

HYDROGENATION OF D-FRUCTOSE AND D-FRUCTOSE/D-GLUCOSE MIXTURES*

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ABSTRACT

D-Fructose and D-fructose/D-glucose mixtures have been hydrogenated in water at 60–80° and 20–75 atm. of hydrogen with Ni, Cu, Ru, Rh, Pd, Os, Ir, and Pt severally as catalysts. The selectivity for the formation of D-mannitol from D-fructose as well as the selectivity for the hydrogenation of D-fructose in the presence of D-glucose with Cu/silica as the catalyst are substantially higher than those for the other catalysts. With Cu/silica as the catalyst, the hydrogenation of D-fructose is first order with respect to the amount of catalyst and the hydrogen pressure, whereas a shift from first- to zero-order kinetics occurs on going from low (<0.3M) to high (>0.8M) concentrations of D-fructose. D-Fructose is preferentially hydrogenated via its furanose forms, presumably by attack of a copper hydride-like species at the anomeric carbon atom with inversion of configuration. Preferential adsorption of pyranose with respect to furanose forms occurs, whereas the furanose forms show a much higher reactivity. The mechanism proposed for the copper-catalysed hydrogenation reaction explains both the enhanced yield of D-mannitol from boric esters of D-fructose and the diastereoselectivity of the hydrogenation of seven other ketoses.

INTRODUCTION

Hydrogenation of D-glucose yields D-glucitol, whereas D-fructose yields a mixture of D-glucitol and D-mannitol which explains why D-mannitol is much more expensive than D-glucitol. However, apart from its pleasant sweet taste and non-carious properties, D-mannitol is in a more favourable position for various applications because of its non-hygroscopicity^{1–4}.

In our search for an alternative procedure for the preparation of D-mannitol, we have developed^{1–3} the combi-process depicted in Fig. 1. The optimal formation of D-mannitol requires a hydrogenation catalyst which (a) is sufficiently active

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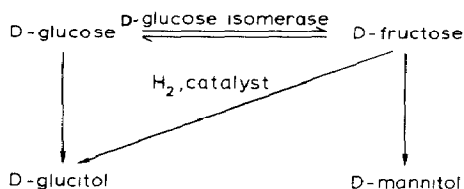


Fig. 1 Combi-process; simultaneous enzymic isomerisation and metal-catalysed hydrogenation of D-glucose/D-fructose mixtures.

under conditions dictated by the enzyme species (60–70°, pH 6.5–8.0)⁵, (b) preferentially hydrogenates D-fructose with respect to D-glucose, and (c) selectively yields D-mannitol in the hydrogenation of D-fructose.

We have therefore studied the behaviour of a series of catalysts in the hydrogenation of D-glucose, D-fructose, and mixtures thereof. As supported copper appeared to be the catalyst of choice, the mechanism and kinetics of the copper-catalysed liquid-phase hydrogenation of monosaccharides have been investigated in more detail.

EXPERIMENTAL

Materials. — Isomaltulose was a gift from Süddeutsche Zucker A.G. The catalysts ruthenium, palladium, rhodium, and platinum, each 5% on carbon, were obtained from Drijfhout Amsterdam. The 10% iridium catalyst was prepared by impregnation of activated carbon (Degussa, 770 mg².g⁻¹) with iridium trichloride followed by reduction with H₂ at 300° and 1 atm. for 3 h. The 5% osmium catalyst was prepared by the reduction of osmium tetroxide in the presence of a suspension of activated carbon in 2-propanol at 60° and 100 atm. of H₂ for 2 h. The 5% ruthenium catalyst was prepared by impregnation of calcium carbonate with a solution of ruthenium trichloride in acetone, followed by reduction with H₂ at 60° and 1 atm. for 3 h. The 60% nickel-on-silica and Raney nickel B 115 Z were obtained from Strem Chemicals and Degussa, respectively. All of the above-mentioned catalysts were used without prior treatment. The 20% copper-on-silica catalyst was prepared by modification of the literature procedure. Thus, the dried catalyst precursor was treated with 10% H₂ and 90% N₂ at 1 atm. and heated from 25° to 400° for 1 h, and then at 400° for 3 h, cooled to room temperature, and stored under nitrogen. The active metal surface of the copper-on-silica was 80–100 m².g⁻¹ Cu, as determined by the dissociation of N₂O. The B.E.T. surface of the silica was 290 m².g⁻¹ SiO₂ (as determined by N₂ adsorption).

