CONFORMATIONAL STUDIES ON PYRANOID SUGAR DERIVATIVES BY N.M.R. SPECTROSCOPY. THE CONFORMATIONAL EQUILIBRIA OF SOME PERACYLATED ALDOPENTOPYRANOSYL HALIDES IN SOLUTION*†

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(Received November 20th, 1970)

ABSTRACT

Conformational equilibria in chloroform-*d* solution have been measured by high-resolution n.m.r. spectroscopy for the tri-*O*-acetyl-D-aldopentopyranosyl bromides having the α-*xylo* (**1**), α-*lyxo* (**3**), β-*ribo* (**5**), and β-*arabino* (**7**) configurations, together with the corresponding chlorides (**2**, **4**, **6**, and **8**). In addition to these thermodynamically more stable anomeric forms, the unstable β anomer (**9**) of **2** was similarly studied. Conformational equilibria were also measured for the tri-*O*-benzoyl-α and β-D-xylopyranosyl chlorides (**10** and **11**) and tri-*O*-benzoyl-β-D-ribopyranosyl bromide (**12**). Data for compounds **1**–**12** are tabulated (Tables I–IX). The *C1* (D) conformation is favored overwhelmingly for **1**, **2**, **3**, and **10**, and very strongly for **4**. The *1C* (D) conformation is favored overwhelmingly for **7**, **8**, **11**, and **12**, very strongly for **5** and **6**, and strongly for **9**, even though **9** and **11** have all four substituents axially attached. At low temperatures, that conformation favored at room temperature tends to become the exclusive form. The polarity of the solvent had little effect on the conformational equilibrium of the chloride **9**, which remained 73–80% in the all-axial *1C* (D) conformation in a range of solvents whose polarities ranged from ε 2.2 (carbon tetrachloride) to 37.5 (acetonitrile). Except on a broad, qualitative basis, the equilibria measured could not be accommodated within the framework of current theories of additive steric and polar contributions.

INTRODUCTION

A program in this laboratory has been concerned with the determination by high-resolution n.m.r. spectroscopy of favored conformation, and conformational populations at equilibrium, for pyranoid sugar derivatives in solution, with the aim of reaching a better understanding of the steric and electronic effects of multiple substituents on the stability of tetrahydropyran ring-systems. In the first paper[9] of this series, it was reported that the large anomeric effect of a halogen atom at C-1

*Supported, in part, by Grant No. GP-9646 from the National Science Foundation. †For previous papers in this series, see Refs. 1–9. ‡NDEA Fellow, 1966–1969. **To whom inquiries should be addressed.

plays an overriding role in determining the favored conformation in chloroform solution for the thermodynamically more stable anomeric forms of the peracetylated aldopentopyranosyl bromides. Each of these "stable" bromides has the halogen atom oriented axially when in its favored conformation. Coxon[10] observed similar behavior with the perbenzoylated α- and β-D-ribopyranosyl halides, where the operation of the anomeric effect was considered to be the principal factor in determining the favored chair conformation at equilibrium. Jennings[11] also observed this phenomenon with some chlorosulfated α- and β-D-aldopentopyranosyl chlorides.

In a subsequent report from this laboratory[8], the conformation of tri-*O*-acetyl-β-D-xylopyranosyl chloride, the thermodynamically less stable anomer, was investigated by n.m.r. spectroscopy, and it was found that, in chloroform solution, the chair conformer having all four substituents axially attached [the *1C* (D) conformation] is favored. This observation, totally unexpected from a consideration of steric factors alone, was attributed to the large anomeric effect of the chlorine atom. In a related study[12], tri-*O*-acetyl- and tri-*O*-benzoyl-β-D-xylopyranosyl fluoride were also found to adopt the *1C* form as the favored conformation.

The favored conformations of a number of peracetylated 1-thioaldopyranose derivatives were next examined with the application of 220-MHz n.m.r. spectroscopy[6,7]. For the D-aldohexose derivatives investigated, the *C1* (D) conformation was strongly favored, most probably because of the large steric effect of the acetoxymethyl group; with the D-aldopentoses, the possibility that the alternative chair conformation was present in appreciable proportion at equilibrium with the apparently favored forms that have the SAc group equatorial at C-1 could not be discounted. The likelihood that both chair forms are interconverting rapidly near room temperature is, in fact, supported by the direct observation of n.m.r. signals for the separate chairlike conformers for 1-thio-β-D-ribopyranose tetraacetate[13] at low temperature. The large difference in the position of the conformational equilibria for the acetylated aldopentopyranosyl halides and the corresponding 1-thiopentose tetraacetates is thought to arise, among other possible factors, from the larger steric influence of the sulfur atom[14] and the smaller magnitude of the electronic axial-directing effect of the SAc group[3,7], as compared with those properties of a halogen atom.

In an extension to aldohexose peracetates, the favored chair form for α-D-idopyranose pentaacetate in acetone or chloroform solution was found to be the *C1* (D) conformation, having four substituents axially and one equatorially attached[4]. The large preponderance of this chair form at equilibrium would not have been predicted by the concept of additive conformational free-energies[15,16], even taking into account the estimated anomeric effect of the acetoxyl group[16]. On the basis of published values[14–16] for these energies, both chair conformers would be expected to be present in substantial proportion, the *1C* (D) conformation being somewhat favored. Attractive interactions between axial acetoxyl groups and other groups in the molecule, or significant repulsive interactions between vicinal equatorial groups, were postulated as possible factors involved in controlling the position of the con-

formational equilibrium for this aldohexose peracetate[4], and the validity of the model[15,16] for additive free-energies in these systems was questioned[4]. There has appeared in the recent literature increasing evidence[17–20] for the non-additivity of conformational free-energy ("A") values for multisubstituted, six-membered ring systems in which electronic interactions between polar groups are possible. Such electrostatic forces, to be discussed further, could be significant in determining the favored conformation of α-D-idopyranose pentaacetate and other systems where these interactions are involved.

From a study of the conformation of β-D-ribopyranose tetraacetate[3,5] in acetone solution, it was, through direct observation of the separate chair conformers by low-temperature n.m.r. spectroscopy, convincingly established for the first time, that pyranoid sugar derivatives can, indeed, exist in rapid equilibrium at room temperature. At −84°, the ratio of the *1C* (D) to *C1* (D) conformers was found to be 2:1. By application of the method of averaging of spin coupling, the equilibrium was found to consist of a 57:43 mixture of the *1C* (D) and *C1* (D) forms at room temperature[1]. For β-D-xylopyranose tetraacetate in acetone solution at room temperature[1], the all-axial, *1C* (D) conformer was found to exist at equilibrium with the all-equatorial, *C1* (D) conformer to the extent of 28%. Low-temperature studies[3] revealed an increase in the proportion of the *C1* (D) form present at equilibrium as the temperature is decreased, in the direction opposite to that found for β-D-ribopyranose tetraacetate. The conformational populations of the remaining six aldopentopyranose tetraacetates in acetone[1,2] were also measured by the n.m.r. spectral method of averaging of spin coupling. A conformational "freeze-out" was observed for β-D-lyxopyranose tetraacetate. Quantitative data are thus available for the conformational equilibria of the eight aldopentopyranose tetraacetates, a complete configurational series of pyranoid sugar derivatives.

In a further extension, the positions of the conformational equilibria in solution for additional examples, to give a total of fifty different peracylated D-aldopentopyranosyl derivatives, have been recorded[1]. The data presented cannot be accommodated within the framework of existing interpretations of steric and polar interactions, except on a very broad, qualitative basis.

The present article reports the conformational equilibria in solution for a number of peracylated aldopentopyranosyl chlorides and bromides in their more stable anomeric forms, and also of tri-*O*-acetyl- and tri-*O*-benzoyl-β-D-xylopyranosyl chloride (the thermodynamically less stable anomers), as determined by n.m.r. spectroscopy at 100 MHz. The role of solvent and temperature in altering the position of each conformational equilibrium was investigated. These studies were undertaken to ascertain the role of competition between the anomeric, and other polar, effects and steric interactions, in determining the conformational populations for poly-*O*-acyl-aldopentopyranosyl halides. The data on the glycosyl bromides constitute a quantitative upgrading of those previously reported[9] by n.m.r. spectral measurements at 60 MHz. The earlier qualitative interpretations are entirely upheld by this more detailed information.

The results are discussed with reference to the studies by Hall and Manville[21] on the conformations of peracylated aldopentopyranosyl fluorides and the work of various investigators on the conformations of 2-halotetrahydropyrans[22–24].

METHODS AND MATERIALS

The thermodynamically stable anomeric forms of various peracetylated aldopentopyranosyl bromides were prepared under conditions involving equilibration in an acetic acid–hydrogen bromide solution. Thus prepared were the known, crystalline tri-*O*-acetyl-D-aldopentopyranosyl bromides having the α-D-*xylo*, β-D-*ribo*, and β-D-*arabino* configurations. Tri-*O*-acetyl-α-D-lyxopyranosyl bromide[25] was obtained crystalline for the first time, by the action of hydrogen bromide in acetic acid on crystalline α-D-lyxopyranose tetraacetate. This glycosyl bromide was somewhat more stable at room temperature than the α-D-*xylo* and β-D-*ribo* analogs.

