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Stereospecific molybdic acid-catalyzed isomerization of 2-hexuloses to branched-chain aldoses

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Abstract

On treatment with a catalytic amount of molybdic acid in aqueous solution, the 2-ketohexoses D-fructose, L-sorbose and D-tagatose undergo a stereospecific intramolecular rearrangement to give the corresponding 2-*C*-(hydroxymethyl)aldoses, 2-*C*-(hydroxymethyl)-D-ribose (D-hamamelose), 2-*C*-(hydroxymethyl)-L-lyxose, and 2-*C*-(hydroxymethyl)-D-xylose, respectively. At equilibrium, the ratio of 2-ketose to 2-*C*-(hydroxymethyl)aldose ranged from 14:1 (fructose) to 32:1 (sorbose). A similar treatment of D-psicose failed to yield a significant amount of the corresponding branched-chain aldose. The equilibria can be shifted with the addition of boric acid to the reaction mixture; under these conditions, ratios of 3:1 and 7:1 were obserwed for D-fructose and L-sorbose, respectively. A mechanistic study with D-(3-^{13}C)fructose afforded D-(1-^{13}C)hamamelose, thus confirming C-3–C-4 bond cleavage with concomitant C-2–C-3 transposition suggested from recent studies with D-(2-^{13}C)fructose.

Keywords: Branched-chain aldoses; 2-*C*-(Hydroxymethyl)aldoses; Molybdic acid-catalysis; Carbon skeleton rearrangement; D-(3-^{13}C)Fructose; Mechanism study

1. Introduction

The mutual interconversion of C-2-epimeric aldoses catalyzed by molybdic acid is known as the Bílik reaction [1–7]. Due to its simplicity, this reaction has been used to prepare several rare aldoses on a commercial scale. Mechanistic studies with regiospecifically hydrogen- and carbon-isotopically labelled and substituted aldoses have revealed a remarkable carbon skeleton rearrangement that accompanies C-2-epimerization in which C-1 of the starting aldose becomes C-2 of the product aldose and vice versa [8–10]. It has been proposed that this exchange of carbon atoms with their substituents is mediated by a tetradentate dimolybdate complex involving four neighboring hydroxyl groups, including one of the aldehydrol hydroxyls. This complex promotes the formation of a new C-1–C-3 bond while simultaneously breaking the C-2–C-3 bond, thereby causing epimerization with concomitant C-1–C-2 transposition. The process as applied to isotopically uniform aldoses formally results in C-2 epimerization only.

Recently it has been shown that treatment of 2-*C*-(hydroxymethyl)-D-glucose and -mannose [11,12] and D-fructose [13] with molybdic acid results in dramatic structural changes.

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The two branched-chain aldoheptoses rearranged stereospecifically and reversibly to D-*manno*-heptulose and D-*gluco*-heptulose, respectively, while D-fructose gave 2-*C*-(hydroxymethyl)-D-ribose (D-hamamelose). The equilibria of these reactions strongly favored the 2-ketoses. The carbon skeleton rearrangement which was expected to accompany these interconversions was confirmed by ^{13}C and ^{1}H NMR studies of the conversion of D-(2-^{13}C)fructose to D-(2-^{13}C)hamamelose [13].

In this report an improved strategy for the preparation of D-hamamelose and studies of the molybdic acid-catalyzed isomerization of three additional 2-ketohexoses (L-sorbose, D-tagatose and D-psicose) to their corresponding 2-*C*-branched aldoses are described. Furthermore, in order to examine the mechanism of this isomerization in more detail, the behavior of D-(3-^{13}C)fructose upon treatment with a catalytic amount of molybdic acid was investigated.

2. Experimental

General methods.—Melting points were determined on an electrothermal Kofler apparatus. Specific optical rotations were measured at 20 °C with an automatic polarimeter (Perkin–Elmer, model 141) using a 10-cm 1-mL cell. The composition of mixtures was examined by descending PC on Whatman No. 1 sheets using the solvent system S_1: 5:1:4 butan-1-ol–ethanol–water, or S_2: 8:2:1 ethyl acetate–pyridine–water as mobile phases, followed by visualization with alkaline silver nitrate. Preparative chromatography was performed on a column (denoted C_1) (95 cm × 1.6 cm) of Dowex 50W X8 (200–400 mesh) in the Ba^{2+} form, using water as the eluant, usually at a flow rate of ~5 mL/h. Evaporations were conducted under reduced pressure at 40 °C.

