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The Acetalation Mechanism of L-Sorbose[1-3]

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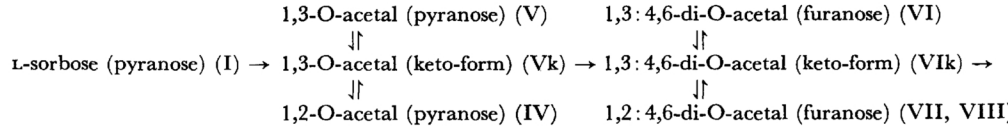
The following reaction mechanism of the acetonation of L-sorbose is proposed:



2,3:4,6-di-*O*-acetal (furanose) (II). The pyranose-to-furanose ring conversion (I→II) proceeds *via* the keto-form intermediates Vk and VIk; VIk is formed by the preferable attack of acetonating reagents on the primary hydroxyl group at the C_6 of Vk followed by cyclization with the hydroxyl group at C_4. The isolation of such keto-form intermediates as were successfully obtained from the acetalations of 1-*O*-methyl- (X) and 1,6-di-*O*-methyl-L-sorboses (XVIII) gave strong support to the above mechanism. This acetonation mechanism can also be used in the other acetalations of I; however, in the case of the benzylidenation there is a possibility that the reaction might be *via* the pathway of 1,3-*O*-acetal (pyranose)⇄1,3-*O*-acetal (furanose) (Vb)→1,3:4,6-di-*O*-acetal (furanose).

The acetonation of L-sorbose (I) is used to prepare a synthetic intermediate, 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (II), for L-ascorbic acid production.[4] However, this process has not yet been subjected to systematic studies despite its relatively lower yield and longer reaction period compared with other process of L-ascorbic acid production. Without any detailed evidence, it has long been believed that the mechanism of the acetonation is that I exists as α-L-sorbofuranose, which is converted into II *via* 2,3-*O*-isopropylidene-α-L-sorbofuranose (III) (mechanism 1).[5] Recently, however, I was confirmed to exist as α-L-sorbopyranose in the 1C conformation by the analyses of the PMR spectra[6] and of the optical rotatory dispersion.[7] The pyranose-to-furanose equilibrium of I was concluded to shift far to the left, as in D-glucose and D-xylose, becuase of its xylo-configuration.[8] Accordingly, the mechanism 1 is unlikely.

A correct mechanism was necessary to improve the reaction conditions of the acetonation. We have proposed previously that the process of the acetonation with acetone in the presence of sulfuric acid should be *via* the pathway of I→1,2-*O*-isopropylidene-α-L-sorbopyranose (IV)→$(IV)_2$→II⇆III (mechanism 2).[9]

Our recent works[10,11] have shown that the acetonation with acetals of acetone affords many kinds of acetonated compounds including the above-described derivatives under controlled conditions. These compounds were 1,3:4,6-di-*O*-isopropylidene-β-L-sorbofuranose (VI) and 1,2:4,6-di-*O*-isopropylidene-α- (VII) and β-L-sorbofuranoses (VIII). Besides these types of compounds, 1,3-*O*-ethylidene-α-L-sorbopyranose (Ve)[12] and 1,3-*O*-benzylidene-

1) Sorboses, Part XVII, for Part XVI see Ref. 3.

2) Some of the results of this paper have been presented in a preliminary form in T. Maeda and K. Tokuyama, *Tetrahedron Letters*, **1968**, 3079, and at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., U. S. A., September, 1968.

3) T. Maeda, K. Tori, S. Satoh and K. Tokuyama, This Bulletin, **42**, 2635 (1969).

4) T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

5) For example, see D. C. DeJoungh and K. Biemann, *J. Am. Chem. Soc.*, **86**, 67 (1964).

6) J. C. Jochims, G. Taigel, A. Seelinger, P. Lutz and H. E. Driesen, *Tetrahedron Letters*, **1967**, 4363.

7) I. Listowsky, S. Englard and G. Avigad, *Carbohyd. Res.*, **2**, 261 (1966).

8) a) R. U. Lemieux, "Molecular Rearrangements," ed. by P. de Mayo, Interscience Pub., New York (1964), Chapter 12; b) S. J. Angyal, "Conformational Analsis," ed. by E. L. Eliel, N. A. Allinger, S. J. Angyal and G. A. Morrison, John Wiley & Sons, New York (1965), Chapter 6.

9) K. Tokuyama, E. Honda and N. Hōki, *J. Org. Chem.*, **29**, 133 (1964).

10) K. Tokuyama and E. Honda, This Bulletin, **37**, 591 (1964).

11) T. Maeda, *ibid.*, **40**, 2122 (1967).

12) T. Maeda, M. Kiyokawa and K. Tokuyama, *ibid.*, **42**, 492 (1969).