Tri-*O*-acetyl-α-D-xylopyranosyl and -β-D-arabinopyranosyl chlorides were obtained crystalline by treating the corresponding free sugars with acetyl chloride and a trace of zinc chloride. The crystalline tri-*O*-acetyl-α-D-lyxopyranosyl and -β-D-ribopyranosyl chlorides were prepared by a modification of the procedure of Korytnyk and Mills[26] for the preparation of per-*O*-acetylglycosyl chlorides having the 1:2-*trans* configuration. Tri-*O*-acetyl-β-D-xylopyranosyl chloride, the less-stable anomeric form, was prepared by a minor modification[8] of the procedure of Korytnyk and Mills[26].

Tri-*O*-benzoyl-α-D-xylopyranosyl chloride, the thermodynamically more-stable anomer, was prepared from crystalline α-D-xylopyranose tetrabenzoate by refluxing a solution of it in chloroform containing titanium tetrachloride until equilibrium was reached (2 h). The corresponding, "unstable" β-D anomer was prepared under kinetic conditions by treating a chloroform solution prepared from crystalline β-D-xylopyranose tetrabenzoate with an excess of titanium tetrachloride for 5 min at room temperature, according to the general procedure of Csűrös and co-workers[27] for the preparation of tetra-*O*-benzoyl-β-D-glucopyranosyl chloride.

The n.m.r. spectra were measured at 100 MHz for 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; they are considered accurate to within ±0.005 p.p.m. The time-averaged $J_{4,5}$ and $J_{4,5'}$ spin couplings employed in the calculation of conformational populations were obtained by ABX analysis[28] of spectra measured at 100-Hz sweep-width. Quantitative conformational assignments from first-order spin-couplings are not considered reliable, because the spacings observed may differ considerably from the absolute coupling-constants $|J|$ owing to second-order effects[29]. 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. The values reported are considered accurate to within ±0.1 Hz.

Conformational populations at 31° were determined from the observed coupling of H-4 with the *trans*-disposed proton at C-5 (this coupling is a time-averaged value for the two chair conformers in rapid equilibrium), taken in conjunction with values for $J_{4e,5e}$ and $J_{4a,5a}$ that had been obtained from the following model compounds. The $J_{4,5a}$ values for the acylated α-D-xylopyranosyl halides were taken as the limiting magnitude of $J_{4a,5a}$ for each compound in the same series. As the spin couplings observed for these α-D-*xylo* halides remained unchanged as the temperature was lowered, it was concluded that each compound was overwhelmingly (>95%) in the *C1* (D) conformation at 31°. The lower limit of the smaller of the $J_{4,5}$ values for the acetylated β-D-arabinopyranosyl halides, obtained by low-temperature studies, was used as the limiting magnitude of $J_{4e,5e}$. From the conformational populations determined from the spin-coupling data, the equilibrium constants and values for free-energy differences given in Tables I, II, VII, and IX were calculated. The limits of accuracy for the calculations were determined from the uncertainty of ±0.1 Hz

TABLE I

CONFORMATIONAL EQUILIBRIA OF PERACETYLATED D-ALDOPENTOPYRANOSYL HALIDES IN CHLOROFORM-*d* AT 31°

Compound	*Configuration and halide*	*Equilibrium constant* (K = C1/1C)	$\Delta G^0_{31°}$ (*kcal. mole*$^{-1}$) *for* 1C (D) ⇄ C1 (D)
1	α-*xylo* Br	>50[a]	<−2.4
2	α-*xylo* Cl	>50[a]	<−2.4
3	α-*lyxo* Br	24	−1.9 ±1.0
4	α-*lyxo* Cl	9.6	−1.4 ±0.5
5	β-*ribo* Br	0.05	+1.8 ±0.9
6	β-*ribo* Cl	0.08	+1.5 ±0.6
7	β-*arabino* Br	0.03	+2.1 ±1.1
8	β-*arabino* Cl	0.02	+2.4 ±1.2
9	β-*xylo* Cl	0.26	+0.81 ±0.32

[a]Almost exclusively *C1* (D) at 31°.

TABLE II

CONFORMATIONAL EQUILIBRIA OF PERBENZOYLATED D-ALDOPENTOPYRANOSYL HALIDES IN CHLOROFORM-*d* AT 31°

Compound	*Configuration and halide*	*Equilibrium constant* (K = C1/1C)	$\Delta G^0_{31°}$ (*kcal. mole*$^{-1}$) *for* 1C (D) ⇄ C1 (D)
10	α-*xylo* Cl	>50[a]	<−2.4
11	β-*xylo* Cl	0.02	+2.4 ±1.2
11	β-*xylo* Cl	0.19[b]	+1.0 ±0.39
12	β-*ribo* Br	0.02	+2.4 ±1.2

[a]Almost exclusively *C1* (D) at 31°. [b]In acetone-d_6.

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 differ from the true couplings in the separate conformers of each compound.

Spectral data for the glycosyl halides **1–12** are given in Tables III–IX.

TABLE III

FIRST-ORDER CHEMICAL SHIFTS[a] OF THE PERACETYLATED D-ALDOPENTOPYRANOSYL HALIDES IN CHLOROFORM-*d*

Compound	*Configuration and halide*	*Chemical shifts*[b] (τ)						
		H-1	*H-2*	*H-3*	*H-4*	*H-5*[c]	[c]*H-5′*	*Acetyl methyl*
1	α-*xylo* Br	3.42d	5.23q	4.45t	4.96o	5.94q	6.15t	7 91, 7.95[d]
2	α-*xylo* Cl	3.75d	5.05q	4.45t	4.98o	5.98q	6.12t	7.91, 7.95 [d]
3	α-*lyxo* Br	3.74d	4.56q	4.30q	4.73s	5.92q	6.23t	7.86, 7.93, 7.98
4	α-*lyxo* Cl	4.07d	4 62q	4.41q	4.75s	5 94q	6.17t	7 87, 7.95, 7.99
5	β-*ribo* Br	3.63d	4.69m	4.36t	4.69m	5 74q	6.02q	7.86, 7.87, 7.99
6	β-*ribo* Cl	3 97d	4.76m	4.45t	4.76m	5.70q	6.04q	7.85, 7 87, 7.98
7	β-*arabino* Br	3.30d	4.94o[e]	4.60q	4 62m	5 79q	6.09q	7 86, 7.90, 7.99
8	β-*arabino* Cl	3.63d	4.73o	4 58q	4.62m	5 74q	6.13q	7.86, 7.90, 7.98
9	β-*xylo* Cl	4.21t	4 97t	4.97t	5.13m	5 62q	6 25[f]	7.89[g]

[a]Data obtained from spectra recorded at 100 MHz. [b]Observed multiplicities: d, doublet; m, complex multiplet; o, octet; q, quartet; s, sextet; t, triplet. [c]The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5′. [d]6-Proton singlet [e]The large coupling of H-4 with H-3, and their small difference in chemical shift, cause further splitting of the H-2 signal through "virtual coupling" (1.4 Hz); this virtual coupling was overlooked in the study[9] at 60 MHz. [f]Broadened quartet. [g]9-Proton singlet.

TABLE IV

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERACETYLATED D-ALDOPENTOPYRANOSYL HALIDES IN CHLOROFORM-*d*

Compound	*Configuration and halide*	*Coupling constants*[a] (*Hz*)					
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$^{b}J_{4,5}$	$^{b}J_{4,5'}$	$J_{5,5'}$
1	α-*xylo* Br	4.0	9.6	9.5	5.8	11.5	−11.3
2	α-*xylo* Cl	3 9	9.6	9.5	5.7	12.1	−11.1
3	α-*lyxo* Br	1.7	3.4	10 2	5.5	11.1	−11.1
4	α-*lyxo* Cl	1.8	3.2	10 1	5.5	11.1	−11.0
5	β-*ribo* Br	1 2	3.8	3.7	1.4	2.0	−13.4
6	β-*ribo* Cl	1.9	3 7	3.7	1.9	2.3	−13 2
7	β-*arabino* Br[c]	3.8	11 5	3.4	0 7	1.8	−13.3
8	β-*arabino* Cl[d]	3 2	11.7	3.0	0.6	1.7	−13.3
9	β-*xylo* Cl	[e]	[e]	[e]	2.8	3.7	−12.9

[a]Data obtained from spectra recorded at 100 MHz at a sweep width of 100 Hz. The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5′. [b]Coupling constants calculated by ABX analysis. [c]"Virtual coupling" 1.4 Hz. [d]"Virtual coupling" 1.3 Hz. [e]First-order couplings not observed.