Apparatus. — Hydrogenations were carried out in a thermostatted Parr 450-mL Hastelloy B autoclave model 4562, which was equipped with a motor-driven impeller stirrer, a sampling device, and two needle valves.

Procedure. — The catalyst and the additives were transferred into the aqueous solution of the carbohydrate to be hydrogenated. The autoclave was sealed, flushed with hydrogen, adjusted to the required temperature, and pressurised with

hydrogen to the required level. The reaction was started by switching on the stirrer. The conversion was monitored by h.p.l.c. of samples withdrawn from the reaction mixture, using an M 6000 A pump (Waters Assoc.), a Rheodyne 7125 injector, an R 401 differential refractometer (Waters Assoc.), and a column (30 cm \times 7.0 mm i.d.) of Aminex A 7 8% cross-linked (Ca^{2+}) resin (7–11 μm) at 85° eluted with degassed and deionised H_2O at 0.6 mL/min. The chromatographic procedure is described in more detail elsewhere⁷.

RESULTS AND DISCUSSION

Catalyst screening. — The hydrogenations of D-glucose, D-fructose, and a 1:1 mixture of D-glucose/D-fructose were carried out in aqueous solution at pH 6–8, 60–70°, and 20–50 atm. of H_2 with the various catalysts.

Table I shows the initial rates for invert sugar (1:1 D-glucose–D-fructose). Since, for most of these catalysts, the areas of the metal surfaces were not determined, these data only give an impression of the activity of the metal surface.

Two selectivities were studied, namely that of the formation of D-mannitol from D-fructose (S_M = D-mannitol formed/D-fructose consumed) and that of the conversion of D-fructose in invert sugar (S_F = D-fructose converted/D-fructose + D-glucose converted). The results are shown in Fig. 2.

Reasonable values for S_F were obtained with Cu/silica, Ru/C, Os/C, and Pt/C. Rh/C showed no preference, whereas D-glucose was preferentially hydrogenated with Pd/C. S_M was independent of the catalyst, except for Cu/silica which showed a selectivity of 0.67, which could be improved to 0.85 by adding borate (Fig. 3). In addition, S_F for Cu/silica was enhanced from 0.88 to 0.92 in the presence of borate. Thus, Cu/silica is the catalyst of choice for the formation of D-mannitol. Application in the combi-process should allow a yield of D-mannitol of $S_M \times S_F \times 100$, i.e., 78%.

TABLE I

ACTIVITIES OF METAL CATALYSTS USED FOR THE HYDROGENATION OF INVERT SUGAR^a

Catalyst	Initial rate ($\text{mol} \cdot \text{h}^{-1} \cdot \text{g}_{\text{metal}}^{-1}$)
100% Raney Ni	0.1
60% Ni/silica	0.04
20% Cu/silica	0.3
5% Ru/C	1.9
5% Ru/ CaCO_3	1.4
5% Rh/C	0.3
5% Pd/C	0.3
5% Os/C	1.6
10% Ir/C	0.8
5% Pt/C	1.9

^aInvert sugar (60 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), H_2O (250 mL), 60°, 20 atm. H_2 .

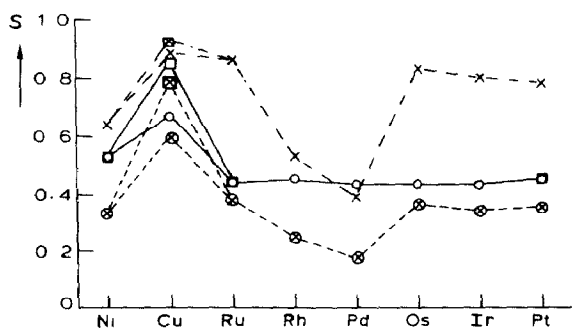


Fig. 2. The influence of catalysts applied on S_M [—○—, D-fructose (30.0 g), H_2O (250 mL), 60° , 20 atm. H_2 , catalyst (0.5 g)] for the hydrogenation of D-fructose; on S_F [—×—, invert sugar (60.0 g), H_2O (250 mL), 60° , 20 atm. H_2 , catalyst (1.0 g)] for the hydrogenation of invert sugar; and on the overall yield (—⊗—) of D-mannitol in the combi-process; $S_F \times S_M$ (—⊗—), S_M in the presence of borate (—□—) (cf. Fig. 3)

