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Conformational Studies of Acetonated α-L-Sorbo- and β-D-Fructopyranoses by Means of Proton Magnetic Resonance Spectroscopy[1]

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The favored conformations of the pyranose rings of several acetonated α-L-sorbo- and β-D-fructopyranoses have been revealed by proton magnetic resonance spectroscopy. The conformations of the rings of the pyranoses are unchanged by the introduction of 1,2-*O*- or 1,3-*O*-isopropylidene groups in α-orientation of L-sorbose, but they are affected by the introduction of the 2,3-*O*-isopropylidene group. These findings support the fact that 2,3-*O*-isopropylidene-α-L-sorbopyranose was not obtained by the acetonation of L-sorbose. The rings of diacetonated D-fructopyranoses with a *cis*-fused acetal ring adopt a distorted conformation; however, those of diacetonated L-sorbopyranoses with a *trans*-fused acetal ring are only slightly distorted from the stable 1C conformation. Angyal's anticipation of the difficult acetalation of the *trans*-glycol of a pyranose has been further experimentally supported.

Our previous studies[3] of the conformations of acetonated L-sorbofuranose rings in solutions by proton magnetic resonance (PMR) spectroscopy showed that their conformations, restricted by the ring strain of the isopropylidene ring, play an important role in the acetonation of L-sorbose. As a part of a program of research into the reaction mechanism of the acetonation,[3,4] we have investigated the conformations of the acetonated L-sorbopyranoses, which were obtained at an initial

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[1] Sorboses Part XVI; for Part XV, see Ref. 2.

[2] T. Maeda, M. Kimoto S. Wakahara and K. Tokuyama, This Bulletin, **42**, 2021 (1969).

[3] T. Maeda, K. Tori, S. Satoh and K. Tokuyama, *ibid.*, **41**, 2495 (1968).

[4] a) K. Tokuyama, E. Honda and N. Hōki, *J. Org. Chem.*, **29**, 133 (1964); b) K. Tokuyama and E. Honda, This Bulletin, **37**, 591(1964); c) T. Maeda, *ibid.*, **40**, 2215 (1967).

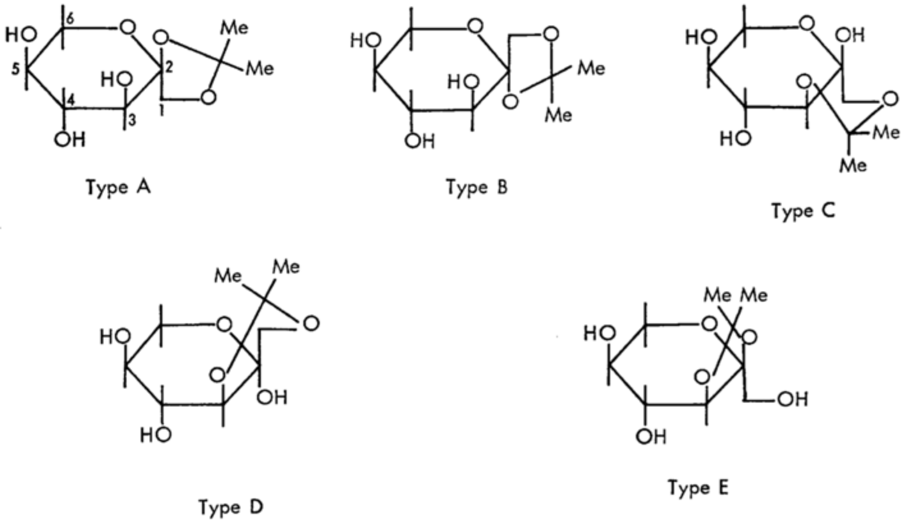
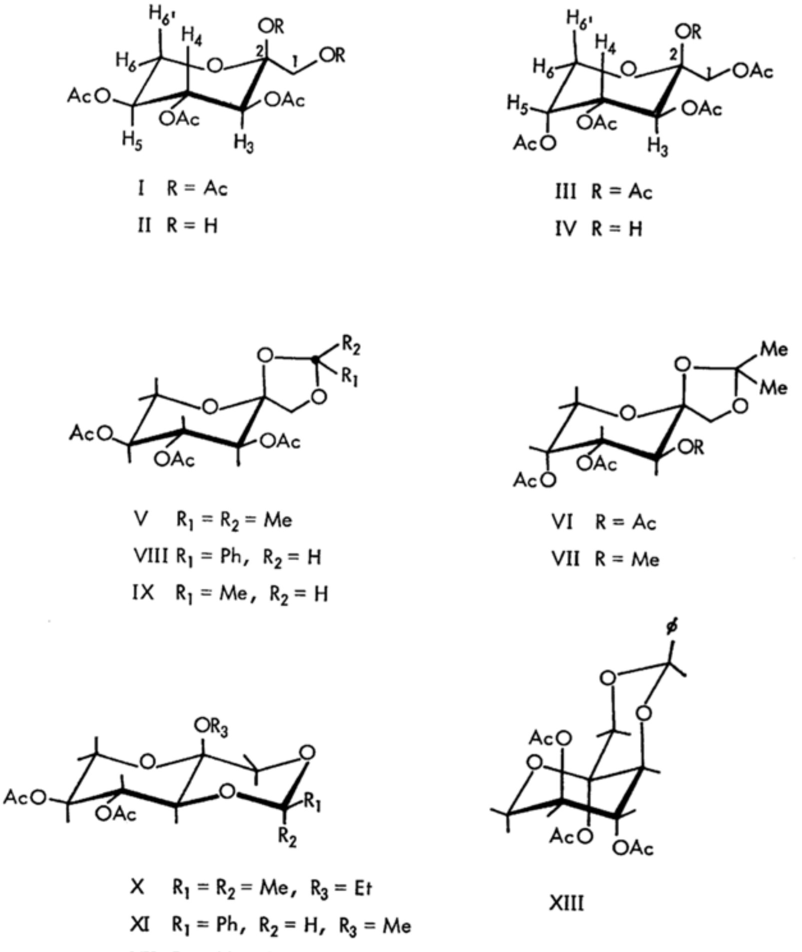


Chart 1



I R = Ac
II R = H

III R = Ac
IV R = H

V $R_1 = R_2 = Me$
VIII $R_1 = Ph$, $R_2 = H$
IX $R_1 = Me$, $R_2 = H$

VI R = Ac
VII R = Me

X $R_1 = R_2 = Me$, $R_3 = Et$
XI $R_1 = Ph$, $R_2 = H$, $R_3 = Me$
XII $R_1 = Me$, $R_2 = H$, $R_3 = Me$

XIII

Chart 2

stage of acetonation.[4–6] In general, there are five possible monoacetonated L-sorbopyranoses; 1,2-*O*-isopropylidene-α- (type A), 1,2-*O*-isopropylidene-β- (type B), 1,3-*O*-isopropylidene-α- (type C), 1,3-*O*-isopropylidene-β- (type D), and 2,3-*O*-isopropylidene-α-L-sorbopyranoses (type E). The benzylidenation[2,7,8] and the ethylidenation[7,9] reactions yielded compounds of the types A and C, while the acetonation produced a type A compound. No compounds of the types B, D and E have yet been isolated; no formation of a type E compound is especially attractive since a derivative of this type can be formed more easily by the acetonation of D-fructose.[10]

Several workers have shown, on the basis of PMR studies, that the pyranose rings of compounds of the type E, such as 1,2-*O*-alkylidene-α-D-glucopyranose[11–14] and 1,2 : 3,4-di-*O*-isopropylidene-α-D-galacto- and β-L-arabinopyranoses (XXIII),[15] adopt distorted chair or skew conformations. In particular, 1,2-*O*-cyanoethylidene-α-D-glucopyranose has been reported to adopt a skew conformation.[11] On the other hand, Trotter and Fawcett[13] pointed out, by X-ray crystal analysis, that this compound is in a distorted, flattened Cl conformation and proposed that the PMR spectra are compatible with the conformation determined in the solid state.