TABLE V

SOLVENT-DEPENDENCE OF FIRST-ORDER, CHEMICAL SHIFTS OF THE PERBENZOYLATED D-ALDOPENTOPYRANOSYL HALIDES[a]

Compound	*Configuration and halide*	*Solvent*	*Chemical shifts*[b] (τ)						
			H-1	*H-2*	*H-3*	*H-4*	[c]*H-5*	[c]*H-5′*	*Benzoyl*
10	*α-xylo* Cl	$CDCl_3$	3.50d	4.55q	3.75t	4.51m	5.67q	5.84t	1.95–2.82
10	*α-xylo* Cl	$(CD_3)_2CO$[d]	3.29d	4.36q	3.79t	4.35m	5.58q	5.78t	1.97–2.73
10	*α-xylo* Cl	C_6D_6[d]	3.67d	4.56q	3.46t	4.52m	——6.00[e]——		1.86–3.29
11	*β-xylo* Cl	$CDCl_3$	3.80[f]	4.56m	4.37m	4.75m	5.31q	5.89sx	1.81–2.83
11	*β-xylo* Cl	$(CD_3)_2CO$[d]	3.60[g]	4.47[h]	4.30[h]	4.59[i]	5.24q	5.79o	1.81–2.72
11	*β-xylo* Cl	C_6D_6[d]	3.99[f]	4.44m	4.26m	4.86m	5.63q	6.27o	1.79–3.19
12	*β-ribo* Br[j]	$CDCl_3$	3.34d	4.25m	3.90t	4.25m	5.50q	5.72q	1.92–2.84

[a]Data obtained from spectra recorded at 100 MHz. [b]Observed multiplicities: d, doublet; m, complex multiplet; o, octet; q, quartet; sx, sextet; t, triplet. [c]The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5′. [d]Measured for 10% (w/v) concentration [e]AB portion of a deceptively simple, ABX system[63]. [f]Broadened singlet [g]Broadened doublet. [h]Broadened triplet. [i]Broadened quartet. [j]Compare with values given in Ref. 10.

TABLE VI

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERBENZOYLATED D-ALDOPENTOPYRANOSYL HALIDES

Compound	*Configuration and halide*	*Solvent*	*Coupling constants*[a] (*Hz*)					
			$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	[b,c]$J_{4,5}$	[b,c]$J_{4,5'}$	$J_{5,5'}$
10	*α-xylo* Cl	$CDCl_3$	3.8	9.8	9.8	5.8	11.5	−11.0
10	*α-xylo* Cl	$(CD_3)_2CO$[d]	3.8	9.6	9.5	5.9	11.5	−11.3
10	*α-xylo* Cl	C_6D_6[d]	3.9	9.7	9.6	*e,f*	*e,f*	*e,f*
11	*β-xylo* Cl	$CDCl_3$	1.7	2.7	[e]	2.0	1.7	−13.4
11	*β-xylo* Cl	$(CD_3)_2CO$[d]	2.3	3.8	3.7	2.5	3.1	−13.2
12	*β-ribo* Br[g]	$CDCl_3$	1.2	4.0	3.9	1.3	1.7	−13.6

[a]Data obtained from spectra recorded at 100 MHz at a sweep width of 100 Hz. [b]The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5′. [c]Coupling constants calculated by ABX analysis [d]Measured for 10% (w/v) concentration [e]First-order coupling not observed [f]Deceptively simple, ABX system[63]. [g]Compare with values given in Ref 10.

RESULTS

General. — In the following spectral analyses, all n.m.r. spectra were measured in chloroform-*d* at 100 MHz, and, unless otherwise indicated, the spectra were well resolved and amenable to complete, first-order analysis.

Tri-O-acetyl-α-D-xylopyranosyl bromide (**1**)

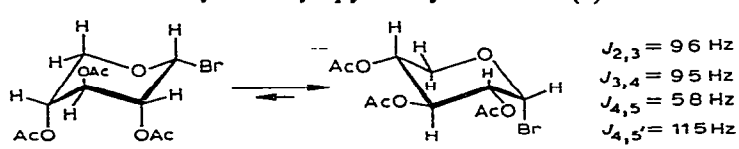


TABLE VII

TEMPERATURE-DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR TRI-*O*-ACETYL-β-D-XYLOPYRANOSYL CHLORIDE (9) IN CHLOROFORM-*d*

Temperature[a] (°C)	*Coupling constants*[b] (*Hz*)		*Equilibrium constant* (K = C1/1C)
	$J_{4,5}$	$J_{4,5'}$	
56	3.0	3.9	0.29
42	2.9	3.8	0 28
3	2.7	3.6	0.25
−19	2.4	3.3	0.20
−33	1.7	2.5	0.10

[a]±2°. [b]Coupling constants calculated by ABX analysis.

TABLE VIII

SOLVENT-DEPENDENCE OF FIRST-ORDER, CHEMICAL SHIFTS FOR TRI-*O*-ACETYL-β-D-XYLOPYRANOSYL CHLORIDE (9)[a]

Solvent	*Chemical shifts*[b] (τ)						
	H-1	*H-2*	*H-3*	*H-4*	[c]*H-5*	[c]*H-5'*	*Acetyl methyl*
CCl_4[d]	4.34t	——5 05–5.32m——			5.70q	6.35[e]	7.94[f]
C_6D_6[g,h]	4 36[i]	—4.71–4.95m—		5 23[e]	5 92q	6 63[e]	8.33, 8 36, 8 40
$C_6D_5CD_3$[h]	4 50[i]	—4 80–5 03m—		5 29[e]	5 98q	6 70[e]	8.33, 8 36, 8 39
$CDCl_3$[g]	4 21t	4 97t	4 97t	5.13m	5.62q	6.25[e]	7.89[f]
$(CD_3)_2CO$[g]	4.09t	——4.92–5.21m——			5.66q	6 21[e]	7.92, 7.94[j]
CD_3CN	4.14t	——4.95–5 24m——			5.69q	6 26[e]	7.94, 7.96[j]

[a]Data obtained from spectra recorded at 100 MHz [b]Observed multiplicities: m, complex multiplet; q, quartet; t, triplet. [c]The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5'. [d]Measured at 10% (w/v) concentration. [e]Broadened quartet. [f]9-Proton singlet. [g]Compare with data recorded at 60 and 100 MHz, given in Ref. 8. [h]Measured for 15% (w/v) concentration. [i]Broadened doublet. [j]6-Proton singlet.

TABLE IX

SOLVENT-DEPENDENCE OF CONFORMATIONAL EQUILIBRIUM FOR TRI-*O*-ACETYL-β-D-XYLOPYRANOSYL CHLORIDE (9)

Solvent	ε	*Coupling constants*[a] (*Hz*)				*Equilibrium constant* (K = C1/1C)	$\Delta G^{\circ}_{31^{\circ}}$ (*kcal. mole*$^{-1}$) *for* 1C (D) ⇄ C1 (D)
		$J_{1,2}$	[b,c]$J_{4,5}$	[b,c]$J_{4,5'}$	$J_{5,5'}$		
CCl_4[d]	2.2	[e]	3.0	3.8	−12.8	0.28	+0.78 ±0 32
C_6D_6[f,g]	2.3	3.3	3.1	3.9	−12.9	0.29	+0.75 ±0.31
$C_6D_5CD_3$	2.4	3.5	3 2	4.1	−12.8	0 32	+0 68 ±0.30
$CDCl_3$[f]	4.8	[e]	2 8	3.7	−12.9	0 26	+0 81 ±0.32
$(CD_3)_2CO$[f]	20.7	[e]	3.1	4.4	−12 8	0 38	+0.59 ±0 38
CD_3CN	37 5	[e]	3.0	4.4	−12.9	0.38	+0.59 ±0.29

[a]Data obtained from spectra recorded at 100 MHz at a sweep width of 100 Hz. [b]The C-5 proton resonating at lower field is designated H-5, and that resonating at higher field is designated H-5'. [c]Coupling constants calculated by ABX analysis. [d]Measured for 10% (w/v) concentration. [e]First-order coupling not observed. [f]Compare with data recorded at 60 and 100 MHz, given in Ref. 8. [g]Measured for 15% (w/v) concentration.

The n.m.r. spectrum is shown in Fig. 1. The measured spin-couplings, which remained unchanged with decreasing temperature, are fully consistent with the *C1* (D) conformation as essentially the exclusive form present. The temperature-independence of the coupling constants suggests that the effect of torsional vibrations[30] on spin couplings is negligible over the temperature range employed in these studies.

