catalysts

Article

Conversion of Glucose to 5-Hydroxymethylfurfural Using Consortium Catalyst in a Biphasic System and Mechanistic Insights

Geraldo Ferreira David [1], Daniela Margarita Echeverri Delgadillo [2], Gabriel Abranches Dias Castro [2], Diana Catalina Cubides-Roman [1], Sergio Antonio Fernandes [2,*] and Valdemar Lacerda Júnior [1,*]

[1] Laboratório de Química Orgânica, Departamento de Química, Universidade Federal do Espírito Santo (UFES), Avenida Fernando Ferrari, 514, Goiabeiras, Vitória 29075-910, ES, Brazil; geraldo_david@yahoo.com.br (G.F.D.); dianacubides@yahoo.com (D.C.C.-R.)

[2] Grupo de Química Supramolecular e Biomimética (GQSB), Departamento de Química, Universidade Federal de Viçosa, Viçosa 36570-900, MG, Brazil; danielamargarita.e@gmail.com (D.M.E.D.); castrogabrielabranches@gmail.com (G.A.D.C.)

* Correspondence: santonio@ufv.br (S.A.F.); valdemar.lacerda@ufes.br (V.L.J.)

Abstract: We found an effective catalytic consortium capable of converting glucose to 5-hydroxy methylfurfural (HMF) in high yields (50%). The reaction consists of a consortium of a Lewis acid ($NbCl_5$) and a Brønsted acid (*p*-sulfonic acid calix[4]arene ($CX4SO_3H$)), in a microwave-assisted reactor and in a biphasic system. The best result for the conversion of glucose to HMF (yield of 50%) was obtained with $CX4SO_3H/NbCl_5$ (5 wt%/7.5 wt%), using water/NaCl and MIBK (1:3), at 150 °C, for 17.5 min. The consortium catalyst recycling was tested, allowing its reuse for up to seven times, while maintaining the HMF yield constant. Additionally, it proposed a catalytic cycle by converting glucose to HMF, highlighting the following two key points: the isomerization of glucose into fructose, in the presence of Lewis acid ($NbCl_5$), and the conversion of fructose into HMF, in the presence of $CX4SO_3H/NbCl_5$. A mechanism for the conversion of glucose to HMF was proposed and validated.

Keywords: biorefinery; niobium; calix[n]arenes

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1. Introduction

Biomass is a renewable source of carbohydrates from which important chemicals can be obtained, such as 5-hydroxymethylfurfural (HMF) [1]. HMF is a versatile substance with a high market value, used in several industries as a fine chemical, medicine, energy, degradable plastic, and others [2]. Its price ranges from 500 to 1500 USD/kg and it has an expected growth of roughly 1.4% over the next years, possibly reaching USD 61 million by 2024 [3].

Glucose is present in large amounts in vegetable biomass, which can also be obtained from agricultural and/or forest residues, and is a promising substrate for HMF production [1,4]. The conversion of glucose to HMF occurs in a two-step process that involves the glucose to fructose isomerization and the subsequent dehydration of fructose to HMF. The direct conversion of glucose to HMF with high yields depends on combining the Lewis acid catalyst, for glucose isomerization in fructose, and the Brønsted acid catalyst, for fructose dehydration to HMF [1,5–7]. The development of a consortium catalyst with both properties (Lewis–Brønsted) is one of the major challenges in the conversion of biomass to HMF.

Several efforts have been made to develop a catalytic system with those features that is simple, efficient, not aggressive to equipment and environment, reproducible on a large scale, and that allows for its recovery and reuse [8–11]. The niobium catalyst and *p*-sulfonic acid calix[4]arene (CX4SO3H) organocatalyst are promising catalysts with the potential to convert carbohydrates, or biomass, into HMF.

Calix[*n*]arenes are used in several chemical transformations and have many advantages, such as high selectivity, easy manipulation, non-corrosiveness, low toxicity, and good thermal and chemical stability [4,12–20].