This paper will deal with conformations of the pyranose rings in twelve acetonated derivatives of α-L-sorbo- and β-D-fructopyranoses by means of PMR spectroscopy. The conformations of these compounds were determined on the basis of the magnitude of their vicinal coupling constants, obtained with reference to those of 1,2,3,4,5-penta- (I), and 1,3,4,5-tetra-*O*-acetyl-α-L-sorbopyranoses (II), 1,2,3,4,5-penta- (III) and 1,3,4,5-tetra-*O*-acetyl-β-D-fructopyranoses (IV), all of which have the 1C conformation, as has previously been reported.[16]

Experimental

Measurements. All the PMR spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz at an ordinary probe temperature by using about 5% (w/v) solutions in chloroform-d ($CDCl_3$), benzene-d_6(C_6D_6), pyridine-d_5(C_5D_5N), dimethylformamide-d_7 (DMF-d_7) and/or dimethyl sulfoxide-d_6 (DMSO-d_6). The charts were calibrated with direct readings of resonance frequencies using a Hewlett-Packard HP-5212 electronic counter with accuracies to within ±0.2 Hz or less. The spin-decoupling experiments were performed on the spectrometer in the frequency-swept and TMS-locked modes by using two Hewlett-Packard HP-200 ABR audio-oscillators and the HP-5212 A counter. The accuracies of the magnitudes of the chemical shifts, τ, and the coupling constants, J, are within about τ 0.02 and 0.2 Hz respectively.

The infrared (IR) spectrum of XXII was measured with a Nippon Bunko DS 402 G infrared spectrometer by using a 4.2 mg/8 m*l* (in 20 mm-cell) solution in carbon tetrachloride.

The melting points were recorded on a Kofler micro-stage apparatus and have been corrected. The optical rotations were measured with a Perkin-Elmer model-141 polarimeter. The concentrations were recorded in percentages.

Analysis of PMR Spectra. In the compounds reported here, the pyranose-ring protons, H_6, $H_{6'}$, H_3, H_4, and H_5, can be classified as composing an ABXYZ spin system. Therefore, it is quite certain that their signals show second-order patterns depending on the $\Delta\nu_{ij}/J_{ij}$ values, where $\Delta\nu_{ij}$ is the value of the difference in chemical shifts between H_i and H_j expressed in frequency unit. The signals of the protons H_1 and H_1' appear, in general, as an AB-type quartet. In order to determine the J values from the signal pattern with accuracies to less than 0.2 Hz, their spectra were analyzed by using the proton double resonance (PMDR) technique and by applying the solvent effects of benzene and pyridine. Since all the compounds examined here contain one or two 1,3-dioxolane rings besides hydroxyl or acetoxy groups, an alteration in the solvent from $CDCl_3$ to C_6D_6 or C_5D_5N can be expected to change their PMR spectral patterns considerably.[17] The altera-

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TABLE 1. CHEMICAL SHIFT IN τ VALUE

Compound	Solvent	H_1 $H_{1'}$	H_3	H_4	H_5	H_6	$H_{6'}$	OAc	$CH_3-\overset{\vert}{\underset{\vert}{C}}-$	Other H	
V	$CDCl_3$	6.04, 6.12	4.98	4.57	5.02	6.13	6.23	7.93, 7.98, 7.99	8.52, 8.58		
	C_6D_6	6.10a)	4.82	4.27	4.89	6.1	6.3b)	8.26, 8.29, 8.37	8.62, 8.64		
VI	$CDCl_3$	6.06a)	4.6		4.8b)	6.22	5.92	7.88, 7.94, 8.03	8.53, 8.59		
	C_6D_6	6.00, 6.04	4.31	4.46	4.58	6.53	6.22	8.25, 8.28, 8.30	8.62 (6H)		
VII	$CDCl_3$	5.91, 5.99	6.45	4.79	4.70	6.31	5.95	7.87, 7.98	8.51, 8.58	OCH_3	7.47
	C_6D_6	5.95a)	6.43	4.41	4.52	6.55	6.25	8.24, 8.26	8.55 (6H)		6.77
X	$CDCl_3$	6.04, 6.40	6.28	4.51	5.01	6.19	6.38	7.99 (6H)	8.56, 8.59	OCH_2CH_3	8.72c)
XIV	$CDCl_3$	5.95, 6.01	5.88	4.42	4.77	6.03	6.21	7.89, 7.91, 7.99	8.43, 8.62		
	C_6D_6	5.54, 5.60	5.93	4.21	4.62	6.13	6.23	8.19, 8.28, 8.29	8.51, 8.73		
	DMF-d_7	5.69a)	5.78	4.49	4.85	6.03	6.18	7.88, 7.92, 8.00	8.47, 8.62		
XVI	$CDCl_3$	5.81, 6.01	6.58	5.92	4.94	6.04	6.55	7.93	8.50, 8.55 (6H), 8.58		
	C_6D_6	5.91, 6.00	6.74	5.77	4.94	6.02	6.54	8.38	8.53, 8.62, 8.66 (6H)		
XVII	$CDCl_3$	5.91, 6.05	6.69	6.14	b)	6.21	6.57		8.50, 8.57 (6H), 8.60	OH	7.22
XVIII	$CDCl_3$	6.05a)	4.84	6.13	6.50	6.02	6.26	7.87	8.51, 8.56 (6H), 8.57		
XIX	$CDCl_3$	6.07, 6.17	4.90	5.7			5.9b)	7.88	8.45, 8.52, 8.60, 8.64		
	C_6D_6	6.06, 6.10	4.62	5.72	~6.13	6.0	6.2b)	8.27	8.45, 8.60, 8.64, 8.79		
	C_5D_5N	5.94, 5.98	4.56	5.52	~5.70	5.7	5.9b)	7.94	8.39, 8.49, 8.53, 8.62		
XX	$CDCl_3$	5.82, 6.02	~6.33	5.8			6.0b)		8.45, 8.46, 8.54, 8.61	OH	7.91
	C_5D_5N	5.41, 5.80	5.92	5.42	~5.70	5.75	5.9b)		8.39, 8.44 (6H), 8.60		5.7—5.8
XI	$CDCl_3$	5.56, 5.94	5.67	5.39	5.75	6.09	6.23	7.91	8.45, 8.52, 8.59, 8.65		
XXII	$CDCl_3$	6.31, 6.35	5.66	5.37	5.77	6.09	6.24		8.45, 8.53, 8.60, 8.65	OH	7.59
	C_6D_6	5.9d)	5.1	5.25b)	5.70	5.91	6.15		8.41, 8.42, 8.50, 8.67		5.25
	DMSO-d_6	6.7e)	5.72	5.43	5.80	6.25	6.47		8.55, 8.65 (6H), 8.72		6.6—6.7

a) Observed as a singlet.
b) Not exactly determined owing to overlapping signals.
c) Methylene signal of OCH_2CH_3 group appeared near at τ 6.45 as A_2 part of A_2X_3.
d) After D_2O addition, the methylene signal was appeared as an AB type quartet at τ 5.89 and 5.97.
e) After D_2O addition, the methylene signal was appeared as an AB type quartet at τ 6.66 and 6.74.

