer for this derivative relative to the tetrabenzoate probably reflects a decrease in the magnitude of the axial-directing influence of the C-1 substituent as a result of the electron-donating effect of the substituted methyl groups on the aromatic rings.

Conformational Equilibrium and Rate of Conformational Inversion in Pyranoid Sugar Derivatives.—In the case of β-D-ribopyranose tetraacetate (**2**), it has already been shown[8,10] by low-temperature nmr spectroscopy in acetone-d_6 that it is possible to observe signals of the separate chair conformers because a substantial proportion of the minor conformer is present at −84°, a temperature at which conformational interconversion is slow on the nmr time scale. A similar "conformational freeze-out" was observed in the spectrum of β-D-lyxopyranose tetraacetate (**8**); at +2° the H-1 signal is a narrow doublet at τ 3.93, whereas at −97° separate signals at τ 4.00 and 3.81 are observed. The relative intensities of these signals give for the *1C*(D) ⇄ *C1*(D) equilibrium at −97° a $\Delta G°$ value of -0.14 ± 0.04 kcal mol^{-1}.

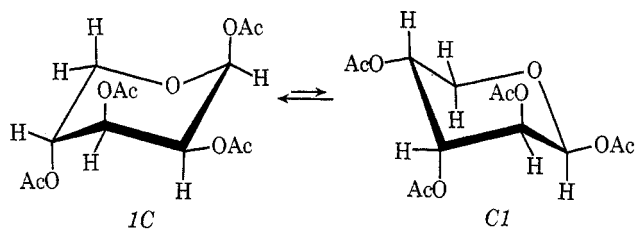
In previous papers on the conformational equilibria of aldopentopyranose tetraacetates,[7,8,10] we reported the frequencies with which one chair conformer of **2** and **8** undergoes ring flip to the alternative chair conformer, as calculated from the equation of Gutowsky and Holm,[32] $k = (\sqrt{2}/2)\pi|\nu_a - \nu_e|$, which relates the rate constant of conformational interconversion to the maximum separation of the signals of an individual proton at conformational "freeze-out." This relationship is strictly valid only when the equilibrium constant for the interconverting species is unity, but when the constant is close to unity, as with β-D-ribopyranose tetraacetate, the error in the calculated rate constant is small. A simple technique has been described[33] that is convenient for calculating rates of conformational interconversion for any two exchanging species at the "coalescence temperature" and thus, by using the Eyring equation, to calculate free energies of activation. Application of this method to the conformational equilibria of β-D-ribopyranose tetraacetate (**2**) and β-D-lyxopyranose tetraacetate (**8**), the only two pentose peracetates for which a conformational "freeze-out" has been detected at temperatures down to −100°, yields the rate data given in Table V and the following free energies of activation, assuming a transmission coefficient of unity.



1C *C1*

2

$K_{-84°} = C1/1C = 0.5$
$\Delta G^{\ddagger}_{1C \rightarrow C1} = 10.6 \pm 0.3$ kcal mol^{-1}
$\Delta G^{\ddagger}_{C1 \rightarrow 1C} = 10.3 \pm 0.3$ kcal mol^{-1}



1C *C1*

8

$K_{-97°} = C1/1C = 1.5$
$\Delta G^{\ddagger}_{1C \rightarrow C1} = 9.6 \pm 0.4$ kcal mol^{-1}
$\Delta G^{\ddagger}_{C1 \rightarrow 1C} = 9.8 \pm 0.4$ kcal mol^{-1}

Interestingly, the free energy differences ($\Delta G°$) for **2** and **8** measured at 31° differ from those measured at the temperature of "conformational freeze-out," indicating that the entropy difference, $\Delta S°$, between the two chair conformers does not equal zero. A similar observation was made previously for β-D-xylopyranose tetraacetate[8] (**6**). The entropy difference between the *1C*(D) and *C1*(D) conformations is positive for the β-D-*ribo* compound but is negative for both the β-D-*xylo* and β-D-*lyxo* derivatives.