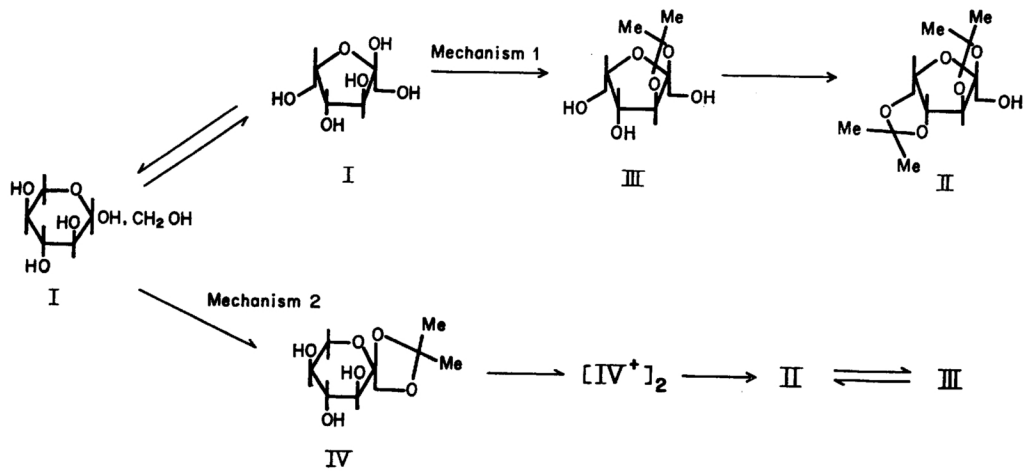


Chart 1

α-L-sorbopyranose (Vb)[13] were obtained from the ethylidenation and the benzylidenation reactions respectively.[14] Ohle[15] reported an unknown diacetonated compound; we identified it as VI by acetonating I with acetone in the presence of cupric sulfate. Patil and Bose[16] reinvestigated his reaction and isolated this unknown product. They also reported the formation of III, VII and 1,2-*O*-isopropylidene-α-L-sorbofuranose (IX).

The mechanism 2 could not explain the formation of the above-described reaction products. It was, then, found necessary to alter it, although the initial formation of IV has been unequivocally established.[9] The present paper presents a novel reaction mechanism of the acetonation, generally the acetalation, of I, a mechanism which accounts for the yielding of new intermediate products.

Results and Discussion

When slightly acidic conditions were used, the acetonation of I afforded II, VI, VII, and VIII.[10,11] On the other hand, mostly II was obtained under highly acidic conditions.[4,9] The acidic treatment of VI in the absence of acetonating reagents easily gave II as the major product and VII and VIII as the minor products, while such a treatment of VII or VIII gave II to only a limited extent. Therefore, the acetonation process must be *via* the pathway of I→(IV⇄VII⇅VI→II⇄III. This pathway sorbopyranose (V))→VIII agreed well with the results of the ethylidenation[12] and the benzylidenation.[13] Although V was not obtained, the formation of Ve and Vb from other acetalations suggested its possible presence.

Formation of Monoacetonated Pyranoses (IV and V). In a preceding paper,[3] we confirmed the conformational role in the stability of the acetonated sorbopyranoses. The results can be summarized as follows: (i) the formation of β-anomers of IV and V is inhibited by their unfavorable steric factors, and (ii) that of 2,3-*O*-isopropylidene-α-L-sorbopyranose can be ruled out because of the strain of the 2,3-*O*-isopropylidene ring, which causes the pyranose ring conformation to be changed from the stable 1C chair to the unfavorable C1 form. Therefore, only IV and V can be formed.

The alcohol structure has a remarkable influence upon the acetal formation in the markedly decreasing order of primary→secondary→tertiary.[17] Among the five hydroxyl groups of the α-pyranose form of I in the 1C conformation, the axial hydroxyl group at C_2 is tertiary and is sterically hindered with axial hydrogens at C_4 and C_6; the three equatorial hydroxyl groups at C_3, C_4 and C_5 are considered to be hindered because of the steric over-crowding. The primary hydroxyl at C_1, which is sterically least hindered, is the most reactive in acetal formation. The conjugate acid of acetone or acetals of acetone reacts with the primary hydroxyl to afford a protonated form, XXI, as an intermediate; this may then be converted into stable

13) T. Maeda, M. Kimoto, S. Wakahara and K. Tokuyama, *ibid.*, **42**, 1686 (1969); *ibid.*, **42**, 2021 (1969).

14) The suffixes e and b used here mean the ethylidenated and benzylidenated analogs, respectively, corresponding to the acetonated analogs.

15) H. Ohle, *Ber.*, **71**, 562 (1938).

16) J. R. Patil and J. L. Bose, a) *J. Indian Chem. Soc.*, **43**, 161 (1966); b) *Indian J. Chem.*, **5**, 598 (1967).

17) R. H. Adkins, *J. Am. Chem. Soc.*, **49**, 2517 (1927); **55**, 299 (1933); **56**, 442 (1934).

IV and V by two possible cyclic acetal formations with hydroxyl groups at C_2 and C_3 respectively. Therefore, the formation of IV and V at the initial stages is quite reasonable. Two compounds of the type V, Ve and Vb, were easily obtained from the ethylidenation[12] and the benzylidenation,[13] however, V itself could not be isolated. This must result from the instability of the axial methyl group at the 2-position of 1,3-dioxane of V, since one of two methyl groups is inevitably axial in the chair conformation of the six-membered *O*-isopropylidene group.[18,19] Of course, the 1,3-*O*-isopropylidene derivative was easily prepared when the hydroxyl at C_2 was blocked.[3] The predominant attack of acetalating agents on the primary hydroxyl groups sterically least hindered accords well with the results of the acetalations of D-glucose and D-galactose,[20–22] which yield 4,6-*O*-acetalated compounds as the initial products. In both acetalations, the primary hydroxyl groups at C_6 are initially attacked by aldehydes or their conjugate acids.