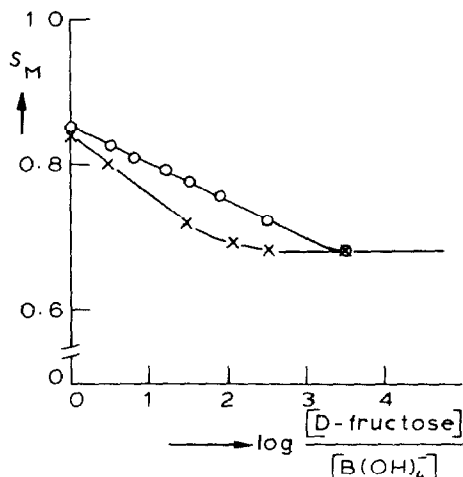


Fig. 3. The influence of borate on S_M for the hydrogenation of D-fructose [D-fructose (30.0 g), H_2O (250 mL), 70° , 50 atm. H_2 , 20% Cu/SiO₂ (1.0 g), in the absence (—○—) and the presence (—×—) of $CaCO_3$ (0.5 g)].

Additives. — In order to keep the D-glucose isomerase sufficiently active during the combi-process, small amounts of $CaCO_3$ (as buffering agent) and Mg^{2+} (as enzyme stabilising agent) were added. These additives had no serious effect on the activity of the metal catalysts. Furthermore, S_F remained essentially the same, whereas S_M increased fractionally, especially for Pt/C (Fig. 4). The addition of borate to the Cu/silica catalyst had a positive effect on the selectivity towards D-mannitol (Fig. 3), and the effect was less pronounced when Ca^{2+} and Mg^{2+} were present. The other catalysts were not affected by borate. The borate/copper phenomenon is discussed below.

Kinetics of the hydrogenation of D-fructose. — Use of Cu/silica and Pt/C at

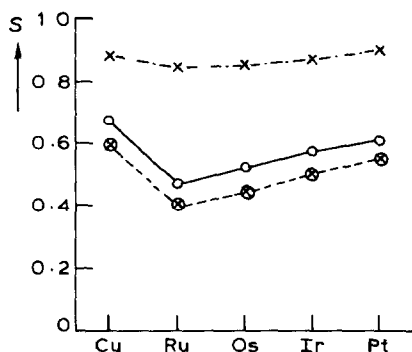


Fig. 4. Selectivities in the presence of Ca^{2+} and Mg^{2+} : S_M [—○—, D-fructose (30.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), H_2O (250 mL), 60° , 20 atm. H_2 , catalyst (0.5 g)], S_F [—×—, invert sugar (60.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), H_2O (250 mL), 60° , 20 atm. H_2 , catalyst (1.0 g)], $S_F \times S_M$ (—⊗—).

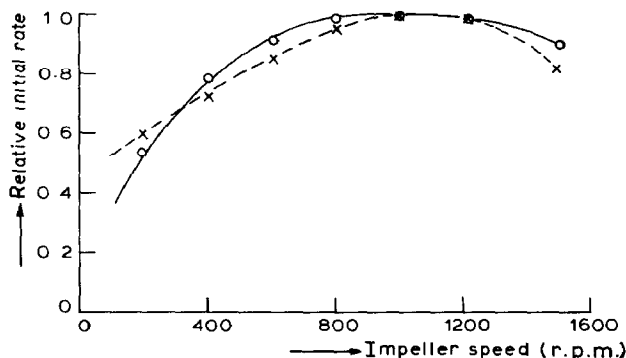


Fig. 5. The influence of the impeller speed on the relative initial rate of D-fructose hydrogenation: D-fructose (30.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), H_2O (250 mL), and 5% Pt/C (0.5 g), 60° , 20 atm. H_2 (—×—) or 20% Cu/silica (1.0 g), 70° , 50 atm. H_2 (—○—).

various rates of agitation showed that the reaction rate was independent of the stirrer speed in the range 800–1200 r.p.m. (Fig. 5), and a speed of 800 r.p.m. was therefore used throughout. The initial rate of the hydrogenation of D-fructose (0.833M) was linearly dependent on the catalyst/D-fructose ratio in the range of 0.003–0.17 (Fig. 6), *i.e.*, the hydrogenation is first order with respect to catalyst.