In order to "freeze-out" a conformational equilibrium in a pyranoid sugar derivative and thus measure directly the conformational equilibrium constant and rate of ring flip, it is necessary to have (1) a reasonably concentrated (5–10%) solution that can be observed in the nmr spectrometer over a wide temperature range without crystallization of the solute, boiling or freezing of the solvent, or development of high viscosity in the solution that would lead to excessive line broadening and loss of necessary spectral detail; (2) a compound in which the proportion of the less favored conformer is sufficient for detection at the temperature of "conformational freeze-out;" and (3) the free energy of activation, $\Delta G^{\ddagger}$, for conformational inversion must be sufficiently large (rate of ring flip sufficiently small) for a "freeze-out" to be obtainable within the temperature limits of the variable temperature accessory of the nmr spectrometer (∼−150 → ∼200°).

Of the 16 aldopentopyranose tetraacetates and tetra-

(32) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 223.
(33) H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

benzoates investigated in the present work, only two have thus far yielded detectable "conformational freeze-outs" at temperatures down to −100°. β-D-Ribopyranose tetraacetate (**2**) and β-D-lyxopyranose tetraacetate (**8**) had a substantial proportion of the less favored chair form present at equilibrium at low temperatures and their free energies of activation (9.6–10.6 kcal mol^{-1}) were high enough to permit accurate determination of the equilibrium constants. The other six tetraacetates did not exhibit "freeze-outs" because at low temperatures the conformational equilibria favored one chair conformer strongly as a result of the shift of the equilibrium position toward the more stable conformation.

It was anticipated that, since β-D-xylopyranose tetrabenzoate (**14**) has an equal amount of each chair form present at equilibrium near room temperature, a "conformational freeze-out" would be detected at low temperatures. However, none was observed in a 1:1 mixture of acetone-d_6 and benzene-d_6 at temperatures down to −90°. That such was the case may be attributed to the high conformational mobility of this derivative even at low temperatures ($\Delta G^{\ddagger}$ <9 kcal mol^{-1}).

The higher rate of conformational interconversion of β-D-xylopyranose tetrabenzoate (**14**), as compared with that of **2** and **8**, is probably due to the presence of four substituents in axial orientation in the *1C*(D) conformation for **14** as compared with only three for **2** and **8**. Schmid and coworkers have shown[34] that, with the syn-diaxial arrangement of two or more methyl substituents on a cyclohexane ring, the relative energy of the transition state for conformational inversion is less markedly increased than is that of the ground state. This factor results in a decrease of the free energy of activation as compared with cyclohexane itself. A "freeze-out" should be observable, however, at temperatures below −100°.

An apparent "conformational freeze-out" was detected for α-D-arabinopyranose tetrabenzoate in a 2:1 mixture of chloroform-*d* and toluene-d_6. However, the spectral dispersion at 100 MHz was insufficient to allow specific assignment of signals.

Conformational Equilibrium and Its Temperature Dependence.—As the temperature is lowered by stages from room temperature, there is detected an increase in the equilibrium proportion of that chair conformer having the lower enthalpy. Which of the two chair forms has the lower enthalpy is not always evident from the equilibrium data at room temperature because the entropy difference ($\Delta S°$) between the two forms does not equal zero, and, therefore, to obtain this information, the equilibrium constant must be measured as a function of the temperature. For the equilibrium process, *1C*(D) ⇄ *C1*(D), a decrease in temperature will result in an increase in the proportion of the *C1*(D) conformation if the enthalpy difference ($\Delta H°$) is negative and an increase in the *1C*(D) form if the enthalpy difference is positive.

The effect of decreasing temperature on conformational population was investigated for the D-aldopentopyranose tetraacetates (**1–8**) and tetrabenzoates (**9–16**), and the results are presented in Table XII. The sign of the enthalpy difference is a function of not only the total stereochemistry of the sugar but also the nature of the substituents on the tetrahydropyran ring. A decrease in the temperature results in an increase in the conformational population of the *C1* form (negative $\Delta H°$) for both α-D-ribopyranose tetraacetate (**1**) and tetrabenzoate (**9**). On the other hand, whereas β-D-lyxopyranose tetraacetate (**8**) and β-D-xylopyranose tetraacetate (**6**) have a negative $\Delta H°$ value, the corresponding tetrabenzoates **16** and **14** have a postive $\Delta H°$ value. Finally, both α-D-arabinopyranose tetraacetate (**3**) and tetrabenzoate (**11**) have a positive value of $\Delta H°$. The differences in the sign of the enthalpy difference reflect the changes in the various steric and electronic interactions that occur in comparing the tetraacetates with the tetrabenzoates. Steric factors appear to control the direction of the enthalpy change for α-D-arabinopyranose tetraacetate (**3**) and tetrabenzoate (**11**), β-D-xylopyranose tetraacetate (**6**), and β-D-lyxopyranose tetraacetate (**8**) since the shift in the equilibrium position with decreasing temperature is toward the chair form having the anomeric substituent in equatorial orientation (unfavorable anomeric effect) but also having fewer syn-diaxial interactions. Electronic forces seem to be the determining factor for the tetrabenzoates **14** and **16**, since the equilibrium shift is now toward that conformer having the C-1 substituent axial (favorable anomeric effect). The remaining tetraacetates and tetrabenzoates all exhibit shifts toward that conformer having the anomeric group axial.

