Supporting information

Tuning Ca-Al-based catalysts composition to isomerize or epimerize glucose and other sugars

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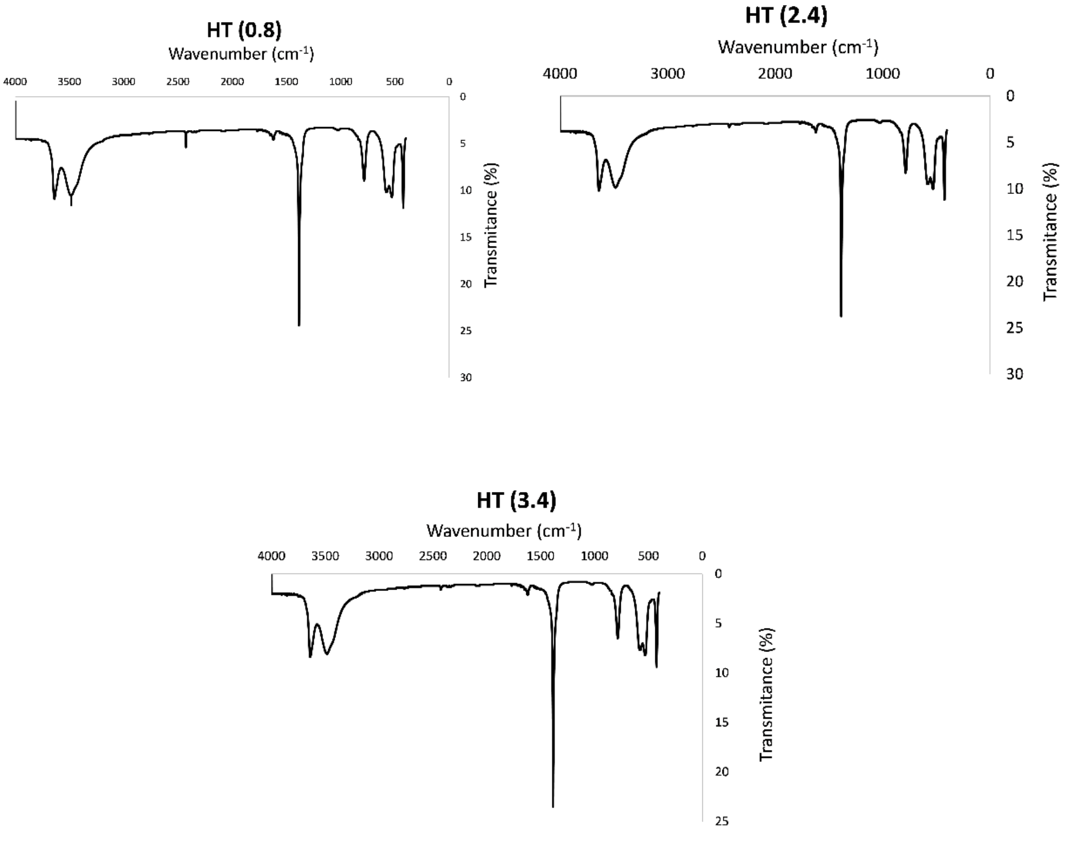
Figure S1: FT-IR spectra of the HT-precursors samples.



HT (0.8)

HT (2.4)

HT (3.4)

Figure S2: CO_2-TPD profiles of the different Ca-Al mixed oxides

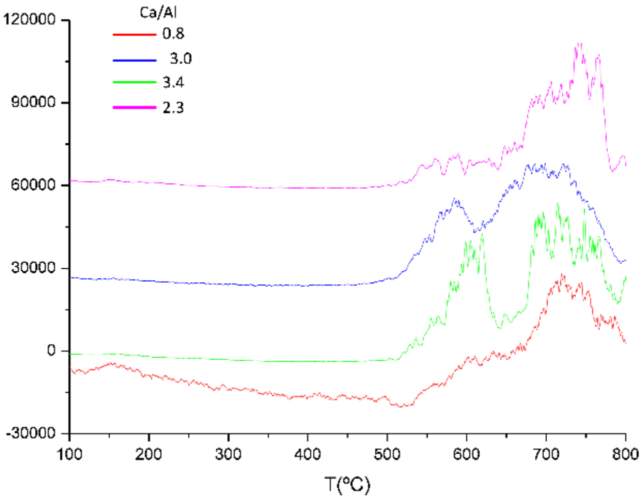
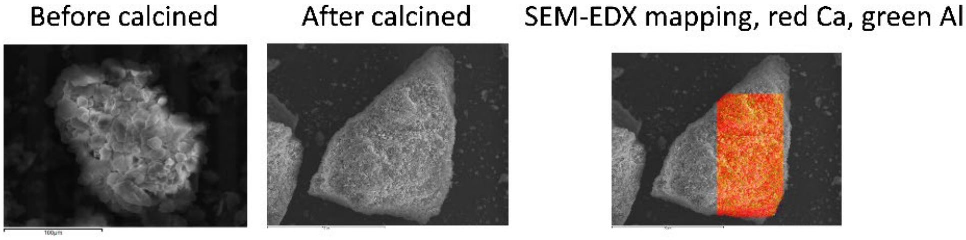
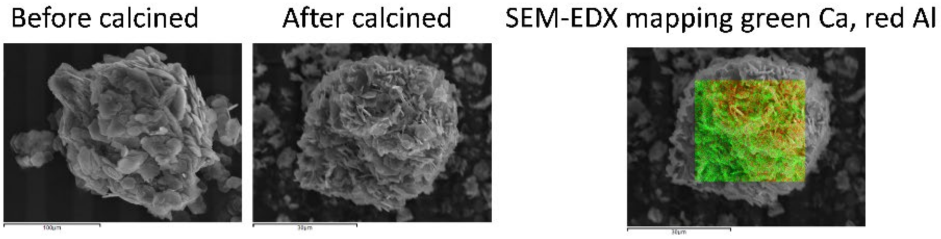


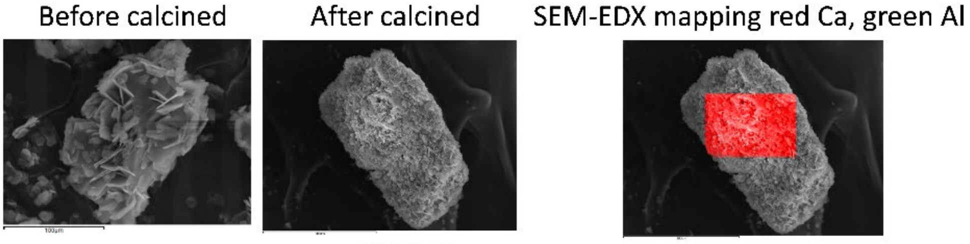
Figure S3: SEM images of HT before calcination, mixed oxides Ca-Al and SEM-EDX mapping of mixed oxides Ca-Al (0.8; 2.4; 3.4), Al (red) Ca (green).



