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> Advance Publication on the web April 16, 2015 by J-STAGE doi:10.1246/bcsj.20150080

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Title: Sulfuric Acid-Catalyzed Dehydration of Sorbitol: Mechanistic Study on Preferential Formation of 1,4-Sorbitan

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Synopsis

1,4-Sorbitan is a precursor to environmentally benign surfactants, which can be produced from biomass via sorbitol. Currently, sulfuric acid-catalyzed dehydration of sorbitol is the most widely used for industrial synthesis of 1,4-sorbitan. In this work, we have studied the mechanism of the sorbitol dehydration by sulfuric acid. Our results show that both thermodynamic and kinetic parameters play significant roles to determine the yield of 1,4-sorbitan. Sorbitol preferentially forms an adduct with sulfuric acid, thereby inhibiting the subsequent dehydration of 1,4-sorbitan to isosorbide. Furthermore, a reaction mechanism is proposed for the dehydration reaction, which involves an S_N2 reaction on primary C1 of sorbitol attacked by OH of secondary C4.

Introduction

Catalytic transformation of waste biomass to fuels and chemicals is a promising technology for decreasing the emission of greenhouse gases causing anthropogenic climate change.¹ Cellulose is the most abundant naturally occurring biopolymer, which places the conversion of cellulose to valuable chemicals as a primary step in bio-refineries. Many research groups have reported the hydrolytic hydrogenation of cellulose to sorbitol over supported metal catalysts under H₂ pressure.² The obtained sorbitol can be converted to useful chemicals such as 1,4-sorbitan (1,4-anhydrosorbitol) and isosorbide (1,4:3,6-dianhydrosorbitol) (Scheme 1). In particular, 1,4-sorbitan is a raw material for

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various environmentally benign surfactants³ [e.g., fatty acid esters (Span) and polysorbates (Tween)]. These compounds are extremely useful as emulsifiers, insecticides, and soft templates for material synthesis.⁴ The emulsifiers can be used in food, cosmetic, and pharmaceutical industries owing to their low-toxicity to human being.⁵ The current annual demand of sorbitan-derived surfactants is more than 10,000 tons worldwide.⁴



Scheme 1. Dehydration of sorbitol.

At present, 1,4-sorbitan is produced commercially by sulfuric acid-catalyzed dehydration of sorbitol with 58% yield.⁶ Use of heterogeneous catalysts for 1,4-sorbitan production can reduce manufacture cost by eliminating problems associated with homogenous sulfuric acid catalyst. Although 1,4-sorbitan can be produced at laboratory scale using solid acid catalysts or hot compressed water, the inherent tendency of 1,4-sorbiton to undergo further dehydration to form isosorbide reduces its yield.⁷ On the contrary, sulfuric acid can give 1,4-sorbitan by preferential dehydration of sorbitol, but the mechanism is not well understood. The purpose of this work is to elucidate the reason for a good yield of 1,4-sorbitan by kinetic study on the dehydration.

Results and Discussion

Here, this section is divided into three parts: (1) catalytic reaction and identification of products, (2) kinetic study, and (3) reaction mechanism.

Catalytic reaction and identification of products. We conducted the dehydration of sorbitol at 403 K without using any solvent. Sorbitol (m.p. 368 K), 1,4-sorbitan (m.p. 385 K), and isosorbide (m.p. 336 K) are liquids at 403 K, which enabled us to perform the reaction under solvent-free conditions. Use of sulfuric acid as catalyst resulted in 93% conversion of sorbitol for 45 min. The main product was 1,4-sorbitan with 58% yield and 63% selectivity based on the conversion of sorbitol (93%) (Scheme 2), which was in good agreement with the results reported earlier.⁶ The primary by-product was isosorbide (16% yield) formed from successive dehydration of 1,4-sorbitan. 2,5-Mannitan

(2,5-anhydromannitol) was also formed as a by-product (3.4%). 2,5-Iditan (2,5-anhydroiditol) and a mono-anhydrohexitol named *AH1* were overlapped in the chromatograms (see Figures S1A and S1C), and their total yield was 8.6%. The yield of another mono-anhydrohexitol labeled as *AH2* was 2.0%. *AH1* and *AH2* were not fully identified, and characterization of the two compounds is described in the next paragraph. A control experiment in the absence of catalyst provided no conversion of sorbitol even after a long reaction time of 180 min, indicating that acid catalyst is necessary for the dehydration of sorbitol.