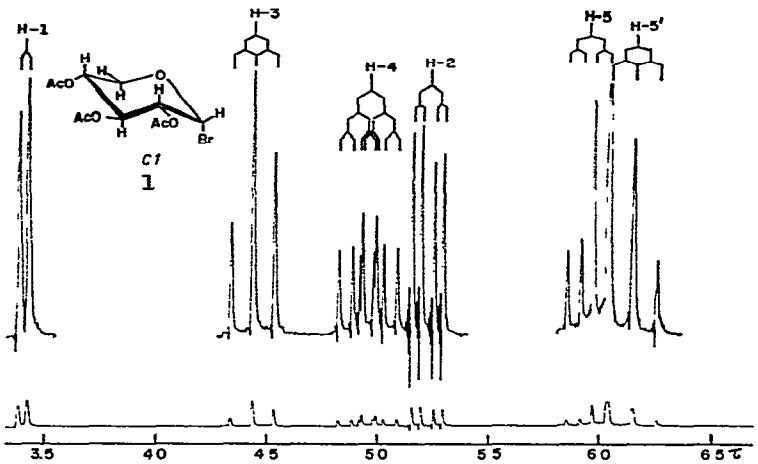
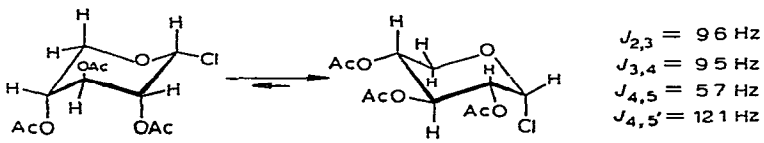


Fig. 1. Partial n m r. spectrum of tri-*O*-acetyl-α-D-xylopyranosyl bromide (**1**) at 100 MHz in chloroform-*d*.

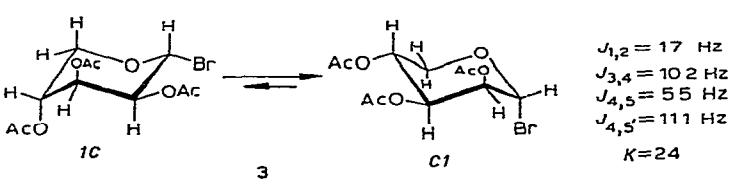
Tri-O-*acetyl*-α-D-*xylopyranosyl chloride* (**2**)



$J_{2,3}$ = 9.6 Hz
$J_{3,4}$ = 9.5 Hz
$J_{4,5}$ = 5.7 Hz
$J_{4,5'}$ = 12.1 Hz
K >50

The spectrum indicates that **2** is essentially all in the *C1* (D) conformation near room temperature, because low-temperature studies did not reveal any changes in the spin-couplings observed.

Tri-O-*acetyl*-α-D-*lyxopyranosyl bromide* (**3**)

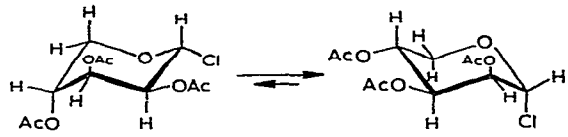


$J_{1,2}$ = 1.7 Hz
$J_{3,4}$ = 10.2 Hz
$J_{4,5}$ = 5.5 Hz
$J_{4,5'}$ = 11.1 Hz
K = 24

The spectrum indicates that the *C1* (D) conformation is the principal chair form present at equilibrium near room temperature[9]. A slight shift of the position of the conformational equilibrium toward the more stable [*C1* (D)] conformation was observed as

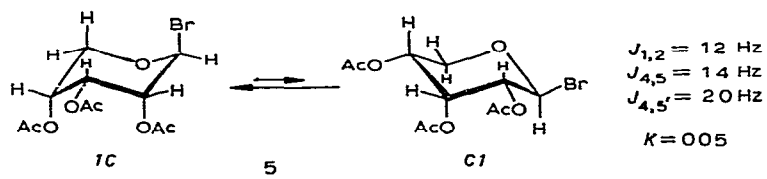
the temperature was lowered. This change was detected by a small decrease in $J_{1,2}$ and a small increase in $J_{4,5'}$.

Tri-O-*acetyl*-α-D-*lyxopyranosyl chloride* (**4**)



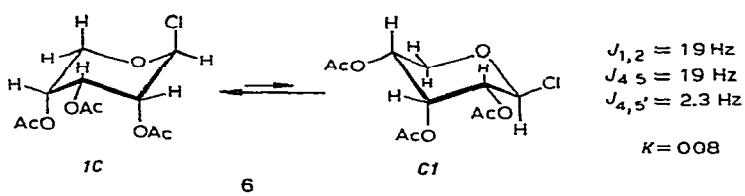
The spectrum is consistent with the *C1* (D) conformation as the preponderant conformer at equilibrium near room temperature. A somewhat greater proportion (~10%) of the *1C* (D) form is present at equilibrium than was found for the bromide **3**. With decreasing temperature, a shift in the conformational equilibrium, toward favoring of the *C1* (D) conformation exclusively, was again detected by a decrease in $J_{1,2}$ and an increase in $J_{4,5'}$. Thus, $J_{1,2}$ decreased from 1.8 Hz at 31° to 1.2 Hz at −33°.

Tri-O-*acetyl*-β-D-*ribopyranosyl bromide* (**5**)



The spectrum indicates that **5** exists principally in the *1C* (D) conformation[9]. The presence of a small proportion (~5%) of the *C1* (D) conformer at equilibrium near room temperature is, however, evident from the observed decrease in the $J_{4,5}$ spin-couplings with decreasing temperature. Such a change in the spin couplings indicates a shift of the conformational equilibrium toward exclusive population by the *1C* (D) conformer.

Tri-O-*acetyl*-β-D-*ribopyranosyl chloride* (**6**)



The spectrum (see Fig. 2) of **6** shows that the *1C* (D) conformation is favored. The proportion (~7.5%) of the *C1* (D) form present at equilibrium near room temperature is somewhat larger than that found for the bromide **5**, but, again, a shift in the equilibrium toward exclusive population by the *1C* (D) form was detected by low-temperature studies.

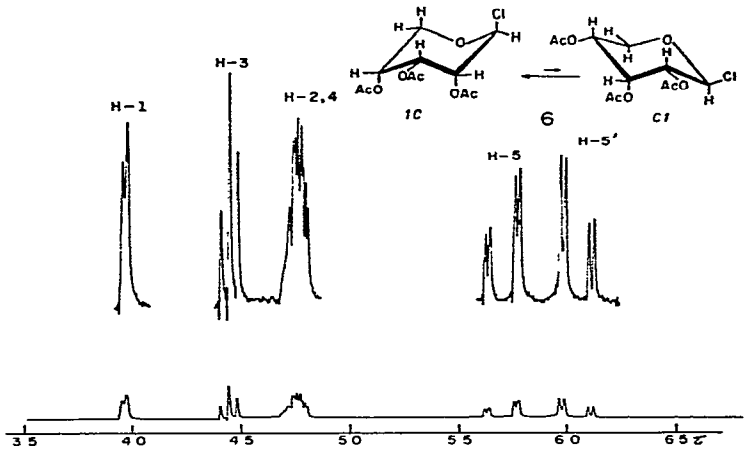
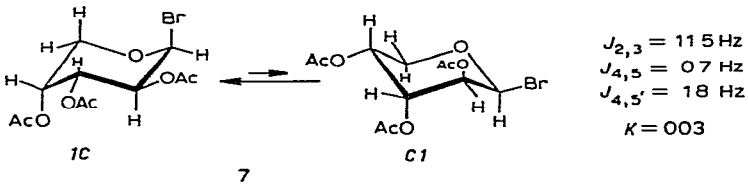


Fig. 2 Partial n.m.r. spectrum of tri-*O*-acetyl-β-D-ribopyranosyl chloride (**6**) at 100 MHz in chloroform-*d*.

Tri-O-*acetyl*-β-D-*arabinopyranosyl bromide* (**7**)



The spectrum (see Fig. 3) indicates that **7** is almost exclusively in the *1C* (D) conformation[9]. The presence of a very small proportion of the other chair conformer at room temperature is evident from the slight decrease observed in the $J_{4,5'}$ value,

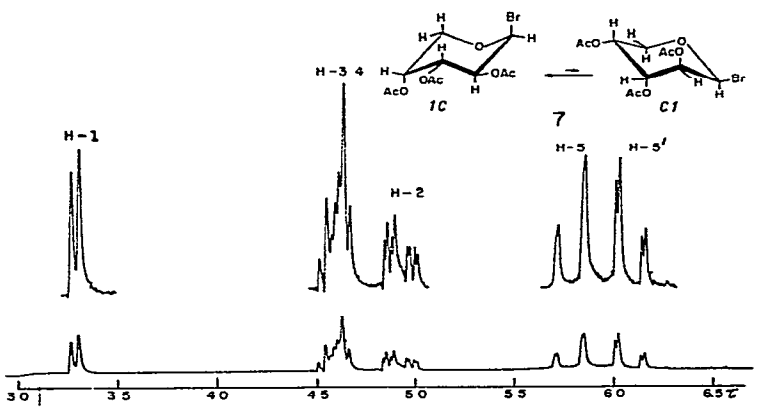
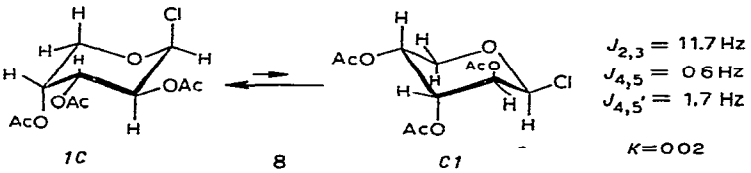


Fig. 3. Partial n m.r. spectrum of tri-*O*-acetyl-β-D-arabinopyranosyl bromide (**7**) at 100 MHz in chloroform-*d*.

