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Efficient Isomerization of Glucose to Fructose over Zeolites in Consecutive Reactions in Alcohol and Aqueous Media

Shunmugavel Saravanamurugan,[†,§] Marta Paniagua,[‡,§] Juan A. Melero,[‡] and Anders Riisager*[,†]

[†]Centre for Catalysis and Sustainable Chemistry, Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

[‡]Chemical and Environmental Technology Department, Universidad Rey Juan Carlos, C/Tulipán s/n, E-28933 Móstoles, Madrid, Spain

Supporting Information

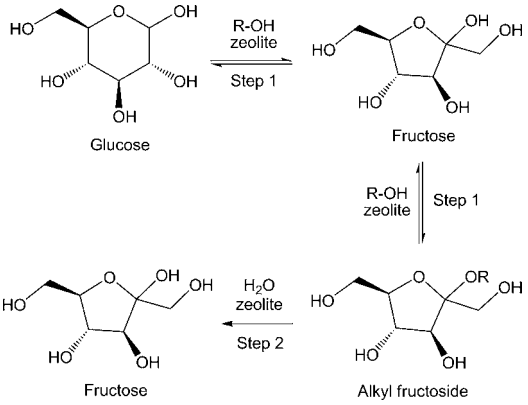
ABSTRACT: Isomerization reactions of glucose were catalyzed by different types of commercial zeolites in methanol and water in two reaction steps. The most active catalyst was zeolite Y, which was found to be more active than the zeolites beta, ZSM-5, and mordenite. The novel reaction pathway involves glucose isomerization to fructose and subsequent reaction with methanol to form methyl fructoside (step 1), followed by hydrolysis to re-form fructose after water addition (step 2). NMR analysis with ^{13}C-labeled sugars confirmed this reaction pathway. Conversion of glucose for 1 h at 120 °C with H-USY (Si/Al = 6) gave a remarkable 55% yield of fructose after the second reaction step. A main advantage of applying alcohol media and a catalyst that combines Brønsted and Lewis acid sites is that glucose is isomerized to fructose at low temperatures, while direct conversion to industrially important chemicals like alkyl levulinates is viable at higher temperatures.

Glucose is the cheapest and the only abundant monosaccharide available in nature among the isomeric hexose sugars glucose, fructose, and mannose.[1] Despite its lower accessibility, fructose is widely used in the food industry as, for example, a sweetener (high-fructose corn syrup), since it contributes many useful physical and functional attributes to food and beverage applications.[2] Currently, the reversible isomerization of glucose to fructose is carried out on large industrial scale in aqueous phase with the enzyme D-glucose/xylose isomerase (GI, EC 5.3.1.5), which possesses high reaction specificity under benign pH conditions and relatively low reaction temperature. However, major drawbacks of the process are inactivation of GI at higher temperatures (above 60 °C), narrow pH operation window, inhibition of GI in the presence of Ca^{2+} ions (prerequisite for the action of amylase when liquefaction, saccharification, and isomerization are carried out simultaneously), requirement of Co^{2+} ions for enzyme activity, and suboptimal concentrations of the product.[3] For these reasons, the enzyme activity is still low from an economic point of view, and a large quantity of enzyme is thus needed to obtain viable throughputs.[4]

As an alternative to GI, glucose can also be transformed into fructose by aldose−ketose isomerization in the presence of a base.[5] However, monosaccharides are unstable in alkaline media, and a high amount of byproducts are formed due to the side reactions.[6] Generally, Brønsted acids are not efficient catalysts for aldose isomerization, although the efficacy may be a function of reaction conditions.[7] Román-Leshkov et al., however, provided conclusive evidence via NMR that Lewis acidity can catalyze sugar isomerization.[6] Zeolites containing tetravalent metal atoms in the tetrahedral positions are well-explored as solid Lewis acid catalysts for many reactions and are widely used in the petroleum industry.[8] Recent studies have shown that the Lewis acid zeolite Sn-BEA is particularly effective for catalyzing the isomerization of a series of pentose and hexose sugars with activities comparable to biological processes[1,6,9] by a mechanism similar to enzymatic catalysts.[10] However, Sn-BEA is not commercially available, comprises tin—a toxic heavy metal—and is by traditional methods cumbersome to synthesize, though improved synthetic routes have very recently been devised.[11]