Scheme 2. Dehydration of sorbitol by sulfuric acid. Reaction conditions: sorbitol 182 mg (1 mmol), sulfuric acid 0.64 mg (6.5 μmol), 403 K, 45 min.

Identification of products is often difficult in a complex mixture of polyalcohols due to the presence of various isomers. In this study, we used techniques such as 1D and 2D nuclear magnetic resonance (NMR) along with liquid-chromatograph/mass spectroscopy (LC/MS) and high-performance liquid chromatograph (HPLC). First, we isolated the products by HPLC equipped with a fraction collector. Then, the isolated products were analyzed by comparing with commercial standards in NMR, LC/MS, and HPLC. The ¹H NMR spectrum, mass spectra, and HPLC charts of the isolated 1,4-sorbitan were consistent with those of the standard sample (Figures 1 and S1). Similarly, we identified other products such as isosorbide, 2,5-mannitan, and 2,5-iditan (see Experimental and Figures S1–S4). Additionally, the LC/MS and NMR analyses revealed that the mono-anhydrohexitol *AH1* was formed (Figures S3 and S4), and ¹H and ¹³C NMR indicated that this product was not either 3,6-sorbitan (3,6-anhydrosorbitol) or 1,4-galactan (1,4-anhydrogalactitol).⁸ We also detected the other mono-anhydrohexitol *AH2* by HPLC (Figure S1). Neither *AH1* nor *AH2*

was identified as 1,5-sorbitan (1,5-anhydrosorbitol) or 1,5-mannitan (1,5-anhydromannitol) since the retention times of *AH1* and *AH2* in HPLC were different from those of 1,5-sorbitan and 1,5-mannitan (Figure S1). Other small peaks were also observed in HPLC, but they were not further investigated as their yields were less than 1%. The yield of all identified products was determined using HPLC, in which standard samples were used to calculate calibration factors. For 2,5-iditan, *AH1*, and *AH2*, the calibration factor of 1,4-sorbitan was used to calculate their yields since regio- or stereoisomers generally give similar calibration factors in a refractive index (RI) measurement.



Figure 1. Identification of 1,4-sorbitan produced from sorbitol. LC/MS spectra recorded by (A) positive ion mode and (B) negative ion mode. The column used is Phenomenex Rezex

RPM-Monosaccharide Pb++. (A): 111 ($[M + H - 3H_2O]^+$), 129 ($[M + H - 2H_2O]^+$), 147 ($[M + H - H_2O]^+$), 165 ($[M + H]^+$). (B): 163 ($[M - H]^-$), 196 ($[M + O_2]^-$). (C) ¹H NMR spectra in D₂O. The assignment of ¹H NMR peaks is summarized in Experimental. All spectra of 1,4-sorbitan obtained from sorbitol are consistent with those of the standard sample.

Kinetic study of sorbitol dehydration by sulfuric acid. We studied the kinetics of sulfuric acid-catalyzed dehydration of sorbitol. Figure 2 shows the time course of sorbitol dehydration by sulfuric acid at 403 K. The amount of sorbitol decreased linearly to 7.4% in the first 45 min, which was followed by a reduction in the rate of reaction. The apparent order of the reaction changed from zeroth to first order at low concentrations of the substrate. This suggests that the reaction is controlled by pre-equilibrium, which is the association equilibrium between the reactant and sulfuric acid in this case. In Figure 2, the yield of 1,4-sorbitan was maximized (58%) at 45 min. Contrastingly, only a small amount of isosorbide was formed in the first 30 min regardless of the accumulation of 1,4-sorbitan. Thereafter, the yield of isosorbide increased at an accelerated pace to reach 72% in 180 min. Since the conversion rate of 1,4-sorbitan to isosorbide increased after a large portion of sorbitol was consumed, we can postulate that sorbitol forms an adduct with sulfuric acid more preferentially than 1,4-sorbitan.



Figure 2. Time course of sorbitol dehydration by sulfuric acid at 403 K. Reaction conditions: sorbitol 182 mg (1 mmol), sulfuric acid 0.64 mg (6.5 µmol). Data points show experimental results and lines are simulation curves based on eqs 4–9. The simulation curves were drawn by considering

preferential adsorption of sorbitol over 1,4-sorbitan and isosorbide ($K_1/K_2 = 4.3$ and $K_1/K_3 = 4.5$). Legend: black diamonds (\blacklozenge) = amount of unreacted sorbitol; red circles (\bullet) = yield of 1,4-sorbitan; and blue triangles (\blacktriangle) = yield of isosorbide. The standard deviations for the difference between experimental data and simulation results were calculated to be 3.9% for sorbitol, 2.2% for 1,4-sorbitan, and 1.1% for isosorbide.