HT (0.8)

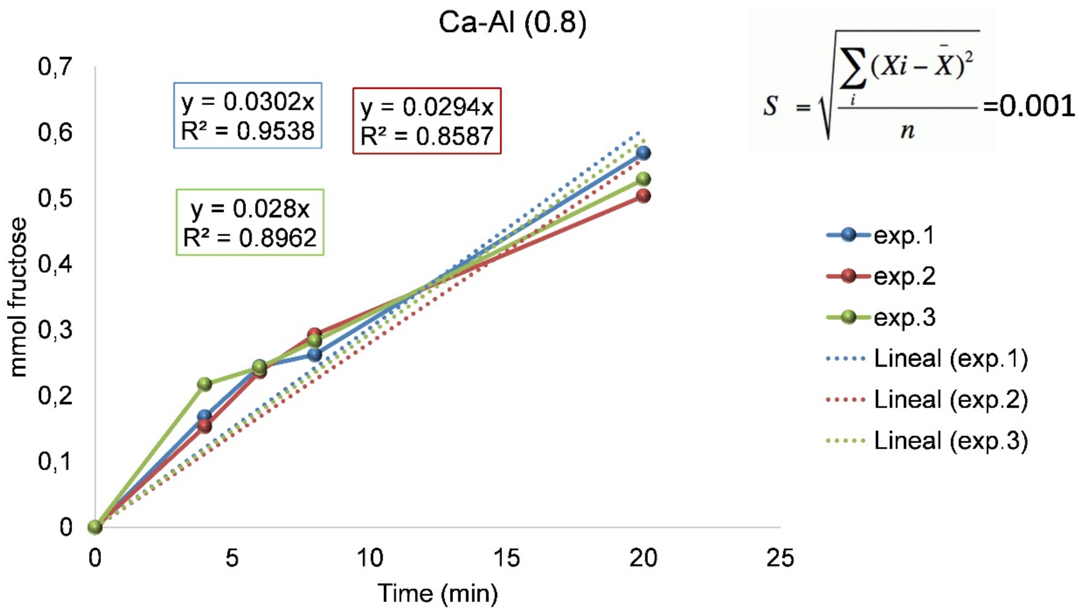


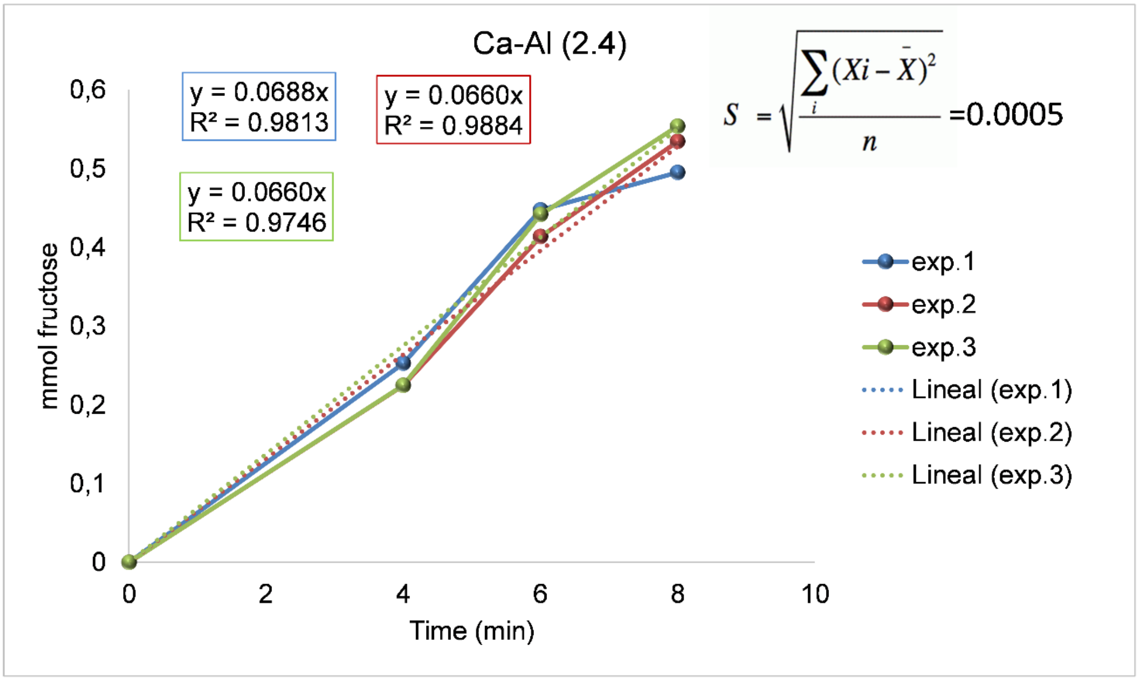
HT (2.4)

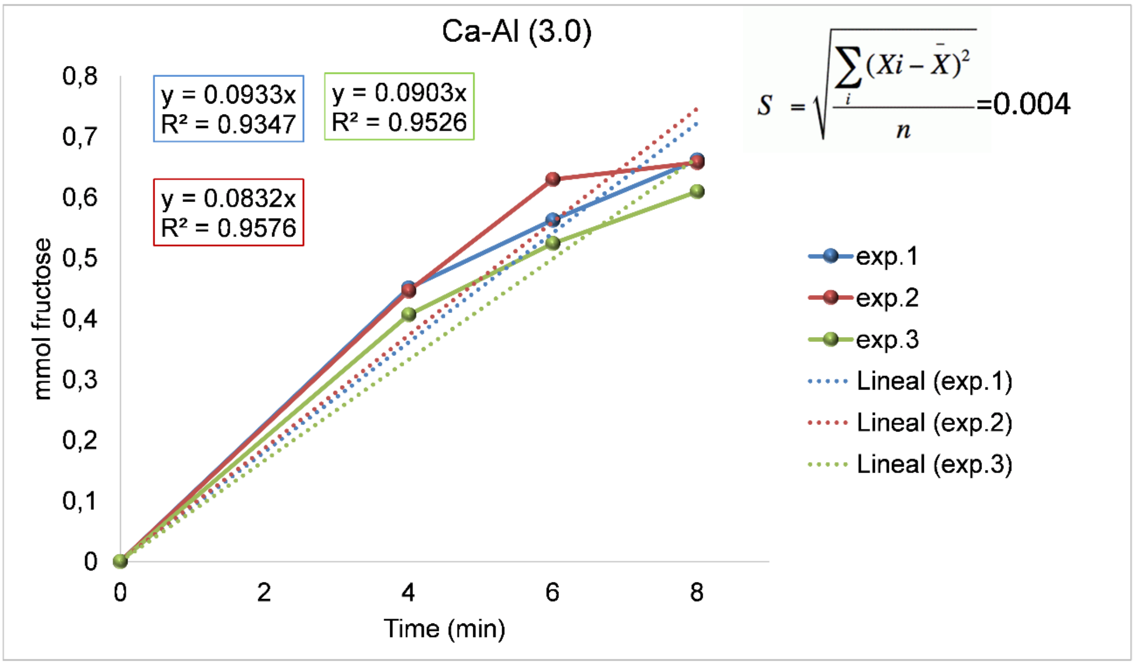


HT (3.4)

Figure S4: Initial isomerization rate and standard deviation for each group of experiments






Ca-Al (3.0)
$S = \sqrt{\frac{\sum_i (Xi - \bar{X})^2}{n}}$=0.004
y = 0.0933x
R² = 0.9347
y = 0.0903x
R² = 0.9526
y = 0.0832x
R² = 0.9576
mmol fructose
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0
2
4
6
8
Time (min)
exp.1
exp.2
exp.3
Lineal (exp.1)
Lineal (exp.2)
Lineal (exp.3)

