Selective Base-Catalyzed Isomerization of Glucose to Fructose

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S Supporting Information

ABSTRACT: Fructose is a key intermediate in the conversion of cellulosic biomass to biofuels and renewable platform chemicals. Biomass-derived glucose can be isomerized to fructose using either Lewis acid or Brønsted base catalysts. Lewis acids are typically preferred as alkaline conditions promote a large number of side reactions. It is widely admitted that only low fructose yields, below 10%, are achievable with inorganic bases. Here, fructose was synthesized with 32% yield using commercially available organic amines. Glucose conversion and fructose selectivity were comparable to Lewis acids, which opens new perspectives for the base-catalyzed pathway.

KEYWORDS: biomass conversion, Brønsted base, glucose isomerization, fructose, tertiary amines
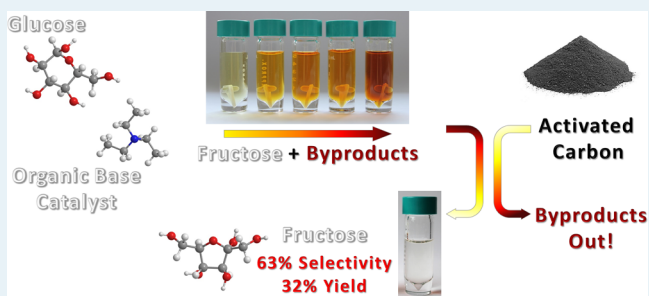
The isomerization of glucose to fructose is a key intermediate step in the synthesis of biofuels and platform chemicals from renewables. Fructose plays a critical role in the production of 5-hydroxymethylfurfural (HMF), 2,5-furandicarboxylic acid (FDCA), and levulinic acid, which are central to the production of plastics, green solvents, lubricants, and valeric biofuels.[1−3] Immobilized enzymes isomerize biomass-derived glucose to fructose with 42% yield, close to the thermodynamic equilibrium.[4] This process has been fully optimized over the past two decades and is currently employed at a large scale for the production of high fructose corn syrup (HFCS).[4−6] However, the enzymatic process suffers several drawbacks; in particular, the enzyme's half-life varies between 80 and 150 days, depending on reactions conditions.[4] Feed purity, pH, temperature, and flow rate need to be carefully controlled in order to prevent the irreversible deactivation of the biocatalyst through chemical and microbial contamination or thermal degradation.[4−6] Therefore, significant efforts are devoted to designing selective chemical catalysts that can operate under a wider range of reaction conditions and at higher temperature in order to improve the reaction kinetics.

Glucose isomerization to fructose is catalyzed both by Lewis acids and Brønsted bases.[7] However, monosaccharides are unstable under strong alkaline conditions and degrade into more than 50 different byproducts.[8,9] It has been widely reported that fructose yields are typically low for Brønsted bases (<10%) and that high selectivity to fructose can only be obtained at low glucose conversion.[7,8,10−18] Therefore, recent works focused on the more promising Lewis acid-catalyzed route.[15,16,19−24] Significant progress has been achieved to produce fructose with high yields both homogeneously and heterogeneously. Moliner et al.'s work on Sn-doped Beta zeolite represents a landmark in this field as the authors demonstrated for the first time that high yields, in the order of 31%, can be achieved with 57% selectivity within 30 min at 110 °C.[15] However, Sn-Beta is not commercially available, and its synthesis is complex.[15] It has also been established that this catalyst deactivates within minutes to a few hours.[25] In this context, we decided to revisit the base-catalyzed isomerization and investigate the potential of organic amines for this reaction. Amines are found in a variety of natural products including food and drugs. Their availability and low toxicity makes them ideal candidates to produce fructose for food, chemical, and fuel applications.