We simulated the time course of sorbitol dehydration by assuming the Michaelis-Menten type mechanism involving a pre-equilibrium of association and a subsequent dehydration step (Scheme 3), where k_1 and k_2 are rate constants for dehydration of sorbitol and 1,4-sorbitan, respectively. Whereas, k_3 , k_4 , and k_5 are rate constants for side reactions of sorbitol, 1,4-sorbitan, and isosorbide. The rates of side reactions were estimated from the carbon balance of sorbitol, 1,4-sorbitan, and isosorbide. The equilibrium constants for association of sulfuric acid with sorbitol, 1,4-sorbitan, and isosorbide are denoted as K_1 , K_2 , and K_3 , respectively. The equilibrium constants are presented below (eqs 1–3).



Scheme 3. Reaction schemes of sulfuric acid-catalyzed dehydration of sorbitol. Rate constants and ratios of association equilibrium constants at 403 K were determined by the fitting simulations based on eqs 4–9 (Figure 2).

$$K_{1} = \frac{[\text{Sorbitol} \cdot \text{H}_{2}\text{SO}_{4}]}{[\text{Sorbitol}]([\text{H}_{2}\text{SO}_{4}]_{0} - [\text{Sorbitol} \cdot \text{H}_{2}\text{SO}_{4}] - [\text{Sorbitan} \cdot \text{H}_{2}\text{SO}_{4}] - [\text{Isosorbide} \cdot \text{H}_{2}\text{SO}_{4}])}$$
(1)
$$K_{2} = \frac{[\text{Sorbitan} \cdot \text{H}_{2}\text{SO}_{4}]}{[\text{Sorbitan}]([\text{H}_{2}\text{SO}_{4}]_{0} - [\text{Sorbitol} \cdot \text{H}_{2}\text{SO}_{4}] - [\text{Sorbitan} \cdot \text{H}_{2}\text{SO}_{4}] - [\text{Isosorbide} \cdot \text{H}_{2}\text{SO}_{4}])}$$
(2)

$$K_{3} = \frac{\left[\text{Isosorbide} \cdot \text{H}_{2}\text{SO}_{4}\right]}{\left[\text{Isosorbide}\right]\left[\left(\text{H}_{2}\text{SO}_{4}\right)_{0} - \left[\text{Sorbitol} \cdot \text{H}_{2}\text{SO}_{4}\right] - \left[\text{Sorbitan} \cdot \text{H}_{2}\text{SO}_{4}\right] - \left[\text{Isosorbide} \cdot \text{H}_{2}\text{SO}_{4}\right]\right]}$$
(3)

where $[H_2SO_4]_0$ is the initial concentration of sulfuric acid. [Sorbitol], [Sorbitan], and [Isosorbide] are the concentrations of sorbitol, 1,4-sorbitan, and isosorbide, respectively. [Sorbitol \cdot H₂SO₄], [Sorbitan \cdot H₂SO₄], and [Isosorbide \cdot H₂SO₄] are the concentrations of sulfuric acid adducts with sorbitol, 1,4-sorbitan, and isosorbide. Accordingly,

$$[\text{Sorbitol} \cdot \text{H}_2 \text{SO}_4] = \frac{K_1 [\text{Sorbitol}] [\text{H}_2 \text{SO}_4]_0}{1 + K_1 [\text{Sorbitol}] + K_2 [\text{Sorbitan}] + K_3 [\text{Isosorbide}]}$$
(4)

$$\left[\text{Sorbitan} \cdot \text{H}_2 \text{SO}_4\right] = \frac{K_2 \left[\text{Sorbitan} \left[\text{H}_2 \text{SO}_4 \right]_0}{1 + K_1 \left[\text{Sorbitol} \right] + K_2 \left[\text{Sorbitan} \right] + K_3 \left[\text{Isosorbide} \right]}$$
(5)

 $[\text{Isosorbide} \cdot \text{H}_2\text{SO}_4] = \frac{K_3[\text{Isosorbide}][\text{H}_2\text{SO}_4]_0}{1 + K_1[\text{Sorbitol}] + K_2[\text{Sorbitan}] + K_3[\text{Isosorbide}]}$ (6)