In this work, we report a new approach for getting unprecedentedly high yields of fructose from glucose in alcohol and aqueous media using commercially available zeolite catalysts containing only silicon and aluminum. The isomerization reaction was carried out in methanol following a two-step batch mode procedure. The reaction pathway for the consecutive reactions for the conversion of glucose to fructose is illustrated in Scheme 1. In the first reaction step, glucose is isomerized to

Scheme 1. Reaction Pathway for Fructose Formation from Glucose in Alcohol and Aqueous Media



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fructose in methanol, which immediately reacts with the reaction media to form methyl fructoside. In a second reaction step, water is added to hydrolyze the methyl fructoside in order to obtain fructose. Notably, both reaction steps can be performed at the same temperature.

One-pot synthesis of fructose from glucose was first examined using different solvent mixtures containing up to 95 wt% of methanol in water (Table S1). The initial presence of water in the media led to low glucose isomerization (maximum yield of 8% of fructose), and no methyl fructoside was formed. In line with this, Johnson et al. reported that a large excess of alcohol is needed, as well as removal of the water formed during the reaction, in order to maximize the conversion of fructose into methyl fructoside.[12] A way to circumvent the unfavorable water inhibition was to perform the reaction as a two-step reaction sequence instead, where the isomerization and etherification were first performed in alcohol, followed by hydrolysis.

In the two-step process, different commercially available zeolite catalysts were tested for the isomerization/etherification of glucose to fructose/methyl fructoside at 120 °C and 1 h, followed by hydrolysis after water addition for another hour. The amount of water and the reaction time required to complete the hydrolysis were found from a preliminary study (see Figure S1). The best reaction results were attained using the large-pore zeolites Y and BEA, with especially the H-USY(6) and H-beta(12.5) catalysts giving high fructose yields of 55 and 40%, respectively. In addition to the pore size of the zeolite, the pore structure was apparently an important factor, since the Y-zeolite framework facilitated formation of a higher yield of methyl fructoside in the first reaction step than the BEA framework. This resulted in an overall improved fructose yield after hydrolysis of the formed methyl fructoside in the second step. Notably, USY—a steamed zeolite—might have extra framework Al compared to the beta zeolites, which could further improve the formation of fructose during both reaction steps.

Basic zeolite catalysts Na-Y and Na-mordenite also isomerized the glucose to a small extent. However, they were unable to catalyze the etherification of fructose to methyl fructoside, producing a maximum yield of 18% of fructose in the two-step process (Table S3). With other acid zeolites (e.g., H-ZSM-5), low glucose conversion was also achieved in the isomerization reaction. Similar results have been obtained in other sugar transformations.[13]

NH_3-TPD analysis of the H-USY(6) and H-beta(12.5) catalysts revealed that they possessed moderate total acidity and ratios of medium (type 1, T_{desorb} = 100−270 °C) to strong (type 2, T_{desorb} = 270−500 °C) acid sites of 1:0.81 and 1:0.52, respectively (Table S2). Notably, all of the other examined zeolites, which gave lower fructose yields, exhibited significantly different type 1:type 2 acid site ratios and/or number of total acid sites. Previously, the Brønsted and Lewis acidity ratio of zeolites has been determined from FT-IR, and here H-USY(6) was shown to possess a larger fraction of Lewis acid sites compared to H-USY(30).[13a] This suggests that the ratio of Lewis and Brønsted acidity is a key factor to maximize the glucose conversion. Moreover, glucose does not isomerize to fructose to form ethyl levulinate over sulfonic acid-functionalized Brønsted acid catalysts. Instead, glucose reacted with ethanol to form ethyl glucopyranoside.[13b,d] These results confirm that Lewis acidity is indeed necessary to carry out the glucose isomerization in alcohol.