Ring Conversion of Monoacetonated Pyranoses to Diacetonated Furanoses. The ring conversion of the pyranoses (IV and V) to the furanose (VI) is the most important step in the acetonation. We can assume the presence of a keto-form intermediate, Vk, which is an equilibrium intermediate between IV and V. The primary hydroxyl group at C_6 of Vk must be most reactive for the same reason as in the case of the α-pyranose form of I. The keto-form intermediate, Vk, reacts with acetonating reagents to afford XXII, which is then converted into VIk, the keto-form of VI, by 1,3-dioxane ring formation at the 4,6-position. Thus-formed VIk is isolated as the furanose form, VI. In this step, another intermediate, XXIII, with 1,3-dioxolane might exist, since it is well known, in the acid-catalyzed acetalations of glycerol, that the 1,3-dioxolanes form rapidly in the initial kinetic phase and that the 1,3-dioxanes are predominant at equilibrium.[23]

This idea that the pyranose-to-furanose conversion can occur through keto-form intermediates was supported by the following evidence. 1-*O*-Methyl-L-sorbose (X)[24] was prepared from 1-*O*-methyl-2,3 : 4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XI)[25] by partial deacetonation with 60% acetic acid to give 1-*O*-methyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XII),[25] followed by further deacetonation with 1N hydrochloric acid at room temperature. As the acetylation of X gave 1-*O*-methyl-3,4,5-tri-*O*-acetyl-α-L-sorbopyranose (XIII) exclusively, X adopts to a pyranose form. The acetonation of X gave 1-*O*-methyl-3,4: 5,6-di-*O*-isopropylidene-L-sorbose (XIV). The IR spectrum (liquid film) of XIV showed an absorption band at 1738 cm^{-1} due to a carbonyl group. The reduction with lithium aluminum hydride in ether yielded an alcohol, which was isolated as a benzoate (XV). The structure of XV was identified as 5-*O*-benzoyl-6-*O*-methyl-1,2:3,4-di-*O*-isopropylidene-D-glucitol; it was synthesized from 6-*O*-benzoyl-1,2:3,4-di-*O*-isopropylidene-D-glucitol (XVI)[26] by the scheme as shown in Chart 2. Therefore, the structure of XIV was established. The further acetonation of X gave XI at the expense of XIV. The pyranose-to-furanose conversion (X→XI) apparently occurred through the keto-form intermediate (XIV). This result unequivocally supported the idea that the pyranose-to-furanose conversion (IV, V→VI) in the acetonation of I can occur through the keto-form intermediates.

1,6-Di-*O*-methyl-L-sorbose (XVIII) was prepared from XII *via* 1,6-di-*O*-methyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XVII) by partial methylation with methyl iodide in the presence of silver oxide, followed by the deacetonation of the 2,3-*O*-isopropylidene group with 1N hydrochloric acid at room temperature. The acetalation of XVIII was expected to afford the derivative of a furanose form, since XVIII can not adopt a pyranose form. The benzylidenation of XVIII with benzaldehyde unexpectedly gave 1,6-di-*O*-methyl-3,5-*O*-benzylidene-L-sorbose (XIX), accompanied by other two monobenzylidenated derivatives.[27] The IR spectrum (Nujol mull) of XIX showed the existence of a band due to carbonyl at 1720 cm^{-1}. The PMR spectra of the acetate of XIX (XX) in $CDCl_3$ and in C_6D_6 showed a triplet at τ 4.55 ($J_{3,4}=J_{4,5}=1.8$ Hz) assignable to the signal of the proton at C_4 bearing acetoxyl group. These spectral data supported the proposed structure. The formation of XIX suggested that even XVIII reacted as a keto-form in the acetalation, and supported the above-described idea.

Formation of the Final Product, II. Thus-formed VIk can be converted into four furanoses, VI, VII, VIII, and II. It is quite natural to assume

18) H. C. Brown, J. H. Brewster and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).
19) E. L. Eliel and Sr. M. C. Knoeber, *ibid.*, **90**, 3444 (1968).
20) T. G. Bonner, E. J. Bourne and D. Lewis, *J. Chem. Soc.*, **1965**, 7453.
21) D. H. Ball, *ibid.*, **1958**, 7905.
22) Z. G. Gros and V. Deufleu, *Chem. Ind. (London)*, **1962**, 1502.
23) a) N. Baggett, J. M. Duxbury, A. B. Foster and J. M. Webber, *Carbohyd. Res.*, **2**, 216 (1966); b) N. Baggett, K. W. Buch, A. B. Foster and J. M. Webber, *J. Chem. Soc.*, **1965**, 3401.
24) J. C. Swoden and I. I. Mao, *J. Org. Chem.*, **25**, 1461 (1960).
25) K. Tokuyama and M. Katsuhara, This Bulletin, **39**, 2728 (1966).
26) H. Mizoiri, A. Sera and R. Goto, *ibid.*, **37**, 1023 (1964).
27) Their structures were not determined.