NMR spectroscopy.—^{1}H (300.13 MHz) and ^{13}C (75.45 MHz) NMR spectra were recorded in D_2O solutions at 40 °C on a Bruker DPX 300 spectrometer equipped with a 5 mm inverse broadband probe with a shielded *z*-gradient. Proton and carbon chemical shifts were expressed relative to internal TSP. 1D ^{1}H NMR spectra were recorded with spectral widths of 1500 Hz and typically 16 transients were accumulated to obtain sufficient signal/noise ratios. Presaturation of the HDO resonance was achieved by low-power irradiation during part of the relaxation delay. A QNP probe (5 mm) was used for the measurement of 1D ^{13}C NMR spectra. Standard 2D techniques with pulse field gradients were used to obtain COSY, HMBC and HSQC data; the latter experiment was performed in the phase sensitive-enhanced pure-absorption mode [14]. A 60 ms delay time was set for the measurement of long-range proton–carbon coupling constants in the HMBC experiment. Spectral widths in heteronuclear experiments were 1200 Hz (^{1}H) and 5000 Hz (^{13}C), and spectra were zero-filled before Fourier transformation to give final digital resolutions of 1.2 and 5.9 Hz/pt, respectively.

Isomerization of hexuloses.—A solution of L-sorbose, D-tagatose or D-psicose (100 mg, 5.6 mmol) in 0.2% aqueous molybdic acid (5 mL) was heated at 80 °C. Samples (0.5 mL) were taken at selected intervals (1, 2, 3, 5, 7, 10 h for L-sorbose and for D-tagatose; 5, 10, 20, 30, 40, 50 h for D-psicose) and treated with Amberlite IRA 400 (HCO_3^-, 3 mL), filtered, and the filtrates were evaporated, exchanged with D_2O and analyzed by ^{1}H NMR. Selected resonances were integrated to determine the ratios of the sugars present.

Preparation of 2-C-(hydroxymethyl)-L-lyxose.—(A) A solution of L-sorbose (1 g, 5.6 mmol) and boric acid (1.4 g, 22.6 mmol) in 2% aqueous molybdic acid (5 mL) was heated at 80 °C for 15 h. The reaction mixture was evaporated to dryness and then again four times from methanol (3 × 10 mL). The residue was dissolved in water (10 mL) and the mixture was treated with Amberlite IRA 400 in the HCO_3^- form (50 mL). The resin was removed by filtration and washed with water (3 × 5 mL). The deionized solution was concentrated and crystallized from MeOH to afford a part of the starting L-sorbose (0.7 g, 3.9 mmol). The mother liquor was fractionated on column C_1. Fraction *1* (eluting between 110 and 130 mL) gave a second portion of recovered L-sorbose (110 mg, 0.6 mmol) after evaporation. Fraction *2* (eluting between 130 and

140 mL) was a 2:1 mixture of L-sorbose and 2-*C*-(hydroxymethyl)-L-lyxose (75 mg). Fraction *3* (eluting between 140 and 160 mL) contained chromatographically pure 2-*C*-(hydroxymethyl)-L-lyxose (92 mg, 0.5 mmol, 9%), which after evaporation was obtained as a colorless syrup: R_f 1.21 (S_2), $[\alpha]_D$ (*c* 1, water) $-3.1 \rightarrow -2.6°$ (24 h); ^{1}H NMR (D_2O, 300.13 MHz): δ 5.01 (H-1 αp), 4.77 (H-1 βp), 3.90 (H-5e βp), 3.82–3.87 (H-4 α, βp), 3.63–3.82 (H-5a, H-5e 3αp), 3.72 (CH_2 (C-2) αp), 3.55–3.68 (CH_2 (C-2) βp), 3.61 (H-3 αp), 3.59 (H-3 βp), 3.21 (H-5a βp); ^{13}C NMR (D_2O, 75.45 MHz): δ 103.49 (C-1 αf), 99.63 (C-1 βf), 97.54 (C-1 βp), 97.19 (C-1 αp), 83.50 (C-2 αf), 82.95 (C-4 βf), 82.17 (C-2 βf), 82.04 (C-4 αf), 78.18 (C-2 αp), 77.64 (C-2 βp), 74.93 (C-3 βp), 74.93 (C-3 βf), 74.21 (C-3 αp), 73.66 (C-3 αf), 69.97 (C-4 αp), 69.97 (C-4 βp), 67.71 (C-5 βp), 66.32 (CH_2(C-2) αp), 65.93 (CH_2(C-2) βf), 65.36 (C-5 βf), 64.11 (CH_2(C-2) αf), 65.93 (CH_2(C-2) βf), 65.36 (C-5 βf), 64.11 (CH_2(C-2) αf), 64.11 (C-5 αp), 63.95 (C-5 αf), 63.32 (CH_2(C-2) βp).