Recently, the great potential of calix[*n*]arenes has been adopted, and in some cases, for thin biorefinery processes, for the synthesis of Julolidines, HMF, levulinate esters, and biomass pretreatment, followed by fast pyrolysis to obtain levoglucosan [4,12,21].

Niobium catalysts are versatile, easy to handle, inexpensive, chemically stable, and commercially available [22,23]. To obtain HMF, the niobium catalyst has been used either on its own or in association with other catalytic systems. The use of niobium phosphate (NbP) as the only catalyst has shown a 15% yield of HMF from glucose at 145 °C and a reaction time of 180 min [24]. Carniti et al. used NbP for the direct conversion of cellobiose to HMF and reached yields between 5% and 10% in the temperature interval 110–130 °C after 3000 min of reaction [25]. The use of niobium acid (NbO) has also been reported. In the work of Catrinck et al., for example, 26% of the HMF yield was obtained from glucose at 152 °C and 120 min [26].

Moreover, when used in association with other systems, niobium has been reported as a promoter or active phase, support, solid acid catalyst, or redox material [5,6,27–32]. Some studies show a higher concentration of acid sites in niobium species, which is a key factor for obtaining HMF, along with high reaction temperatures and long reaction times [6,7,33,34].

In the work of Kreissl et al., a yield of 36% was reported when using mesoporous Nb_2O_5 as catalyst, and the reaction was performed in an autoclave at 500 rpm stirring speed, at 180 °C, for 180 min [35], whereas Liu et al. obtained a 26.8% yield in the conversion of glucose into HMF using Nb_2O_5, at 180 °C, for 180 min [36]. Using niobic acid, Huang et al. (2020) immobilized on regenerated cellulose, reaching 27.8% of the HMF and yield using glucose as substrate in a glass reactor at 150 °C for 250 min [37]. Meanwhile, Torres-Olea et al. evaluated the glucose dehydration to HMF, and found a yield of 44% using Nb_3Zr_7 as an acid catalyst after 90 min at 175 °C [6].

Herein, we report an efficient method for the conversion of glucose into HMF using the consortium catalyst, $CX4SO_3H/NbCl_{5,}$ in a biphasic system (water/NaCl and methyl isobutyl ketone (MIBK)) in a MW reactor. To achieve the best results, different conditions such as temperature, reaction time, catalytic load, and different Lewis acids were evaluated.

2. Results and Discussion

2.1. Evaluation of Different Niobium Catalysts in HMF Synthesis

Different types of niobium catalysts ($NbCl_5$, Nb_2O_5, $NbOPO_4$, and HNb_3O_8) were evaluated under the initial reaction conditions: 0.25 mmol glucose (45 mg), $CX4SO_3H$ 5 wt%, niobium-based catalyst 7.5 wt%, MW, 150 °C, and 10 min of time reaction using water/NaCl and MIBK as the biphasic system.

In our results, when using $CX4SO_3H/Nb_2O_5$ or $HNb_3O_{8,}$ a yield of 19% of HMF was obtained for the two consortium catalysts (Figure 1). When using $CX4SO_3H/NbOPO_4$ or $NbCl_5$ consortium catalysts for the conversion of glucose to HMF, yields of 23% and 42% were obtained, respectively (Figure 1).

Once it was determined that the $CX4SO_3H/NbCl_5$ consortium catalyst was the best system for the conversion of glucose into HMF, we further investigated the proportion between Brønsted and Lewis acids in the catalytic system.