An activation energy of 14.7 kcal/mol for the hydrogenation of D-fructose over Cu/silica in the range 60 – 90° was obtained from Fig. 7. The hydrogenation of D-fructose over Cu/silica appeared to be first order with respect to hydrogen pressure (Fig. 8). A typical plot for the hydrogenation of D-fructose over Cu/silica (Fig. 9) indicated the reaction to be between zero and first order with respect to D-fructose concentration at $0.3 < [F] < 0.8$, zero order at $[F] > 0.8$, and first order at $[F] < 0.3$ M. This is demonstrated by the logarithmic relation between $[F]$ and $d[F]/dt$ as shown in Fig. 10. Thus, the rate-limiting step is the attack of hydrogen on D-fructose adsorbed on the surface of the catalyst. The products D-mannitol and D-glucitol

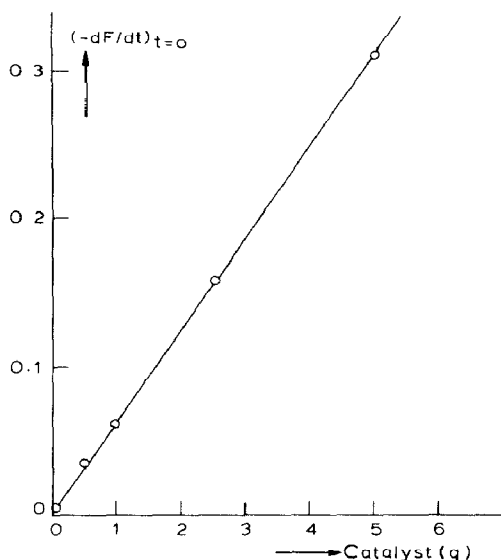


Fig. 6. The influence of the amount of Cu/silica on the initial rate of hydrogenation of D-fructose: D-fructose (30.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ (0.1 g), H_2O (200 mL), 70° , 50 atm. H_2 .

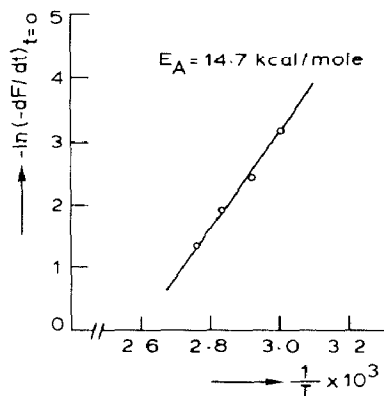


Fig. 7. Arrhenius plot of the initial reaction rates for the hydrogenation of D-fructose: D-fructose (30.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ (0.5 g), 20% Cu/silica (1.0 g), H_2O (200 mL), 50 atm. H_2 at 60° , 70° , 80° , and 90° .

TABLE II

INFLUENCE OF D-MANNITOL AND D-GLUCITOL ON THE RATE OF HYDROGENATION OF D-FRUCTOSE^a

Composition	Initial rate (mol.h ⁻¹)
D-Fructose (30 g)	0.044
D-Fructose (60 g)	0.045
D-Fructose (30 g) + D-mannitol (30 g)	0.041
D-Fructose (30 g) + D-glucitol (30 g)	0.042
D-Fructose (30 g) + D-mannitol (15 g) + D-glucitol (15 g)	0.043

^a CaCO_3 (0.5 g), MgSO_4 (0.4 g), 20% Cu/SiO₂ (1.0 g), H_2O (200 mL), 70° , 50 atm. H_2 .

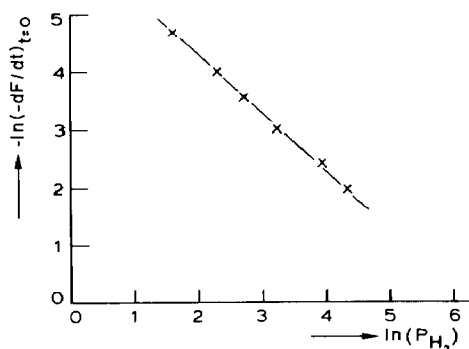


Fig. 8. The influence of the pressure of hydrogen (atm.) on the initial rates for the hydrogenation of D-fructose: D-fructose (30.0 g), $MgSO_4$ (0.3 g), $CaCO_3$ (0.5 g), $Na_2B_4O_7 \cdot 10 H_2O$ (0.1 g), 20% Cu/silica (1.0 g), H_2O (200 mL), 70° .