Work-up of fraction *4* (eluting between 170 and 200 mL) gave L-fructose (12 mg, 0.07 mmol, 1%) as a syrup: $[\alpha]_D$ (*c*1, water) $+95°$ (24 h). Obtained data were in accordance with those published previously [15].

(B) The same procedure conducted without the addition of boric acid to the reaction mixture afforded 32 mg (0.2 mmol, 3%) of 2-*C*-(hydroxymethyl)-L-lyxose and 9 mg (0.05 mmol, 1%) of L-fructose.

Preparation of 2-C-(hydroxymethyl)-D-xylose.—A solution of D-tagatose (7 g, 38.9 mmol) in 0.2% aqueous molybdic acid (35 mL) was heated at 80 °C for 15 h. After cooling, the reaction mixture was treated batchwise with Amberlite IRA 400 in the HCO_3^- form (300 mL). The resin was removed by filtration and washed with water (3 × 30 mL). The deionized solution was concentrated, and the residue was crystallized from MeOH to afford a part of the starting D-tagatose (5.5 g, 30.6 mmol). The mother liquor was twice fractionated on column C_1. A 3:1 mixture of starting D-tagatose and 2-*C*-(hydroxymethyl)-D-xylose (0.63 g) eluted first (eluting between 150 and 170 mL and containing a substantial fraction of the latter sugar). Subsequent rechromatography on C_1 afforded a 1:1 mixture of the two sugars (0.12 g; eluting between 160 and 165 mL). Final preparative PC (Whatman No. 3, solvent S_2, 12 h; R_f 1.27 for D-tagatose, 1.69 for 2-*C*-(hydroxymethyl)-D-xylose) afforded pure 2-*C*-(hydroxymethyl)-D-xylose (40 mg, 0.6 mmol, 0.5%): mp 108–110 °C (EtOH), $[\alpha]_D$ (*c* 1, water) $+29.6 \rightarrow +16.5$ (24 h) [16]. ^{1}H δ 5.05 (H-1 αp), 4.70 (H-1 βp), 4.07 (H-5e βp), 3.86 (CH_2 (C-2) βp), 3.83 (H-3 αp), 3.67–3.78 (CH_2 (C-2) αp), 3.73 (H-5a, H-5e αp), 3.69–3.74 (H-4 α, βp), 3.57 (H-3 βp), 3.37 (H-5a βp). ^{13}C NMR (D_2O, 75.45 MHz): δ 100.61 (C-1 βp), 95.18 (C-1 αp), 78.02 (C-3 βp), 77.56 (C-2 αp), 76.01 (C-2 βp), 76.01 (C-3 αp), 70.75 (C-4 αp), 70.75 (C-4 βp), 66.67 (C-5 βp), 64.86 (C-5 αp), 64.13 (CH_2(C-2) αp), 63.60 (CH_2(C-2) βp).

Preparation of D-hamamelose.—D-Fructose (0.5 g, 2.8 mmol) and boric acid (0.7 g, 11.3 mmol) were dissolved in 2% aqueous molybdic acid (2.5 mL) and the reaction conditions and purification of products followed those for the preparation of 2-*C*-(hydroxymethyl)-L-lyxose. Three chromatographic fractions were obtained. Fraction *1* (eluting between 115 and 135 mL) contained D-sorbose, which was crystallized from MeOH to yield 45 mg (0.25 mmol, 9%) of product; mp 164 °C, $[\alpha]_D$ (*c* 1.0, water) + 42°; R_f 0.91 (S_1); R_f 0.96 (S_2). These data and the ^{13}C chemical shifts were in accordance with those published previously [15,17]. Fraction *2* (eluting between 175 and 205 mL) contained recovered D-fructose (280 mg, 1.6 mmol, 57%). Concentration and crystallization of fraction *3* (eluting between 225 and 300 mL) gave pure D-hamamelose (101 mg, 0.6 mmol, 20%), mp 110–111 °C (absolute ethanol), $[\alpha]_D$ (*c* 1, water) $+7.5 \rightarrow -7.1°$; R_f 1.26 (S_1); R_f 1.88 (S_2). These data were in accordance with data published previously [18].