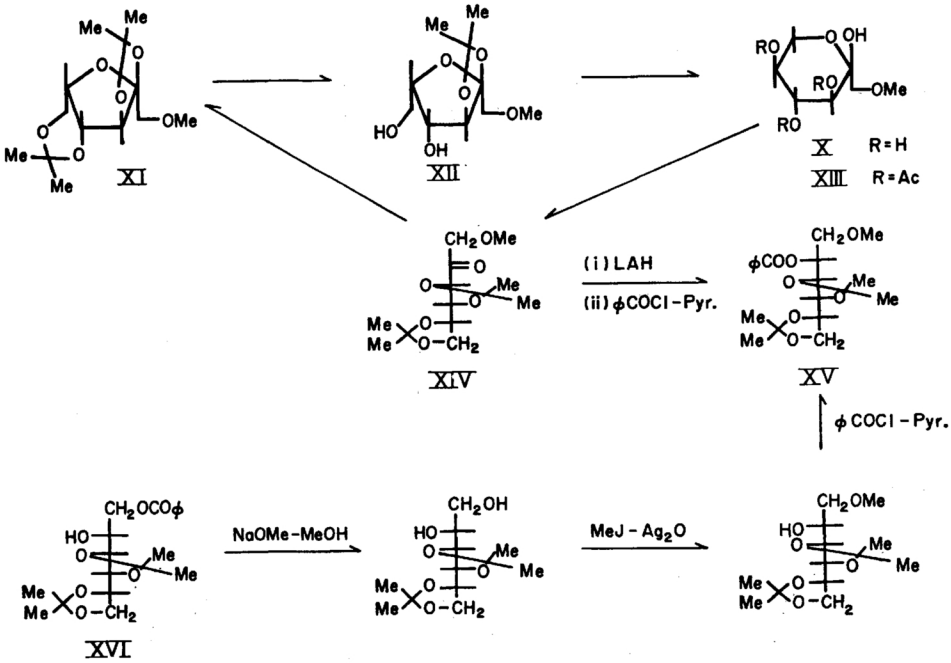


Chart 2

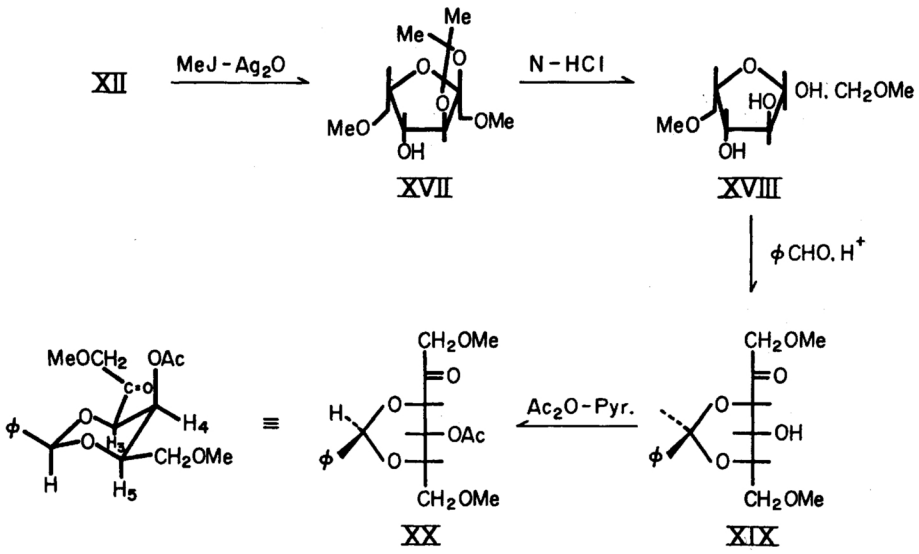


Chart 3

the existence of an equilibrium of furanoses, VII, VIII⇄VIk⇄VI, corresponding to that of pyranoses, IV⇄Vk⇄V. The stabilities of these diacetonated furanoses have been previously reported.[28] All these furanoses have a 4,6-*O*-isopropylidene group, which locks their furanose ring to the half-chair conformation of the C_3-*exo*-C_4-*endo* type. The 2,3-*O*-isopropylidene group of II and the 1,3-*O*-isopropylidene group of VI also lock the furanose ring in the same direction. Therefore, II and VI are more stable than the others. As Brown, Brewster, and Schechter pointed out,[18] a five-membered isopropylidene ring is more stable than a six-membered one. II is the most stable form among the diacetonated furanoses. Thus, VIk can be converted into II preferably.

As has been described above, it may be concluded

28) T. Maeda, K. Tori, S. Satoh and K. Tokuyama, This Bulletin, **41**, 2495 (1968).

