

The Dehydration of Ketohexoses into 5-Chloromethyl-2-furaldehyde. The Isolation of Diketohexose Dianhydrides

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(Received July 16, 1983)

Synopsis. The isolation of diketohexose dianhydrides, produced during the dehydration of D(–)-fructose and L(–)-sorbitose with concentrated hydrochloric acid, in a mixture containing water, an organic solvent and a catalytic amount of a surface-active agent is described.

The chemistry of 2,5-disubstituted furan derivatives has attracted attention recently in connection with the transformation of carbohydrates into useful organic intermediates. We ourselves have previously reported an improved method for synthesizing 5-chloromethyl-2-furaldehyde (CFAL), a potent intermediate of synthetic pyrethroid, in a high yield from saccharides with mineral acids.¹⁾ The present work will describe the isolation and structural determination of diketohexose dianhydrides produced during the early stage of the reaction.

Experimental

In a typical run, D(–)-fructose, 4 equiv. of concd hydrochloric acid, and a catalytic amount of a cationic surface-active agent ($C_{12}H_{25}N^+(CH_3)_3Cl^-$) were mixed and stirred at 15–20 °C for 2 h ("pre-reaction solution"). This "pre-reaction solution" was then added, drop by drop, to an inert organic solvent (benzene, toluene, or chlorobenzene), and maintained at 80 °C for about 30 min with stirring. After the temperature of the solution had been allowed to drop to room temperature under continuous stirring (1–2 h), a small amount of water and some active charcoal were added and the mixture was stirred further. The organic layer separated after filtration was washed with a saturated aqueous NaCl solution twice, dried over anhydrous sodium sulfate, and concentrated to obtain CFAL in a yield of 70%.²⁾

Results and Discussion

The polarimetric analysis of the "pre-reaction solution" revealed that the addition of a catalytic amount of a surface-active agent accelerated the pyranose-furanose mutarotation rate of D(–)-fructose twice as much as in a solution containing D(–)-fructose and concd hydrochloric acid. The HPLC analysis of the "pre-reaction solution"³⁾ revealed that the two compounds, **1** and **2** (total 45%;⁴⁾ 1/2=2.5/1) were equilibrated with the remaining D(–)-fructose **3** (55%) at the end of the "pre-reaction." The isolation of these products using HPLC or cellulose-column chromatography⁵⁾ was carried out, and then they were studied spectroscopically. **1** and **2** were attributed to be difructose dianhydrides.⁶⁾ The D-fructose rings in **2** were found by periodate oxidation to be pyranoid moieties only; **1** possessed one pyranoid and one furanoid residue. The proton signals of ¹H NMR⁷⁾ of the peracetylated difructose dianhydrides in benzene-*d*₆ were resolved to permit first-order analysis; each of these sugars was thus found to possess three rings, one substituted 1,4-

dioxane and two D-fructose.⁸⁾ The conformations of the ring systems and the anomeric configurations were determined by means of ¹³C NMR⁷⁾ (Table 1). The structures of **1** and **2** were found to be 1',2-anhydro-1-*O*-α-fructopyranosyl-(1C)-β-D-fructofuranose-(E3) ($[\alpha]_D^{20} = -36^\circ$; *c* 3.5, H₂O) and 1',2-anhydro-1-*O*-α-D-fructopyranosyl-(1C)-α-D-fructopyranose-(Cl) ($[\alpha]_D^{20} = -49^\circ$; *c* 3.1, H₂O) respectively, which coincided with the known difructose dianhydrides.⁹⁾ A ¹³C NMR study¹⁰⁾ of the remaining D(–)-fructose fraction, **3** ($[\alpha]_D^{20} = -41^\circ$ – -44° ; *c* 2.6, H₂O, 2 h), by means of the measurement