TABLE 2. COUPLING CONSTANTS J IN Hz

Compound	$J_{1,1'}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	Other J
I[a)]	11.8	9.9	9.1	6.1	10.5	11.0	
II[a)]	11.8	9.9	9.3	6.1	10.7	11.0	
III[a)]	12.0	10.2	3.3	1.9	1.2	13.0	
IV[a)]	11.6	10.2	3.2	1.9	1.2	13.0	
V	9.4	9.8	9.4	6.1	10.2	11.2	
VI	9.0	10.4	3.2	1.8	1.3	13.2	
VII	8.8	10.0	3.4	1.8	1.3	13.2	
VIII[b)]	9.2	9.6	9.3—9.6	d)	d)	d)	
IX[c)]	9.0	9.7	~9	d)	d)	d)	
X	12.5	10.0	9.2	6.2	10.5	11.0	$J_{CH_2CH_3}=7.0$
XI[b)]	12.0	10.0	9.3	6.3	10.7	10.7	
XII[c)]	12.0	9.8	~9	6.2	10.2	11.0	
XIII[e)]	12.0	2	3	2	2	13	$J_{1,3}\leq 1.0$, $J_{4,6'}\leq 1.0$
XIV	11.8	3.8	3.7	5.3	6.8	12.3	$J_{4,6}=0.5$
XV[f)]	—	3.15	3.15	—	9.6	—	
XVI	9.0	9.6	10.0	5.5	10.0	11.2	
XVII	9.0	9.5	10.0	5.5	10.0	11.2	$J_{5,OH}=3.5$
XVIII	g)	10.4	8.8	5.3	9.7	10.5	
XIX	9.1	7.8	~5.0	~1.8	~1.8	d)	
XX	8.2	7.8	5.0	d)	d)	d)	$J_{3,OH}$[d)]
XXI	12.0	2.5	8.0	1.5	1.0	13.0	$J_{1,OH}=3.8, 9.2$
XXII	11.6	2.5	8.0	1.5	1.0	13.0	
XXIII[a)]	—	2.5	8.0				

a) Reported in Ref. 16. b) Reported in Ref. 8. c) Reported in Ref. 9.
d) Obscured. e) Reported in Ref. 2. f) Reported in Ref. 12.
g) Observed as a singlet.

tion in the solvent frequently changed their signal patterns into those which can be analyzed by the first-order approximation. However, in some cases the signal patterns can be analyzed by the usual procedure.[18] The chemical shifts and J values obtained are summarized in Tables 1 and 2.

Materials. 1,2-*O*-Isopropylidene-3-*O*-methyl-4,5-di-*O*-acetyl-*β*-D-fructopyranose (VII). A solution of 1,2 : 4,5-di-*O*-isopropylidene-3-*O*-methyl-*β*-D-fructopyranose[19] (2.0 g) in 60% aq. acetic acid (10 m*l*) was warmed at 45°C for 4 hr. The complete removal of the solvent under reduced pressure gave a syrup; the syrup was immediately acetylated with acetic anhydride (20 m*l*) and pyridine (20 m*l*) at room temperature for 3 hr. The mixture was then poured onto crushed ice and neutralized with an excess of sodium hydrogencarbonate. The solution was extracted with chloroform; the chloroform solution was washed with water, 2N HCl, and water, and dried with anhydrous magnesium sulfate, after which the solvent was removed. The recrystallization of a residue from water and methanol gave VII in a good yield. It had a mp of 101—102°C, $[\alpha]_D^{21}$ −130.8 (*c* 1.027, acetone). Found: C, 52.96; H, 6.97%. Cacld for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97%.

Ethyl 1,3-*O*-Isopropylidene-4,5-di-*O*-acetyl-*α*-L-sorbopyranoside (X). A mixture of ethyl *α*-L-sorbopyranoside[20] (0.8 g), acetone dimethylketal (15 m*l*) and *p*-toluenesulfonic acid (70 mg) was stirred vigorously at room temperature. A clear solution was soon obtained. After 15 min, the fine crystals which precipitated were collected by filtration. The crystals were recrystallized from ethyl acetate and then acetone. Ethyl 1,3-*O*-isopropylidene-*α*-L-sorbopyranoside was obtained as needles (0.46 g), mp 178—179°C, $[\alpha]_D^{22}$ −60.4 (*c* 0.998, acetone). Found: C, 53.11; H, 7.98%; mol wt, 247. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.26%; mol wt, 248. The needles (1.09 g) were acetylated with acetic anhydride (1 m*l*) and pyridine (1 m*l*) for 18 hr in a refrigerator. The mixture was then poured into ice water (10 g) and made alkaline with sodium bicarbonate. The solution was extracted with chloroform, and the chloroform was washed with a 2N hydrochloric acid solution. The dried extract was evaporated to give X as a syrup (130 mg); $[\alpha]_D^{23}$ −48.6 (*c* 0.970, acetone). Found: C, 54.48; H, 7.44%. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28%.

Results and Discussion

Monoacetonated Derivatives. *i) 1,2-O-Isopropylidene Compounds (Types A and B).* Figure 1 shows the PMR spectrum of 1,2-*O*-isopropyli-

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[19] a) J. C. Irvine and J. P. Scott, *J. Chem. Soc.*, **103**, 564 (1913); b) K. Freudenberg and A. Doser, *Ber.*, **56**, 1243 (1923).

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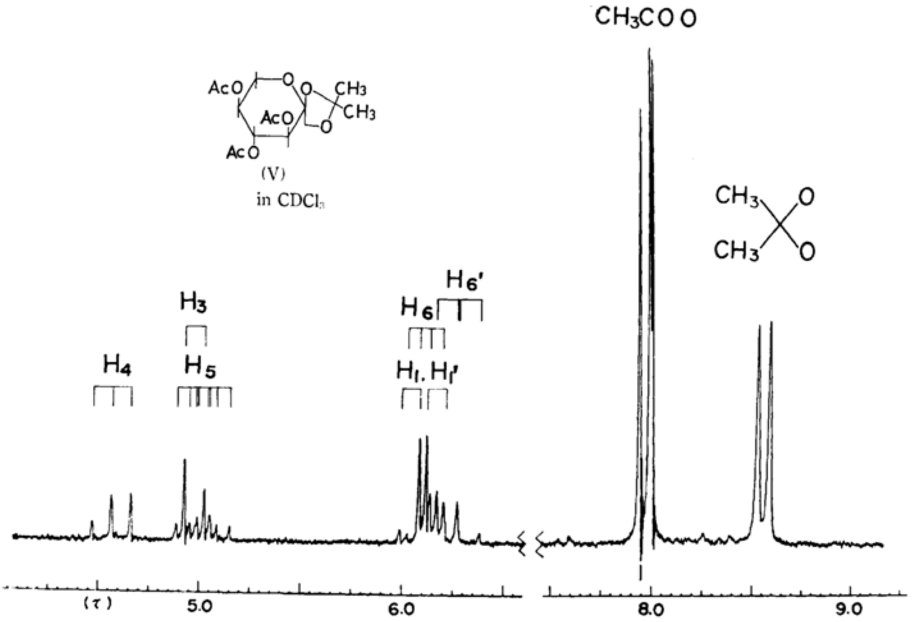