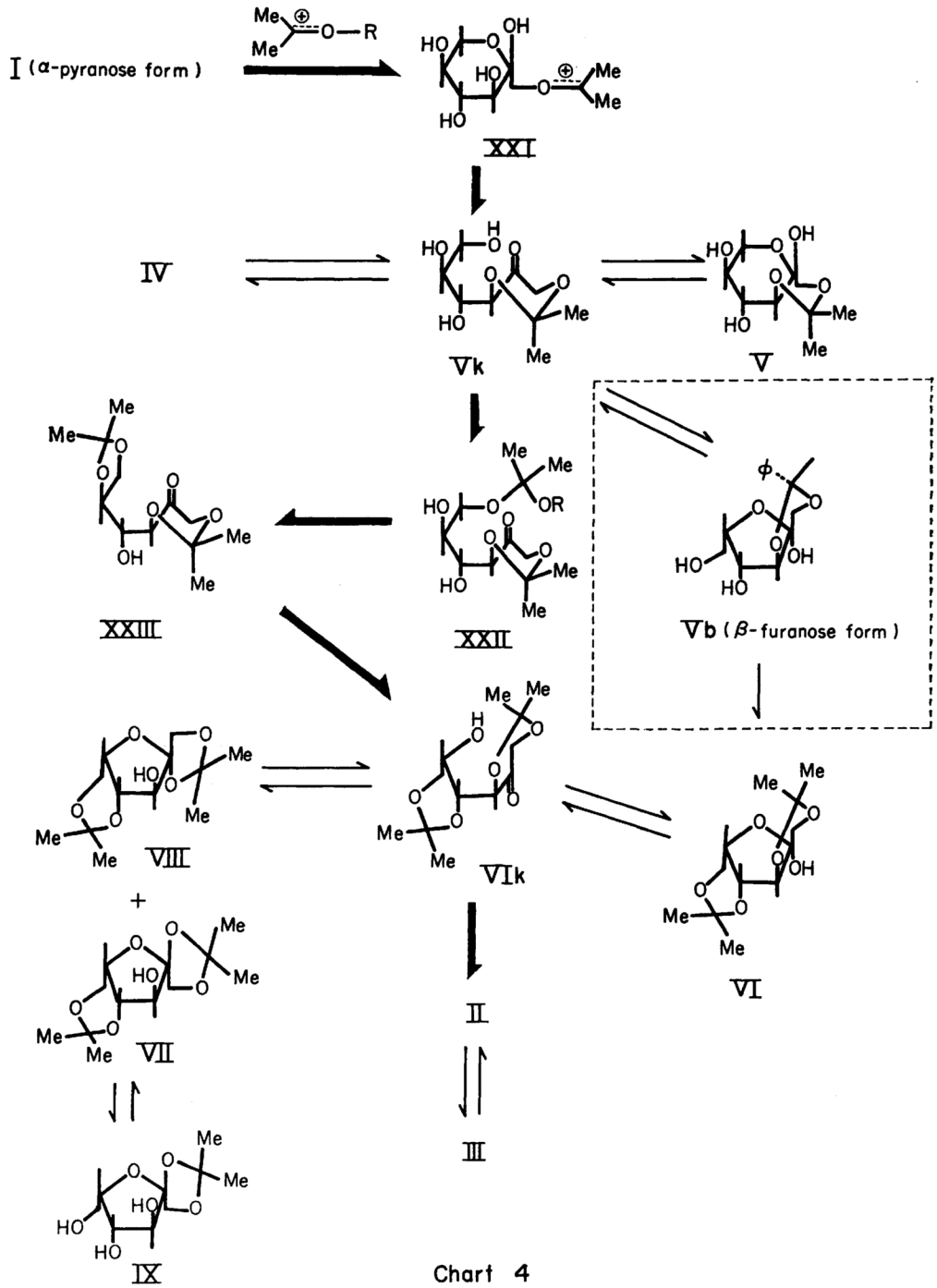


Chart 4

that the acetonation occurs *via* keto-form intermediates. The process of the acetonation proceeds *via* the pathway of

$$\begin{array}{ccccc} & & \text{IV} & & \text{VI} \\ & & \downarrow\uparrow & & \downarrow\uparrow \\ \text{I} \rightarrow & \text{Vk} & \rightarrow & \text{VIk} & \rightarrow \text{II}. \\ & & \downarrow\uparrow & & \downarrow\uparrow \\ & & \text{IV} & & \text{VII,VIII} \end{array}$$

The pathway is shown in detail in Chart 4, which includes minor pathways. The benzylidenation and the ethylidenation gave similar products under acidic conditions similar to those of the acetonation. Therefore, it may reasonably be concluded that the proposed mechanism for the acetonation can be generally applied to acetalations.

In the case of the benzylidenation,[13] the *β*-

furanose form of 1,3-*O*-benzylidene-L-sorbose (Vb) was found; the analyses of the PMR spectra and of the acetylation products of Vb clearly showed the existence of an equilibrium between the α-pyranose and the β-furanose forms.[13] The compound exists as the β-furanose form in a crystalline state and as an equilibrium mixture of the α-pyranose form, the keto-form and the β-furanose form in a solution. It is difficult to explain the preference of the β-furanose form of Vb only in the benzylidene derivative on the basis of the steric effect. Some additional polar factor of the 1,3-*O*-benzylidene ring must possibly be assumed,[13] since the acetate of the unstable β-pyranose form is abnormally obtained from the acetylation of Vb in the same proportion as that of the α-pyranose form. The existence of the β-furanose form of Vb suggests the possibility that the benzylidenation, proceeds exceptionally, *via* the β-furanose form of Vb.

We have shown that the process of the acetonation with acetone should be *via* the pathway of I→IV→$(IV)_2$→II⇄III because of the second-order reaction at the step from IV to II.[9] The intermediate IV was concluded to be acetonated with another molecule of IV, but not with acetone. The present kinetic study shows that the addition of a large amount of acetone dimethylketal to a solution of IV in acetone containing sulfuric acid changed the reaction order from the second-order to the first-order. This means that the acetals of acetone attack more easily than acetone does; the dimeric intermediate $(IV)_2$ should thus be XXII, in which the "OR" group is L-sorbose moiety. The preferable attack of the acetals must be caused by the stabilities of the intermediates XXII; the reaction with acetone gave XXII of the hemiacetal type (R=H), which should naturally be less stable than XXII of the acetal type (R=alkyl or sorbose) formed from the reaction with acetals of acetone.