An interesting observation is that β-D-ribopyranose tetraacetate (**2**) has a negative enthalpy difference, even though the *1C*(D) conformer has a syn-diaxial interaction between two acetoxy groups. This illustrates the strong influence of the anomeric effect in directing the conformational stability of pyranose sugars having an acetoxy group at the anomeric position. However, the additional syn-diaxial interactions in the *1C*(D) conformation of **3**, **6**, and **8** are accompanied by a change in the sign of $\Delta H°$.

TABLE XII

EFFECT OF DECREASING TEMPERATURE ON THE CONFORMATIONAL EQUILIBRIA FOR THE PERACETYLATED AND PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6

Compd	Configuration	ΔH	ΔK (*C1*/*1C*)	Shift in equilibrium for *1C*(D) ⇄ *C1*(D)
1	α-D-*ribo* OAc_4	−	+	→
9	α-D-*ribo* OBz_4	−	+	→
2	β-D-*ribo* OAc_4	+	−	←
10	β-D-*ribo* OBz_4	+	−	←
3	α-D-*arabino* OAc_4[a]	+	−	←
11	α-D-*arabino* OBz_4[a]	+	−	←
4	β-D-*arabino* OAc_4	+	−	←
12	β-D-*arabino* OBz_4	+	−	←
5	α-D-*xylo* OAc_4	−	[b]	[b]
13	α-D-*xylo* OBz_4	−	[b]	[b]
6	β-D-*xylo* OAc_4	−	+	→
14	β-D-*xylo* OBz_4[a]	+	−	←
7	α-D-*lyxo* OAc_4[c]	−	+	→
15	α-D-*lyxo* OBz_4[d]	−	+	→
8	β-D-*lyxo* OAc_4	−	+	→
16	β-D-*lyxo* OBz_4[e]	+	−	←

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°. [c] $J_{1,2}$ = 3.0 Hz at +31°; 2.2 Hz at −51°. [d] $J_{1,2}$ = 3.1 Hz at +31°; 1.7 Hz at ∼−50°. [e] $J_{4,5'}$ = 3.8 Hz at +31°; 2.3 Hz at ∼−40°.

(34) H. G. Schmid, A. Jaeschke, H. Friebolin, S. Kabuss, and R. Mecke, *Org. Magn. Resonance*, **1**, 163 (1969).

The fact that **6** and **8** have ΔH° values of a different sign than **14** and **16** is an indication of the enhanced anomeric effect and other electronic interactions for the tetrabenzoates. In spite of these electronic factors, α-D-arabinopyranose tetrabenzoate still has a positive ΔH° value.

The temperature dependence of the $J_{1,2}$ coupling has been measured for β-D-xylopyranose tetraacetate (**6**) in acetone-d_6[8] and β-D-ribopyranose tetrabenzoate (**10**) and β-D-xylopyranose tetrabenzoate (**14**) in chloroform-*d*. The results for the latter two compounds are given in Table VI. For both tetrabenzoates there is observed a regular decrease in the magnitude of $J_{1,2}$, as would be expected from a shift in the equilibrium that would favor the *1C*(D) form (H-1 and H-2 diequatorial) increasingly at lower temperatures.