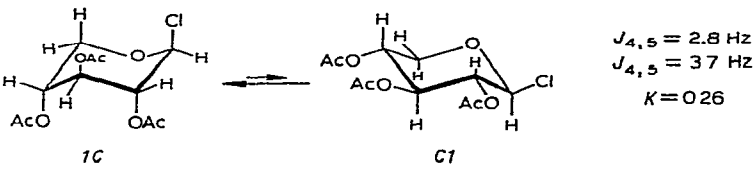
to a limit of 1.5 Hz, as the temperature was lowered. Some second-order effects are observed because the chemical-shift difference between the H-3 and H-4 signals is small; the absolute value of $J_{2,3}$ may be slightly different from the first-order value of 11.5 Hz.

Tri-O-*acetyl*-β-D-*arabinopyranosyl chloride* (**8**)



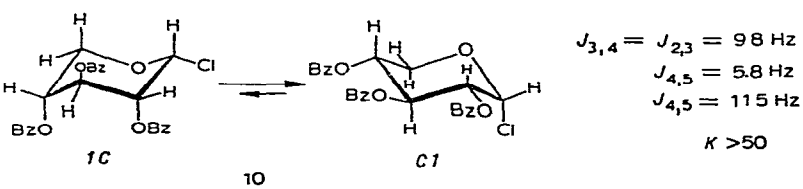
As with bromide **7**, the chloride **8** exists almost exclusively in the *1C* (D) conformation. A slight decrease in the $J_{4,5'}$ coupling-constant is detected as the temperature is decreased, providing evidence for the presence of a very small proportion of the *C1* (D) conformer at equilibrium. The reservations concerning the $J_{2,3}$ value noted for the bromide **7** are also applicable with **8**, for similar reasons.

Tri-O-*acetyl*-β-D-*xylopyranosyl chloride* (**9**)



The spectrum indicates that the all-axial, *1C* (D) conformer is the major chair form present at equilibrium near room temperature[8]. There is, however, an appreciable proportion (~20%) of the all-equatorial, *C1* (D) form present at equilibrium; this is reflected in the decrease in the $J_{4,5}$ coupling-constants with lowering of the temperature, indicating a shift of the equilibrium position toward more exclusive population by the *1C* (D) form. The H-1 signal, although a narrow doublet in benzene-d_6 or toluene-d_8, is observed with chloroform-*d* as a narrow triplet as a result of second-order effects, because the H-2 and H-3 signals differ little in chemical shift. In Table VII are given the changes in the $J_{4,5}$ and $J_{4,5'}$ values in chloroform solution, and the equilibrium constants derived, as a function of the temperature.

Tri-O-*benzoyl*-α-D-*xylopyranosyl chloride* (**10**)



The n.m.r. spectrum (see Fig. 4) is fully consistent with the assignment of **10** as the α-D anomer in the *C1* conformation. The H-1 signal appears at low field (τ 3.50) as

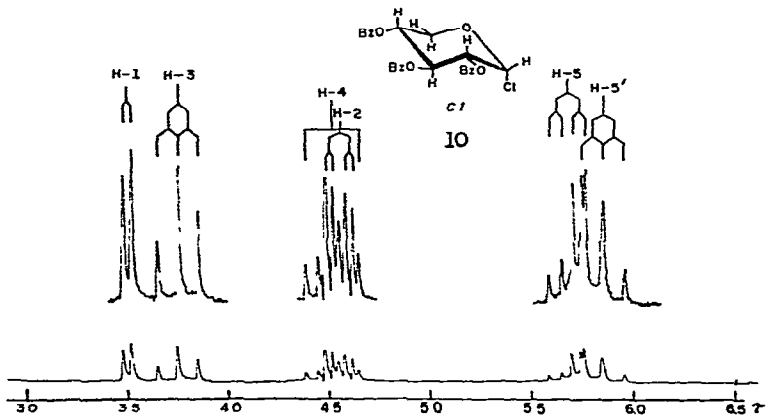
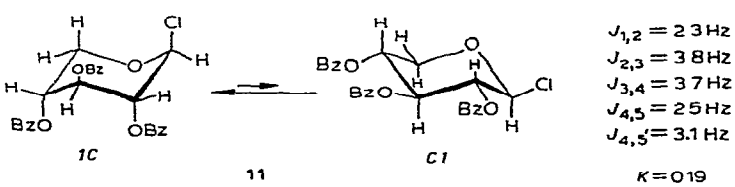


Fig. 4. Partial n.m.r. spectrum of tri-*O*-benzoyl-α-D-xylopyranosyl chloride (**10**) at 100 MHz in chloroform-*d*.

a doublet ($J_{1,2}$ = 3.8 Hz), indicating that H-1 and H-2 are gauche-disposed. The H-2 signal appears as a quartet through additional large (9.8 Hz) coupling with H-3, in accord with a *trans*-diaxial arrangement of H-2 and H-3. The H-3 signal appears as a wide triplet, as the result of equal coupling with the axial protons at C-2 and C-4; its resonance at a relatively low field, τ 3.75, is attributable to the deshielding effect of the chloro group at C-1 in *syn*-diaxial relationship with H-3. The H-4 signal appears as a multiplet, the X portion of an ABXY (where $\nu_X - \nu_Y$ is large compared with $J_{X,Y}$) system, due to coupling of H-4 with the protons on C-5 (AB portion) and on C-3 (Y portion). The H-5 signals appear as a typical AB portion of an ABX system, and the two protons show a geminal coupling of −11.0 Hz. The quartet at τ 5.67 is assigned to the equatorial H-5, and shows $J_{4a,5e}$ = 5.8 Hz. The higher-field triplet (τ 5.84) is assigned to the axial H-5 atom, and has $J_{4a,5a}$ = 11.5 Hz, indicating a *trans*-diaxial relationship with H-4.

All of the foregoing data fully support the structure assigned. The vicinal couplings remained unchanged with decreasing temperature, indicating that **10** exists essentially all in the *C1* (D) conformation, both at and below room temperature.

Tri-O-*benzoyl*-β-D-*xylopyranosyl chloride* (**11**)



The spectrum of this compound in acetone-d_6 supports the β-D assignment and indicates that **11** exists preponderantly in the *1C* (D) (all-axial) conformation. The signal assignments are based on spin-decoupling experiments. The broadened multiplets in the spectrum indicate substantial, long-range coupling among the ring

protons, as would be expected from the many "W" conformational arrangements[31] found in the *1C* (D) form.

The H-1 signal appears at lowest field (τ 3.60) as a narrow doublet ($J_{1,2}$ 2.3 Hz), with broadening of each line indicative of the anticipated, long-range coupling with H-3. The H-2 signal appears as a triplet at τ 4.47 ($J_{2,3}$ 3.8 Hz), again with each line broadened from long-range coupling. The H-3 signal, also broadened, appears as a triplet at τ 4.30, and has $J_{3,4}$ = 3.7 Hz. The H-4 signal is observed at higher field (τ 4.59) as a broadened quartet, the X portion of an ABXY system, through coupling with the protons on C-5 (AB portion) and on C-3 (Y portion). The quartet at τ 5 24 is assigned to the axial H-5 proton in the *1C* (D) conformation; $J_{4e,5a}$ = 2.5 Hz. The higher-field quartet of narrow doublets at τ 5.79 is assigned to the equatorial H-5 proton ($J_{4e,5e}$ = 3.1 Hz), which is long-range coupled to H-3.

The spectrum of **11** in chloroform-*d* (see Fig. 5) indicates even more exclusive population by the *1C* (D) conformation (K = 0.02) in this solvent.