The reaction rates corresponding to each reactant can be represented by using reaction time t as

$$\frac{d[\text{Sorbitol}]}{dt} = -(k_1 + k_3)[\text{Sorbitol} \cdot \text{H}_2\text{SO}_4] \quad (7)$$

$$\frac{d[\text{Sorbitan}]}{dt} = k_1[\text{Sorbitol} \cdot \text{H}_2\text{SO}_4] - (k_2 + k_4)[\text{Sorbitan} \cdot \text{H}_2\text{SO}_4] \quad (8)$$

$$\frac{d[\text{Isosorbide}]}{dt} = k_2[\text{Sorbitan} \cdot \text{H}_2\text{SO}_4] - k_5[\text{Isosorbide} \cdot \text{H}_2\text{SO}_4] \quad (9)$$

The simulation curves (lines) based on eqs 4–9 fit well with the experimental data (dots) in Figure 2. According to the calculation, the rate constant k_1 (4.7 × 10⁻² min⁻¹) was only 1.7 times larger than k_2 (2.7 × 10⁻² min⁻¹) (Scheme 3). Furthermore, k_3 (1.1 × 10⁻² min⁻¹) and k_4 (3.8 × 10⁻³ min⁻¹) were lower than k_1 , which was consistent with the low yields of by-products such as 2,5-mannitan and 2,5-iditan. The rate constant k_5 was <1.0 × 10⁻⁴ min⁻¹, indicating high stability of isosorbide under the reaction conditions. For the association equilibrium constants, the K_1/K_2 and K_1/K_3 ratios were estimated to be 4.3 and 4.5, respectively. This indicates that the association of sulfuric acid with sorbitol is 4.3 and 4.5 times stronger than that with 1,4-sorbitan and isosorbide. If this preferential association did not occur (e.g., $K_1 = K_2 = K_3$), the maximum yield of 1,4-sorbitan would be at most 40% (Figure S5). In this case, in order to achieve the original yield of 1,4-sorbitan (58%), the rate of the dehydration of sorbitol to 1,4-sorbitan needs to be 3.2 times larger than that of the subsequent transformation of 1,4-sorbitan. In other words, the value of $k_1/(k_2 + k_4)$ should be greater than 3.2. In reality, the calculated value for $k_1/(k_2 + k_4)$ is only 1.2 as both sorbitol and 1,4-sorbitan dehydration are similar acid-catalyzed reactions. Therefore, we conclude that the inhibition of association between sulfuric acid and 1,4-sorbitan due to the large K_1/K_2 ratio prevents the successive dehydration of 1,4-sorbitan. The above results support the hypothesis by Takagaki *et al.* that molecular recognition is the key for selective formation of 1,4-sorbitan.^{7j}

Reaction mechanism for dehydration of sorbitol by sulfuric acid. As mentioned in the previous section, sorbitol undergoes dehydration after the formation of adduct with sulfuric acid. Here, we discuss the mechanism of the dehydration based on the product distribution (Scheme 2). Five types of mechanisms are possible for the 1,4-dehydration of sorbitol (Scheme 4): (1) S_N2 reaction at primary C1 attacked by a secondary OH of C4, 9 (2) S_N1 reaction at C1 attacked by the OH of C4, (3) S_N2 reaction at secondary C4 attacked by a primary OH of C1, (4) S_N1 reaction at C4 attacked by the OH of C1, and (5) tandem $S_N 2$ - $S_N 2$ reactions caused by a vicinal OH and a terminal OH.¹⁰ Taking into account the higher selectivity of 1,4-sorbitan, the mechanism 1 is the most probable pathway for the following reasons. In the mechanism 1, the S_N2 reaction at C1 is favorable with less steric hindrance and retention of the configuration of sorbitol. This 1,4-dehydration selectively provides 1,4-sorbitan. In the mechanism 2, the formation of primary carbenium ion at C1 is energetically unfavorable. According to the density functional theory (DFT) calculations for dehydration of sugar alcohol by Nimlos et al., 1,2-hydride shift simultaneously occurs to form secondary carbenium ion, which is more stable than primary carbenium ion.¹¹ Therefore, it is less likely that the reaction proceeds through mechanism 2. The S_N2 reaction at C4 (mechanism 3) should result in the formation of 1,4-galactan as a major product. As this product has not been detected, this mechanism can be excluded. Similarly, the mechanism 4 is implausible as the formation of secondary carbenium ions should yield a mixture of 1,4-sorbitan and 1,4-galactan, but the latter was not observed in our