The base-catalyzed isomerization of glucose to fructose follows the Lobry de Bruyn−Alberda van Ekenstein (LdB−AvE) mechanism, named after the two scientists who discovered in 1895 that glucose is transformed into fructose in the presence of a base.[10,26] Ring and open-chain forms of glucose coexist in aqueous solutions. The base reacts with glucose and promotes the formation of the 1,2-enediol intermediate (Scheme 1).[26] A proton is then transferred from C-2 to C-1 and O-2 to O-1 to form fructose.[26] At the same time, more complex reaction pathways involving the 2,3-enediol anion, aldolization/retro-aldolization, β-elimination, and benzilic rearrangements produce a variety of undesired byproducts.[11] The nature and the ratio of these byproducts depend on pH, temperature, and the chemical composition of

Scheme 1. Reaction Mechanism for the Base-Catalyzed Isomerization of Glucose to Fructose
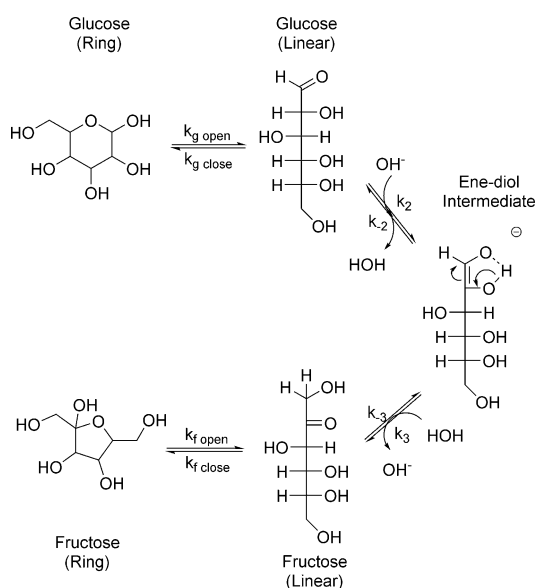
the inorganic base catalyst. Cations, in particular Ca^{2+} (from calcium hydroxide), form cation–ketose complexes which promote retro-aldolization byproducts.[11] We noticed when reviewing the published literature that most experiments were carried out with strong inorganic bases, which favor a high glucose conversion but at the expense of a low selectivity to fructose.[8,11] Here, amines provide additional advantages as (i) they cannot form cation–ketose complexes, and (ii) amines present a much broader range of pK_a values than inorganic bases. They offer significantly more flexibility to optimize the selectivity to fructose, even at high glucose conversion.

Representative amines were selected and tested in order to explore any differences in catalytic activity due to chemical structure (acyclic vs cyclic amine), nature of the functional group (primary, secondary, tertiary amine), and pK_a. A list of the tested compounds along with their properties and catalytic performance are reported in Table 1. The catalytic tests were performed with 10% (w/w) glucose in water for easier comparison with data available on Sn-Beta.[15] The reaction was allowed to proceed for 30 min. The reaction vials were then quenched in an ice bath and the solutions were analyzed by ultra performance liquid chromatography (UPLC) equipped with photodiode array (PDA) and evaporative light scattering

Table 1. Catalytic Results for the Amine-Catalyzed Isomerization of Glucose to Fructose[a]

amine	type[b]	pK_a	X_{Glu}[c]	S_{Fru}[d]	Y_{Fru}[e]	Y_{Man}[f]
morpholine	sec	8.4	39	43	17	2
piperazine	sec	9.8	45	62	28	3
ethylenediamine	pri	10.8	42	60	25	3
triethylamine	ter	10.8	57	54	31	5
piperidine	sec	11.2	56	51	29	5
pyrrolidine	sec	11.3	49	59	29	3

[a]Catalytic tests performed with a 10% (w/w) glucose/water solution, 10 mol % N relative to glucose, 100 °C, 30 min. All results are reported within ±1%. [b]Amine type: pri = primary, sec = secondary, ter = tertiary. [c]Glucose conversion (%). [d]Fructose selectivity (%). [e]Fructose yield (%). [f]Mannose yield (%).

(ELS) detectors. Triplicates were performed to ensure the reproducibility of the obtained data. The standard error was always smaller than 1% (Supporting Information).