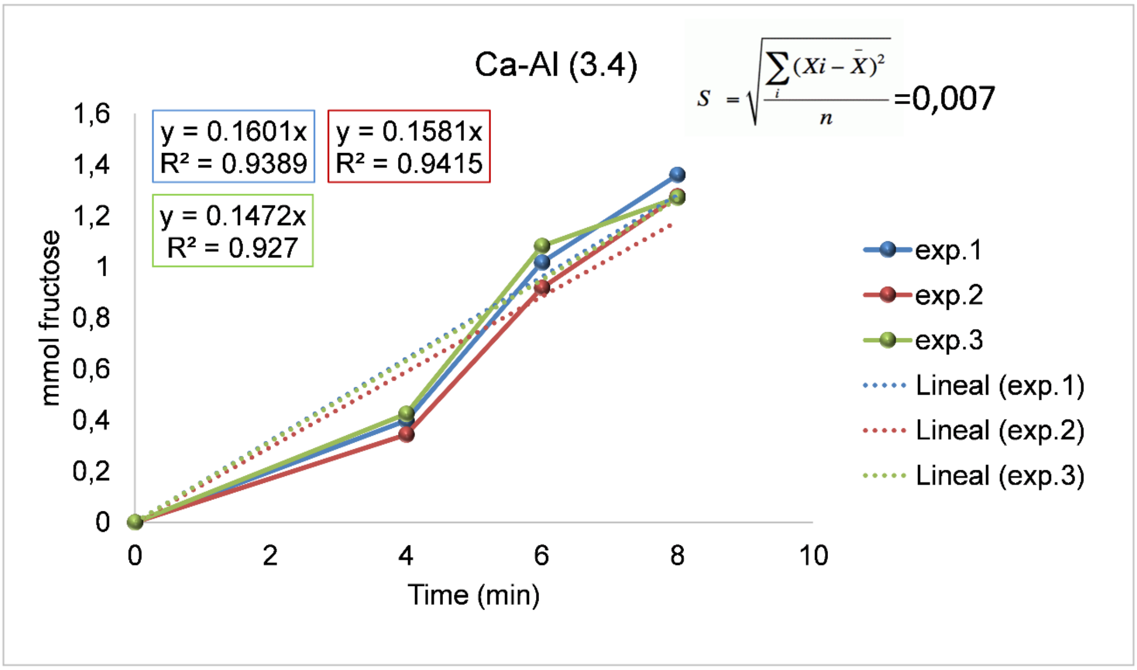

Ca-Al (3.4)
$S = \sqrt{\frac{\sum_i (Xi - \bar{X})^2}{n}}$=0,007
y = 0.1601x
R² = 0.9389
y = 0.1581x
R² = 0.9415
y = 0.1472x
R² = 0.927
mmol fructose
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0
2
4
6
8
10
Time (min)
exp.1
exp.2
exp.3
Lineal (exp.1)
Lineal (exp.2)
Lineal (exp.3)

Figure S5: HPLC of the reaction mixture performed in the conditions: $[Glucose]_i$=0.55M, 0.05g catalyst, 5 mL H_2O, PN_2=10bar, T=393K.

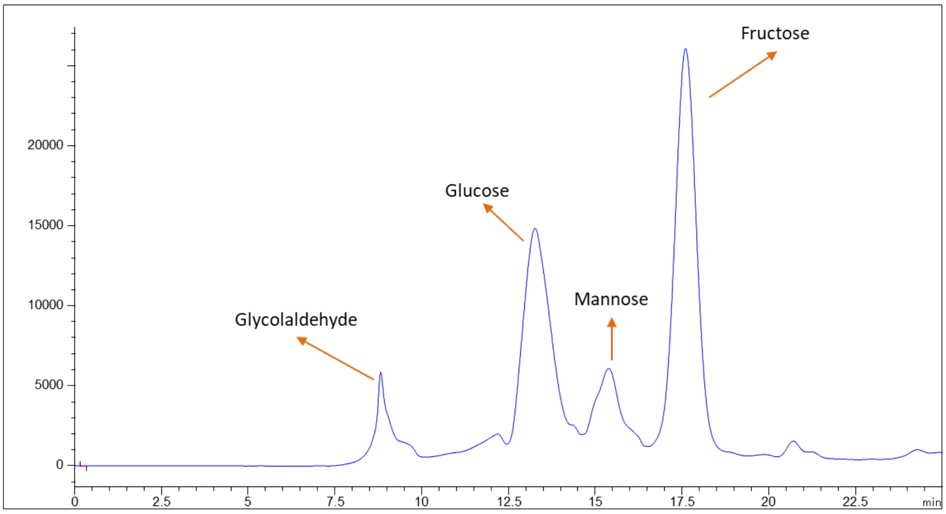
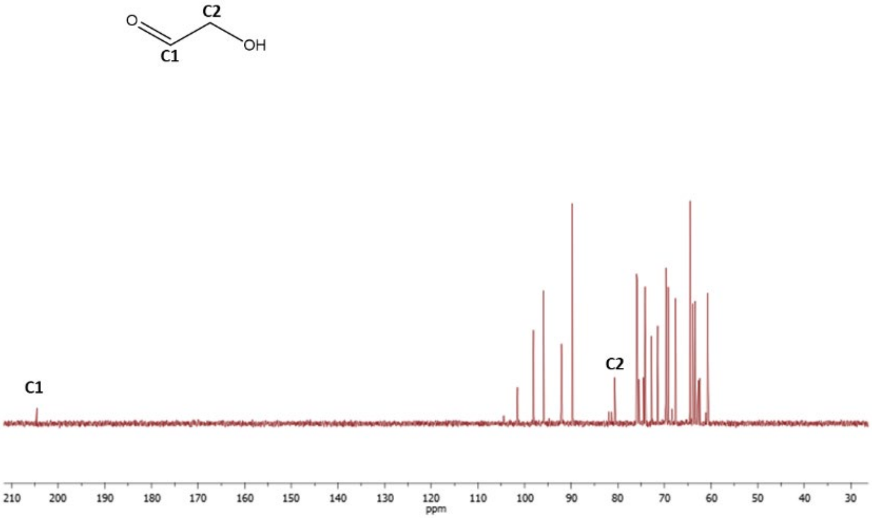


Figure S6: ^{13}C-NMR of the reaction mixture, the same as above. Solvent used: mixture of H_2O+D_2O



The rest of the signals are belonged to the mixture of the α and β isomers of glucose + fructose. Due to the dilution grade of the products, ^{1}H NMR was not clear, and did not help to identify the mixture therefore. For this reason, it is not included.

Figure S7: Comparison on the isomerization of fructose in absence and presence of glycolaldehyde.

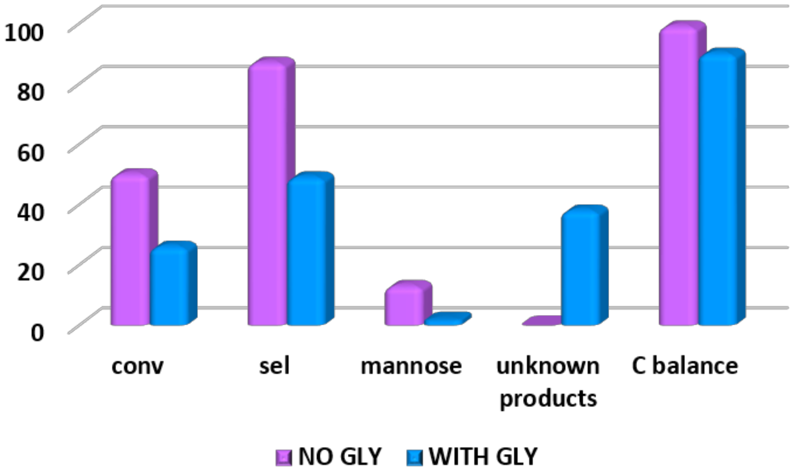


Figure S8: Overlapped HPLC of the kinetic analysis shown in Figure 7.