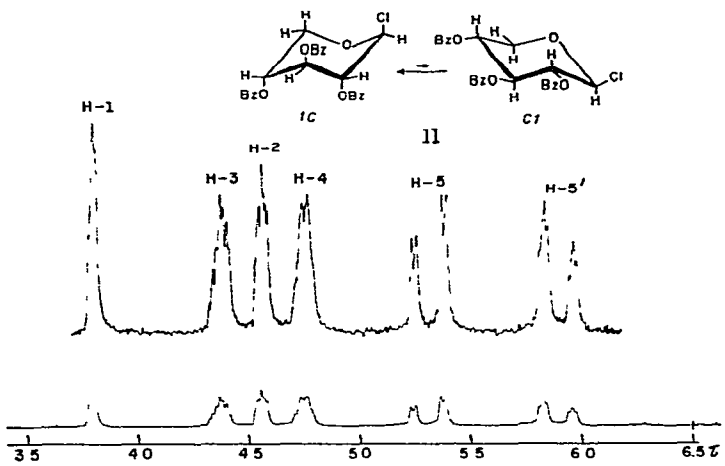
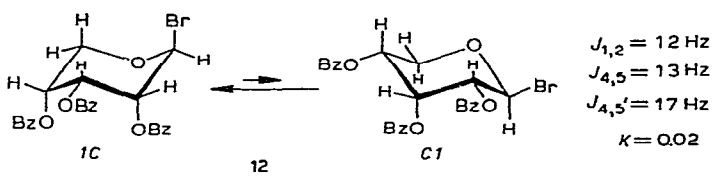


Fig 5. Partial n.m.r. spectrum of tri-*O*-benzoyl-β-D-xylopyranosyl chloride (**11**) at 100 MHz in chloroform-*d*

Tri-O-*benzoyl*-β-D-*ribopyranosyl bromide* (**12**)



The spectrum indicates that **12** exists overwhelmingly in the *1C* (D) conformation near room temperature[10]. As the temperature was lowered, the $J_{4,5'}$ value decreased from 1.7 Hz at 31° to ~1.5 Hz at −10°. This slight change indicates that the conformational population is still more exclusively *1C* (D) at the lower temperature.

DISCUSSION

Chemical shifts and structure. — From Table III, it may be seen that the chemical shifts of the individual protons in each of the bromides correspond closely to those for the corresponding chlorides, except that the H-1 signal in the bromides appears 0.33 p.p.m. to lower field than in the chlorides. This effect can be accounted for by the larger deshielding effect of the C–Br bond than of the C–Cl bond[32]. Changing the halogen from bromine to chlorine had little effect on the chemical shifts of the *syn*-diaxial protons H-3 and H-5.

Effects of solvent on chemical shifts. — Table VIII gives the solvent dependence of the observed chemical shifts for tri-*O*-acetyl-β-D-xylopyranosyl chloride (**9**). The signals for acetyl methyl protons are observed ~0.4 p.p.m. to higher field in benzene and toluene (relative to the nonaromatic solvents). The upfield shift of acetate signals in n.m r. spectra measured in aromatic solvents is well known[7,33,34] and is attributable to the magnetic–anisotropic character of the aromatic molecule. The shifts induced by the aromatic solvent on the methine and methylene protons of the ring are both positive and negative,[7,34] the direction presumably being dependent on the geometry of the solvent–solute collision complex.

In Tables V and VI are given the n m.r. spectral data recorded for tri-*O*-benzoyl-α-D-xylopyranosyl chloride (**10**) in chloroform-*d*, acetone-d_6, and benzene-d_6. The ring-proton signals of **10** in chloroform-*d* are all at lower field than those measured for the acetylated analog **2**. The difference in the chemical shifts may arise partly from the greater electronegativity of the benzoyloxy group, but the ring protons in **10** may also be in the deshielding zone of the π-system of the benzoate groups.

As was observed for **10** and **2**, the ring-proton signals for tri-*O*-benzoyl-β-D-xylopyranosyl chloride (**11**) are all at lower field than those measured for the acetylated analog **9** (compare Tables V and VIII). This effect was noted for solutions in chloroform-*d*, acetone-d_6, and benzene-d_6. In benzene-d_6, substantial upfield and downfield shifts are observed for certain of the pyranoid ring-protons.

The chemical shifts of the acetyl methyl protons for compounds **1**–**9** in chloroform-*d* (see Table III) are in general accord with expectations for equatorial and axial acetoxyl-group signals that are indicative of such arrangement[35,36].

Temperature dependence of the equilibria. — In those examples in which a contribution from the less-favored conformer could be detected at room temperature, it was found that, as the temperature was lowered, the favored form became increasingly more preponderant, tending to become the exclusive form detectable at low temperature. Thus, for tri-*O*-acetyl-β-D-xylopyranosyl chloride (**9**), the favored, all-axial form, which was present to the extent of 77% at 56°, reached 90% at −33° (see Table VII). This change is in a direction opposite from that observed[3] for β-D-xylopyranose tetraacetate, and it indicates that the halogen atom has a much greater axial-directing influence than the acetoxyl group.

No conformational "freeze-outs" were observed for any of the halides **1**–**12**, because, at very low temperature (−85°), the equilibrium had in all cases been shifted

to the more-stable conformation to such an extent that the proportion of the other chair form present was negligible, and undetectable by the technique used.

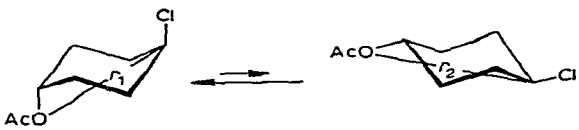
In their studies of the peracylated aldopentopyranosyl fluorides[21], Hall and Manville observed effects that they termed "deviations" in the spin-coupling data for the β-D-*xylo* and α-D-*arabino* derivatives. They were unable to determine whether such "deviations" were caused by a time-averaging process between the two chair forms or by a distortion of the ring symmetry. In view of the present variable-temperature studies, it appears that Hall and Manville had observed mainly a time-averaging process, although some degree of ring distortion may also have been involved. The compounds that exhibited the greatest divergence were those having the largest number of axially attached substituents. Indeed, it is exactly for these systems that the minor chair conformer might make an appreciable contribution to the equilibrium, resulting in the observed difference between the spin couplings measured for these derivatives and those for the more conformationally homogeneous derivatives.

Effect of configuration and structure on conformational equilibria. — General. All of the data presented on the equilibria for compounds **1–12** support the general qualitative principle that the halogen atom at C-1 has a strong tendency to adopt the axial orientation, even at the expense of forcing several, or even all, of the three acyloxy groups into the axial orientation, a hitherto-supposed unfavorable situation with respect to steric destabilization, particularly when up to two sets of *syn*-diaxial interactions are involved.

The bromides **3** and **5** still more strongly favor that conformation having the halogen atom axial than do the corresponding chlorides **4** and **6**, indicating that the axial-directing influence of the bromo substituent exceeds that of the chloro substituent. This observation is in agreement with data on 2-halotetrahydropyrans, for which it was estimated[23] that the anomeric effect of the bromo group is 0.5 kcal.mole^{-1} larger than that of the chloro group. For the bromide **1** and the corresponding chloride analog **2**, the *C1* (D) conformation, having the halogen atom axially attached, is so strongly favored in each that the n.m.r. spectral method used is insensitive for detection of quantitative differences between the two halogens; the same is true of the bromide **7** and the corresponding chloride **8**, for which the *1C* (D) conformation is overwhelmingly favored.

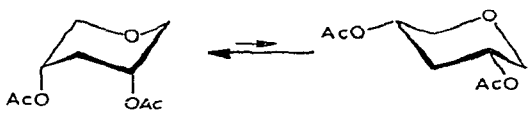
Quantitative discrepancies between behavior observed and that predicted from "conformational free-energies". The preponderance of the all-axial *1C* (D) conformation for tri-*O*-acetyl-β-D-xylopyranosyl chloride (**9**) would not have been predicted from a consideration of values suggested[14–16] for conformational free-energies and for the anomeric effect of the chloro group[23]. Indeed, the all-equatorial form would have been predicted to be the favored form. The experimental results for **9**, and also for α-D-idopyranose pentaacetate[4], suggest that the concept of additive conformational free-energies may not be valid for polysubstituted pyranoid ring-systems. Deviations from additivity of conformational free-energies have also been observed by other workers, and the results obtained provide a rationale for the observed preponderance of the *1C* (D) form of **9** at equilibrium.

Thus, work on 1,4-disubstituted cyclohexanes[17] has shown that, when two polar groups (X) are in the 1,4-*trans*-orientation, marked divergence from additivity of conformational free-energies occurs, and that the *trans*-diaxial form is more favored than would have been anticipated. Such an arrangement is found for the *1C* (D) conformer of **9**, wherein the axially attached chloro group at C-1 is *trans* to the axial acetoxyl group at C-4. The attractive interaction between the partial charges created at C-1 and X-4 and at C-4 and X-1 from the polarization of the C–X bonds is



thought[17] to be greater in the diaxial form than in the diequatorial form, because the distance r_1 is less than the distance r_2.

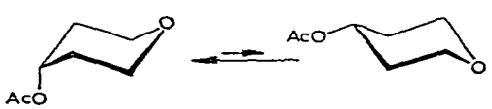
Anderson and co-workers[18] examined the conformational equilibrium of 3-acetoxytetrahydropyran and observed that the values of the free-energy difference between chair conformers, measured in several solvents, were far from the values predicted merely from steric considerations. They found that the conformer having the acetoxyl group axial is more favored than had been anticipated. They rationalized this difference in terms of dipole–dipole interactions of the substituent group with the resultant dipole of the two C–O bonds in the ring. For compound **9**, the *1C* (D) conformer, which has two such axial acetoxyl groups, could be substantially stabilized by attractive, electronic interactions of this kind.