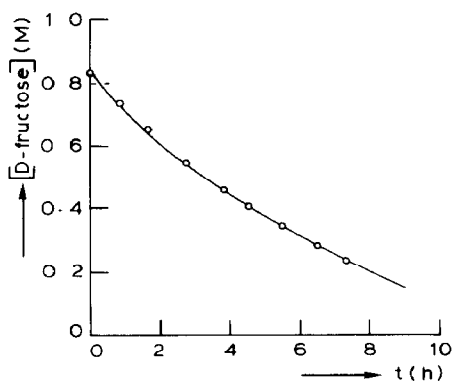
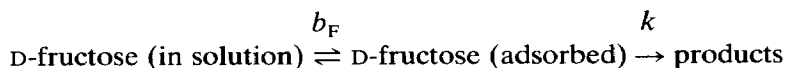


Fig. 9. Concentration *versus* time for a typical hydrogenation of D-fructose: D-fructose (30.0 g), $MgSO_4$ (0.3 g), $CaCO_3$ (0.5 g), $Na_2B_4O_7 \cdot 10 H_2O$ (0.1 g), 20% Cu/silica (1.0 g), H_2O (200 mL), 70° , 50 atm. H_2 .

affected neither the rate of hydrogenation of D-fructose (see Table II), nor the stereoselectivity.

The kinetic picture observed is easily explained using Langmuir–Hinshelwood kinetics:



$$r = \frac{-d[F]}{dt} = k\Theta_F = k \frac{b_F[F]}{1 + b_F[F] + \Sigma bC}.$$

Here, k includes the hydrogen pressure and the amount of catalyst, and ΣbC is the sum of the contributions of water, D-glucitol, D-mannitol, and the hydrogen to the denominator of the Langmuir–Hinshelwood expression. If $b_F[F] \gg 1 + \Sigma bC$, then $r \approx k$ (zero order in D-fructose); if $b_F[F] \ll 1 + \Sigma bC$, then $r \approx k[F]$ (first order in D-fructose).

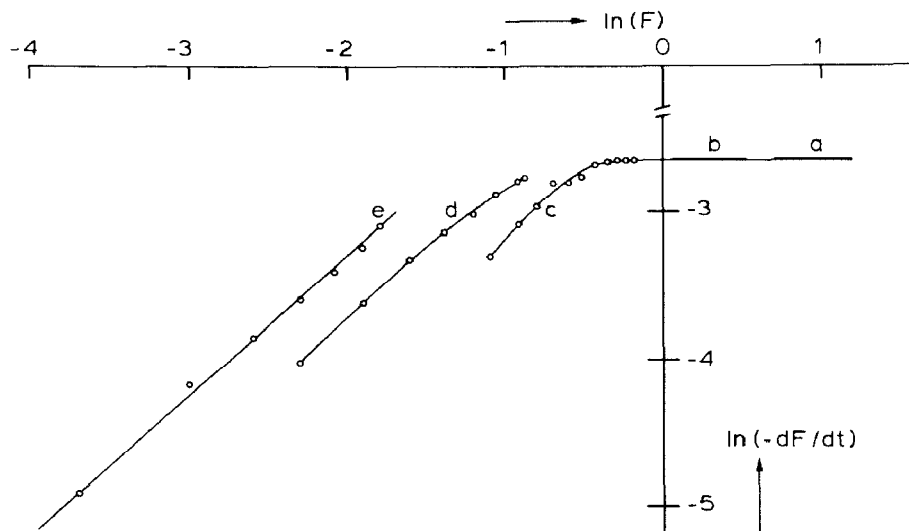


Fig. 10 The influence of the concentration of D-fructose on its initial rate of hydrogenation: MgSO_4 (0.3 g), CaCO_3 (0.5 g), $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ (0.1 g), 20% Cu/silica (1.0 g), H_2O (200 mL), 70° , 50 atm. H_2 ; D-fructose a (120.0 g), b (60.0 g), c (30.0 g), d (15.0 g), and e (6.0 g).

The selectivity (S_F) for the conversion of D-fructose in the hydrogenation of invert sugar over Cu/silica is determined by both the adsorption and reaction rate constants of D-fructose and D-glucose, *i.e.*, $S_F = k_F b_F / k_G b_G$.