In the reactions of glucose with the Y and BEA catalysts, the combined yields of fructose and glucose were between 70 and 83% (Table 1). A significant product, eluting on HPLC between the glucose and fructose (with retention time similar to that of mannose), could account for the rest of the converted glucose. In an attempt to identify the intermediate product and to examine the equilibrium of the three isomeric sugars—glucose, fructose, and mannose—a time-course study was carried out for each sugar over Na-mordenite under identical reaction conditions, assuming that the basic zeolite would suppress the formation of methyl fructoside during the first reaction step as well as the intermediate product if it was not mannose. The results confirmed that glucose isomerized to mannose and fructose to some extent in the presence of basic zeolite in methanol and vice versa (Figure S2). However, after isomerization reactions with mannose or fructose in methanol using the acidic H-USY(6) or H-beta(12.5) zeolites, only traces of glucose were observed in HPLC, implying that the formation of methyl fructoside perturbed the equilibrium between the sugars. A complementary reaction study with D-[1-^{13}C]- and D-[2-^{13}C]glucose and mannose was further carried out in the presence of H-USY(6) in methanol-d_4 and D_2O. The results from ^{13}C NMR analysis of the reaction solutions revealed here no carbon signals corresponding to formation of glucose from mannose or mannose from glucose (Table S4; see Scheme S1 for the tautomers). However, two new major peaks (δ/ppm = 102.7 and 109.0 ppm), which did not correlate with standards of methyl glucosides, appeared in the experiments with the 1-^{13}C-labeled sugars. We speculate that these peaks originate from methyl mannosides which account for the remainder of the converted glucose. However, additional work is needed to establish this identity positively. No other significant product peaks were detected in the glucose reaction with this catalyst, thus implying that there were no other degradation products formed. Additionally, the reaction solution remained colorless after the reaction, indicating that humins were not formed in significant amounts. Importantly, it was also possible to get similar reaction results (51% of fructose) and avoid sugar degradation by carrying out the reaction at lower reaction temperature (80 °C) and longer reaction time (24 h).

The influence of reaction time on fructose conversion in methanol over H-USY(6) was further studied at 80 °C to get additional understanding of the reactivity and to ascertain the reaction pathway proposed. In line with the initial experiments at

Table 1. Product Distribution (mol%) Obtained for Glucose Conversion over Commercial Zeolites after the Two-Step Reaction Sequence[a]

			product distribution		
zeolite	Si/Al ratio	step	glucose	fructose	methyl fructoside
H-Y	2.6	1	56	16	19
		2	54	20	18
H-USY	6	1	30	22	33
		2	28	55	4
	30	1	63	26	<1
		2	63	24	<1
H-beta	12.5	1	29	23	22
		2	30	40	8
	19	1	39	21	16
		2	43	29	8
	150	1	90	0	0
		2	89	0	0

[a]Step 1: 75 mg of catalyst, 125 mg of glucose, 4 g of methanol, 1 h, 120 °C. Step 2: 4 g of water, 1 h, 120 °C.

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120 °C, methyl fructoside was practically the only product formed (Figure S3), as also observed in previous work.[12] When water was added to the reaction solution during the second reaction step, the initial fructose was recovered, as expected. Moreover, ^{13}C NMR analysis of reaction products formed with D-[2-^{13}C]fructose and methanol-d_4 revealed the presence of characteristic peaks of methyl fructoside (δ/ppm = 100.8, 104.5, and 108.5). These three peaks were ascribed to methyl β-D-fructopyranoside, methyl β-D-fructofuranoside, and methyl α-D-fructofuranoside, respectively[12] (tautomers shown in Scheme S1). After the hydrolysis step, the three peaks were shifted to lower chemical shift values (δ/ppm = 98.3, 101.9, and 104.7), corresponding to the re-formation of fructose. In an experiment starting with D-[2,5-^{13}C]glucose, similar intermediate products were identified unambiguously, confirming the proposed glucose isomerization reaction pathway to fructose. Additionally, only fructose and methyl fructoside (and trace glucose) were formed when mannose was used as starting sugar, suggesting that the use of methanol as solvent in the isomerization of glucose to fructose is a way to impede establishment of the equilibrium of the C_6 sugar isomers described in water.[9a]

Changing the solvent from methanol to the higher alcohols ethanol and 1-propanol led to the formation of the corresponding alkyl fructoside. The same pathway as described for methanol was observed, resulting in an increased amount of fructose after addition of water in the second reaction step (Figure 1). However, the fructose etherification with higher