It is very interesting that the reaction also proceeds when such a non-acidic catalyst as cupric sulfate was used; even in this case, however, the medium became slightly acidic because the formation of the complex of I with cupric ion freed the sulfuric acid. Therefore, it can be said that this reaction is also a kind of acid-catalyzed acetonation. Thin-layer chromatographic analyses showing the presence of the common intermediates IV—VIII supported this conclusion. Patil and Bose[16b] suggested a pathway of IV→IX→VII, which is similar to mechanism 1. Their suggestion is unlikely for the same reason that the mechanism 1 is. Further, there is no driving force to transform the pyranose IV into the furanose IX. The formation of IX might be due to the equilibrium with VII, as III is formed from II.

Experimental

All the melting points were recorded on a Kofler micro-stage apparatus and have been corrected.

The optical rotations were determined in an acetone solution unless otherwise stated, and the concentrations were recorded in percentages.

The PMR spectra were measured on a Varian A-60A spectrometer using 5% solutions of the samples in either chloroform-d ($CDCl_3$) or benzene-d_6 (C_6D_6), with TMS as the internal standard. The range of chemical shifts shown means merely that the signals occurred somewhere in the range.

Thin-layer chromatography was carried out on a silica gel plate using either acetone-chloroform (1 : 9 v/v, solvent A) or *n*-hexane-ether (2 : 1 v/v, solvent B) for both detection and preparation. The R_f values of the products were reported for II—VIII. The separated materials were located with iodine vapor of 0.2% resorcin in 10% ethanolic phosphoric acid (Seliwanoff test),[29] followed by heating on an oven. The separations of the reaction products were carried out by preparative thin-layer chromatography (PTC) unless otherwise noted. In some cases, the developed zones were extracted with acetone. The evaporation of the acetone *in vacuo* gave materials. The solvents used were removed under reduced pressure at below 40°C.

Transformation of 1,3:4,6-Di-*O*-isopropylidene-β-L-sorbofuranose (VI). i) A mixture of VI[11] (1.0 g), acetone dimethylketal (5 m*l*), chloroform (5 m*l*), and *p*-toluenesulfonic acid (TsOH) (50 mg) was stirred at room temperature for 4 hr. The solution was neutralized with methanolic sodium methoxide and then concentrated. The chloroform solution of the residue was washed, dried, and evaporated to a crystalline syrup (1.05 g). The recrystallization of the syrup from benzene gave the starting material, VI (170 mg). From the mother liquor, VI[11] (41 mg), 1,2:4,6-di-*O*-isopropylidene-α- (VII)[10,11] (71 mg) and β-L-sorbofuranoses (VIII)[11] (13 mg) were isolated.

ii) A solution of VI (1.0 g), chloroform (5 m*l*), ether (10 m*l*), and TsOH (55 mg) was stirred at 45—48°C for 3 hr and then worked up in a way similar to that described above. A syrup (1.0 g) was obtained, and from the syrup 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (II)[4] (27 mg), VII (94 mg), VIII (30 mg), and VI (88 mg) were isolated.

Transformation of VII and VIII. A mixture of VII (500 mg), chloroform (3 m*l*), ether (5 m*l*), and TsOH (28 mg) was stirred at 40—45°C for 3 hr and then worked up in a way similar to that described above. A crystalline syrup was obtained. The recrystallization of the syrup gave the starting material (VII) (230 mg). From the mother liquor, a syrup (41 mg) was obtained; the thin-layer chromatogram of the syrup showed the starting material (VII) as a major spot and II and VI as minor spots. Similar results were obtained from the reaction of VIII under the same conditions.

1-*O*-Methyl-L-sorbose (X). A solution of 1-*O*-methyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XI) (30.5 g) in 60% aq. acetic acid (110 m*l*) was warmed at 40°C. After 3 hr, the solution was evaporated completely. The distillation of the residue gave 1-*O*-methyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XII) (26.7 g), bp 148—150°C/2 mmHg. XII (10 g) was

29) A. Anno and N. Seno, "Jikken Kagaku Kōza," Bd. 23, ed. by Chem. Soc. Japan, Maruzen, Tokyo (1957), p. 374.

hydrolyzed with 1N hydrochloric acid (100 ml) at room temperature. After 2 days, the reaction mixture was neutralized with a slight excess of Amberlite IR-45 and then evaporated to give X as a syrup (7.8 g), $[\alpha]_D^{24}$ −32.9 (*c* 0.471, water). Found: C, 43.29; H, 7.38%. Calcd for $C_7H_{14}O_6$: C, 43.29; H, 7.27%.

Acetylation of X. A mixture of X (2.0 g), acetic anhydride (10 ml), and pyridine (10 ml) was reacted in a refrigerator. After 16 hr, the solution was poured onto crushed ice and made alkaline with sodium bicarbonate. The chloroform extract was washed with 1N hydrochloric acid, and water, and then dried. The evaporation of the solvent gave crude crystals (1.8 g). The recrystallization of the crystals from ether gave 1-*O*-methyl-3,4,5-tri-*O*-acetyl-α-L-sorbopyranose (XIII) (0.98 g) as needles. It had mp 115.5—117°C, $[\alpha]_D^{24}$ −16.4 (*c* 1.026). Found: C, 49.01; H, 6.37%. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29%. PMR ($CDCl_3$)[30] τ: 7.92, 7.97 and 7.99 (OAc), 6.57 (OCH_3), 6.08 (OH), 6.6—6.7 (C_1-protons), 5.07 (H_3, doublet, $J_{3,4}$=9.5 Hz), 4.47 (H_4, doublet-doublet, $J_{4,5}$=9.5 Hz), 5.05 (H_5, multiplet), 6.1—6.3 (C_6-protons).