Separate hydrogenations of D-glucose and D-fructose (0.833M) over Cu/silica in water at 70° and 50 atm. of H_2 yielded a value for k_F/k_G of 27. Under the same conditions, the co-adsorption of D-glucose was examined by measuring the decrease in initial rate for the hydrogenation of D-fructose on the addition of increasing amounts of D-glucose (Fig. 11). Using the expression

$$r_0 \sim \frac{k_F b_F [F]}{b_F [F]_0 + b_G [G]_0} = \frac{k_F [F]_0}{[F]_0 + (b_G/b_F)[G]_0},$$

it follows that $b_G/b_F = 3$, *i.e.*, D-glucose is adsorbed more strongly than D-fructose. So the overall selectivity S_F of 9 observed for the hydrogenation of invert sugar is brought about by a 27-fold higher reactivity of D-fructose, which is partly counteracted by a 3-fold stronger adsorption of D-glucose.

Mechanism of the hydrogenation of D-fructose over Cu/silica. — The furanose, pyranose, and open-chain forms of D-fructose present in aqueous solution will have different adsorptivities for the surface of the catalyst, and characteristic rates of hydrogenation. These factors will determine which form is preferentially hydrogenated. Also possible are hydrogenation of the free carbonyl group and the 1,2-enediol form, and hydrogenolysis of either a pyranose or a furanose form.

Ruddlesden *et al.*⁸ found 1,3,4,5,6-penta-*O*-acetyl-*keto*-D-fructose to be resistant to hydrogenation under conditions where 1,3,4,5-tetra-*O*-acetyl-D-fructo-

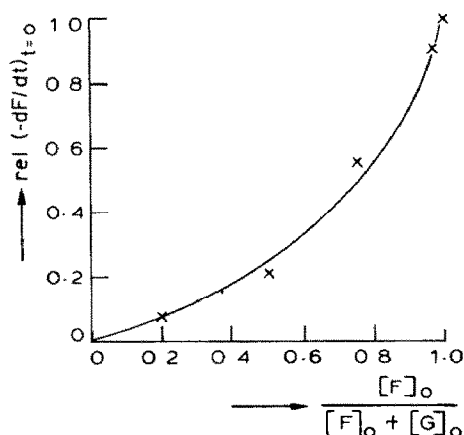
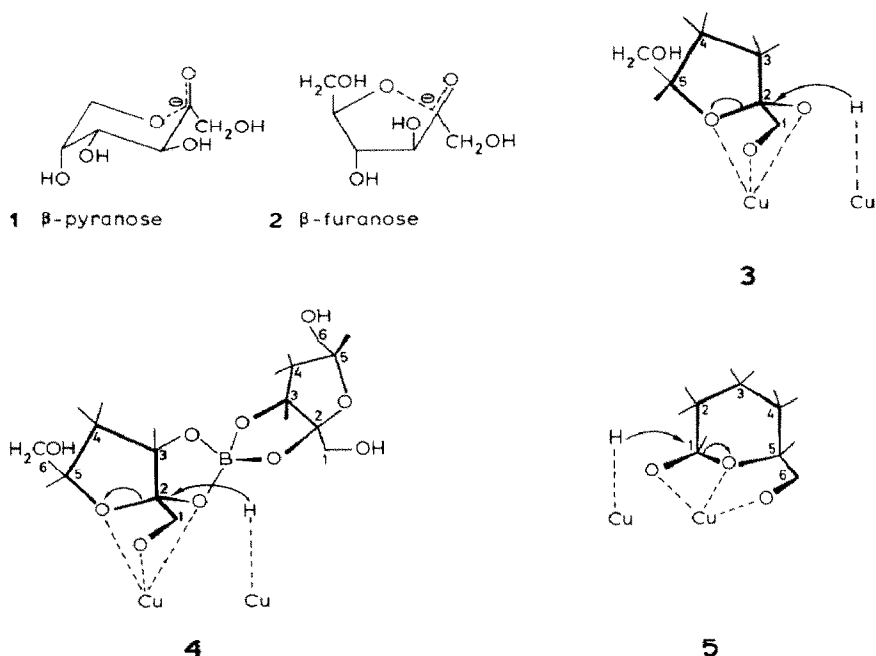


Fig. 11. The influence of D-glucose on the relative initial rate of the hydrogenation of D-fructose: D-fructose (30.0 g), MgSO_4 (0.3 g), CaCO_3 (0.5 g), $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ (0.1 g), 20% Cu/silica (1.0 g), H_2O (200 mL), 70° , 50 atm. H_2 .

pyranose reacted, and only one ^2H was introduced at position 2 on deuteration of D-fructose. We have also shown that, on deuteration, the ^2H was introduced at position 2 for D-fructose (D_2O , 70° , 50 atm. D_2) and one ^2H at position 1 for both D-glucose and D-mannose (D_2O , 100° , 50 atm. D_2) when Cu/silica was the catalyst. Hydrogenolysis is unlikely since the methyl D-fructosides did not react under the above-mentioned conditions. On prolonged reaction at 120° , the methyl D-fructosides were converted into methanol, D-mannitol, and D-glucitol, but no 2-O-methyl-D-mannitol or 2-O-methyl-D-glucitol was formed. Clearly, hydrogenation occurs after hydrolysis of the methyl D-fructosides into methanol and D-fructose. It is possible that the mechanism involves a cyclic structure with an ionised, anomeric hydroxyl group.