Isomerization of D-(3-^{13}C)fructose.—A solution of D-(3-^{13}C)fructose (170 mg, 0.9 mmol) in 0.2% aqueous molybdic acid (1.8 mL) was heated at 80 °C for 5 h. After cooling, the reaction mixture was stirred with Amberlite IRA-400 in the HCO_3^- form (2 mL) for 15 min, filtered, and the resin was washed with water (3 × 3 mL). The filtrate was concentrated under diminished pressure to give a

light-yellow syrup (175 mg). ^{1}H and ^{13}C NMR spectra revealed the presence of three components, namely, D-(3-^{13}C)sorbose, D-(3-^{13}C)fructose and D-(1-^{13}C)hamamelose. Separation of this mixture on column C_1 at a flow rate of 5 mL/h afforded three fractions. Fraction *1* (eluting between 90 and 105 mL) contained D-(3-^{13}C)sorbose (4.5 mg, 0.03 mmol, 3%), fraction *2* (eluting between 125 and 155 mL) contained recovered D-(3-^{13}C)fructose (150 mg, 0.8 mmol, 88%), and fraction *3* (eluting between 185 and 235 mL) contained D-(1-^{13}C)hamamelose (12 mg, 0.07 mmol, 7%).

3. Results and discussion

The treatment of L-sorbose with 0.2% aqueous molybdic acid at 80 °C for 5 h gave a mixture of L-sorbose and 2-*C*-(hydroxymethyl)-L-lyxose in a 32:1 ratio. The ratio was determined by integration of separated ^{1}H signals between 3.42 and 3.53 ppm of L-sorbose (the H-1b and H-4 signals of α-L-sorbopyranose, respectively) and the anomeric signals of the branched chain L-lyxose (4.75–5.25 ppm). This ratio can be considered to be a good estimate of the thermodynamic equilibrium since it remained unchanged even after an additional 5 h of reaction. When the reaction was performed in the presence of four equivalents of boric acid (relative to the ketose starting material), a new ratio of 7:1 was achieved and the product 2-*C*-(hydroxymethyl)-L-lyxose was obtained in 12% yield. Similar co-application of boric acid in the preparation of D-hamamelose from D-fructose gave a 20% yield of the branched-chain aldose. This modification makes the method more useful from a preparative viewpoint, since a yield of only $\sim 7\%$ is obtained in the absence of boric acid.

Molybdic acid-catalyzed isomerization of D-tagatose under similar reaction conditions without boric acid led to a 19:1 ratio of the ketose to 2-*C*-(hydroxymethyl)-D-xylose (obtained by integration of H-6b signals of the α- and β-pyranose forms of the former and the anomeric signals of the latter) after 5 h of reaction. In contrast, the molybdic acid-catalyzed isomerization of D-psicose under identical reaction conditions did not afford the expected 2-*C*-(hydroxymethyl)-D-arabinose as determined by ^{1}H NMR, even after 50 h of reaction. The addition of boric acid to the reaction mixture failed to shift the equilibria with D-tagatose and D-psicose towards the corresponding 2-*C*-(hydroxymethyl)aldoses.

The different yields of 2-*C*-(hydroxymethyl)aldoses produced by 2-ketose rearrangement under the conditions of the Bílik reaction may be caused by different amounts of cyclic and acyclic molybdate complexes of the 2-ketohexoses in the reaction mixtures. For D-tagatose and especially D-psicose, catalytically inactive cyclic species are expected to predominate in aqueous solution [19–21]. In contrast, D-fructose and L-sorbose, which have the threo configuration at the C-3–C-4 fragment, form mainly acyclic molybdate complexes, which are expected to be catalytically active [13].