Acetonation of X. A mixture of X (8.7 g), acetone dimethylketal (150 ml), TsOH (260 mg), and dried chloroform (80 ml) was stirred at room temperature. After 3.5 hr, the reaction mixture was made alkaline with sodium bicarbonate and then extracted with chloroform. The dried chloroform was evaporated to give a syrup (10.3 g), which was then used; (i) for the isolation of 1-*O*-methyl-3,4:5,6-di-*O*-isopropylidene-L-sorbose (XIV), and (ii) for further acetonation. (i) The syrup (1.5 g) was separated into XIV (195 mg, R_f=0.3) and XI (240 mg, R_f=0.5) by PTC with ether-*n*-hexane (2 : 3 v/v). XIV: syrup, $[\alpha]_D^{24}$ +10.5 (*c* 1.861). Found: C, 56.63; H, 8.07%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%. (ii) The syrup (1.0 g) was further treated with acetone dimethylketal (15 ml) and TsOH (500 mg) at 41—42°C. No XIV was detected in the TLC. After 5.5 hr, the solution was worked up by the above-described procedure. XI (590 mg) was thus obtained.

Reduction of XIV with Lithium Aluminum Hydride. A mixture of XIV (866 mg), lithium aluminum hydride (0.45 g) and ether (30 ml) was stirred at room temperature. After 7 hr, excess lithium aluminum hydride was deactivated with ether saturated with water. The precipitates were filtered off, and then the filtrate was evaporated. The resulting syrup, dissolved in chloroform, was washed with water and dried. The evaporation of the solvent gave a syrup (726 mg), which was immediately benzoylated with benzoyl chloride (1 ml) and pyridine (15 ml), without further purification. 5-*O*-Benzoyl-6-*O*-methyl-3,4:5,6-di-*O*-isopropylidene-D-glucitol (XV) (422 mg, R_f=0.65) was isolated by PTC with benzene-ether (4 : 1 v/v) from the crude product (1.15 g). XV: syrup, $[\alpha]_D^{24}$ +13.1 (*c* 0.566). Found: C, 63.19; H, 7.48%. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42%.

Preparation of XV from 6-*O*-Benzoyl-1,2:3,4-di-*O*-isopropylidene-D-glucitol (XVI). XVI (1.0 g) was debenzoylated with methanolic sodium methoxide by the procedure of Mizoiri *et al.*[26] to give 1,2:3,4-di-*O*-isopropylidene-D-glucitol, which was methylated with methyl iodide (20 g) in the presence of silver oxide (1.0 g) under refluxing for 10 hr. The resulting 6-*O*-methyl-1,2:3,4-di-*O*-isopropylidene-D-glucitol (150 mg) was isolated as a syrup in the pure state from the reaction product (0.93 g) by PTC using the solvent A (R_f=0.50). The treatment of the syrup with bezoyl chloride and pyridine, followed by purification by PTC, gave a benzoate (88 mg) which was identified with XV by a study of its TLC and IR spectrum.

1,6-Di-*O*-methyl-L-sorbose (XVIII). A mixture of XII (10 g), methyl iodide (250 g) and silver oxide (30 g) was refluxed for 1.5 hr. Precipitates were then filtered off, and the filtrate was evaporated completely. The resulting syrup was dissolved in *n*-hexane (100 ml) and washed with water (50 ml×10). The aqueous layer was extracted with chloroform (100 ml×3), dried, and evaporated to give 1,6-di-*O*-methyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XVII) (9.5 g). XVII was hydrolyzed with 1N hydrochloric acid (110 ml) at room temperature. After 3 days, the solution was neutralized with Amberlite IR-45, washed with benzene, and then evaporated to give a syrup (5.5 g) which solidified after standing several days in a desiccator. The recrystallization from ethyl acetate gave XVIII as prisms (4.0 g), mp 78—80°C, $[\alpha]_D^{24}$ −5.3 (*c* 0.997, chloroform). Found: C, 46.15; H, 7.71%. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75%.

Benzylidenation of XVIII. A mixture XVIII (8.7 g), benzaldehyde (27 ml), and TsOH (47 mg) was stirred at room temperature. After 1 hr the reaction mixture was neutralized with sodium bicarbonate. The dried chloroform extract was evaporated to give a syrup (5.8 g) in which three major compounds were detected by TLC with solvent A; their R_f values were 0.50, 0.44, and 0.23 respectively. PTC with the same solvent gave needles (0.31 g, R_f 0.23) and a syrup mixture of two unknown compounds (2.28 g) (R_f 0.50 and 0.44). The recrystallization of the needles from ether gave 1,6-di-*O*-methyl-3,5-*O*-benzylidene-L-sorbose (XIX) (89 mg), mp 89—93°C, $[\alpha]_D^{20}$ −6.0 (*c* 0.329). Found: C, 60.92; H, 6.83%; mol wt 300. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80%; mol wt, 296. Unknown compounds with higher mobilities[27] were isolated by repeated PTC; a compound of R_f 0.50: syrup, 45 mg, $[\alpha]_D^{22}$ −6.9 (*c* 1.011). Found: C, 61.09; H, 6.92%; mol wt, 329. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80%; mol wt, 296; a compound of R_f 0.44: syrup, 100 mg, $[\alpha]_D^{22}$ −1.9 (*c* 0.627). Found: C, 60.78; H, 7.04%; mol wt, 305. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80%; mol wt, 296.