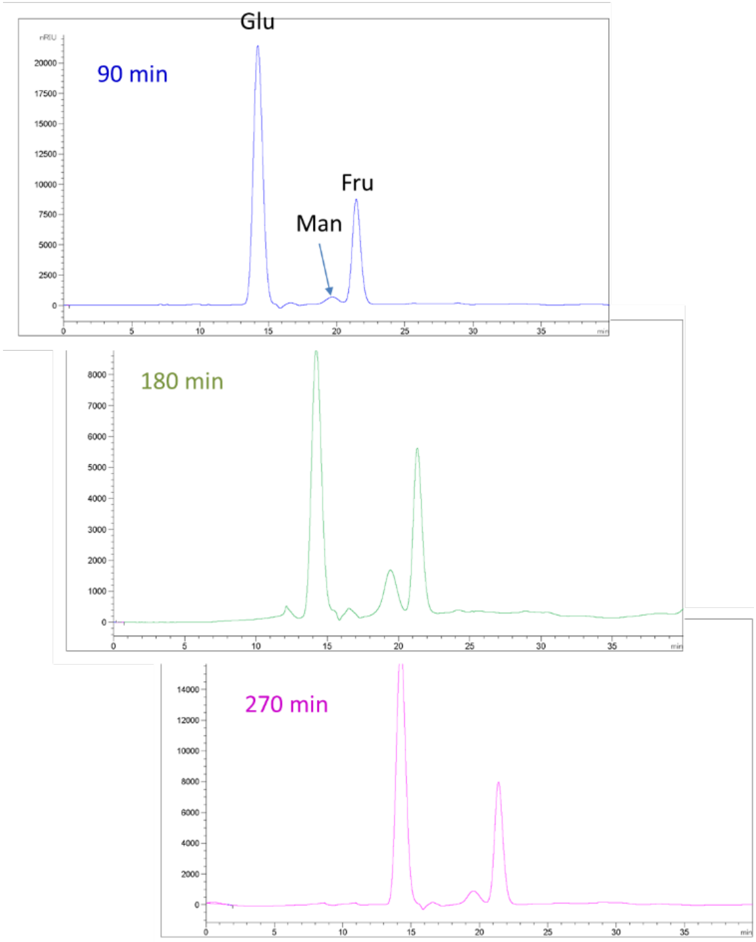


Figure S9: XRD analysis of the fresh and used catalyst for the isomerization to fructose.

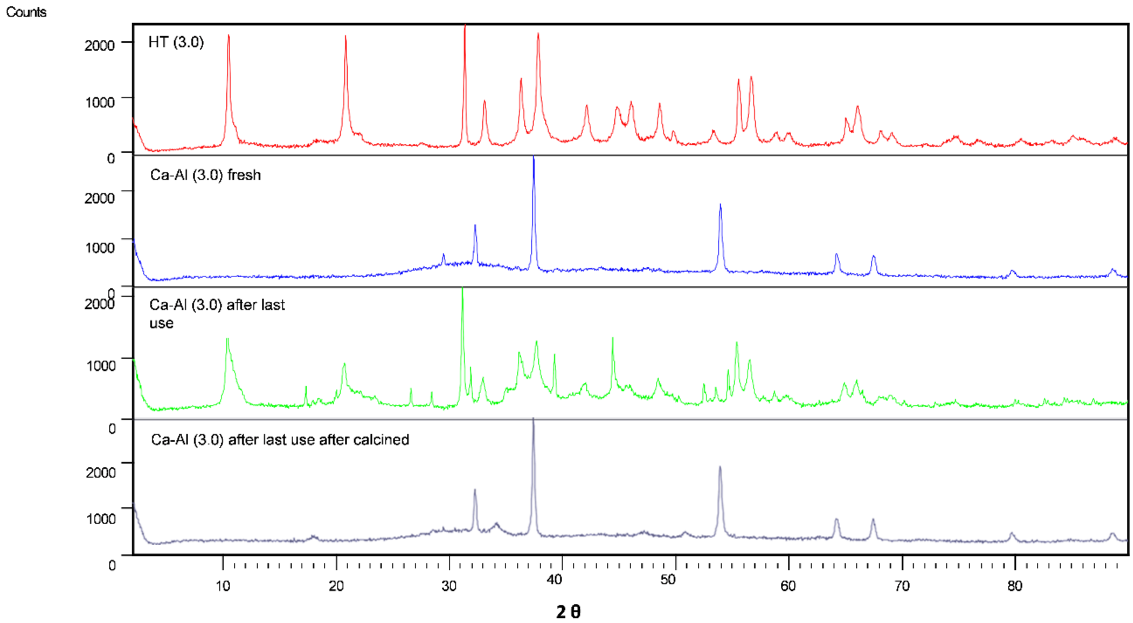


Table S1: ICP analysis of the catalysts after isomerization to fructose or epimerization to mannose.

Entry	Reaction	run	Ca (mg) by ICP	Al (mg) by ICP	Ca loss (%)*	Al loss (%)*
1	Isomerization	fresh	79.4	24.4	-	-
2		1st	77.4	24.1	2.5	1.2
3		5th	77.3	24	2.6	1.6
4	Epimerization	fresh	69.3	19.9	-	-
5		1st	67.3	19.8	2.8	0.5
6		5th	67.2	19.8	2.9	0.5

* by comparing with reference value of fresh catalyst

Green metrics calculations:

Atom Economy:

$$Atom\ economy = \frac{Molecular\ weight\ of\ fructose}{\sum Molecular\ weight\ of\ all\ of\ the\ products\ generated\ in\ the\ reaction}$$

E-factor:

$$E\ factor = \frac{weight\ of\ undesirable\ products\ (waste)}{weight\ of\ fructose}$$

As it was reported by other authors [1], E-factor could be calculated considering catalysts and solvents as wastes or not considering them. For our calculations solvent was not consider because in the three cases water, the greenest and non-contaminant solvent, was used. Therefore, we have considered excluding water from these calculations. Anyway, water was considered in Ecoscale calculations (see below). However, the catalysts were considered in this E-factor since they could add toxicity to the reaction. This fact will be explained in more detail below.

Thus, E-factor for the different systems evaluated in this paper was calculated as follows:

Our system

(1) Total amount of reactants = 0.50g (Glucose) + 0.05g (catalyst) = 0.55g

(2) Amount of final product (Fructose) = 0.21g

Amount of waste = (1) - (2) = 0.34g

E-factor = Amount of waste / amount of products = 0.34 / 0.21 = 1.61

Enzymatic system

Data from the Experimental part showed in ref. 47 (cited in the manuscript) were considered for the calculations of the E-Factor of the enzymatic system, mainly because it was impossible to found the industrial operational parameters of this process due to the trade secret of the industrial process.