The mechanism of transformation of D-fructose to D-hamamelose has been studied recently by ^{1}H and ^{13}C NMR spectroscopy using ^{13}C-labeled ketose [13]. D-(2-^{13}C)-Fructose was converted to D-(2-^{13}C)-hamamelose stereospecifically, as determined from 1D and 2D NMR spectra in which additional $^{1}H-^{1}H$ splittings (^{1}H spectra) and the appearance of ^{13}C resonances corresponding to the quarternary C-2 were observed. In the present study, further evidence of an intramolecular C-1–C-2–C-3 rearrangement was obtained using D-(3-^{13}C)fructose as the starting ketose, affording D-(1-^{13}C)hamamelose as the product. The reaction of D-(3-^{13}C)fructose with molybdic acid gave a 14:1 ratio of ketose to branched-chain aldose which was identical to ratios obtained from similar reactions with unlabeled D-fructose and D-(2-^{13}C)fructose. The 300 MHz ^{1}H NMR spectrum of the D-(1-^{13}C)hamamelose product is shown in Fig. 1. The anomeric regions of the ^{1}H spectra of natural D-hamamelose and of D-hamamelose obtained from D-(3-^{13}C)fructose differ considerably. In the latter spectrum, two sets of four signals due to anomeric protons correspond to the four forms of D-(1-^{13}C)hamamelose in aqueous solution, namely, α-furanose (5.25

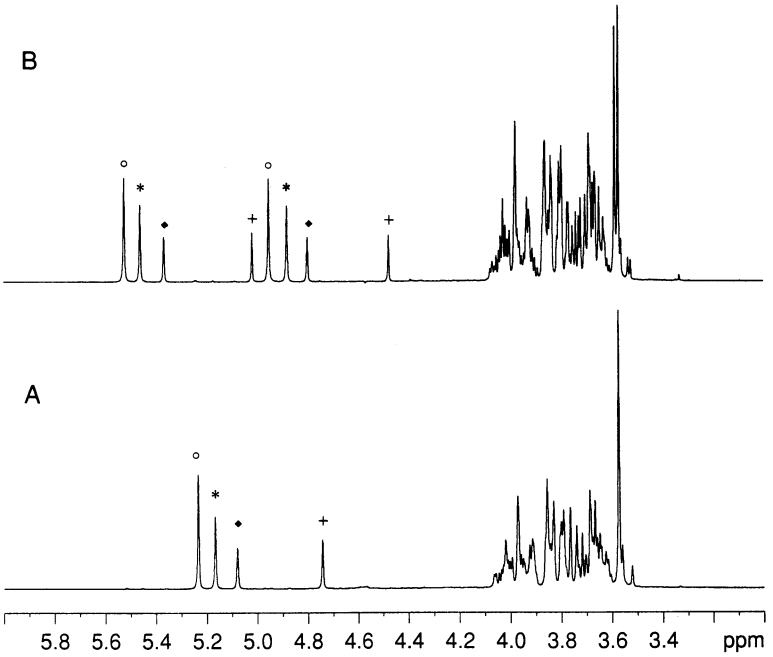
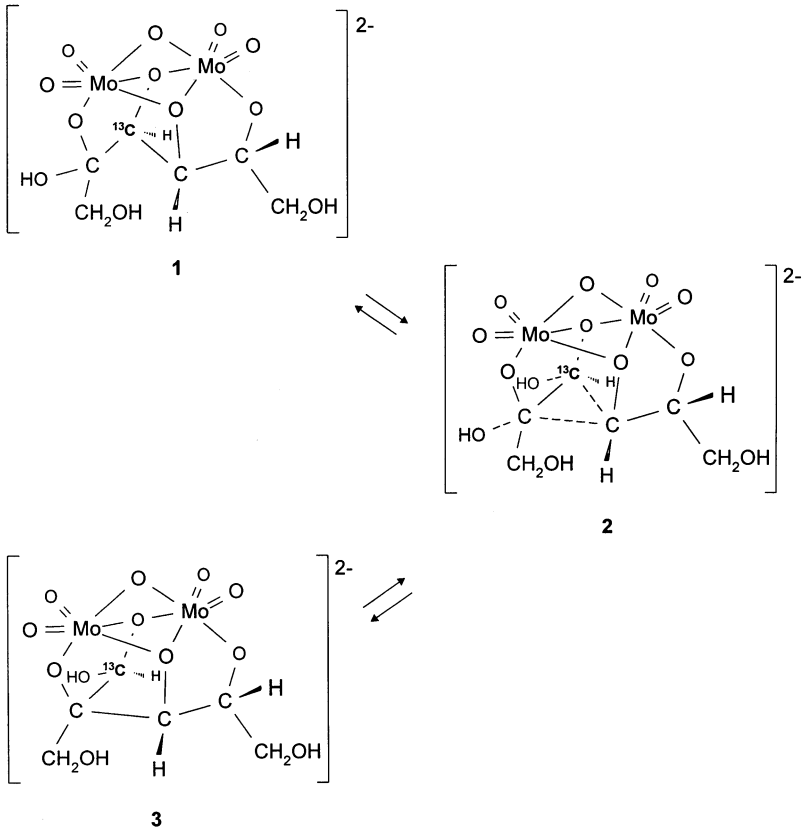