Conformational Equilibrium and Its Solvent Dependence.—That solvent polarity does not affect in any regular manner the position of conformational equilibria for tetrasubstituted tetrahydropyran ring systems is evident from a study of the solvent dependence of the conformational populations of β-D-ribopyranose tetraacetate[7] (**2**), β-D-xylopyranose tetrabenzoate[6] (**14**), and tri-*O*-acetyl-β-D-xylopyranosyl chloride.[4] In Table VII is given the $J_{1,2}$ coupling for **2** and in Table VIII the $J_{1,2}$ and $J_{2,3}$ couplings for **14** in various deuterated solvents as a function of the dielectric constant. These couplings provide a measure of the equilibrium constant since they represent a time average between a diaxial arrangement of the coupled protons in the *C1*(D) conformation and a diequatorial orientation in the alternative *1C*(D) conformation. As the solvent polarity was increased, there was not observed any regular increase in the vicinal spin couplings as would have been expected from an increase in the proportion of the *C1*(D) conformation having the anomeric substituent equatorial. Such a shift would have resulted had there been a decrease in the magnitude of the anomeric effect with increasing solvation of the interacting dipoles. Evidently, any solvation of the dipoles involved in the operation of the anomeric effect must be approximately cancelled by other effects resulting from change of solvent.

Similar observations have been made by Lemieux and coworkers from an examination of solvent effects on the conformational equilibrium of a monosubstituted tetrahydropyran[35] and a trisubstituted tetrahydropyran.[36]

Factors Influencing Conformational Stability.—Various empirical treatments have been advanced for predicting the conformational preferences of polysubstituted tetrahydropyran ring systems, based on additive contributions of steric interactions[37,38] and with the polar contribution of the anomeric effect.[17,39,40] The data presented in the present work cannot be accommodated within the framework of these existing interpretations except on a very broad, qualitative basis, even with adjustment of the magnitudes estimated for the various steric and polar elements. These results, and the observation of Lemieux and Pavia[36] that the magnitude of nonbonded interactions between atoms that have unshared pairs of electrons depends on the substituent on these atoms, point out the need for more accurate determinations of steric interactions by methods such as those reported by Wolfe and Campbell[41] and Tichý and coworkers[42] for the evaluation of syn–diaxial interactions, and that of Tichý and coworkers[43,44] and Aycard and coworkers[45] for the determination of vicinal–gauche interactions. Vicinal–gauche interactions in a tetrahydropyran ring may be expected to vary according to the position and configuration of the substituents because of the "nonideal" geometry of the heterocyclic ring and the consequent variations from the "ideal" values in the dihedral angles around the ring.

In addition, other factors, such as polar contributions from other than the C-1 substituent, attractive interactions between syn–diaxial substituents,[46] vicinal–gauche interactions,[44,45] and specific solvation effects such as hydrogen bonding and formation of charge–transfer complexes, must also be reconsidered in attempting to interpret quantitatively the conformational distributions of polysubstituted, six-membered ring systems, especially when a ring heteroatom is involved.

Assignment of 1-Acetyl Methyl Group Signals by Means of Specifically Deuterated Derivatives.—The nmr spectra in chloroform-*d* of the tetraacetates having the β-D-*ribo* (**2**), α-D-*arabino* (**3**), β-D-*xylo* (**6**), and α-D-*lyxo* (**7**) configurations were compared with those of the corresponding analogs **18**, **19**, **20**, and **21** that had been specifically deuterated in the 1-acetyl methyl group. The spectra of **18**, **19**, **20**, and **21** were identical in all respects with those of **2**, **3**, **6**, and **7**, respectively, except that one three-proton singlet in the spectra of the latter group was absent in those of the former, and this signal in **2**, **3**, **6**, and **7** could thus be assigned unambiguously to the 1-acetyl methyl group. The spectra of the deuterated derivatives were also measured in acetone-d_6 and in benzene-d_6. Assignments of the signals are given in Table IX. The signal of the 1-*O*-acetyl group is observed in chloroform-*d* and acetone-d_6 at lower field than all of the other acetoxy group signals for **2**, **6**, and **7**, but for the α-D-*arabino* derivative (**3**), the 1-acetoxy signal is observed at next to lowest field. Similar deuteration experiments have established that the 1-acetoxy group resonates at lower field than the other acetoxy groups in β-D-glucopyranose pentaacetate[47] in chloroform-*d* and in 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose[48] in chloroform-*d* and acetone-d_6. The present results show that, in nonaromatic solvents, the 1-