reaction. In the mechanism 5, if the first S_N2 reaction occurs at C3 or C5, the stereochemistry of sorbitol is maintained to produce 1,4-sorbitan as shown in Scheme 4. However, the first S_N2 reaction is possible by OH group on C4 to C3 (mechanism 5') or C5 (mechanism 5"). Such reactions would result in the formation of 3,6-sorbitan (L-isomer) or 3,6-talitan (3,6-anhydrotalitol, L-isomer), but these were not detected in our products. Hence, we propose that the selective 1,4-dehydration of sorbitol by sulfuric acid occurs by the mechanism 1, viz., the S_N2 reaction at C1.



Scheme 4. Possible reaction pathways for 1,4-dehydration of sorbitol.

Conclusions

Sulfuric acid-catalyzed dehydration of sorbitol produced 1,4-sorbitan in 58% yield with 63% selectivity at 403 K. Kinetic study shows that both sorbitol and 1,4-sorbitan undergo dehydration by acid catalysts as indicated by similar rate constants ($k_1/k_2 = 1.7$). However, the ratio of association equilibrium constants ($K_1/K_2 = 4.3$) is high. Therefore, the association of sorbitol with sulfuric acid is substantially more favorable than that of 1,4-sorbitan with sulfuric acid, and further dehydration of 1,4-sorbitan to isosorbide is effectively inhibited. Accordingly, we believe that control of the association equilibrium constant (K) is essential in addition to an increase in the rate constant (k) to maximize the yield of 1,4-sorbitan. This insight is useful for designing novel catalysts for the selective synthesis of anhydropolyols.

Experimental

Reagents. Sulfuric acid was obtained from Wako Pure Chemical Industries, sorbitol and isosorbide from Tokyo Chemical Industry, 1,4-sorbitan and 1,5-sorbitan from Toronto Research Chemicals, 1,5-mannitan and 2,5-mannitan from Sigma-Aldrich. Distilled water and deuterated solvents [deuterium oxide and dimethyl sulfoxide-d₆ (DMSO-d₆)] were supplied by Wako Pure Chemical Industries and Acros Organics, respectively.

Dehydration of sorbitol. Sulfuric acid (13 mg) was dissolved in diethyl ether (10 mL), and then powder of sorbitol (3.64 g) was added to the solution. After drying diethyl ether under vacuum, sulfuric acid-impregnated sorbitol was obtained. The dehydration reaction was conducted without using solvent in an eggplant flask (50 mL). The melting points of sorbitol, 1,4-sorbitan, and isosorbide are 368, 385, and 336 K, respectively, which have enabled us to conduct the dehydration reaction in the absence of solvents at 403 K. The sulfuric acid-impregnated sorbitol [containing sorbitol 182 mg (1 mmol) and sulfuric acid 0.64 mg (6.5 μ mol)] was charged into the flask. The flask was immersed in an oil bath at 403 K. The volume of reactant was 1.32×10^{-4} L [calculated from the amount of sorbitol charged (182 mg) and the density of sorbitol at 403 K (0.726 $\times 10^{-6}$ L mg⁻¹)¹²] during the reaction at 403 K, and this value was used for the simulation based on eqs 4–9. After the reaction, 20 mL of water was added to the mixture at room temperature to dissolve the products. The water-soluble compounds were analyzed by HPLC [Shimadzu LC10-ATVP, RI and ultraviolet (210 nm) detectors] with a Shodex SUGAR SH1011 column (ø8 × 300 mm, mobile phase: water 0.5 mL

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min⁻¹, 323 K) and a Phenomenex Rezex RPM-Monosaccharide Pb++ column (ϕ 7.8 × 300 mm, mobile phase: water 0.6 mL min⁻¹, 343 K). Yields of products and sorbitol recovery were determined by an absolute calibration method.