(1) Total amount of reactants = 0.43g (Glucose) + 0.02 g (enzyme) = 0.45g

(2) Amount of final product = 0.21g

Amount of waste (1) - (2) = 0.24g

E-factor = 1.15

Sn-β system

(1) Total amount of reactants = 0.50g (Glucose) + 0.01 g (catalyst) = 0.51 g

(2) Amount of final product = 0.12 g (Conversion = 30%, selectivity = 80%)

Amount of waste = 0.39g

E-factor = 3.25

Ecoscale

This factor was calculated by using the tools providing on internet (Webpage: http://ecoscale.cheminfo.org/calculator) free for users. Besides, the information reported by Patiny and co-workers [2] was also used. Table S2 shows the penalty points to calculate Ecoscale in general terms while Tables S3, S4 and S5 show Ecoscale calculations for our system, the enzymatic system, and the Sn-β system, respectively. It is necessary to point out that: i) the solid catalyst synthesis and ulterior activation was considered for both our catalytic system (Table S3) and the Sn-b system (Table S5); and ii) a final separation step via classical chromatography was included for all the evaluated systems (see Tables S3 to S5).

Table S2. Penalty points to calculate Ecoscale. Adapted with the permission of Beilstein-Institut.

Parameter	Penalty points
1. Yield	(100 – %yield)/2
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< \$10)	0
Expensive (> \$10 and < \$50)	3
Very expensive (> \$50)	5
3. Safety[a]	
N (dangerous for environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	2
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3
5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction[e]	3
Classical chromatography	10

[a]Based on the hazard warning symbols. [b] Dropping funnel, syringe pump, gas pressure regulator, etc. [c] Microwave irradiation, ultrasound or photochemical activation, etc. [d]scCO$_2$, high pressure hydrogenation equipment, etc. [e]If applicable, the process includes drying of solvent with desiccant and filtration of desiccant.

Table S3. Ecoscale for our system

Parameter	Penalty points
1. Yield	29
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< \$10)	-
Expensive (> \$10 and < \$50)	-
Very expensive (> \$50)	-
3. Safety[a]	
N (dangerous for environment)	-
T (toxic)	-
F (highly flammable)	-
E (explosive)	-
F+ (extremely flammable)	-
T+ (extremely toxic)	-
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	-
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	-
(Inert) gas atmosphere	1
Glove box	-
5. Temperature/time	
Room temperature, < 1 h	-
Room temperature, < 24 h	-
Heating, < 1 h	-
Heating, > 1 h	3
Cooling to 0°C	-
Cooling, < 0°C	-
6. Workup and purification	
None	-
Cooling to room temperature	-
Adding solvent	-
Simple filtration	-
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	-
Solid phase extraction	-
Distillation	-
Sublimation	-
Liquid-liquid extraction[e]	-
Classical chromatography	10
Total	**52**

Table S4. Ecoscale for the enzymatic system

Parameter	Penalty points
1. Yield	26
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< \$10)	-
Expensive (> \$10 and < \$50)	-
Very expensive (> \$50)	-
3. Safety[a]	
N (dangerous for environment)	-
T (toxic)	-
F (highly flammable)	-
E (explosive)	-
F+ (extremely flammable)	-
T+ (extremely toxic)	-
4. Technical setup	
Common setup	-
Instruments for controlled addition of chemicals[b]	-
Unconventional activation technique[c]	-
Pressure equipment, > 1 atm[d]	-
Any additional special glassware	-
(Inert) gas atmosphere	-
Glove box	-
5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	-
Heating, < 1 h	-
Heating, > 1 h	-
Cooling to 0°C	-
Cooling, < 0°C	-
6. Workup and purification	
None	-
Cooling to room temperature	-
Adding solvent	-
Simple filtration	-
Removal of solvent with bp < 150°C	-
Crystallization and filtration	1
Removal of solvent with bp > 150°C	-
Solid phase extraction	-
Distillation	-
Sublimation	-
Liquid-liquid extraction[e]	-
Classical chromatography	10
Total	**63**

Table S5. Ecoscale for Sn-β system

Parameter	Penalty points
1. Yield	38
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< \$10)	0
Expensive (> \$10 and < \$50)	(2*3)
Very expensive (> \$50)	5
3. Safety[a]	
N (dangerous for environment)	5
T (toxic)	2*5
F (highly flammable)	-
E (explosive)	-
F+ (extremely flammable)	-
T+ (extremely toxic)	-
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	-
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	-
Glove box	-
5. Temperature/time	
Room temperature, < 1 h	-
Room temperature, < 24 h	-
Heating, < 1 h	-
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	-
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	-
Removal of solvent with bp > 150°C	-
Solid phase extraction	-
Distillation	-
Sublimation	-
Liquid-liquid extraction[e]	-
Classical chromatography	10
Total	**14**

Table S6: Optimization of the reaction conditions for the synthesis of HT-precursors.

Entry	Addition rate (mL/h)	[NaOH] (mol/L)	[Ca] ; [Al] (mol/L)	Ca/Al molar ratio Theoretical / Measured by ICP	Surf. Area (BET) (m^2/g)
1	20	2	1.4 ; 0.34	4 / 3.1	6.9
2	20	2 [Ca^{2+}] 3 [Al^{3+}]		3 / 3.1	6.7
3	10			3 / 2.5	5.9
4	20		0.75 ; 0.25	3 / 3.1	5.3
5	20		2.98 ; 0.99	fail	-

Figure S10: Comparison on XRD of entry 1 (red), 2 (blue)

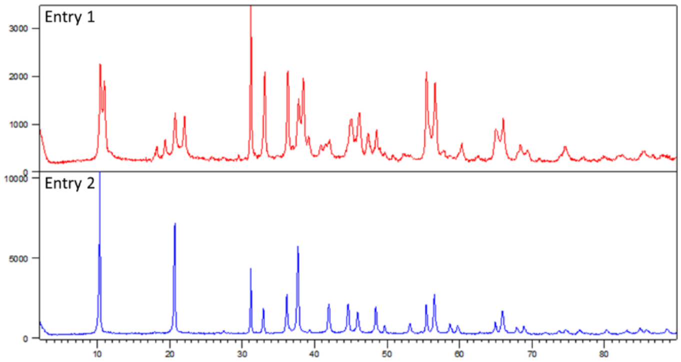


Figure S11: Comparison on XRD of entry 3 (green), 2 (blue)

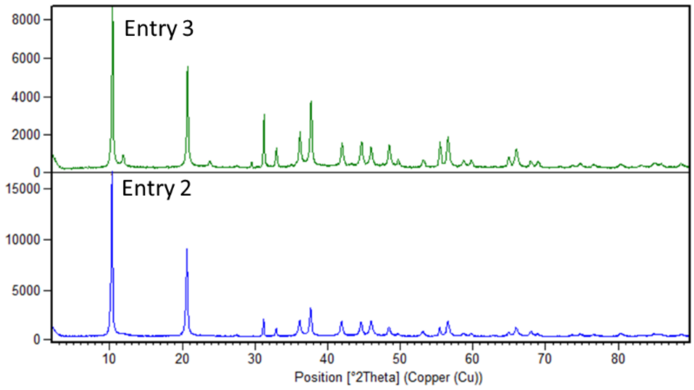


Figure S12: Comparison of entry 4 (pink), 2 (blue).