^{13}C -N.m.r. spectroscopy of monosaccharides has shown that, upon ionisation of D-fructose, the C-2-O ring bond is weakened and that the anomeric C-O $^-$ bond acquires partial double-bond character⁹ (**1** and **2**). It is believed that interaction of ketoses and aldoses with such metals as copper may generate such ionised species which are susceptible to attack by hydrogen at the anomeric carbon (*cf.* the mechanism proposed¹⁰ for benzyl C-O hydrogenolysis). The importance of ionised species is indicated by the accelerating effect of base in the hydrogenation of D-fructose over platinum and rhodium¹¹. The electron distribution in the ionised species in combination with the proposed attack of a hydride-like species favours an $\text{S}_{\text{N}}2$ type of reaction with inversion of configuration of the anomeric carbon (**3**). Therefore, we propose that D-mannitol is formed from β -D-fructose, whereas D-glucitol is formed from α -D-fructose¹².

In this context, isomaltulose (6-O- α -D-glucopyranosyl-D-fructofuranose) is a useful model compound since only the α - (20%) and β -furanose (80%) forms are present in aqueous solution at room temperature. Hydrogenation of isomaltulose



(Cu/SiO₂, 100°, 50 atm. H₂) gave 67% of 6-*O*- α -D-glucopyranosyl-D-mannitol and 33% of 6-*O*- α -D-glucopyranosyl-D-glucitol, indicating that the precursor β - and α -furanose structures react at similar rates and have similar adsorptivities.

D-Fructose exists in aqueous solution (at 66°) essentially as an equilibrium of β -pyranose (55%), β -furanose (35%), and α -furanose (10%) forms. However, hydrogenation over Cu/silica gave 67% of D-mannitol and 33% of D-glucitol, a result which parallels closely that for isomaltulose and suggests that the pyranose form probably plays a minor role in the hydrogenation reaction.

The suggested lower reactivity of the pyranose form accords with the results of the competitive hydrogenation of D-mannose and D-talose. In aqueous solution, D-mannose is present solely as its pyranose form at 31°, whereas 30% of D-talose is present as furanose forms at 44°. Hydrogenation (Cu/silica, 70°, 50 atm. H₂, H₂O) of a 1:1 D-mannose/D-talose mixture showed that the initial rate of reaction of D-talose was 2.7 times higher than that of D-mannose.

In an analogous way, the preferential products of hydrogenation of L-sorbose, D-tagatose, D-psicose, D-xylulose, and D-ribulose, as expected from their respective α/β -furanose ratios for aqueous solutions, will be D-glucitol, allitol, D-talitol, D-arabinitol, and D-ribitol, respectively, which accords with the results of Ruddlesden *et al.*⁸ using Cu/silica as the catalyst.

Therefore, we propose that the hydrogenation of D-fructose (and other ketoses) over Cu/silica involves the formation of an ionised furanose species adsorbed on the copper surface by coordination of O-1, O-2, and O-5 (3), and attack of a hydride-like species from the copper surface from the anti-ring-O side with