TABLE 1. ¹³C NMR CHEMICAL SHIFTS^{a)} OF **1** AND **2**

Assignment	Chemical shifts of ¹³ C resonances of	
	1 ^{b)}	2 ^{c)}
C-2		
β-D-Fructofuranose	103.1	
β-D-Fructopyranose		
α-D-Fructopyranose	96.5	95.6, 94.2
C-3, C-4, C-5		
β-D-Fructofuranose	84.4, 82.7, 78.6	
D-Fructopyranose	69.8, 69.8, 69.4	71.6, 71.2, 69.3, 69.3
C-1, C-6		
Pyranose	64.3, 62.4	64.0, 63.6
Furanose	62.1, 62.1	61.6, 61.2, 60.0

a) Chemical shifts are expressed in δ downfield from the ¹³C resonance of Me₄Si. b) Measured in D₂O. c) Measured in DMSO-*d*₆.

TABLE 2. CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE METHINE AND METHYLENE PROTONS OF HEXAACETATES^{a)} OF **4** AND **5**

Proton	Chemical shifts, δ (Coupling constants/Hz in benzene- <i>d</i> ₆)	
	4	5
H-1	4.02	3.71
H-1	3.71	3.71
H-1'	3.65	3.84
H-1'	3.50	4.09
H-3 (<i>J</i> 3,4)	5.53 (10.4)	5.62 (10.5)
H-4 (<i>J</i> 4,5)	5.75 (3.7)	5.82 (3.6)
H-5 (<i>J</i> 5c,6a)	5.46 (1.6)	5.48
H-6 (<i>J</i> 5c,6e)	3.42 (1.7)	3.41
H-6 (<i>J</i> 6c,6a)	3.52 (–12)	3.53 (–11)
H-3' (<i>J</i> 3',4') ^{b)}		5.44 (1.7)
H-4' (<i>J</i> 4',5') ^{b)}		5.23 (5.6)
H-5' (<i>J</i> 5',6')	5.39 (8.7)	4.09 (3.6)
H-6' (<i>J</i> 5',6')	3.57 (4.5)	4.30 (4.5)
H-6' (<i>J</i> 6',6')	3.90 (–10)	4.54 (–11)

a) Acylation conditions: A 0.9-g portion of **4** (or **5**) in pyridine (12 ml) was reacted with acetic anhydride (8 ml) at 15 °C for 3 d (yield=70%). b) As the signals for H-3', H-4', and H-5' in the second pyranoid ring of **4** were not resolved, its conformation was determined by an analysis of the H-6' resonance patterns.

TABLE 3. ^{13}C NMR CHEMICAL SHIFTS^{a)} OF **4** AND **5**

Assignment	Chemical shifts of ^{13}C resonances of	
	4 ^{b)}	5 ^{b)}
C-2		
α -L-Sorbofuranose		100.5
β -L-Sorbopyranose	97.9, 97.7	
α -L-Sorbopyranose		95.2
C-3, C-4, C-5		
α -L-Sorbofuranose		83.9, 81.9, 77.0
C-3, C-4, C-5		
L-Sorbopyranose	74.0, 72.3, 72.3	74.1, 72.5, 70.0
	71.9, 69.9, 69.0	
C-1, C-6		
Pyranose	62.9, 62.5, 62.2	62.6, 62.6
Furanose	59.6	62.0, 61.9

a) Chemical shifts are expressed in δ downfield from the ^{13}C resonance of Me_4Si . b) Measured in D_2O .

of the integration of the peak intensities, clarified the equilibrium composition at 20 °C: α -D-fructofuranose 25%, β -D-fructofuranose 17%, β -D-fructopyranose 57%. It should be noted that the isolated **1** was converted into CFAL in a yield of only about 40%²⁾ under the present reaction conditions.