Fig. 1. PMR spectrum of V in $CDCl_3$ at 100 MHz.

dene 3,4,5-tri-*O*-acetyl-α-L-sorbopyranose (V)[4c] in $CDCl_3$ at 100 MHz. Two singlets in the high field (τ 8.52 and 8.58) are due to the isopropylidene methyls; they appear somewhat broad compared with those due to the acetoxyl methyls at τ 7.93, 7.98 and 7.99, because of the long-range coupling over 4 σ bonds.[21] The signals of H_6 and $H_{6'}$ appear as a quartet at τ 6.13 ($J=(-)11.2$ and 6.1 Hz) and a quartet at τ 6.23 ($J=(-)11.2$ and 10.2 Hz) respectively. An AB-type quartet at τ 6.04 and 6.12 ($J=(-)11.8$ Hz) can be assigned to H_1 and $H_{1'}$. Among the three signals arising from H_3, H_4 and H_5 at low fields, the doublet at τ 4.98 ($J=9.8$ Hz) should be assigned to H_3; the doublet at τ 4.57 ($J=9.8$ and 9.4 Hz), to H_4, and the octet at τ 5.02 ($J=9.4$, 6.1 and 10.2 Hz), to H_5. A similar analysis of the spectrum of V in C_6D_6 gave the results shown in Tables 1 and 2. The *J* values determined from the two spectra agreed well with each other. A comparison of the *J* values obtained with those of I and II (see Table 2) confirmed that the pyranose ring of V has the 1C conformation, in which all the secondary acetoxyl groups are equatorial. 1,2-*O*-Benzylidene- (VIII)[8] and 1,2-*O*-ethylidene-3,4,5-tri-*O*-acetyl-α-L-sorbopyranoses (IX)[9] were also believed to be in the conformation (see Table 2).

The spectrum of an analogous derivative of D-fructose, 1,2-*O*-isopropylidene-3,4,5-tri-*O*-acetyl-β-D-fructopyranose (VI),[22] whose C_5-acetoxyl group is expected to be axial, was examined in $CDCl_3$; two quartets due to H_6 and $H_{6'}$ appeared at τ 5.92 ($J=(-)13.2$ and 1.3 Hz) and 6.22 ($J=(-)13.2$ and 1.9 Hz) respectively. The signals of H_1 and $H_{1'}$ coincide as a singlet as τ 6.06. The signals due to other ring protons are too complicated to be analyzed. The spectrum in C_6D_6 shows somewhat separated signals (Fig. 2). Double irradiation at the resonance center of H_6 and $H_{6'}$ at τ 6.53 and 6.22 caused a multiplet at τ 4.58 to collapse into a doublet ($J=3.2$ Hz). The multiplet is clearly assignable to H_5 (Fig. 2b). The remaining doublet and quartet, at τ 4.31 ($J=10.4$ Hz) and τ 4.46 ($J=10.4$ and 3.2 Hz), should be assigned to H_3 and H_4 respectively.

To confirm the assignment of the spectra of of VI, 1,2-*O*-isopropylidene-3-*O*-methyl-4,5-di-*O*-acetyl-β-D-fructopyranose (VII) was also studied. VII was prepared from 1,2:4,5-di-*O*-isopropylidene-3-*O*-methyl-β-D-fructopyranose[19] by hydrolysis with 60% acetic acid, followed by acetylation. The spectra of VII in $CDCl_3$ and in C_6D_6 are readily analyzed. Doublets at τ 6.45 in $CDCl_3$ and at τ 6.43 in C_6D_6 ($J=10.0$ Hz) due to H_3; the quartets at τ 4.79 in $CDCl_3$ and τ 4.41 in C_6D_6 ($J=10.0$ and 3.4 Hz) due to H_4, and the octets at τ 4.70 in $CDCl_3$ and τ 4.52 in C_6D_6 to H_5 are quite distinct. The *J* values obtained ($J_{3,4}=10.0$—10.4 and $J_{4,5}=3.2$—3.4 Hz) from VI and VII agreed well with those obtained from III and IV, which have been established to adopt the 1C conformation.[16] The lower-field part of C_6-methylene proton signals [VI, 5.92 ($CDCl_3$) and 6.22 (C_6D_6); VII, 5.95 ($CDCl_3$) and 6.25 (C_6D_6)]

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21) For example, see S. Sternhell, *Rev. Pure and Appl. Chem.*, **14**, 15 (1964).

22) E. Fisher and H. Noth, *Ber.*, **51**, 339 (1918).

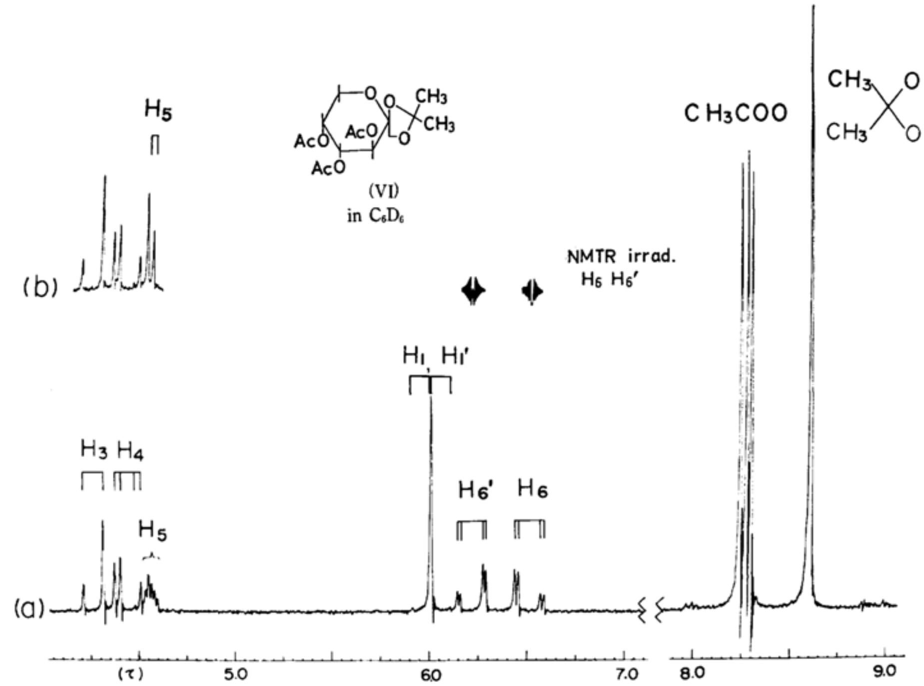

Fig. 2. PMR spectra of VI in C_6D_6 at 100 MHz.
(a) Normal spectrum (b) PMDR spectrum

can be assigned to the axial protons ($H_{6'}$) although the assignment does not obey the general rule[23] that the signal of an axial proton of a pyranose ring appears at a higher field than does that of an equatorial proton. The fact is accounted for by the long-range shielding effects of the acetoxyl group at C_5 in the *trans*-diaxial relation to $H_{6'}$.