Product identification. The products were identified by means of NMR methods [JEOL, JNM-ECX-400 (¹H 400 MHz, ¹³C 100 MHz) and JNM-ECX-600 (¹H 600 MHz, ¹³C 150 MHz) including ¹H NMR spectroscopy, proton-decoupled ¹³C NMR spectroscopy, distortionless enhancement by polarization transfer (DEPT), and ¹³C–¹H heteronuclear multiple quantum coherence (HMQC) technique, Figures 1, S4, and S5]. LC/MS [Thermo Fisher Scientific, LCQ Fleet, atmospheric pressure chemical ionization (APCI), Figures 1, S2, and S3] was conducted under the same conditions as described above for HPLC using the Phenomenex Rezex RPM-Monosaccharide Pb++ column. The structures of identified products (e.g., 1,4-sorbitan, isosorbide, 2,5-mannitan, and 2,5-iditan) are shown in Scheme 2. Mono-anhydrohexitols, denoted as *AH1* and *AH2*, were also observed by HPLC (Figure S1). Although 2,5-iditan and *AH1* were not separated by HPLC, they were detected by NMR (Figure S4).

1,4-Sorbitan: ¹H NMR (400 MHz, D₂O): δ 4.27 (1H, d, J = 4.0 Hz, H–C2), 4.21 (1H, d, J = 2.8 Hz, H–C3), 4.13 (1H, dd, J = 10, 4.0 Hz, H–C1), 3.90 (1H, dd, J = 8.8, 2.8 Hz, H–C4), 3.85 (1H, dd, J = 8.8, 6.0, 2.8 Hz, H–C5), 3.78 (1H, dd, J = 12, 2.8 Hz, H–C6), 3.70 (1H, d, J = 10 Hz, H–C1), 3.61 (1H, dd, J = 12, 6.0 Hz, H–C6). H–C1 and H–C6 were distinguished by means of ¹H NMR in DMSO-d₆ solvent. In DMSO-d₆, the peaks for H–C6 are observed as *ddd* due to coupling with one proton of the hydroxyl group in addition to two aliphatic protons, whereas the peaks of H–C1 are in a *dd* form due to coupling with one proton of the hydroxyl group in addition to 5 (reaction product), found 165 (commercial standard); [M – H]⁻ calculated 163, found 163 (reaction product), found 163 (commercial standard).

Isosorbide: ¹H NMR (400 MHz, D₂O): δ 4.64 (1H, dd, *J* = 5.2, 4.4 Hz, *H*–C4), 4.49 (1H, d, *J* = 4.4 Hz, *H*–C3), 4.39 (1H, ddd, *J* = 7.0, 7.0, 5.2 Hz, *H*–C5), 4.32 (1H, d, *J* = 3.2 Hz, *H*–C2), 3.89–3.96 (2H, *H*–C1 and *H*–C6), 3.87 (1H, dd, *J* = 10.4, 3.2 Hz, *H*–C1), 3.49 (1H, dd, *J* = 9.0, 7.2 Hz, *H*–C6). Some of the ¹H NMR peaks at 3.89–3.96 and 3.87 ppm were overlapped with the peaks of *AH1* (Figure S4A). The ¹³C NMR and DEPT peaks of isosorbide in Figure S4B could not be distinguished from noise due to its low concentration.

2,5-Mannitan: LC/MS: [M + H]⁺ calculated 165, found 165 (reaction product), found 165

(commercial standard); $[M - H]^-$ calculated 163, found 163 (reaction product), found 163 (commercial standard).

2,5-Iditan: ¹H NMR (600 MHz, D₂O): δ 4.21–4.25 (4H, *H*–C2, *H*–C3, *H*–C4, and *H*–C5), 3.80 (2H, dd, *J* = 11.4, 4.8 Hz, *H*–C1 and *H*–C6), 3.73 (2H, dd, *J* = 11.4, 7.2 Hz, *H*–C1 and *H*–C6). ¹³C NMR (150 MHz, D₂O): δ 81.3 (CH, C3 and C4), 77.5 (CH, C2 and C5), 61.0 (CH₂, C1 and C6). The ¹H NMR peaks at 4.21–4.25, 3.80, and 3.73 ppm were overlapped with those of *AH1* (Figure S4A). The assignment of the ¹³C NMR peaks is based on reference 13. LC/MS for reaction product [M + H]⁺ calculated 165, found 165; [M – H][–] calculated 163, found 163.