Fructose yields are typically low, below 10%, when strong inorganic bases are used as catalysts.[7,8,10−18] In contrast, our preliminary tests (Table 1) clearly show that organic amines, and in particular triethylamine, isomerize glucose to fructose with similar selectivity (54%) and yield (31%) as Sn-Beta.[15] Differences in performance were observed for the tested amines (Figure 1a−e). Glucose conversion increased with pK_a, although no correlation was found between pK_a and both selectivity and yield of fructose; this lack of correlation could suggest that additional effects due to the solvation of the amine or interaction between the amine and the carbohydrates may play a role that remains to be elucidated. Theoretical calculation performed for the dehydration of fructose to HMF demonstrated that the higher selectivity observed in water–dimethylsulfoxide (DMSO) mixtures can be explained by solvent effects.[27] DMSO reduces the number of water molecules in fructose's vicinity and protects it from side reactions.[27] Organic amines may play a similar role during glucose isomerization.

The Maillard reaction represents one possible pathway of byproduct formation. It is well-known in food sciences that primary and secondary amines react with reducible sugars through the Maillard reaction to form colored products.[28] The kinetics involved in this nonenzymatic browning reaction are complex and vary with the structure of the amine. The Maillard reaction is significantly faster in the presence of primary amines than with secondary amines, which is consistent with the darker solution observed for ethylenediamine (Figure 1e and Supporting Information) compared to piperidine (Figure 1d); tertiary amines are not expected to react based on the proposed reaction mechanism.[29]
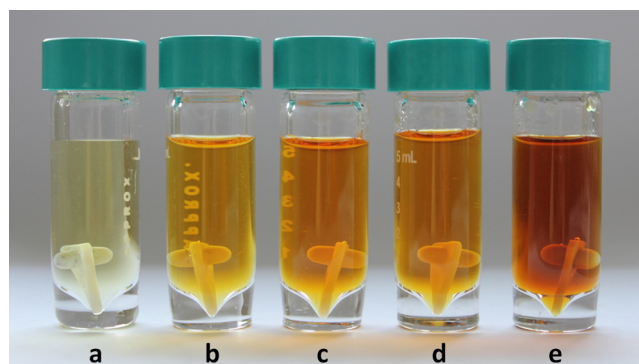

Figure 1. Photograph of the reaction vials showing the formation of colored degradation products. (a–c) Triethylamine after reaction at 100 °C for 5, 10, and 15 min; (d) piperidine and (e) ethylenediamine after 15 min at 100 °C.

The Maillard reaction is particularly undesired in the present work as this stoichiometric reaction would consume both the reactant and the catalyst. Therefore, the reacted solutions were analyzed using UV–vis spectrometry and ^1H NMR spectroscopy (Supporting Information) to get more insights on the contribution from the Maillard reaction under the tested conditions. UV–vis spectra of the reacted solutions containing primary and secondary amines were red-shifted relative to the spectrum of triethylamine. The magnitude of the shift was consistent with the expected kinetics: 42 nm for ethylenedi-

amine (primary amine) and 2−14 nm for the secondary amines (Supporting Information). The similarities between the UV−vis spectra of secondary and tertiary amines suggest that most colored byproducts observed with secondary amines are the result of thermal degradation of the carbohydrates, which is the process involved in caramelization.[30] ^{1}H NMR investigations further confirmed that triethylamine does not participate in the Maillard reaction and is not consumed under reaction conditions (Supporting Information).

The effect of temperature, reaction time, and catalyst loading were further investigated for triethylamine (Table 2). Selectivity

Table 2. Effect of Reaction Parameters on the Catalytic Activity of Triethylamine (TEA)[a]

entry	TEA concn (mol %)	temp (°C)	time (min)	X_{Glu}[b]	S_{Fru}[c]	Y_{Fru}[d]	Y_{Man}[e]
1	2	100	30	31	74	23	2
2	5	100	30	45	61	27	4
3	10	100	30	57	54	31	5
4	20	100	30	69	39	27	7
5	30	100	30	75	33	25	7
6	10	60	30	15	65	10	<1
7	10	80	30	45	63	28	<1
8	10	120	30	58	49	28	7
9	10	100	10	48	61	29	<1
10	10	100	20	51	63	32	<1
11	10	100	40	56	53	30	5
12	10	100	50	54	57	31	5