(35) R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, **47**, 4427 (1969).
(36) R. U. Lemieux and A. A. Pavia, *ibid.*, **47**, 4441 (1969).
(37) R. E. Reeves, *J. Amer. Chem. Soc.*, **72**, 1499 (1950); *Advan. Carbohyd. Chem.*, **6**, 107 (1951).
(38) R. B. Kelly, *Can. J. Chem.*, **35**, 149 (1957).
(39) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, Chapter 6, pp 375–377.
(40) S. J. Angyal, *Angew. Chem., Int. Ed. Engl.*, **8**, 157 (1969).
(41) S. Wolfe and J. R. Campbell, *Chem. Commun.*, 877 (1967).
(42) M. Tichý, A. Orahovats, and J. Sicher, *Collect. Czech. Chem. Commun.*, **35**, 459 (1970).
(43) J. Sicher and M. Tichý, *ibid.*, **32**, 3687 (1967).
(44) M. Tichý, S. Vašíčková, S. V. Arakelian, and J. Sicher, *ibid.*, **35**, 1522 (1970).
(45) J. P. Aycard, H. Bodot, R. Garnier, R. Lauricella, and G. Pouzard, *Org. Magn. Resonance*, **2**, 7 (1970).
(46) Reference 39, Chapter 2, p 46.
(47) K. Heyns, W-P. Trautwein, and F. G. Espinosa, *Angew. Chem., Int. Ed. Engl.*, **6**, 955 (1967).
(48) D. Horton, W. E. Mast, and K. D. Philips, *J. Org. Chem.*, **32**, 1471 (1967).

acetoxy group usually gives the lowest field, acetoxy group signal, but there are exceptions to this behavior.

The well-known upfield shift of acetate signals in nmr spectra caused by aromatic solvents[49] was also observed for **2**, **3**, **6**, and **7**. In all four cases these signals were detected ~0.4 ppm to higher field in benzene-d_6 than their positions in nonaromatic solvents. It is noteworthy that, when the spectra are measured in benzene-d_6, the signal of the 1-*O*-acetyl group for **2** and **7** is shifted to highest field and to second highest field position for **3** and **6**. These data may be useful for further studies concerning the orientation of the substituents, and molecules of the solvent sheath, with solutions in aromatic solvents.

Further Observations on Chemical Shifts.—The chemical shifts observed for the anomeric proton of each chair conformer of β-D-ribopyranose tetraacetate (**2**) at "conformational freeze-out" at −84° accord with the generalization[13,20] that axial protons usually resonate at higher field than equatorial protons in a similar chemical environment. By Lemieux's empirical rules[20] on the effect of configuration on chemical shift, the estimated value for chemical shift of H-1e is τ 3.85 (observed τ 3.93) and that for H-1a is τ 4.00 (observed τ 4.19). A similar correlation can be made for β-D-lyxopyranose tetraacetate (**8**) at −97°, where signals for both conformers are detected. The estimated value for the chemical shift of H-1e is τ 3.85 (observed τ 3.81) and that for H-1a is τ 4.05 (observed τ 4.00). Differences between the calculated and the observed values may be due in part to variation of the equatorial and axial proton resonances with temperature.[50]

The signals for the acetate protons of β-D-ribopyranose tetraacetate (**2**) at 31° comprised a simple, 4-line pattern having the chemical shifts given in Table I. At −84°, the temperature at which signals for the seprate chair conformers were observed, the acetate region became more complex, as expected, with the appearance of five broad signals at τ 7.79, 7.82, 7.84, 7.96, and 8.04. Low-temperature studies were performed on the analogous derivative specifically deuterated in the 1-acetyl methyl group (**18**) to determine whether the two higher field singlets corresponded to the 1-acetoxy groups of the *C1*(D) and *1C*(D) conformers of **2**. If such had been the case, integration of the signals would have provided another measure of the conformational equilibrium. However, at −84° these two signals were still present, indicating that signals of the 1-acetyl methyl groups are located in the overlapping, lower field band of signals.