The above-mentioned facts, that the pyranose rings of the compounds V—VII adopt 1C conformations, show that the introduction of a 1,2-*O*-isopropylidene ring causes no changes in the stable 1C conformation of the parent pyranose ring.[24] It is noteworthy that no such type B compounds such as *β*-anomer of V, are formed. This can be attributed to the fact that the 1,2-*O*-isopropylidene ring orients the pyranose ring in the same direction as does the influence of the anomeric effect of a methoxyl group as has been reported in the case of L-sorbofuranose.[3] The type B compounds, if they are formed, might exist in an unstable Cl chair or as a mixture of 1C and Cl forms similar to the case of methyl 1,3,4,5-tetra-*O*-acetyl-*β*-L-sorbopyranoside.[16]

ii) 1,3-O-Isopropylidene Compounds (Types C and D). Ethyl 1,3-*O*-isopropylidene-4,5-di-*O*-acetyl-α-L-sorbopyranoside (X) was prepared from the acetonation of ethyl α-L-sorbopyranoside,[21] followed by acetylation. The spectrum of X in $CDCl_3$ is somewhat complicated as a result of the overlapping of the signals. The signals of the methylene protons of the *O*-ethyl group constitute the A_2 part of an A_2X_3 system,[25] which partially overlaps with the higher field part of the C_1-methylene proton signals, H_3, H_6, and $H_{6'}$. The ring protons display a well resolved pattern and could be easily analyzed (Fig. 3). The *J* values obtained from the ring proton signals similar to those of I, II, and V show that the pyranose ring of X should have the 1C chair form. Therefore, X was confirmed to exist as a stable conformation of a *trans*-decalin type. The analogous compounds, methyl 1,3-*O*-benzylidene-(XI)[8] and 1,3-*O*-ethylidene-α-L-sorbopyranosides[9] (XII) also have conformation similar to that of X, judging from their *J* values. Therefore, the easy formation of 1,3-*O*-benzylidene- or 1,3-ethylidene-α-L-sorbopyranose from the acetalation of L-sorbose is reasonable. It is exceptionsl that no 1,3-*O*-isopropylidene-α-L-sorbopyranose is detected from the acetonation; its absence is probably responsible for the high instability of an axial methyl

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23) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London (1959), p. 115.

24) a) J. C. Jochims, G. Taigel, A. Seelinger, P. Lutz and H. E. Driesen, *Tetrahedron Letters*, **1967**, 4363; b) I. Listowsky, S. Englard and G. Avigad, *Carbohyd. Res.*, **2**, 261 (1966).

25) The complicated signal results from the hindrance of the free rotation of the ethyl group around the O–C bond; see Ref. 16.

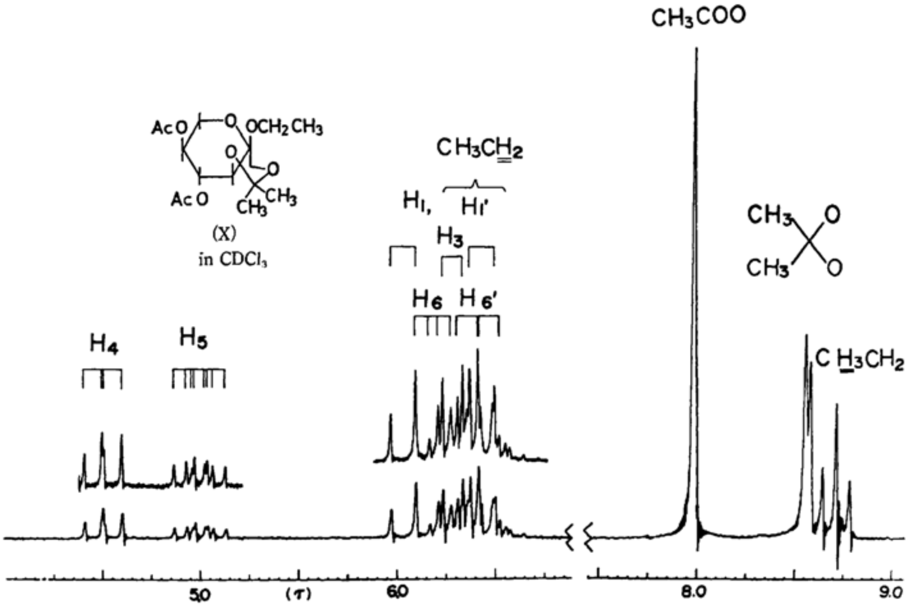
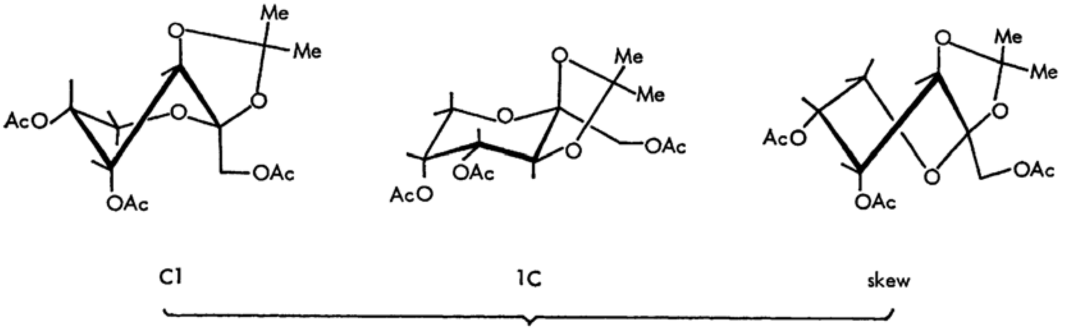


Fig. 3. PMR spectrum of X in $CDCl_3$ at 100 MHz.



XIV

Chart 3

group at the 2-position of 1,3-dioxane.[26] This is known as the Brown-Brewster-Schechter rule.[27]

The type D compounds, the β-anomers of X—XII, have not been detected from the acetalations.[2,4,7–9] Their absence results from their stereochemical instabilities. For instance, an examination of the Dreiding models indicates that they must be in an unstable conformation of a *cis*-decalin type and of the Cl chair form. Our recent studies[2] have supported this suggestion: the pyranose ring of 1,3-*O*-benzylidene-2,4,5-tri-*O*-acetyl-β-L-sorbopyranose (XIII) has been concluded to have the conformation indicated by the models.

iii) 2,3-O-Isopropylidene Compound (Type E). The spectrum of 2,3-*O*-isopropylidene-1,4,5-tri-*O*-acetyl-β-D-fructopyranose (XIV) in $CDCl_3$ exhibits well-separated patterns; the signals were readily assigned as is shown in Fig. 4. Double irradiation at the resonance center of H_4 at τ 4.42 caused the collapse of the doublet assignable to H_3 at τ 5.88 (J=3.8 Hz) into a singlet, and that of the quartet due to H_6 at τ 6.03 (J=0.5, 5.3 and 12.3 Hz) into a sharp quartet (J=5.3 and 12.3 Hz) (Fig. 4b). Therefore, the presence of a long-range coupling between H_4 and H_6 was established.

Rees *et al.*[12] pointed out that 1,2-*O*-isopropylidene-3,4,6-tri-*O*-acetyl-α-D-glucopyranose (XV), the corresponding aldose derivative, has a distorted, flattened Cl chair conformation. Its reported J values are recorded in Table 2. The $J_{3,4}$ and $J_{4,5}$ values in XIV are not greatly different from corresponding values, $J_{2,3}$ and $J_{3,4}$, of XV.[13] Therefore, the pyranose ring of XIV seems to have a distorted, flattened 1C form. The values of the coupling constants, $J_{5,6}$ and $J_{5,6'}$, in the 1C

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[26] E. L. Eliel and Sr. M. C. Knoeber, *J. Am. Chem. Soc.*, **90**, 3444 (1968).