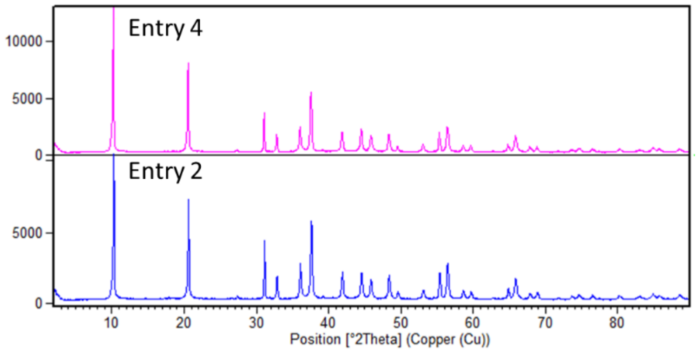
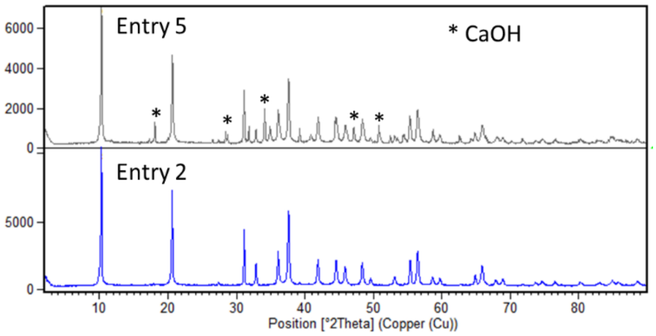


Figure S13: Comparison of entry 5 (grey), 2 (blue).



Kinetics of Glucose isomerization and epimerization reactions

Catalytic results showed in Figures 7 and 9 of the manuscript were obtained from reactions repeated several times, as it is shown in Figures S14 and S15. The data accuracy was checked being within normal error limits, taking into account experimental errors such as HPLC measurements and experimental proceeds.

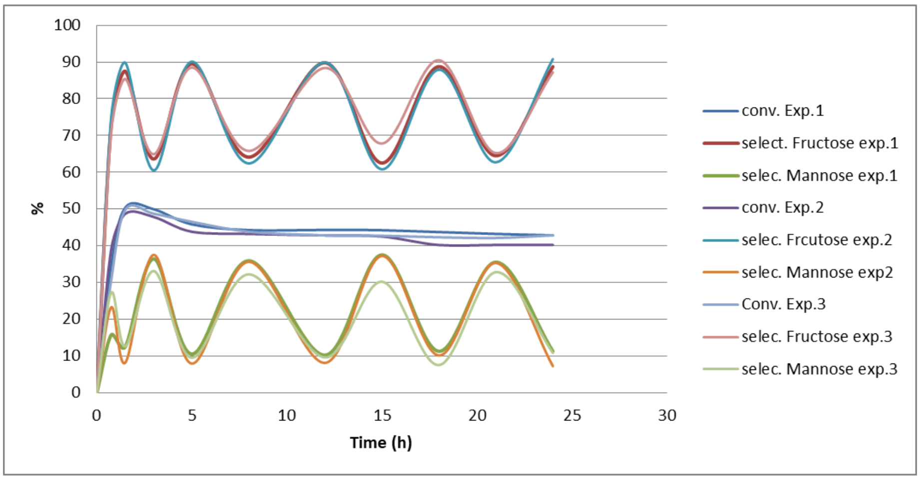


Figure S14. Kinetics of the isomerization of glucose using Ca-Al (3) as catalyst.

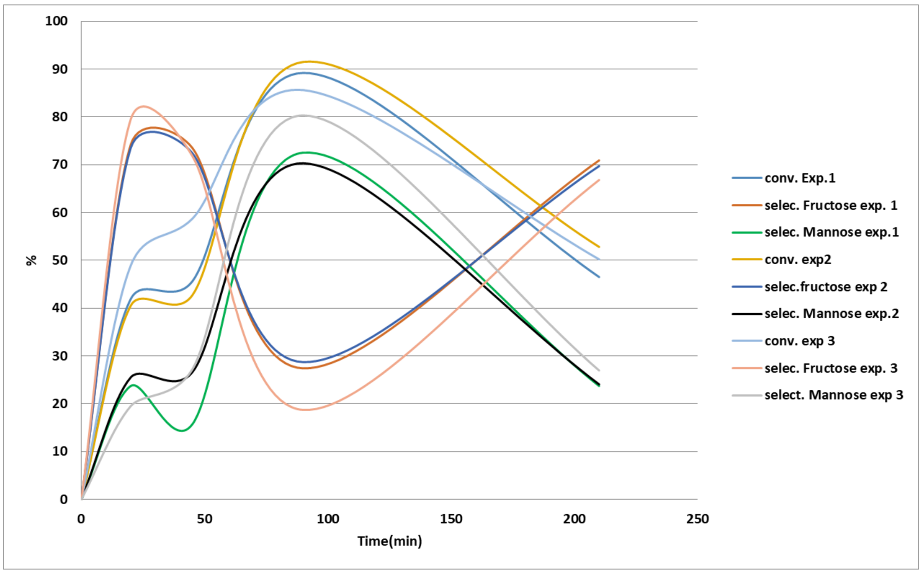


Figure S15. Kinetics of the epimerization of glucose using Ca-Al (3.4) as catalyst.

Rate constants k1 for the isomerization to fructose and k2 for the epimerization to mannose were calculated from the slope of the graphic in Figure S14 and S15, respectively, where the reaction is in the equilibrium, obtaining the following values: k1 = 0.020 min^{-1} and k2 = 0.021 min^{-1}, Figures S16 and S17.

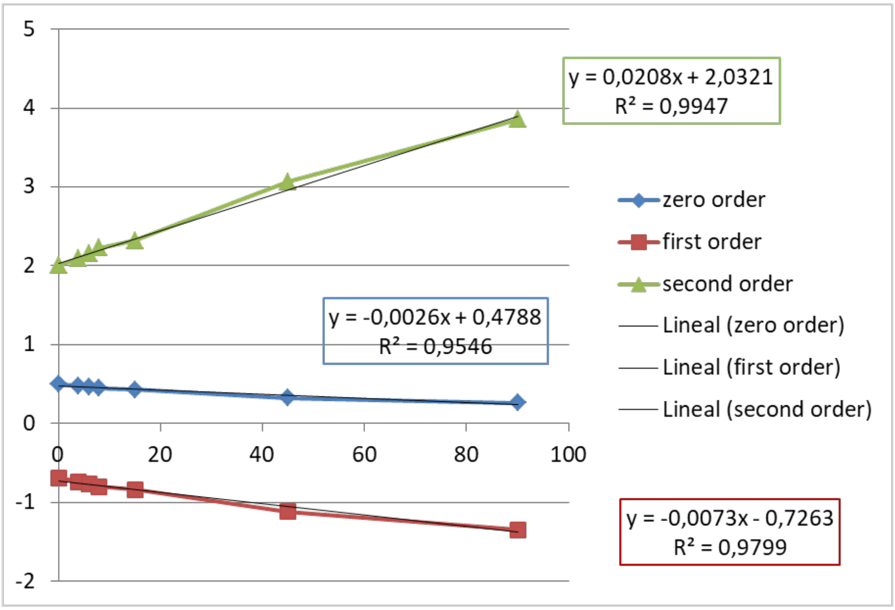


Figure S16. Calculations performed to elucidate the kinetic model for isomerization of glucose to fructose.