Studies of Configurational Equilibria.—By equilibrating 15% (w/v) solutions of each of the D-aldopentopyranose tetraacetates (**1**–**8**) at 27° in 1:1 acetic anhydride–acetic acid, 0.1 *M* in perchloric acid, the α,β anomeric equilibria for the pairs **1** and **2**, **3** and **4**, **5** and **6**, and **7** and **8** were established. The compositions of these mixtures were determined by nmr spectroscopy and the equilibrium data are recorded in Table XIII. The data are in excellent agreement with literature values[17] (determined by optical rotatory methods) for the first three pairs. The equilibrium constant for the interconversion **7** ⇄ **8**, here determined as 0.20 at 27° by approach from both sides of the equilibrium, differs substantially from the value (0.08 at 25°) previously[17] reported.

TABLE XIII

ANOMERIC EQUILIBRIA OF D-ALDOPENTOPYRANOSE TETRAACETATES AT 27° IN 1:1 ACETIC ANHYDRIDE—ACETIC ACID, 0.1 *M* IN PERCHLORIC ACID

Anomeric pair	Equilibrium constant, $K = \beta/\alpha$	$\Delta G°$, kcal mol^{-1}, for $\alpha \rightleftarrows \beta$ at 27°
Tetra-*O*-acetyl-α,β-D-ribopyranose (**1** and **2**)	3.4	−0.73 ± 0.03
Tetra-*O*-acetyl-α,β-D-arabinopyranose (**3** and **4**)	5.4	−1.01 ± 0.03
Tetra-*O*-acetyl-α,β-D-xylopyranose (**5** and **6**)	0.23	+0.89 ± 0.03
Tetra-*O*-acetyl-α,β-D-lyxopyranose (**7** and **8**)	0.20	+0.98 ± 0.05

Experimental Section

General Methods.—Evaporations were performed below 50° under diminished pressure. Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer Model 141 polarimeter in a 1-dm, narrow-bore polarimeter tube. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137 spectrophotometer. Microanalyses were determined by W. N. Rond. Thin layer chromatography (tlc) was performed with 0.25-mm layers of silica gel G (E. Merck, Darmstadt, Germany) activated at 120° as the adsorbent and sulfuric acid as the indicator. Column chromatography was performed with silica gel (7734, Merck) as the adsorbent with 1 g of mixture to be separated per 30 g of adsorbent, and the components were eluted with the solvents specified.

Nmr Spectra.—Spectra were recorded at 100 MHz with a Varian HA-100 nmr spectrometer operating in the frequency-sweep mode at a probe temperature of 31 ± 1°. Unless otherwise noted, spectra were measured at a concentration of 20% (w/v). Solutions also contained 5% (w/v) of tetramethylsilane (τ 10.00) as an internal standard and to provide a lock signal. Variable-temperature measurements were made with a Varian V-4341/V-6057 variable-temperature accessory and a Varian V-6040 controller. Calibration in the low-temperature range was effected with a sample of methanol, and ethylene glycol was used for high-temperature calibration. The temperatures are considered accurate to within ±2°. Coupling constants for the equilibrium studies were obtained by second-order analysis of ABX spin systems from spectra recorded at a sweep width of 100 Hz; they are considered accurate to within ±0.1 Hz. All other coupling constants reported were obtained on a first-order basis as direct peak spacings from spectra measured at a sweep width of 100 Hz and are considered precise to within ±0.1 Hz. Chemical shifts are on the τ scale and were taken from the chart recording and/or were measured electronically by using the "Diff 1" position on a Varian V-4354A internal reference nmr stabilized controller in conjunction with a Varian V-4315 frequency counter; values are considered accurate to within ±0.005 ppm.

Preparation of β-D-Ribopyranose Tetraacetate (2).—D-Ribose (Pfanstiehl Laboratories, Inc., Waukegan, Ill.) was acetylated with acetic anhydride and pyridine by the procedure of Levene and Tipson[51] to give crystalline **2**, mp 109–110° (lit.[51] mp 110°).

α-D-Ribopyranose Tetraacetate (1).—β-D-Ribopyranose tetraacetate (**2**) was equilibrated with acetic anhydride and zinc chlo-

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(50) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 3251 (1968).

(51) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **92**, 109 (1931).

ride by the procedure of Zinner[52] to give syrupy **1**, $[\alpha]^{20}D$ +50.1° (*c* 1.08, chloroform) [lit.[52] $[\alpha]^{22}D$ +50.7° (*c* 3.14, methanol)].