[27] H. C. Brown, J. H. Brewster, and H. Schechter, *ibid.*, **76**, 467 (1954).

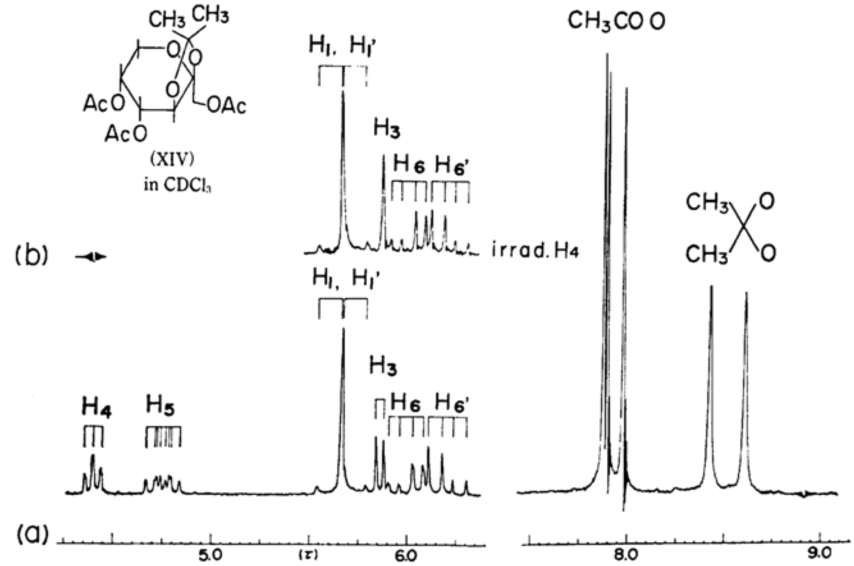
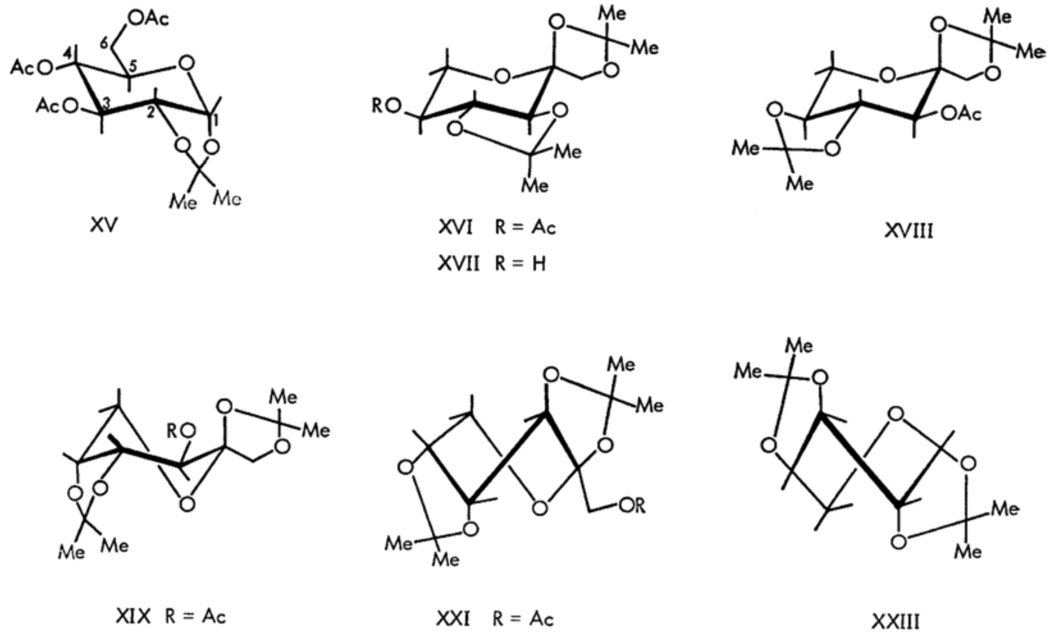


Fig. 4. PMR spectra of XIV in $CDCl_3$ at 100 MHz.
(a) Normal spectrum (b) PMDR spectrum



XV

XVI R = Ac
XVII R = H

XVIII

XIX R = Ac
XX R = H

XXI R = Ac
XXII R = H

XXIII

Chart 4

conformation can be expected to be about 2 Hz from the Karplus correlation,[28] since the H_5 is inevitably situated in the bisectional conformation between H_6 and $H_{6'}$. However, the values of $J_{5,6}$ (5.3 Hz) and $J_{5,6'}$ (6.8 Hz) deviate from the correlation in even a qualitative sense. Other possible skew conformations, among which one depicted in Chart 2 is the most probable, appear highly unlikely judging from the comparison of J values in 2,3 : 4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (XXII),[10] which adopts a skew conformation, as will be described below. Therefore, the distorted Cl conformation is most likely for the pyranose ring of XIV. The presence of the long-range coupling between H_4 and H_6 also sup-

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[28] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).

ported this conclusion, because it seems that H_4 and H_6 should have an equatorial conformation if we apply the "W-letter" rule.[21] As the $J_{5,6}$ value is smaller than the normal $J_{a,a}$ value, and since $J_{5,6'}$ is larger than $J_{a,e}$, the pyranose ring must be flattened. This conformation of XIV is fixed in a temperature range from 37 to 150°C in DMF-d_7 because the J values are unchanged in this temperature range.

The results show that the fused 2,3-*O*-isopropylidene group locked the pyranose ring in an unexpected direction. This is the reason why 2,3-*O*-isopropylidene-α-L-sorbopyranose is not detected in the acetonation of L-sorbose. If this compound were formed, it should adopt an unstable Cl conformation because of the ring strain of the 2,3-*O*-acetal. This unfavorable steric requirement must inhibit its formation.

Diacetonated Derivatives. It has been pointed out[29] that, in order to form the *O*-isopropylidene derivative of a vicinal glycol group of a pyranose a decrease in the projected angle in the chair form imposes little strain on the *cis*-configuration, whereas the acetonation of *trans*-glycol with acetone is impossible since a decrease in the projected angle of *trans*-one would cause severe distortion. Thus, a *trans*-fused 1,3-dioxolane formed from the acetonation with acetone dimethylketal is expected to be formed without such a distortion, that is, it should deform the pyranose ring to which it attached only slightly. We investigated 1,2 : 3,4-di-*O*-isopropylidene-α-L-sorbopyranose (XVII),[4c] its acetate (XVI),[4c] and 1,2 : 4,5-di-*O*-isopropylidene-3-*O*-acetyl-α-L-sorbopyranose (XVIII).[4c]

The spectrum of XVI in $CDCl_3$, shown in Fig. 5 exhibits well-separated signals, which were easily assigned. The assignment was further confirmed by the aid of solvent shifts in C_6D_6 and by comparison with the spectra of XVII in $CDCl_3$ and in C_6D_6. In the case of XVIII, the spectrum in $CDCl_3$ shown in Fig. 6 was rather complicated. Double irradiation at the resonance center of a doublet at τ 4.84 (J=10.4 Hz) due to H_3 caused the collapse of a quartet at τ 6.13 (J=10.4 and 8.8 Hz) assignable to H_4 into the doublet (J=8.8 Hz) (Fig. 6b). The assignment of the remaining signals are quite obvious, as is shown. The J values of XVI—XVIII for ring protons ($J_{3,4}$=9.5—10.4, $J_{4,5}$=8.8—10.0, $J_{5,6}$=5.3—5.5 and $J_{5,6'}$=9.7—10.0 Hz) indicate that their ring conformations are slightly distorted 1C forms compared with those of I, II, and V. In these conformations, and 1,3-dioxolane at the 3,4- and 4,5-positions must adopt half-chair conformations.