Fig. 1. The 300 MHz ^{1}H NMR spectrum of D-hamamelose in aqueous solution at 40 °C. (A) Conventional spectrum of the natural abundance compound. Four signals between 4.76 and 5.25 ppm are due to anomeric protons, namely, α-furanose (5.25 ppm, ○), β-furanose (5.18 ppm, ∗), β-pyranose (5.09 ppm, ◆) and α-pyranose (4.76 ppm, +). (B) Spectrum of D-hamamelose obtained from the reaction of D-(3-^{13}C)fructose with a catalytic amount of molybdic acid. Signals of the anomeric protons are split into doublets due to the presence of ^{13}C at C-1 of the product branched-chain aldose. The magnitudes of the one-bond proton–carbon coupling constants between ^{1}H-1 and ^{13}C-1 vary according to anomeric configuration and cyclic form; in furanose forms, 171.3 Hz (α anomer) and 173.9 Hz (β anomer), and in pyranose forms, 170.0 Hz (β anomer) and 162.6 Hz (α anomer).

ppm), β-furanose (5.18 ppm), β-pyranose (5.09 ppm) and α-pyranose (4.76 ppm). Each anomeric proton is coupled by 160–175 Hz to the enriched ^{13}C nucleus at C-1 in the synthesized D-hamamelose. The magnitudes of these $^1J_{C1-H1}$ values depend on both anomeric configuration and ring form. In furanose forms, $^1J_{C1-H1}$ values were 171.3 Hz (α anomer) and 173.9 Hz (β anomer), whereas in the pyranoses 170.0 Hz (β anomer) and 162.6 Hz (α anomer) were observed[1]. Thus, the ^{13}C-substituted C-3 in the postulated D-(3-^{13}C)-fructose tetradentate dimolybdate complex **1** (Scheme 1) is transposed to C-1 in the D-(1-^{13}C)hamamelose product. We postulate the involvement of transient state **2** during the interconversion, where a new C-2–C-4 bond forms with concomitant cleavage of the original ^{13}C-3–C-4 bond. This rearrangement was also monitored by ^{13}C NMR spectroscopy. ^{13}C NMR spectra of D-(2-^{13}C)fructose and D-(3-^{13}C)fructose and the product branched-chain aldoses are shown in Fig. 2. From D-(2-^{13}C)fructose (Fig. 2A), D-(2-^{13}C)hamamelose was formed (Fig. 2C), whereas D-(3-^{13}C)-fructose (Fig. 2B) yielded D-(1-^{13}C)hamamelose (Fig. 2D). Thus, in the former rearrangement the carbonyl carbon of D-fructose was converted to the quarternary, branching carbon in D-hamamelose, whereas in the latter the C-3 atom of D-(3-^{13}C)fructose became C-1 in D-(1-^{13}C)hamamelose, as concluded from ^{1}H NMR data. In addition, Fig. 2 shows ^{13}C NMR spectra (Fig. 2E,F) of a secondary product generated during the reaction of D-fructose with molybdic acid, namely, D-sorbose. Although obtained in low yield, D-sorbose is also formed during the conversion of D-fructose to D-hamamelose. However, as observed in the ^{13}C spectra, the formation of D-sorbose is *not* accompanied by carbon-skeleton rearrangement; D-(2-^{13}C)fructose generates D-(2-^{13}C)sorbose (Fig. 2A,E) and D-(3-^{13}C)-fructose generates D-(3-^{13}C)sorbose (Fig. 2B,F). Isotope tracing clearly demonstrates the differences of both processes upon molybdic

[1] The pyranose forms of D-hamamelose prefer the $^1C_4$ conformation, and thus the C-1–H-1 bond is equatorial in the β anomer [22].