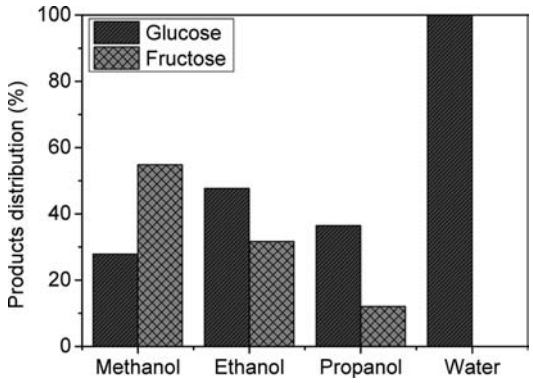

Figure 1. Comparison of different solvents for the conversion of glucose to fructose. Step 1: 75 mg of H-USY(6), 125 mg of glucose, 4 g of solvent, 1 h, 120 °C. Step 2: 4 g of water, 1 h, 120 °C.

alcohols seemed more difficult to accomplish, possibly due to steric impediments. Therefore, less fructose and more by-products were obtained here in comparison to reactions with methanol. In the reaction with ethanol, formation of the byproduct ethyl D-glucopyranoside was confirmed by GC-MS, corroborating that glucose not only isomerized to fructose but also reacted directly with the alcohol, resulting in decreased fructose yield. Changing the reaction parameters did not significantly improve the fructose yields for the ethanol experiments. Importantly, the vital role of the alcohol for the isomerization of glucose remained, however, clear compared to aqueous media where no fructose formation occurred.

Another important aspect to examine is the viability of the catalytic system for the isomerization reaction with increased initial glucose concentration. Accordingly, experiments with different initial concentrations of glucose were also carried out over H-USY(6). Figure 2 shows a progressive decrease in the

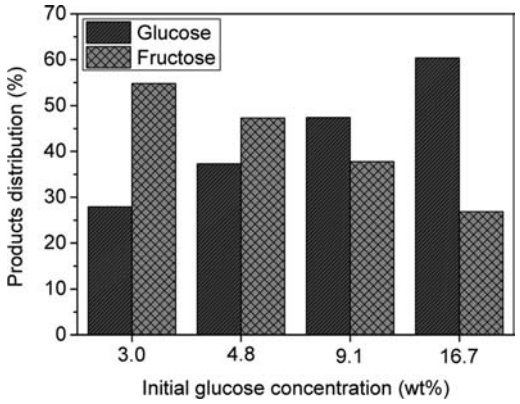

Figure 2. Effect of the initial glucose concentration for glucose conversion. Step 1: 75 mg of H-USY(6), 4 g of methanol, 1 h, 120 °C. Step 2: 4 g of water, 1 h, 120 °C.

obtained yield of fructose from 55 to 27% when the glucose concentration was changed from 3.0 to 16.7 wt%, probably as a consequence of more water being formed during the etherification step in the more concentrated systems. However, a moderate fructose yield of 38% was obtained with up to about 9.1 wt% of initial glucose concentration. This yield increased further to 46% at longer reaction time, thus approaching a result similar to that achieved with lower initial glucose concentration. Likewise, the yield of fructose could be enhanced from 27 to 38% when the reaction time was prolonged for the experiment with 16.7 wt% glucose, while the presence of molecular sieves (4 Å) unexpectedly lowered the yield from 27 to 12%.

The reaction system with H-USY(6) and 3 wt% initial glucose concentration in methanol was also examined with different glucose-to-catalyst mass ratios between 1.7:1 and 12.5:1, and the reaction time was optimized during each reaction step to achieve high yields of fructose (Table 2). The results clearly

Table 2. Influence of the Mass Ratio of Glucose to H-USY(6) Catalyst on the Product Distribution (%) in the Two-Step Reaction Sequence[a]

				product distribution	
m_{cat} (mg)	m_{glu}:m_{cat} ratio	step	time (h)	glucose	fructose
10	12.5:1	1	21	39	20
		2	3	37	51
15	8.3:1	1	5	40	18
		2	3	38	52
25	5.0:1	1	4	32	19
		2	3	33	53
50	2.5:1	1	3	32	20
		2	1	33	55
75	1.7:1	1	1	30	22
		2	1	28	55

[a]Step 1: 10–75 mg of H-USY(6), 125 mg of glucose, 4 g of methanol, 120 °C. Step 2: 4 g of water, 120 °C.

demonstrated that it was possible to achieve above 50% of fructose for all the systems examined if the reaction times were adjusted properly. Moreover, the combined yield of glucose and fructose could be increased from 83% (1.7:1 mass ratio) to between 88 and 91% at higher mass ratios, indicative of suppression in the formed intermediates.