The conformation of a pyranose ring is not very much distorted by the introduction of a *trans*-acetal group, but it is much influenced by a *cis*-acetal group, as is confirmed below. In the spectrum of 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (XIX)[23] in $CDCl_3$, an AB-type quartet

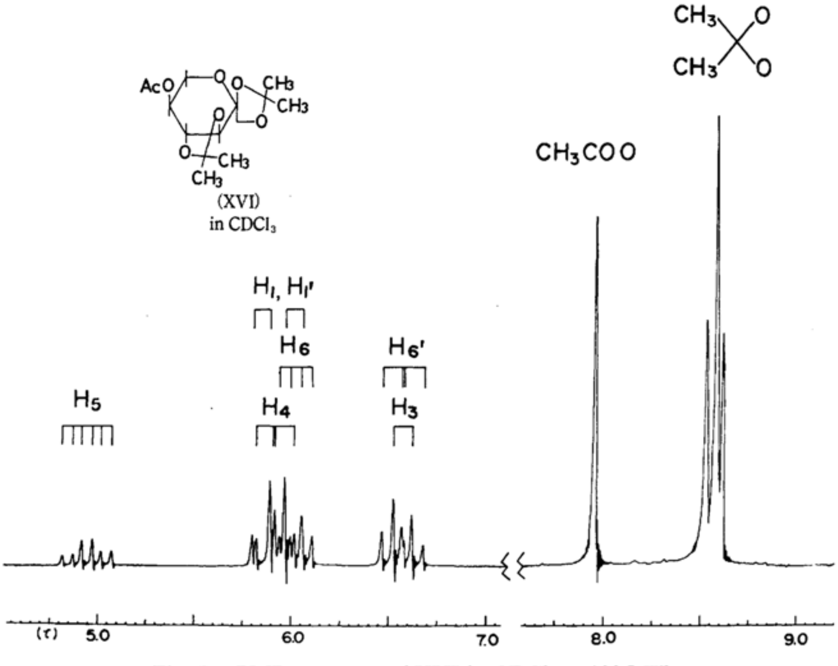

Fig. 5. PMR spectrum of XVI in $CDCl_3$ at 100 MHz.

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[29] a) S. J. Angyal and C. G. MacDonald, *J. Chem. Soc.*, **1952**, 686; b) R. U. Lemieux, "Molecular Rearrangements," ed. by P. De Mayo, Interscience Publishers, New York, N. Y. (1964), Chapter 12.

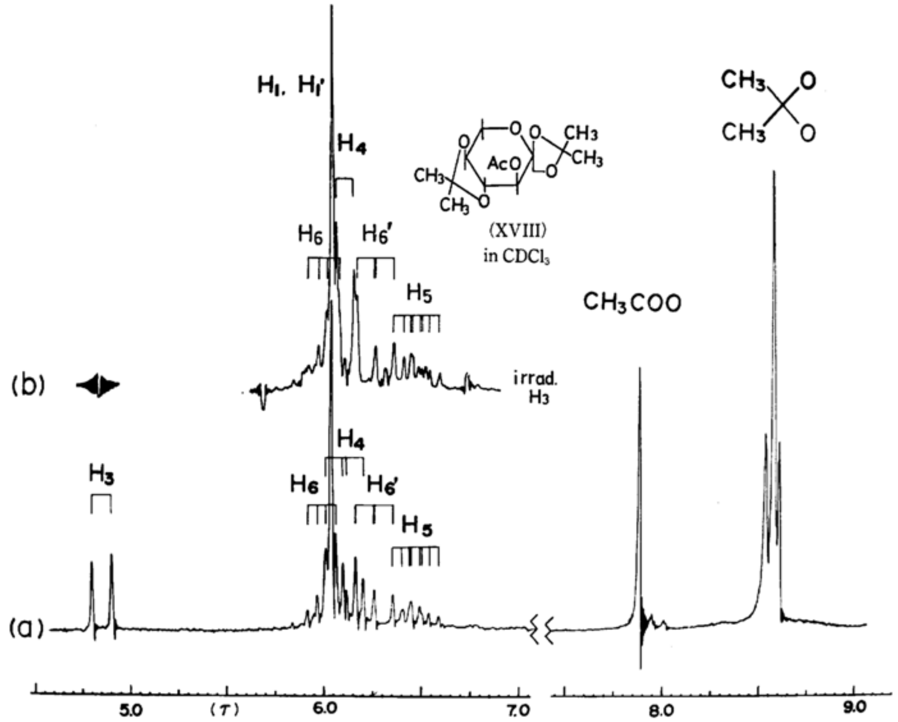

Fig. 6. PMR spectra of XVIII in $CDCl_3$ at 100 MHz.
(a) Normal spectrum (b) PMDR spectrum

assignable to H_1 and $H_{1'}$ appears at τ 6.07 and 6.17 (J=9.1 Hz). The signal due to H_3 is observed at τ 4.90 as a doublet (J=7.8 Hz). The signals of other ring protons are too close to each other to analyze in a simple way. In C_6D_6 and in C_5D_5N, the signals of the ring protons were more separated, although some of them appear as second-order patterns. The spectrum in the last solvent was assigned as is shown in Fig. 7a. Double irradiation at the resonance center of the double at τ 4.56 (J=7.8 Hz) due to H_3 causes the collapse of the multiplet assignable to H_4 around τ 5.52 into a doublet (J=5.0 Hz) (Fig. 7b). Even in these solvents, the signals due to H_5, H_6, and $H_{6'}$ are too close to each other to analyze. The analysis of the spectrum of the deacetyl derivative of XIX (XX)[10a,30] gave similar results. Judging from the J values ($J_{3,4}$=7.8 and $J_{4,5}$=5.0 Hz), the projected angles of $\phi_{3,4}$ seems to decrease, and those of $\phi_{4,5}$ to increase, as compared to the case of VI. Therefore, the conformation of the pyranose ring is more distorted by a *cis*-fused dioxolane than by a *trans*-fused one, as is to be expected.

Finally, we investigated the conformation of 2,3 : 4,5-di-*O*-isopropylidene-β-D-fructopyranose (XXII)[10] and its acetate (XXI).[10] Cone *et al.*[15]

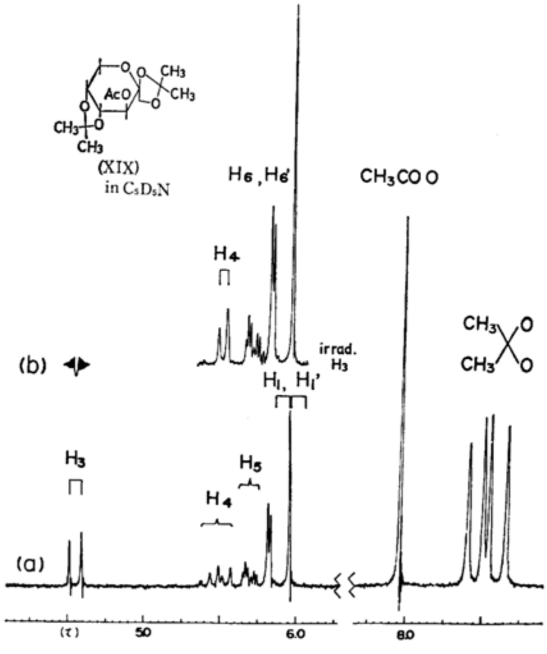

Fig. 7. PMR spectra of XIX in C_5H_5N at 100 MHz.
(a) Normal spectrum (b) PMDR spectrum

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[30] a) J. C. Irvine and A. Hynd, *J. Chem. Soc.*, **95**, 1220 (1909); b) J. C. Irvine and C. S. Garrett, *ibid.*, **97**, 1277 (1910); c) J. C. Irvine and J. Patterson, *ibid.*, **121**, 2146 (1922); d) H. Ohle, *Ber.*, **60**, 1168 (1927).