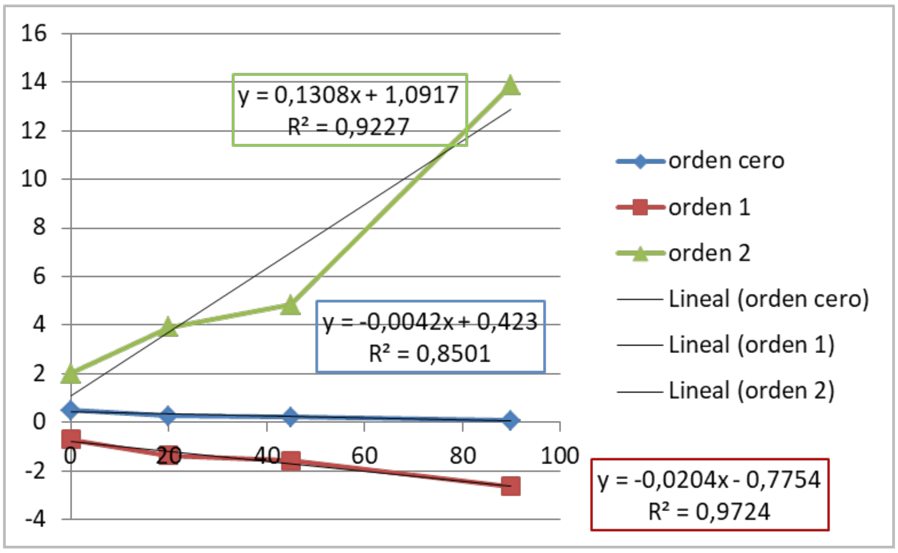


Figure S17. Calculations performed to elucidate the kinetic model for epimerization of glucose to mannose.

Although in the first case (Fig. S16), apparently the data adjust for both first-order (R^2 = 0.9979) and second-order (R^2 = 0.9947) models, the first-order model is the more plausible for a heterogeneous catalyst mechanism and it was preferred for the glucose-to-fructose isomerization. In the case of the epimerization to mannose, a first-order model adjusts pretty well with the data (Fig. S17). The equations proposed for both reactions rates are the following:

Isomerization to fructose: $\mathrm{v} = k[Glucose]$

Epimerization to mannose: $\mathrm{v} = k[Glucose]$

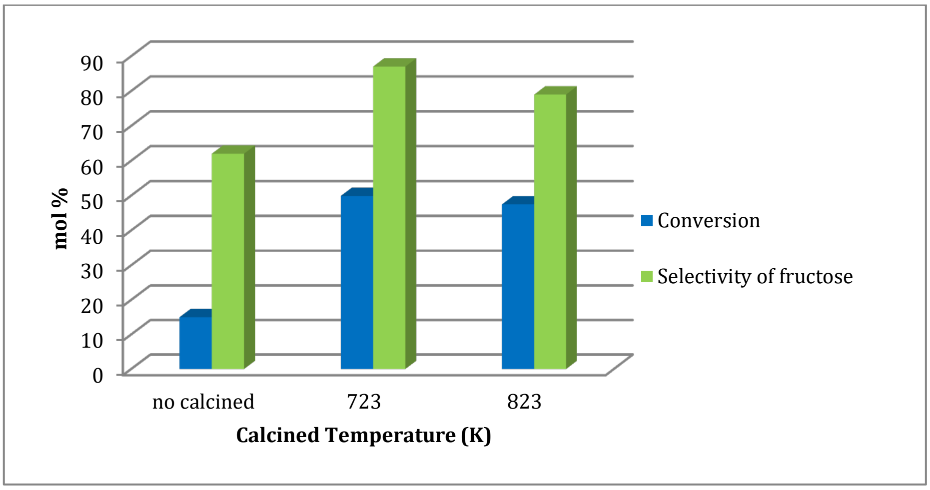
In this sense, and taking into account that both constants have practically the same value, this could be more consistent with the kinetic model of *Competitive First Order Reactions*, where the equations for fructose and mannose (calculated by a well-known mathematical model) are the following:

$$[B]=[k_1[A]_0-(k_1+k_2)-(k_1+k_2)_t]_t\,;\quad [C]=k_2[A]_0k_1+k_2[1-e^{-(k1+k2)t}]$$

Where A = glucose; B = fructose; and C = mannose.

Different calcination temperatures

Figure S18: Correlation between calcination temperature, glucose conversion and fructose selectivity.



As synthesized Ca-Al hydrotalcite-type materials (without calcination) possess a poor reactivity in the isomerization reaction because they present the layered structure of double metallic hydroxides typical of hydrotalcite-type materials, where water and nitrate anions from metal precursors are still present in the interlayer system, thus reducing basicity and activity of the catalysts. Once the hydrotalcite-precursor is calcined (at 723 K during 4 h, see Experimental), interlayered water and precursors moieties are eliminated and the corresponding Ca-Al mixed oxide structure is obtained, as it is confirmed by XRD measurements of the solids before and after calcination (see Fig. 1 in the manuscript). The temperature and methodology (from room temperature until 723 K with a temperature rate of 2 °C/min under air atmosphere, and then kept at 723 K during 4 h under N_2 atmosphere) followed for calcination treatment were selected based on previous studies performed in our Institution (ITQ, UPV – CSIC) by working with different Metal-Al mixed oxides derived from hydrotalcite-type materials. [3, 4] In this sense, the activity of the more active Ca-Al-based catalyst (Ca/Al molar ratio = 3), synthesized with two different calcination temperatures (723 and 823 K), were investigated. Figure S18 shows the correlation between calcination temperature, glucose conversion, and selectivity to fructose. As can be seen, best results were attained when the Ca-Al material was calcined at 723 K. No great differences in glucose conversion were observed when the calcination temperature was increased up to 823 K, just a small decrease in selectivity to fructose. However, the Ca-Al material without calcination showed much lower activity (in terms of both glucose conversion and selectivity to fructose) than the calcined ones. Therefore, the Ca-Al-based catalyst calcined at 723 K (selected temperature) was chosen as the most active catalyst.

Mechanism by NMR

The reaction using glucose-2-d_1 as substrate was performed in the same conditions as those described for the isomerization of glucose to fructose with unlabeled glucose. We could elucidate the rate-determining step in the glucose isomerization due to the decrease in the isomerization rate when using glucose-2-d1. This indicates the C2–H bond cleavage as the rate-determining step. Table S7 shows a comparison between the two reactions.

Table S7. Isotope effect on the isomerization of glucose.

Substrate	Conversion (%)	Fructose yield (%)
Glucose	50	43
Glucose-2-d_1	25	18

Reaction conditions: [Glucose] = 0.55M, 0.05 g catalyst, 5 mL D_2O, PN_2 = 10 bar, temperature = 363 K, reaction time = 90 min.

More investigations were performed to clarify the mechanism by NMR spectroscopy. Due to the reaction was done in D_2O, the low concentration of the compounds hindered to follow the reaction by ^{1}H-NMR; therefore, it was followed by ^{13}C-NMR. If the mechanism goes via LdB-AvE, the common mechanism for base-catalyzed isomerization, the products synthesized from glucose-2-d_1 could lack a deuterium atom in their structure, therefore C1, called *a,b* in α-fructofuranose and *c,d* in β-fructofuranose, Figure S19, would be classified by ^{13}C and DEPT-135 as secondary carbon. However, when the reaction was performed and following by NMR, this *a, b* was classified as tertiary carbon and give positive peaks in DEPT-135 and *c, d* as secondary carbon giving negative peaks. Under these results seems that both mechanisms, basic and acid-catalyzed are got involved. The reaction was repeated several times giving the same ^{13}C spectrums. In Figure S20 is showed LdB-AvE mechanism while Figure S21 shows isomerization catalyzed by Lewis acid catalysts. Although the first mechanism is the more plausible for our catalytic system, the NMR studies performed are not conclusive.