α-D-Arabinopyranose Tetraacetate (3).—D-Arabinose was acetylated with acetic anhydride and sodium acetate according to the procedure of Hudson and Dale[53] for the preparation of the L enantiomorph to give crystalline **3**, mp 96–97°, $[\alpha]^{22}D$ −43.8° (*c* 1.00, chloroform) [lit.[53] values for the L enantiomorph, mp 97°; $[\alpha]^{22}D$ +42.5° (*c* 2.67, chloroform)].

β-D-Arabinopyranose Tetraacetate (4).—α-D-Arabinopyranose tetraacetate (**3**) was equilibrated with acetic anhydride and zinc chloride by the procedure of Hudson and Dale[53] for the preparation of the L enantiomorph to give crystalline **4**, mp 85°, $[\alpha]^{22}D$ −155.6° (*c* 0.98, acetone) [lit.[53] values for the L enantiomorph, mp 86°; $[\alpha]^{21}D$ +147.2° (*c* 4.82, chloroform)].

β-D-Xylopyranose Tetraacetate (6).—D-Xylose was acetylated by the procedure of Hudson and Johnson[54] to give crystalline **6**, mp 127–128° (lit.[54] mp 128°).

α-D-Xylopyranose Tetraacetate (5).—A modification of the procedure of Pacsu[55] for the anomerization of β acetates to their α form was used. To a solution of β-D-xylopyranose tetraacetate (**6**, 7.0 g, 22 mmol) in dry dichloromethane was added anhydrous stannic chloride (4.7 g, 18 mmol). The reaction mixture was refluxed for 5 hr, cooled, and then extracted twice with ice–water. The organic extract was washed once with 10% sodium hydrogen carbonate solution and once with ice–water. It was dried by passage over a pad of anhydrous magnesium sulfate and concentrated to a thick syrup. Crystallization of the syrup from ethanol–petroleum ether and three recrystallizations from ether–petroleum ether (bp 30–60°) gave **5** as thin, white needles: yield 5.4 g (77%); mp 56–58°; $[\alpha]^{24}D$ +92.9° (*c* 1.06, acetone) [lit.[54] mp 59°; $[\alpha]^{20}D$ +89.3° (*c* 5.02, chloroform)].

α-D-Lyxopyranose Tetraacetate (7).—D-Lyxose was acetylated with acetic anhydride and sodium acetate by the procedure of Reyle and Reichstein[56] to give crystalline **7**, mp 123–124° (lit.[57] mp 124°).

β-D-Lyxopyranose Tetraacetate (8).—The mother liquor from the preparation of α-D-lyxopyranose tetraacetate (**7**) was concentrated to a thick syrup, which was dissolved in a minimal volume of benzene and passed through a column of silica gel according to the procedure of Zinner and Brandner[57] to give syrupy, chromatographically homogeneous **8**, $[\alpha]^{22}D$ −79.7° (*c* 0.94, acetone) [lit.[57] $[\alpha]^{20}D$ −83.4 ± 0.8° (chloroform)].

β-D-Ribopyranose Tetrabenzoate (10).—D-Ribose was benzoylated with benzoyl chloride and pyridine according to the procedure of Fletcher, *et al.*,[58] to give crystalline **10**, mp 129–130° (lit.[58] mp 131°).

α-D-Ribopyranose Tetrabenzoate (9).—The mother liquor from the preparation of β-D-ribopyranose tetrabenzoate (**10**) was concentrated to a thick syrup which was dissolved in the minimal volume of benzene and passed through a column of silica gel with benzene as the eluent. The first fractions contained more of the β-D anomer [R_f 0.43 (19:1 benzene–ether)] and the middle fractions contained a mixture of the β-D and α-D anomers. The last fractions contained the chromatographically homogeneous α-D anomer **9** obtained as an amorphous glass: $[\alpha]^{28}D$ +62.4° (*c* 1.01, chloroform); R_f 0.35 (19:1 benzene–ether)]. The α-D anomer has not been previously reported in a pure form.[25]

Anal. Calcd for $C_{33}H_{26}O_9$: C, 69.96; H, 4.63. Found: C, 70.18; H, 4.80.

α-D-Arabinopyranose Tetrabenzoate (11).—D-Arabinose was dissolved in boiling pyridine and the resulting solution was kept for 24 hr at room temperature. The solution was then benzoylated as described by Fletcher and Hudson[59] to give crystalline **11**, mp 163–164° (lit.[59] mp 164–165°).