Scheme 1.

acid treatment of isotopically substituted D-fructoses (Scheme 2). ^{13}C-3 of D-(3-^{13}C)fructose (**4**) becomes ^{13}C-1 in the primary product, D-(1-^{13}C)hamamelose (**5**), while the secondary product of the transformation, D-(3-^{13}C)sorbose (**6**), remains labeled at C-3. If D-sorbose is formed from D-fructose via a process similar to the Lobry de Bruyn–Alberda van Ekenstein isomerization [23], other isomerization products such as D-psicose, D-tagatose and 3-ketoses might also be expected. However, careful examination of the NMR spectra of reaction mixtures generated from D-(2-^{13}C)fructose and D-(3-^{13}C)fructose did not show the presence of products other than D-(2-^{13}C)hamamelose and D-(2-^{13}C)sorbose in the former case [13] and D-(1-^{13}C)hamamelose and D-(3-^{13}C)sorbose in the latter case. In addition, total respective recoveries of all the isotopically substituted sugars after purification by chromatography were 98.0 and 97.8%, respectively.

These results suggest the existence of a D-fructose $\rightleftharpoons$ D-sorbose interconversion analogous to the secondary reaction pathway proposed previously [8,9,24,25] during the molybdate-catalyzed epimerization of aldoses. In this secondary process, the C-2–C-3 *threo*-diastereoisomeric aldoses mutually interconvert without carbon-skeleton rearrangement. This secondary process is probably accompanied by a mutual exchange of the C-2–H and C-3–H hydrogen atoms similar to that originally suggested for the primary process [10]. Interestingly, the treatment of D-(2-^{13}C; 2-^{2}H)xylose with molybdic acid essentially eliminated this secondary process, presumably due to the deuterium isotope effect retarding proton abstraction; in this case, only D-(1-^{13}C; 1-^{2}H)lyxose was formed as the product of the primary process [8].

Of the 2-ketohexose $\rightleftharpoons$ 2-*C*-(hydroxymethyl)aldose interconversions studied herein, the most useful preparatively is the D-fructose to D-hamamelose interconversion. Since a catalytic amount of molybdic acid is used (1:100 when expressed as the mole ratio of dimolybdate to sugar), the observed 14:1 ratio of ketose to branched-chain aldose prob-

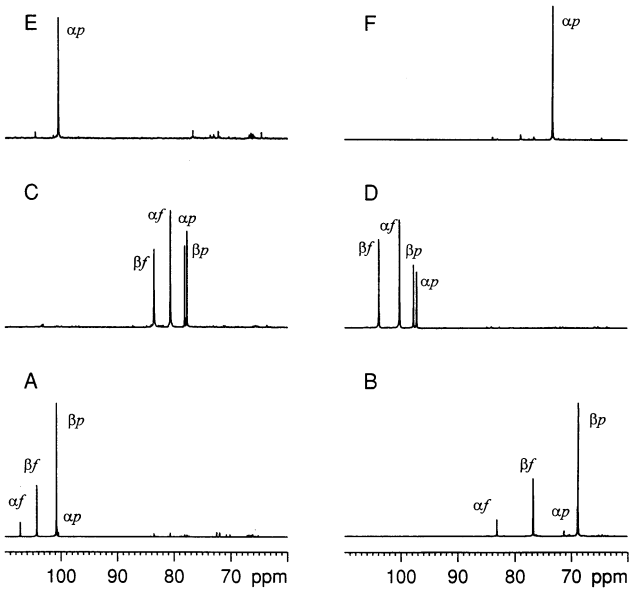


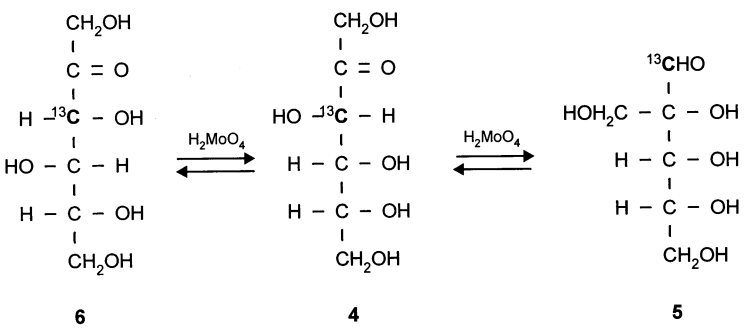
Fig. 2. The 75.5 MHz ^{1}H-decoupled ^{13}C NMR spectra, in aqueous solution at 40 °C, of the starting ^{13}C-enriched compounds (A,B) and the synthetic products obtained from isomerization reactions (C–F). D-(2-^{13}C)Fructose (A); D-(3-^{13}C)fructose (B); D-(2-^{13}C)hamamelose (C) and D-(2-^{13}C)sorbose (E) obtained from D-(2-^{13}C)fructose; D-(1-^{13}C)hamamelose (D) and D-(3-^{13}C)sorbose (F) obtained from D-(3-^{13}C)fructose.