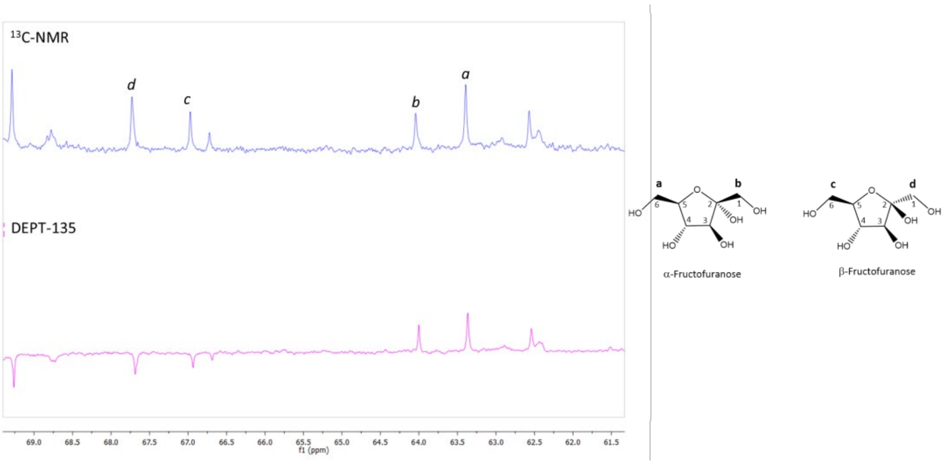


Figure S19. ^{13}C-NMR and DEPT-135 spectra in the range of 61-69 for the reaction mixture obtained from glucose-2-d$_1$

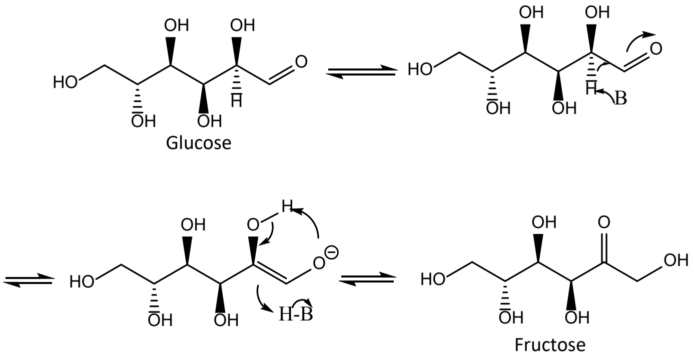


Figure S20. Isomerization of Fructose via LdB-AvE mechanism catalyzed by basic catalysts (B).

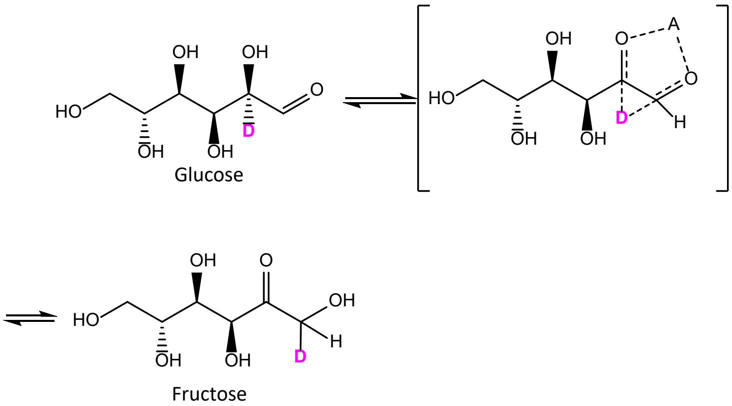


Figure S21. Isomerization of Glucose to fructose via intramolecular 1,2-hydride shift catalyzed by Lewis acids (A).

Additional Explanation for Fructose/Mannose Selectivity

Catalytic results showed in Figures 7 and 9 of the manuscript were obtained from reactions repeated several times (see Figures S14 and S15 above). The data accuracy was checked carefully, and we are confident that these data are not arising from either the error or the coincidence. Therefore, the experimental evidences suggest an oscillating system in this case. In this sense, there are many oscillating chemical reactions reported in literature closely related to glucose isomerization [5]. In this reference, the author explain some oscillating reactions, providing mechanism and examples. Even if isomerization of glucose to fructose does not appear, the glycolytic pathway via enzymatic system is described as an example of oscillating reactions [5], which is related to glucose isomerization.

In addition to that, some key points of our research and recent reports that could support our experimental results are discussed in the next paragraphs.

On one hand, Y. Wang et al. [6] have studied nitrogen-doped mesoporous carbon materials as catalysts for the isomerization of glucose to fructose. They did not observe an oscillating reaction but after a certain reaction time, a decrease in the fructose yield is observed. As the reaction was not kept during more time, it was not possible to observe a new increase in the fructose yield; but does not mean that it could not occur. At the same time, the authors affirm "literally" that "*the maximum yield of fructose varying with temperature verify that isomerization reaction of glucose to fructose is an endothermic reversible reaction, which was consistent with the literature"* [7,8] and that "*basicity cannot only promote the direct glucose isomerization into fructose, but also the further glucose or fructose transformation"*. In this sense, two facts are connected with our observations:

i) The isomerization is a reversible reaction, which depends on temperature. As matter of fact, we did not observe any oscillation when experiments were performed at lower temperature or at atmospheric pressure. And,
ii) The high basicity of our catalysts could promote the transformation of fructose to glucose, as we have observed when fructose is getting at substrate; glucose is obtained as the major reaction product (See Table 5 in the manuscript).

Moreover, R. Otomo et al. [9] have observed the same decrease in fructose yield with the increased reaction time. The authors explained this decrease because of fructose degradation but without providing any evidence supported by adequate analysis; therefore, the possibility of mannose formation is opened.

On the other hand, there is other fact to consider that is the analysis procedure of the reaction mixture. To our knowledge, the proper HPLC-type column allowing detecting the entire product isomers derived from glucose is an 8% cross-linked resin-Ca (or Pb) ionic form. Conversely, the authors in the above-mentioned papers use different columns, such as Welch Ultimate XB-NH_2 and ROA-Organic acids, respectively. These HPLC columns are not able to give high resolution to separate and detect the mixture of glucose, fructose and mannose. Therefore, errors may exist in the analysis of the reaction mixture that prevents the detection of all of the components present in the mixture.

Another point that we would like to clarify refers to the reaction conditions here employed. In our case, we performs experiments at 10 bar of N_2 pressure. Classically, the isomerization of glucose is performed at atmospheric pressure, as many works confirm. The equilibrium constant for the reaction is calculated at that pressure; thus, pressure increasing in an equilibrium type system will displace the reaction to the formation of products, in our case fructose, reaching another equilibrium state.

Finally, it is important to emphasize that the oscillating system was only evidenced when the glucose isomerization reaction was done in a batch reactor at 393 K and 10 bars of pressure during longer times, this allowing us to observe the variation between fructose and mannose selectivity, while glucose conversion remains practically constant (see Fig. 7 in the manuscript). On the contrary, when the experiment was carried out at lower temperatures (<363 K) and at atmospheric pressure only fructose was observed as the main product. More importantly, experiments carried out at shorter contact times in a continuous flow fixed-bed catalytic reactor (at >363 K and atmospheric pressure) over our Ca-Al-type catalysts mainly gives fructose as product with excellent selectivity [9].

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