β-D-Arabinopyranose Tetrabenzoate (12).—D-Arabinose was benzoylated with benzoyl chloride and pyridine according to the procedure of Fletcher and Hudson[59] to give crystalline **12**, mp 159–161° (lit.[59] mp 160–161°).

α-D-Xylopyranose Tetrabenzoate (13).—D-Xylose was benzoylated with benzoyl chloride and pyridine by the procedure of Major and Cook[60] to give crystalline **13**, mp 119–121° (lit.[61] mp 119–120°).

β-D-Xylopyranose Tetrabenzoate (14).—D-Xylose was benzoylated by the procedure of Fletcher and Hudson[61] to give crystalline **14**, mp 175–177° (lit.[61] mp 177°).

α-D-Lyxopyranose Tetrabenzoate (15).—D-Lyxose was benzoylated with benzoyl chloride and pyridine by the procedure of Fletcher, *et al.*,[62] to give crystalline **15**, mp 137–139° (lit.[62] mp 138–139°).

β-D-Lyxopyranose Tetrabenzoate (16).—The mother liquor from the preparation of α-D-lyxopyranose tetrabenzoate (**15**) was concentrated to a thick syrup. The syrup was passed through a column of neutral alumina as described by Fletcher, *et al.*,[25] to give crystalline **16**, mp 117–120° (lit.[25] mp 118–122°).

β-D-Ribopyranose Tetra-*p*-toluate (17).—To a solution of D-ribose in pyridine was added dropwise a solution of *p*-toluoyl chloride in pyridine according to the procedure of Zinner and Belau[26] to give crystalline **17**, mp 171–172° (lit.[26] mp 172–173°).

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-β-D-ribopyranose (18).—To a solution of tri-*O*-acetyl-β-D-ribopyranosyl chloride (3.1 g, 11 mmol) in acetonitrile (30 ml) was added silver acetate-d_3 (1.9 g, 11 mmol). The mixture was heated on a steam bath for 3 hr, cooled, and then filtered over a Celite pad to remove precipitated silver chloride. The resulting solution was concentrated to a thick syrup which was crystallized from 95% ethanol. Recrystallization from 95% ethanol gave **18**, yield 2.4 g (72%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **2**. The nmr spectra of **18** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **2** except that the 3-proton singlets at τ 7.876, 7.89, and 8.37, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-α-D-arabinopyranose (19).—This compound was prepared in the same manner as **18**, starting from tri-*O*-acetyl-β-D-arabinopyranosyl chloride (1.0 g) and silver acetate-d_3 (0.6 g), to give crystalline **19**, yield 0.82 g (75%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **3**. The nmr spectra of **19** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **3** except that the 3-proton singlets at τ 7.89, 7.93, and 8.31, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-β-D-xylopyranose (20).—This compound was prepared in the same way as **18**, starting from tri-*O*-acetyl-β-D-xylopyranosyl chloride (3.5 g) and silver acetate-d_3 (2.1 g), to give crystalline **20**, yield 2.6 g (69%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **6**, except that the 3-proton singlets at τ 7.903, 7.936, and 8.37, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-α-D-lyxopyranose (21).—A solution of tri-*O*-acetyl-α-D-lyxopyranosyl bromide (2.0 g, 5.9 mmol) in acetonitrile (20 ml) to which was added silver acetate-d_3 (1.2 g, 7.1 mmol) was stirred at room temperature for 1 hr. After filtration over a Celite pad to remove precipitated silver bromide, the solution was concentrated to a thick syrup, which crystallized from 95% ethanol. Recrystallization from 95% ethanol gave **21**, yield 1.3 g (70%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **7**. The nmr spectra of **21** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **7** except that the 3-proton singlets at τ 7.85, 7.85, and 8.36, respectively, were absent.

Registry No.—**1**, 4257-95-8; **2**, 4049-34-7; **3**, 19186-37-9; **4**, 25243-38-3; **5**, 4257-98-1; **6**, 4049-33-6; **7**, 4026-34-0; **8**, 25227-11-6; **9**, 13035-41-1; **10**, 7473-43-0; **11**, 30319-42-7; **12**, 22434-99-7; **13**, 30319-44-9; **14**, 22435-09-2; **15**, 7702-27-4; **16**, 30319-46-1; **17**, 30319-47-2.

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