Catalyst reusability has also been evaluated for the most active catalyst, H-USY(6). Figure 3 depicts the results of five

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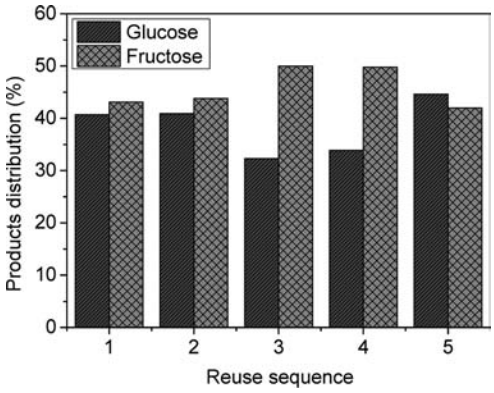

Figure 3. Reuse of H-USY(6) for glucose conversion. Step 1: glucose to catalyst mass ratio = 1.7, 4 g of methanol, 1 h, 120 °C. Step 2: 4 g of water, 1 h, 120 °C.

consecutive catalytic runs performed reusing the catalyst under the optimal reaction conditions. After each catalytic run the catalyst was recovered by filtration, washed thoroughly with methanol, and dried overnight at 140 °C before being reused in the following reaction. In all five consecutive catalytic runs, the fructose yield remained constant at about 40−50% with a similar product distribution. This clearly demonstrates that the catalytic performance of the zeolite is preserved in the consecutive runs, and that the catalyst system is highly suitable for reuse. Furthermore, after the fifth reaction run, the catalyst was calcined at 550 °C for 6 h and then subjected to surface area analysis. The formal BET area and pore volume of H-USY(6) before use were measured to be 708 m^2/g and 0.2436 cm^3/g, respectively. After the fifth reaction run, there were practically no changes in the formal BET area (707 m^2/g) and pore volume (0.2463 cm^3/g), thus corroborating that the structural integrity of H-USY(6) remained unchanged after the reaction cycles.

In conclusion, commercial large-pore zeolites have been demonstrated to provide excellent catalytic performance in the isomerization of glucose and subsequent etherification in methanol. Applying these findings, a new two-step reaction route to produce fructose from glucose was introduced, which was ascertained by ^{13}C NMR analyses using isotope-labeled sugars. The best result for formation of fructose was obtained using the zeolite H-USY(6) with optimal levels and distribution of Brønsted and Lewis acidity (Si/Al ratio = 6). Using this catalyst, it proved possible to maintain a high fructose yield of 50−55%, with remaining 30−40% glucose even with low catalyst loading (glucose-to-catalyst mass ratio = 12.5:1) at prolonged reaction times. These values resembles the equilibrium yields obtained of glucose (44−47%) and fructose (53−55%) in the enzymatic isomerization reaction of glucose with glucose isomerase.[14] The solid catalyst could furthermore be reused in five consecutive reaction runs, upholding the same initial activity and structural integrity.

The introduced reaction approach has further been extended to conversion of C_5 sugars, confirming that xylose follows the same reaction pathway as described for glucose (results will be reported in due course). This clearly demonstrates the generality of the concept and enables potential new catalytic applications of zeolites with combined Brønsted and Lewis acid sites in reaction protocols where sugar isomerization is favored at low temperature and direct transformation to industrially important chemicals (e.g., alkyl levulinates) is facilitated at higher temperature.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, NMR and NH_3-TPD data, and some catalytic results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ar@kemi.dtu.dk

Author Contributions

[§]S.S. and M.P. contributed equally to the work.

Notes

The authors declare no competing financial interest.

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