In the same way, the treatment of L(–)-sorbose with 4 equiv. of concd hydrochloric acid in the presence of a catalytic amount of a surface-active agent (e.g., $\text{C}_{16}\text{H}_{33}\text{N}^+(\text{CH}_3)_3\text{Cl}^-$ or $\text{C}_{12}\text{H}_{25}\text{N}^+(\text{CH}_3)_3\text{Cl}^-$) under stirring at 20 °C for 4 h afforded two compounds, **4** and **5** (total 20%), equilibrated with the remaining L(–)-sorbose (80%). The isolation of **4** and **5** using HPLC³⁾ was then carried, and the spectroscopic data were obtained. **4** and **5** were thus identified as disorbose dianhydrides.¹¹⁾ The L-sorbose rings in **4** were found by periodate oxidation to be pyranoid moieties only; **5** possessed one furanoid and one pyranoid residue. A ^1H NMR⁷⁾ of the peracetylated disorbose dianhydrides (Table 2) showed the conformational structures of **4** and **5** to be 1',2-anhydro-1-O-L-sorbopyranosyl-L-sorbopyranose and 1',2-anhydro-1-O-L-sorbopyranosyl-L-sorbofuranose respectively. ^{13}C NMR was used to determine the anomeric configurations of the two compounds (Table 3). The structures of **4** and **5** were thus identified as new disorbose dianhydrides, 1',2-anhydro-1-O- β -L-sorbopyranosyl-(1C)- β -L-sorbopyr-

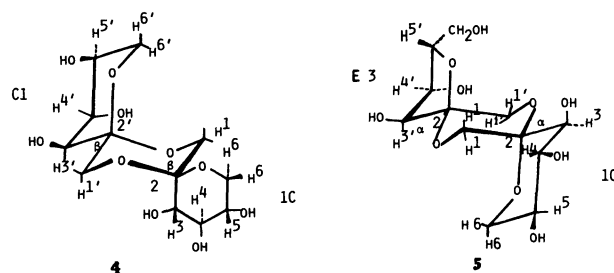


Fig. 1. Disorbose dianhydrides.

anose-(Cl) ($[\alpha]_{\text{D}}^{20} = -107^\circ$; c 0.17, H_2O) and 1',2-anhydro-1-O- α -L-sorbopyranosyl-(E3)- α -L-sorbopyranose-(1C) ($[\alpha]_{\text{D}}^{20} = -121^\circ$; c 0.40, H_2O) respectively (Fig. 1).

References

- 1) K. Hamada, H. Yoshihara, and G. Suzukamo, *Chem. Lett.*, **1982**, 617.
- 2) GC analysis: LAC-2R 446/ H_3PO_4 , 2 m, 130 °C.
- 3) HPLC study: μ -BONDAPAK, Carbohydrates, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 85/15$, 2 ml/min, RI. The "pre-reaction solution" was neutralized with Et_3N . Maltose was used as the Internal Standard.
- 4) **1** and **2**: total 25%, $1/2 = 1.5/1.0$ ("pre-reaction solution" without the addition of a catalytic amount of a surface-active agent).
- 5) Cellulose: 4 cm $\times$ 70 cm; $\text{CH}_3\text{COOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O} = 6/3/1-3/3/4$.
- 6) **1=2**: CI-MS, m/z 163 ($\text{C}_6\text{H}_{12}\text{O}_6$ (fructose)- H_2O)+1; FD-MS, m/z 347 2 ($\text{C}_6\text{H}_{12}\text{O}_6$ (fructose)- H_2O)+Na; elemental analysis; **1** Found: C, 46.4; H, 7.1%. **2** Found: C, 45.1; H, 6.3%.
- 7) ^1H NMR: 200 MHz, Varian XL-200, FT-NMR.
- 8) ^{13}C NMR: 50.3 MHz, Varian XL-200, FT-NMR.
- 9) R. W. Binkley, W. W. Binkley, and A. A. Grey, *Carbohydr. Res.*, **28**, 365 (1973).
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- 11) D. Doddrell and A. Allerhand, *J. Am. Chem. Soc.*, **93**, 2779 (1971).
- 12) FD-MS: **4**, m/z 347; **5**, m/z 347. Elemental analysis: **4** Found: C, 45.3; H, 6.0%. **5** Found: C, 46.2; H, 6.1%. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_{10}$: C, 44.5; H, 6.2%.