ably reflects the thermodynamic equilibrium. A recently described analogous interconversion of D-fructose to D-hamamelose catalyzed by Ni(II)–diamine complexes gave a 56% yield of the latter sugar in an analytical-scale reaction [26,27]. In this case, however, equimolar amounts of D-fructose and catalyst were used, and thus the Ni(II)–diamine-catalyzed process is not expected to give a true thermodynamic ratio of the interconverting free sugars but rather that of their Ni(II) complexes. In this respect the process is similar to the boric acid-assisted molybdic acid-catalysis reported herein, where the thermodynamic equilibrium of interconverting sugars is shifted to those species forming stronger sugar–borate complexes. Preliminary results with calcium hydroxide, which is also known to catalyze a similar carbon-skeleton rearrangement of aldoses having the threo arrangement at their C-2–C-3 fragments [28–30], revealed that carbon atom transposition may occur when some ketoses are treated with an equimolar amount of the hydroxide, yielding 2-*C*-(hydroxymethyl)aldose products.

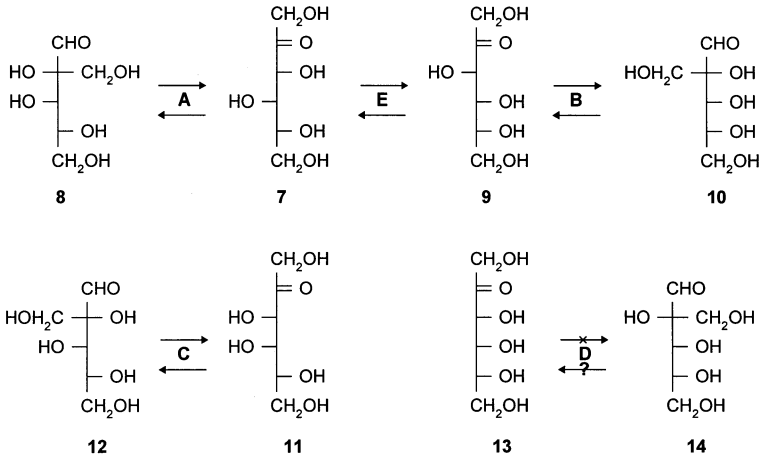
4. Conclusions

Molybdic acid catalyzes two types of interconversions among the sugars shown in Scheme 3. D-Sorbose[2] (**7**), D-fructose (**9**) and D-tagatose (**11**) treated with this catalyst undergo highly stereospecific carbon-skeleton rearrangements (**A**, **B**, **C**) to produce equilibrium mixtures containing 2-*C*-(hydroxymethyl)-D-lyxose[2] (**8**), 2-*C*-(hydroxymethyl)-D-ribose (D-hamamelose, **10**) and 2-*C*-(hydroxymethyl)-D-xylose (**12**), respectively. These equilibria highly favor the hexuloses; ketose and branched-chain aldose ratios of 32:1, 14:1 and 19:1, respectively, have been determined by NMR. Due to the apparently extensive production of catalytically inactive molybdate complexes of D-psicose (**13**), interconversion **D** starting from **13** was not observed; this reaction remains to be investigated from **14**. Importantly, reaction equilibria for

[2] Although L-sorbose and its isomerization product, 2-*C*-(hydroxymethyl)-L-lyxose, were studied in this paper, their enantiomers are shown in Scheme 3 in order to indicate the structural relationships among the interconverting sugars within one enantiomeric series.



Scheme 2.



Scheme 3.

L-sorbose and D-fructose can be shifted significantly towards the 2-*C*-(hydroxymethyl)-pentoses when boric acid is included in the reaction mixture. Moreover, L-sorbose and D-fructose also undergo a competitive secondary isomerization process to a small extent, apparently catalyzed by molybdic acid, affording L-fructose and D-sorbose, respectively; this process (**E**) is shown in Scheme 3 for the D-enantiomers **7** and **9**.

The proposed mechanism of the molybdic acid-catalyzed carbon-skeleton rearrangement of ketoses to 2-*C*-(hydroxymethyl)aldoses, studied earlier with the use of D-(2-^{13}C)-fructose, was tested further with the use of D-(3-^{13}C)fructose. The results indicate that the rearrangement proceeds in a fashion analogous to the carbon-skeleton rearrangement of aldoses catalyzed by molybdate ions.

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