1C *C1*

Stolow and co-workers[19] have observed a transannular, substituent effect in their studies on conformational equilibria of the type:

where Z is an electron-attracting group. The proportion of that conformer having the substituent axial is found to increase with the electron-withdrawing ability of the Z group. Although the exact nature of this electronic effect has not yet been explained[19], such a transannular interaction could play a role in stabilizing the *1C* (D) form of compound **9**.



1C *C1*

Finally, the results obtained by Hageman and Havinga[20], from their studies of the conformational properties of some *trans*-1,2-dihalocyclohexanes and their alkyl derivatives, serve as another warning against applying the idea of additive, conformational free-energies in situations where several interacting substituents are present on the ring. The deviations from additivity may in part be due to 1,2-dipolar interactions that cause the vicinal-diaxial form to be more favored than would be expected purely from steric factors. The all-axial *1C* (D) conformer of **9** may be further stabilized by such polar interactions of vicinal substituents.

The position of the conformational equilibrium for tri-*O*-benzoyl-β-D-xylopyranosyl chloride (**11**) is, again, not predictable on the basis of additive conformational free-energies and the anomeric effect of the chloro group. The electronic factors already discussed for the acetylated analog **9** presumably play a similar role in determining the favored conformation of **11**. The equilibrium for the benzoyl derivative **11** lies even more in favor of the *1C* (D) conformer than does that for **9**. In fact, the benzoylated chloride **11** has only about 2% of the all-equatorial [*C1* (D)] form present at equilibrium in chloroform-*d* at room temperature, whereas the acetylated analog **9** has about 20%. A similar shift in the conformational equilibrium, further favoring the *1C* (D) conformer, was observed on passing from tri-*O*-acetyl-β-D-ribopyranosyl bromide (**5**) to the corresponding tri-*O*-benzoyl analog (**12**) (see Tables I and II) This shift may, in part, be attributable to enhancement, by the more-electronegative benzoyloxy groups, of the magnitude of the anomeric effect of the halo substituent. The other electrostatic interactions considered for **9** may also be enhanced by replacing the acetoxyl groups with benzoyloxy substituents. Without further data, it is difficult to evaluate quantitatively the relative contributions of each factor. Attractive interaction between the *syn*-diaxial benzoyloxy groups at C-2 and C-4 of the *1C* (D) conformer[1] may also be involved. Inspection of molecular models suggests that the gauche interaction between a pair of vicinal benzoyloxy substituents should be very similar to that between a pair of acetoxyl groups; the interaction between benzoyloxy groups may be slightly smaller than that between acetoxyl groups, because the more-electronegative benzoyl group would cause greater delocalization of unshared pairs of electrons on the oxygen atom by which it is attached to the ring

Configurational dependence of vicinal and geminal spin-couplings. — Vicinal couplings From the $J_{4,5}$, $J_{4,5'}$, and $J_{5e,5a}$ coupling-constants (see Table IV) and conformational equilibrium constants (see Table I) observed for the peracetylated aldopentopyranosyl halides, it may be seen that there is a decreasing trend for $J_{4,5'}$ as the equilibrium constant (*C1*/*1C*) decreases. As there is a *trans*-diaxial disposition of H-4 and H-5*a* in one chair form, the decrease in $J_{4,5'}$ can be ascribed to an increase in the proportion of that chair conformer having H-4 equatorial. The lower-field, H-5 signal also exhibits coupling with H-4 that decreases as the equilibrium constant decreases, but, in this instance, the coupled protons in both conformers are *gauche*-disposed.

However, vicinal spin-couplings also depend on the orientation of substituents

relative to the coupled protons[37,38]. As predicted from Booth's generalizations[38], the $J_{4,5}$ coupling-constant decreases as the proportion of the *1C* (D) conformer, having an axial (electronegative) acetoxyl group at C-4, increases.

Geminal couplings. Molecular-orbital theory[39] predicts that the geminal spin-coupling should increase algebraically with the equilibrium proportion of that conformer in which the electron-withdrawing, acetoxyl group at C-4 bisects the angle subtended by the geminal protons on C-5 (experimental studies have established that proton geminal couplings in sp^3 hybridized systems are negative[40]). As may be seen from Tables I and IV, there is a general algebraic increase in the $J_{5e,5a}$ spin coupling as the proportion of the *C1* (D) conformer increases, but the trend is not monotonic. However, the size of this coupling does provide a qualitative estimate of the conformational population. The $J_{5e,5a}$ couplings reported by Hall and Manville[21] for tri-*O*-acyl-β-D-xylopyranosyl and -α-D-arabinopyranosyl fluorides are not really anomalous; instead, they provide further evidence that, for these derivatives, the less-favored chair form makes a greater contribution to the equilibrium at room temperature than it does in the other systems examined.

Influence of solvent on conformational equilibria. — The data presented in Table IX show that the conformational equilibrium for tri-*O*-acetyl-β-D-xylopyranosyl chloride (**9**) is largely independent of the polarity of the solvent (compare refs. 1 and 2). This observation contrasts with those made for the equilibria of 2-substituted tetrahydropyrans[41,42], which exhibit a decrease in the magnitude of the axial-directing effect with an increase in the dielectric constant of the solvent Results for related systems[43,44] emphasize that effects of the solvent on the position of conformational equilibria are not always explicable merely on the basis of the polarity of the solvent.

It is, therefore, clear that solvation of the dipoles involved in the operation of the anomeric effect is not the only factor that needs consideration when dealing with polysubstituted tetrahydropyran derivatives. As an illustration of the complexity of the problem, an acyloxy substituent has associated with it two dipoles that act in opposite directions, and the presence of several such groups on a tetrahydropyran ring renders very difficult an assessment of which conformation is the more polar and should thus become more favored with increasing polarity of the solvent. The rotational conformation of groups attached to the ring will first have to be determined, before any attempt can be made to calculate conformational dipole-moments in the way used for the 2-alkoxytetrahydropyrans[42].

The chemical nature of the solvent must also be taken into account, because solvent–solute interactions should have a significant influence on conformational tendencies. Interactions between polar solutes and polar solvents increase as the dipole moment of either the solute or the solvent increases[45]. Aromatic solvents can form complexes with the solute by virtue of charge-transfer[45,46]. The strength of such complexes is conformationally dependent, as has been demonstrated by Abraham and co-workers[47] by their results on the rotational isomerism of substituted ethanes;

they found that aromatic solvents have a greater tendency to interact* with the conformer of higher dipole moment (gauche conformer), to the extent of 0.4 kcal. mole^{-1}. Such solvents as chloroform[49] and methanol, which can form hydrogen bonds with the solute, may affect the position of conformational equilibria by altering electrostatic interactions of the tetrahydropyran ring[43] and by increasing the conformational free-energies of the ring substituents[50]. Such solvents as acetone and acetonitrile, which can accept a hydrogen bond, may interact intermolecularly with the more acidic hydrogen atoms of the ring, as, for example, the anomeric protons of an acetylated glycosyl halide.

The internal pressure of a solvent should have an effect on the conformational population of a conformationally mobile compound, since specific conformations can be expected to have different molar volumes[51]. The population of that conformer having the smaller molar volume should increase with increasing solvent pressure[50,51]. The shift in the equilibrium will depend on the polarity of the solvent, because the more polar solvents have larger internal pressures. These considerations will be most important with those compounds, such as the *β*-D-*xylo* derivatives, for which the two chair forms differ the most in their numbers of axial and equatorial groups. It is known that the dimethylcyclohexanes having axial-equatorial substituents have a smaller molar volume (higher density) than the diastereoisomeric, diequatorial forms[52].

Accurate predictions of solvent effects in conformational problems involving polysubstituted tetrahydropyrans will, therefore, require a much more detailed understanding of the various phenomena discussed.

EXPERIMENTAL

General. — 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 and a 1-dm, narrow-bore, polarimeter tube. Infrared spectra were recorded with a Perkin–Elmer "Infracord" Model 137 infrared spectrophotometer. Microanalyses were made by W. N. Rond. T.l.c. 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. Pure, anhydrous chloroform was prepared by passing U.S.P. chloroform through a column of neutral alumina (Woelm) immediately before use.

N.m.r spectra. — Spectra were recorded at 100 MHz with a Varian HA-100 n.m.r. spectrometer operating in the frequency-sweep mode at a probe temperature of 31 ±1°. Unless otherwise noted, spectra were recorded for a concentration of 20% (w/v). Solutions also contained 5% (w/v) of tetramethylsilane (τ = 10.00) as the internal standard and to provide a lock signal. Spin-decoupling experiments were

*For examples of the effect of benzene on the conformational equilibria of cyclic, vicinal dihalides, see Ref. 48.

performed with the HA-100 instrument operating in the frequency-sweep mode. 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 recorded are considered accurate to within $\pm 2°$. 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; they are considered accurate to within ± 0.1 Hz. Chemical shifts are given 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 p.p.m. N.m.r. spectral data are given in Tables III–IX.