[a]Catalytic tests performed with a 10 wt % glucose/water solution using triethylamine as a catalyst. All results are reported within ±1%. [b]Glucose conversion (%). [c]Fructose selectivity (%). [d]Fructose yield (%). [e]Mannose yield (%).

to fructose decreased with increasing catalyst concentration and/or reaction temperature, which is consistent with previous work on NaOH.[17,31] Our preliminary results indicate that a yield of 27−32% can be obtained for a wide range of reaction conditions, making it a rather flexible process. Most of the fructose is formed within minutes: the yield was of 29% after 15 min and reached 31% after 30 min of reaction at 100 °C and a catalyst loading at 10 mol % relative to glucose.

Separation and purification of reaction media is often challenging, especially when homogeneous catalysts are employed. We explored the possibility to selectively remove the undesired colored byproducts by simple purification using activated carbon. The solution was mixed after reaction (Entry 10) with 5 wt % of Darco KB-G activated carbon and stirred for 1 h. The mixture was then filtered and analyzed by UV−vis spectroscopy, UPLC, and ^{1}H NMR. The solution became colorless after filtration indicating that the colored byproducts adsorbed on the activated carbon (Figure 2). The UV−vis spectra of the solution before and after purification confirmed that the peaks at 286 and 340 nm, which can be respectively assigned to the 1,2-enediol intermediate and the colored byproducts[28,32,33] disappeared after filtration. The disappearance of the 1,2-enediol anion is most likely due to the pH drop from 10 to 6.5 measured after removing the activated carbon from the solution.[34] The weak contribution at 260 nm in the spectrum after purification could be assigned to the neutral acyclic aldehyde form of glucose[35] or to oxidation products formed by contact with air.[34] Analysis of the purified solution by UPLC indicated that the glucose and fructose concen-
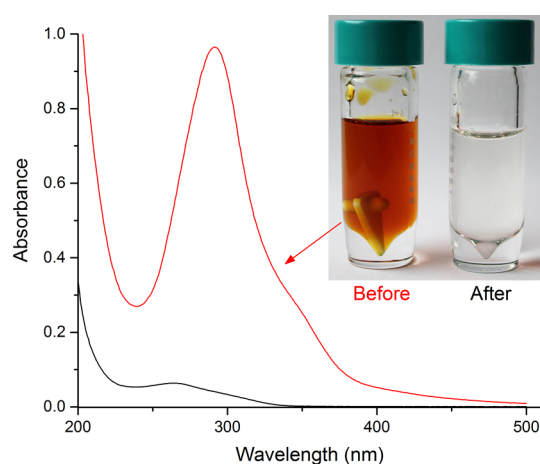

Figure 2. UV−vis spectra of the reacted solution (Entry 10) before (red) and after (black) purification with activated carbon. Inset: photograph of the corresponding vials.

trations remained unchanged, meaning that the activated carbon removed the undesired colored compounds selectively. Other byproducts were not detected by ^{1}H NMR (Supporting Information). Glucose, fructose, and triethylamine can be further separated by chromatography, using a similar technique as in industry to collect the fructose-rich stream (HFCS) and return the glucose- and triethylamine-rich streams to the reaction vessel.[25]

In summary, we demonstrated that amines catalyze the isomerization of glucose to fructose with the same performance as state of the art Lewis acid catalysts. A yield of 32% with a selectivity to fructose of 63% were reached after 20 min at 100 °C. These results open new perspectives for the production of HFCS and renewable chemicals from cellulosic biomass. Triethylamine offers several additional advantages compared to Lewis acids. First, TEA is commercially available with >99.5% purity at a low cost, $3−12/kg for bulk orders. In addition, TEA is industrially produced from renewables by alkylation of ammonia with bioethanol.[36] Finally, TEA has a relatively low toxicity and photochemically degrades within 90−240 min.[37,38]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501197w.

Detailed experimental procedures, detailed catalytic results with error bars, ^{1}H NMR spectrum after purification with activated carbon (PDF).

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Notes
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