Acetylation of XIX. XIX (78 mg) was acetylated with acetic anhydride (1 ml) and pyridine (1 ml). The same work-up as in the acetylation of X produced a crude acetate (91 mg). The recrystallization from ether gave 1,6-di-*O*-methyl-4-*O*-acetyl-3,5-*O*-benzylidene-L-sorbose (XX) (54 mg) as needles, mp 98—99.8°C, $[\alpha]_D^{24}$ −46.9 (*c* 0.384). Found: C, 60.24; H, 6.54%. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55%. PMR ($CDCl_3$) τ: 7.93 (OAc), 6.58 and 6.64 (OCH_3), 4.32 (benzylic proton), ~6.6 (methylene protons at C_1), 5.33 (H_3, doublet, $J_{3,4}$=1.8 Hz), 4.55 (H_4, doublet-doublet, $J_{4,5}$=1.8 Hz), 5.88 (H_5, multiplet) and 6.4—6.6 (methylene protons at C_6); PMR (C_6D_6) τ: 8.35 (OAc), 6.82 and 6.88 (OCH_3), 4.72 (benzylic proton), 5.72 and 5.84 (methylene protons at C_1, $J_{1,1}$=18.3 Hz), 5.92 (H_3, doublet, $J_{3,4}$=1.8 Hz), 4.55 (H_4, doublet-doublet,

30) The *J* values supported the pyranose structure of XIII.[3]

$J_{4,5}$=1.8 Hz), 6.13 (H_5, multiplet) and 6.5—6.6 (methylene protons at C_6).

Kinetic Measurements of the Reaction of IV with Acetone Dimethylketal. Kinetic measurements were made polarimetrically[31] at 15, 25, and 35°C. A Yanagimoto Automatic Recording Polarimeter, model OR-1, was used. Acetone (5 m*l*) containing conc. sulfuric acid (45 mg) was added to a 10 m*l* solution of IV (300 mg) and acetone dimethylketal (3.00 g) in acetone at the appropriate temperature. The solution was transformed into 10 cm polarimeter cell for optical rotation determination. The data are shown in Fig. 1 and Table 1.

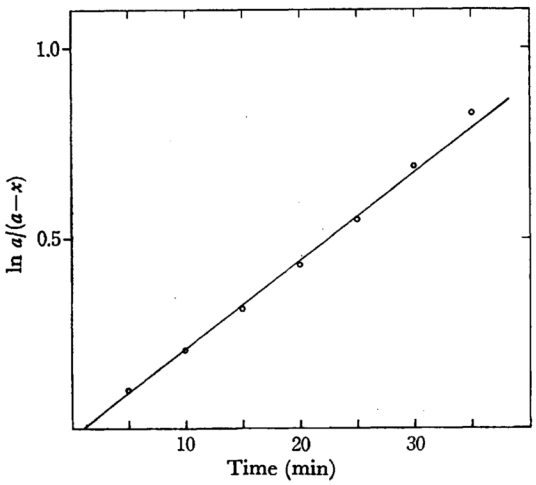


Fig. 1. Values of concentration function *vs.* time at 25°C.

TABLE 1. THE RATE CONSTANTS

Reaction temp.	Rate constants $\times 10^{-4}$ (sec^{-1})
15	1.52
25	3.80
35	8.62

Acetonation of I in Acetone. A mixture of I (5.0 g), acetone (500 m*l*), and sulfuric acid (121 mg) was stirred at 30°C for 5 hr. The solution was then neutralized by a few drops of a sodium hydroxide solution. The unreacted I was filtered and washed with acetone. The combined filtrate was evaporated to give a syrup; this syrup was then dissolved in chloroform, washed with water, and dried, and the chloroform was evaporated. The recrystallization of the residual syrup (750 mg) from *n*-hexane gave VI (59.5 mg). From the mother liquor, II (53.6 mg), VII (89.4 mg), VIII (62.0 mg), and VI (42.7 mg) were isolated by repeated PTC (solvent A).

Acetonation of I in the Presence of Cupric Sulfate. A mixture of I (5.0 g), acetone (500 m*l*), and anhydrous cupric sulfate (50 g) was stirred for 8 hr at room temperature. After the cupric sulfate and the unreacted I had been removed by filtration, the neutralized solution with a few drops of a 2N sodium hydroxide solution was worked up in a way similar to the acetonation of I in acetone. II (140 mg), VII (273 mg), VIII (114 mg), and VI (114 mg) were obtained.

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31) Under the reaction conditions employed, II as the major product and traces of 1-*O*-methoxyisopropyl-2,3:4,6-*O*-isopropylidene-α-L-sorbofuranose[11] were detected as products in the thin-layer chromatograms. The further acetonation of II under these conditions fortunately did not affect the kinetic measurements.