Tri-O-acetyl-α-D-xylopyranosyl bromide (**1**). — *β*-D-Xylopyranose tetraacetate was treated with acetic acid saturated with hydrogen bromide by the procedure of Levene and Tipson[53] for the preparation of **5**, to give crystalline **1**, m.p. 100–102° (lit.[54] m.p. 102°).

Tri-O-acetyl-α-D-xylopyranosyl chloride (**2**). — D-Xylose (Pfanstiehl Laboratories, Inc., Waukegan, Illinois) was boiled with acetyl chloride and a trace of zinc chloride according to the procedure of Hudson and Johnson[55], to give crystalline **2**, m.p. 105° (lit.[56] m.p. 105°).

Tri-O-acetyl-α-D-lyxopyranosyl bromide (**3**). — A modification of the procedure of Levene and Wolfrom[25] was used. A solution of crystalline α-D-lyxopyranose tetraacetate[57] (1.5 g, 4.7 mmoles) in anhydrous chloroform (15 ml) was treated with acetic acid (15 ml) saturated in the cold with dry hydrogen bromide gas, and the solution was kept for 2 h at room temperature. The mixture was then poured into a separatory funnel containing cold, anhydrous chloroform (30 ml), and washed rapidly with three portions of ice–water. The organic layer was dried (sodium sulfate) and evaporated under diminished pressure to a thick syrup, which was crystallized from anhydrous ether–petroleum ether (b.p. 30–60°). Three recrystallizations from the same solvent system gave **3** as huge, clear needles; yield 1.2 g (75%); m.p. 118°; $[\alpha]_D^{26}$ +143.8 ±3° (*c* 1.04, anhydrous chloroform); λ_{max}^{KBr} 5.71 (C=O), 7.30, 7.98, 8.13, 8.79, 9.45, 9.89, 10.65, 11.04, 11.20, 11.63, and 14.74 μm.

Anal. Calc. for $C_{11}H_{15}BrO_7$: C, 38.96; H, 4.42; Br, 23.56. Found: C, 39.16; H, 4 51; Br, 23.71.

This bromide **3** had hitherto been reported[9,25] only as a syrup. The crystalline product was somewhat more stable at room temperature than the α-D-*xylo* and *β*-D-*ribo* analogs, but it decomposed with the evolution of hydrogen bromide gas upon standing. It could be kept for longer periods, however, by storage at 0° over Drierite and sodium hydroxide pellets.

Tri-O-acetyl-α-D-lyxopyranosyl chloride (**4**). — A modification[8] of the procedure

of Korytnyk and Mills[26] for the preparation of acetylated glycosyl chlorides having the 1,2-*trans* configuration was used. A solution of crystalline α-D-lyxopyranose tetraacetate[57] (1.5 g, 4.7 mmoles) in anhydrous chloroform (15 ml) was stirred with anhydrous aluminum chloride (1.1 g) for 2 h at room temperature. The mixture was then diluted with benzene and washed with 3 portions of ice–water. The organic layer was dried by passage through a pad of anhydrous magnesium sulfate, and evaporated to a thick syrup, which was crystallized from anhydrous ether–petroleum ether (b.p. 30–60°), and recrystallized twice from the same solvent system to give **4** as thick, colorless needles; yield 1.1 g (80%); m.p. 95.5–96.5°; $[\alpha]_D^{27}$ +90.3 ±2° (*c* 1.03, anhydrous chloroform) [lit.[57] m.p. 96°, $[\alpha]_D^{20}$ +91.0° (*c* 4.14, chloroform)]; λ_{max}^{KBr} 5.71 (C=O) 7.29, 7.98, 8.17, 8.73, 9.41, 9.85, 10.64, 11.04, 11.18, 11.62, and 13.73 μm.

Anal. Calc. for $C_{11}H_{15}ClO_7$: C, 44.83; H, 5.13; Cl, 12.03. Found: C, 45.13; H, 5.20; Cl, 12.14.

Tri-O-acetyl-β-D-ribopyranosyl bromide (**5**). — β-D-Ribopyranose tetraacetate was treated with acetic acid saturated in the cold with dry hydrogen bromide gas, according to the procedure of Levene and Tipson[53], to give **5**, m.p. 94–95° (lit.[53] m.p. 96°).

Tri-O-acetyl-β-D-ribopyranosyl chloride (**6**). — β-D-Ribopyranose tetraacetate dissolved in anhydrous chloroform was stirred with anhydrous aluminum chloride by the general procedure given for the preparation of **4**, to give crystalline **6**; yield 77%, m.p. 94–95° (lit.[58] m.p. 95°).

Tri-O-acetyl-β-D-arabinopyranosyl bromide (**7**). — A solution of crystalline α-D-arabinopyranose tetraacetate in anhydrous chloroform was treated with acetic acid saturated in the cold with dry hydrogen bromide, by the general procedure given for the preparation of **3**, to give crystalline **7**, m.p. 139–140° (lit.[59] m.p. 139°).

Tri-O-acetyl-β-D-arabinopyranosyl chloride (**8**). — D-Arabinose (Pfanstiehl Laboratories, Inc., Waukegan, Illinois) was treated with acetyl chloride and a trace of zinc chloride according to the procedure of Brauns[60], to give crystalline **8**, m.p. 151–152° (lit.[61] m.p. 151–152°).

Tri-O-acetyl-β-D-xylopyranosyl chloride (**9**). — A minor modification[8] of the procedure of Korytnyk and Mills[26] for the preparation of the thermodynamically "unstable" *O*-acetylated glycosyl chlorides was employed to give crystalline **9**, m.p. 112–113° (lit.[26] m.p. 112–113°).

Tri-O-benzoyl-α-D-xylopyranosyl chloride (**10**). — To a solution of α-D-xylopyranose tetrabenzoate (3.0 g, 5.3 mmoles) in anhydrous chloroform (25 ml) was added anhydrous titanium tetrachloride (0.6 ml, 5.5 mmoles). The mixture was boiled under reflux for 2 h, cooled, and diluted with 1,2-dichloroethane. The resulting solution was successively washed once with ice–water, 10% aqueous sodium hydrogen carbonate solution, and ice–water, dried by passage through a pad of anhydrous magnesium sulfate, and evaporated to a syrup which was crystallized from chloroform (8 ml) and ether (50 ml). Two recrystallizations from anhydrous ether–petroleum ether (b.p. 30–60°) gave pure **10**; yield 2.4 g (94%), m.p. 144–146°; $[\alpha]_D^{20}$ +88.1 ±2°

(*c* 1.20, anhydrous chloroform); λ_{max}^{KBr} 5.81 (C=O), 6.91, 7.82, 8.02, 8.48, 9.14, 9.75, 10.94, 11.32, 13.52, and 14.21 μm (aryl).

Anal. Calc. for $C_{26}H_{21}ClO_7$: C, 64.93; H, 4.40; Cl, 7.37. Found: C, 64.77; H, 4.36; Cl, 7.64.

Tri-O-benzoyl-β-D-xylopyranosyl chloride (**11**). — This compound was prepared by a modification of the general procedure of Csűrös *et al.*[27] for the synthesis of the thermodynamically "unstable" tetra-*O*-benzoyl-β-D-glucopyranosyl chloride. A solution of crystalline β-D-xylopyranose tetrabenzoate (3.0 g, 5.3 mmoles) in anhydrous chloroform was treated with an excess of anhydrous titanium tetrachloride (1.5 ml, 14 mmoles) and then stirred for 5 min at room temperature. The reaction was immediately quenched by pouring the mixture into a separatory funnel and washing it rapidly with ice–water (twice). The organic layer was dried by passage through a pad of anhydrous magnesium sulfate, and evaporated to a syrup that was crystallized from ether–petroleum ether (b.p. 30–60°). Two recrystallizations from the same solvent mixture gave **11** as fine, colorless needles; yield 2.0 g (80%), m.p. 143–144°, $[\alpha]_D^{20}$ −108.3 ±3° (*c* 1.07 anhydrous chloroform); λ_{max}^{KBr} 5.81 (C=O), 6.92, 7.62, 7.84, 8.01, 8.51, 9.11, 9.73, 10.64, 11.69, and 14.15 μm (aryl).

Anal. Calc. for $C_{26}H_{21}ClO_7$: C, 64.93; H, 4.40; Cl, 7.37. Found: C, 65.02; H, 4.63; Cl, 7.38.

Tri-O-benzoyl-β-D-ribopyranosyl bromide (**12**). — β-D-Ribopyranose tetrabenzoate was dissolved in 1,2-dichloroethane, and the solution treated with acetic acid presaturated in the cold with hydrogen bromide as described by Fletcher *et al.*[62], to give crystalline **12**, m.p. 150–152° (lit.[62] m.p. 151–153°).

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