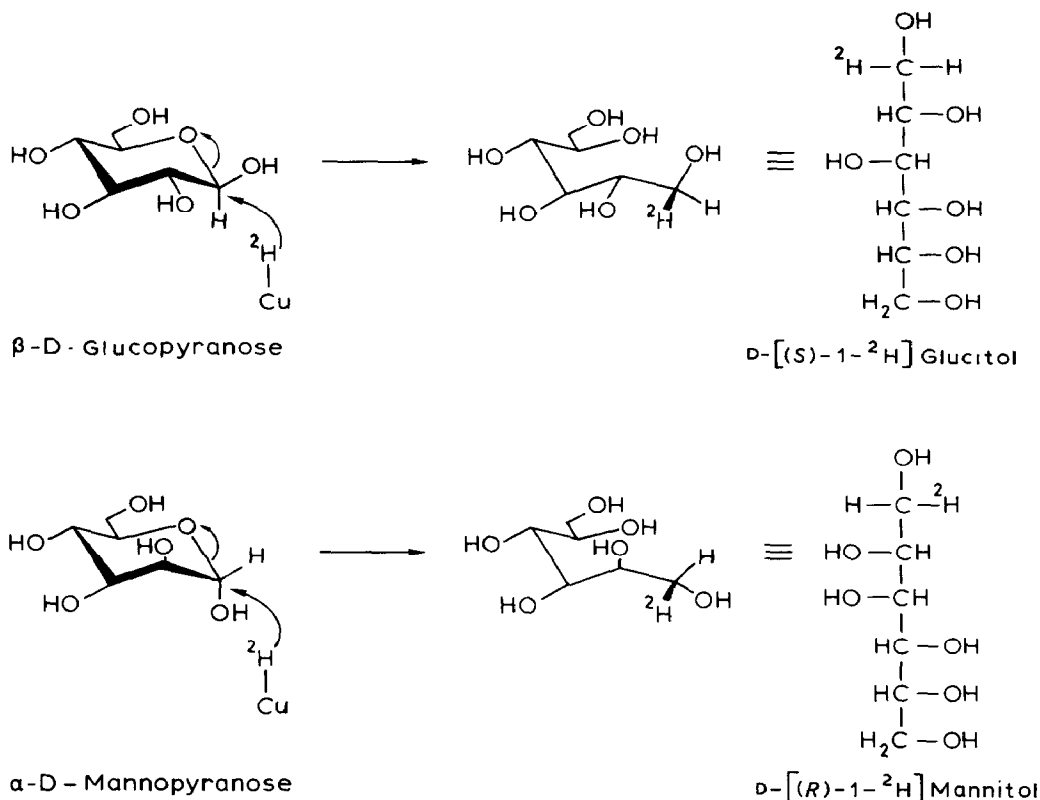


Fig. 12. Stereoselective attack of ^2H on $\beta\text{-D-glucopyranose}$ and $\alpha\text{-D-mannopyranose}$.

inversion of configuration at the anomeric carbon.

Effect of borate addition. — In the presence of borate, hydrogenation of D-fructose and isomaltulose over Cu/silica gave enhanced yields of D-mannitol (80–90%) and 6-O- $\alpha\text{-D-glucopyranosyl-D-mannitol}$ (75%), respectively. ^{11}B - and ^{13}C -n.m.r. spectra show that, under these conditions, a 1:2 borate-sugar ester is formed, involving the β -furanose form¹³ (4). The effect of borate can be understood on the basis of the above mechanism if it is assumed that the boric ester is hydrogenated preferentially. Since small amounts of borate affect the selectivity, relatively strong adsorption of the boric ester on the copper surface must occur. The selectivity of Ru/C, Pt/C, and Raney Ni was not influenced by the addition of borate, probably because these metal surfaces have a low affinity for borate esters.

As shown in Fig. 3, the presence of CaCO_3 (as a buffering agent) partly counteracted the effect of borate. ^{11}B - and ^{13}C -n.m.r. spectroscopy showed that CaCO_3 inhibited the formation of borate esters unless the borate concentration exceeded the amount of CaCO_3 .

Mechanism of the hydrogenation of aldoses over Cu/silica. — In aqueous solution, D-glucose and D-mannose are present as their α - and β -pyranose forms.

Molecular models indicate that the adsorption of the β -pyranose form will be more favourable through the coordination of O-1, O-5, and O-6 (5). If the reactivities of the adsorbed α - and β -pyranose forms are similar, the mechanism proposed above would predict that D-glucose will be preferentially converted into D-[(S)-1- 2 H]glucitol upon deuterogenation, but for D-mannose (35% β -pyranose) the selectivity for the formation of D-[(S)-1- 2 H]mannitol should be smaller (Fig. 12).

D-Glucose and D-mannose were deuterogenated (D₂O, 120°, 50 atm. D₂), and the relative amounts of the (R) and (S) isomers of D-[1- 2 H]glucitol and of D-[1- 2 H]mannitol were determined by 1 H-n.m.r. spectroscopy of the respective 1,4:3,6-dianhydro derivatives^{14,15}. Thus, D-glucose yielded 80% of D-[(S)-1- 2 H]glucitol, whereas D-mannose gave a 1:1 (R)/(S) mixture of the D-[1- 2 H]mannitols, thus supporting the proposed mechanism.

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