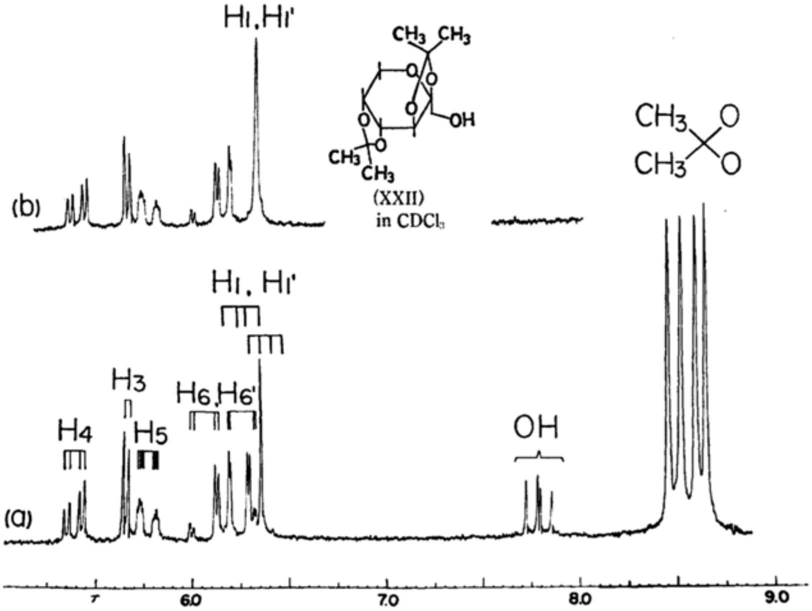

Fig. 8. PMR spectra of XXII in $CDCl_3$ at 100 MHz.
(a) Normal spectrum (b) PMDR spectrum

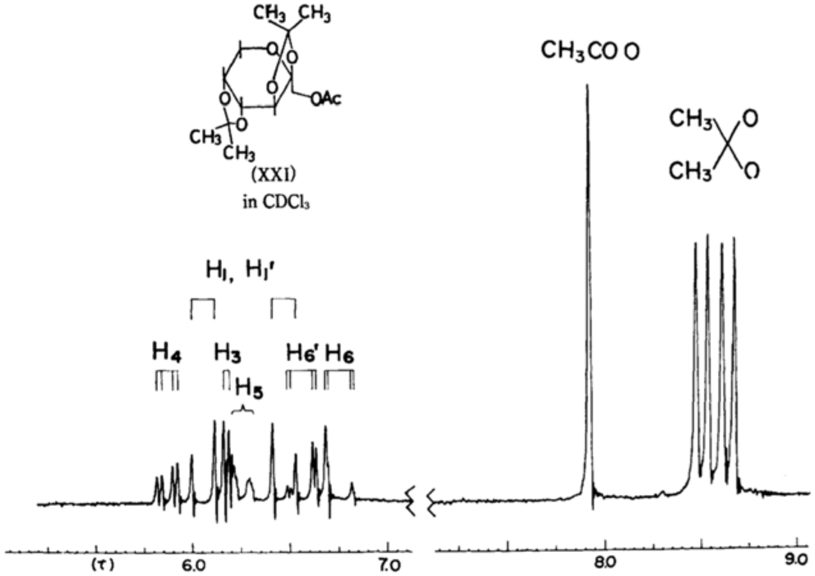

Fig. 9. PMR spectrum of XXI in $CDCl_3$ at 100 MHz.

reported that 1,2:3,4-di-*O*-isopropylidene-α-D-galacto- and β-L-arabinopyranose (XXIII) adopt a skew conformation. Our finding that XIV, the partially deacetonated derivative of XXII, adopts the Cl conformation reasonably led us to anticipate that the pyranose rings of XXI and XXII might adopt a skew conformation, much as the acetonated aldoses have the same arabino-configuration as XXI and XXII. The signals due to the ring protons of XXII are well-separated and are assigned as is shown in Fig. 8a, where the signals due to the $C\underline{H}_2O\underline{H}$ group appear as an ABX-type signal, but the addition of deuterium oxide to the solution examined changed the signal into an AB type quartet (J=12.0 Hz) (Fig. 8b). From the ABX pattern,[18] $J_{1,1'}$, $J_{1,OH}$, and $J_{1',OH}$ were calculated to be 12.0, 3.8, and 9.2 Hz respectively.

The infrared spectrum of XXII in a dilute solution of carbon tetrachloride shows the presence of two OH bands at 3518 and 3640 cm^{-1}; the distances between OH–O have been calculated[31] to be about 1.5 and 2.34 Å respectively. The close proximity between OH–O (1.5 Å) gave valuable information concerning the conformation; an examination of the Dreiding models indicates that the intramolecular hydrogen-bonding of this OH toward C_4–O in the skew conformation depicted in Chart 2, and in other conformations, it is difficult to form the hydrogen-bonding. The latter hydrogen-bonding may exist between C_1–OH and ring-O or C_2–O in that conformation.

The spectrum of XXI in $CDCl_3$ exhibits well-separated signals and was easily analyzed; the results are shown in Fig. 9. The coupling constants obtained from the spectra of both XXI and XXII are in good agreement with those reported for those of XXIII[15] (see Table 2). Thus, the IR spectrum of XXII and the PMR spectra of XXI and XXII are uniquely compatible with the skew conformation.

In conclusion, the compounds of the types A and C have the same 1C conformation as α-L-sorbopyranose. On the other hand, the compounds of the types B, D, and E compounds have distorted conformations. Therefore, the formation of the type A and C compounds at the initial stages of the acetalations of L-sorbose[2,4,5,7–9] is reasonable. We have also established that the conformation of a pyranose is much more influenced by the introduction of a *cis*-fused acetal ring than by that of a *trans*-fused one. This fact experimentally supported Angyal's anticipation[29] of the difficult acetalation of the *trans*-glycol of a pyranose. The easy formation of the type E compound XXII from the acetalation of D-fructose[10] is very interesting, although the reasonable type A compound XX[30] appeared as the initial product. This fact can be explained in the light of the present finding in terms of the distortion of XX, which causes C_3–OH to be so close to C_2–O as to enable them to form the 1,3-dioxolane at the 2,3-position, unlike as in the parent D-fructopyranose.

The authors are deeply grateful to Professor Toshihiko Okamoto, the University of Tokyo, and Dr. Ken'ichi Takeda, Director of this laboratory, for their encouragement.

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[31] The distances were calculated according to Y. Matsui M. Takasuka and T. Kubota, *Ann. Rept. Shionogi Res. Lab.*, **15**, 125 (1965), and T. Kubota, M. Takasuka and Y. Matsui, *ibid.*, **16**, 63 (1966).