Mono-anhydrohexitol (*AH1*): ¹H NMR (600 MHz, D₂O): δ 4.29 (1H, d, *J* = 4.2 Hz), 4.15 (1H, dd, *J* = 10.5, 4.2 Hz), 3.92 (1H, dd, *J* = 9.0, 2.4 Hz), 3.88 (1H, ddd, *J* = 9.0, 6.0, 3.0 Hz), 3.64 (1H, dd, *J* = 12, 6.0 Hz). ¹³C NMR (150 MHz, D₂O): δ 80.7 (CH), 77.2 (CH), 76.7 (CH), 74.3 (CH₂), 69.9 (CH), 64.6 (CH₂). Several ¹H NMR peaks were overlapped with those of 2,5-iditan and isosorbide (Figure S4A). The chemical shifts of the ¹H NMR peaks indicate that this unidentified compound is not 3,6-sorbitan or 1,4-galactan.⁸ The retention times of *AH1* in HPLC analyses are different from those of 1,5-sorbitan or 1,5-mannitan (Figure S1). LC/MS for reaction product [M + H]⁺ found 165; [M – H]⁻ found 163.

Mono-anhydrohexitol (*AH2*): The retention times of *AH2* in HPLC analyses are different from those of 1,5-sorbitan or 1,5-mannitan (Figure S1). LC/MS for reaction product $[M + H]^+$ found 165; $[M - H]^-$ found 163.

The authors would like to thank Dr. Y. Koyama (Hokkaido University) for the discussion of NMR assignments and Dr. Y. Yamakoshi (Hokkaido Research Organization) for the LC/MS analysis. This work was supported by a Grant-in-Aid for the Japan Society for the Promotion of Science (JSPS) Research Fellows.

Supporting Information: HPLC data for products in sorbitol dehydration by sulfuric acid, LC/MS and NMR spectra of products, and simulation curves with the assumption of $K_1 = K_2 = K_3$. This material is available free of charge on the web at https://www.jstage.jst.go.jp/browse/bcsj.

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Scheme captions

- Scheme 1. Dehydration of sorbitol.
- **Scheme 2.** Dehydration of sorbitol by sulfuric acid. Reaction conditions: sorbitol 182 mg (1 mmol), sulfuric acid 0.64 mg (6.5 μmol), 403 K, 45 min.
- Scheme 3. Reaction schemes of sulfuric acid-catalyzed dehydration of sorbitol. Rate constants and ratios of association equilibrium constants at 403 K were determined by the fitting simulations based on eqs 4–9 (Figure 2).
- Scheme 4. Possible reaction pathways for 1,4-dehydration of sorbitol.

Figure captions

- Figure 1. Identification of 1,4-sorbitan produced from sorbitol. LC/MS spectra recorded by (A) positive ion mode and (B) negative ion mode. The column used is Phenomenex Rezex RPM-Monosaccharide Pb++. (A): 111 ([M + H 3H₂O]⁺), 129 ([M + H 2H₂O]⁺), 147 ([M + H H₂O]⁺), 165 ([M + H]⁺). (B): 163 ([M H]⁻), 196 ([M + O₂]⁻). (C) ¹H NMR spectra in D₂O. The assignment of ¹H NMR peaks is summarized in Experimental. All spectra of 1,4-sorbitan obtained from sorbitol are consistent with those of the standard sample.
- **Figure 2.** Time course of sorbitol dehydration by sulfuric acid at 403 K. Reaction conditions: sorbitol 182 mg (1 mmol), sulfuric acid 0.64 mg (6.5 µmol). Data points show experimental results and lines are simulation curves based on eqs 4–9. The simulation curves were drawn by considering preferential adsorption of sorbitol over 1,4-sorbitan and isosorbide ($K_1/K_2 = 4.3$ and $K_1/K_3 = 4.5$). Legend: black diamonds (\blacklozenge) = amount of unreacted sorbitol; red circles (\bullet) = yield of 1,4-sorbitan; and blue triangles (\blacktriangle) = yield of isosorbide. The standard deviations for the difference between experimental data and simulation results were calculated to be 3.9% for sorbitol, 2.2% for 1,4-sorbitan, and 1.1% for isosorbide.



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Graphical Abstract

Sulfuric Acid-Catalyzed Dehydration of Sorbitol: Mechanistic Study on Preferential Formation of 1,4-Sorbitan

Mizuho Yabushita, Hirokazu Kobayashi, Abhijit Shrotri, Kenji Hara, Shogo Ito, and Atsushi Fukuoka

Sulfuric acid produces 1,4-sorbitan from sorbitol by controlling thermodynamics and kinetics. Sorbitol preferentially forms an adduct with sulfuric acid, which suppresses further dehydration of 1,4-sorbitan to isosorbide.