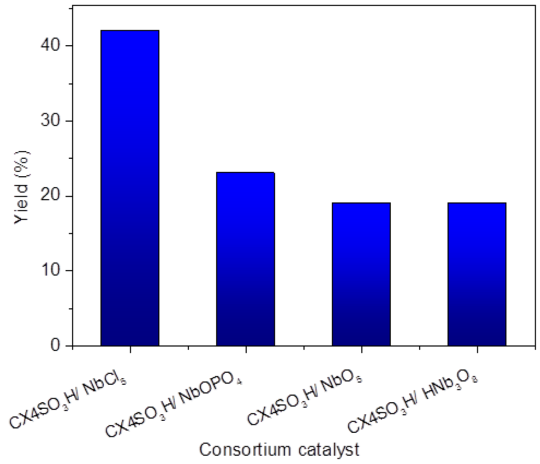
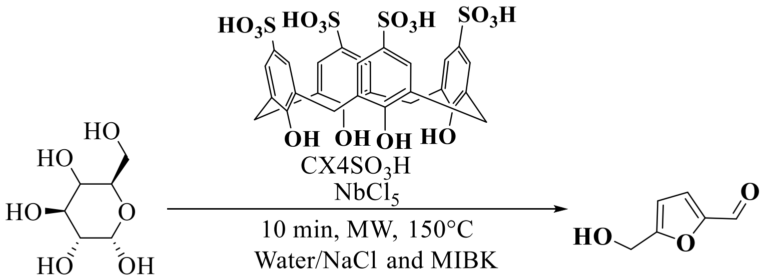


Figure 1. Comparison of different Lewis acids (niobium) fixed holding of CX4SO$_3$H Brønsted acid catalysts.

2.2. Evaluation of CX4SO$_3$H/NbCl$_5$ Consortium Catalyst Ratio

To investigate the need for a consortium catalyst (CX4SO$_3$H/NbCl$_5$) for the conversion of glucose into HMF, different ratios between Brønsted and Lewis acids were evaluated (Table 1). Initially, we evaluated CX4SO$_3$H (5 wt%) and different proportions of NbCl$_5$ (0–10 wt%) (Table 1, Entries 1–5). In the absence of NbCl$_5$, a marginal yield of only trace was obtained (Table 1, Entry 1). For amounts of 2.5, 5.0, and 7.5 wt% NbCl$_5$, the yield of HMF increased to 42%, and for 10 wt%, the yield decreased to 29% (Table 1, Entries 2–5). After establishing that 7.5 wt% NbCl$_5$ is the best ratio for the conversion of glucose into HMF, we evaluated different proportions of CX4SO$_3$H (Table 1, Entries 6–9). In the absence of CX4SO$_3$H, a 20% yield of HMF was obtained (Table 1, Entry 6). With the addition of increasing amounts of CX4SO$_3$H, the conversion of glucose into HMF reached a maximum value of 42% with the CX4SO$_3$H/NbCl$_5$ consortium (Table 1, Entry 4). For CX4SO$_3$H amounts greater than 5 wt%, the HMF yield decreased to 39% and 32% (Table 1, Entries 8 and 9) and the formation of humins was observed.

Table 1. Evaluation of ratio CX4SO$_3$H/NbCl$_5$ consortium catalyst.



Entry	CX4SO$_3$H (% wt)	NbCl$_5$ (% wt)	Temperature (°C)	Yield (%)
1	5.0	0.0	150	trace
2	5.0	2.5	150	27
3	5.0	5.0	150	31
4	5.0	7.5	150	42
5	5.0	10.0	150	29
6	0.0	7.5	150	20
7	2.5	7.5	150	30
8	7.5	7.5	150	39
9	10.0	7.5	150	32

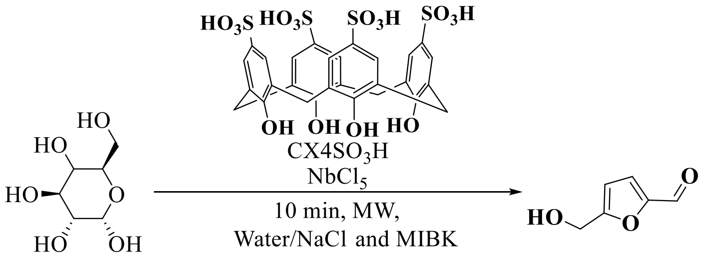
Reagents and conditions: 0.25 mmol of glucose (45 mg), water/NaCl and MIBK/(1/3 *v*/*v*).

Several works [38–41] have been published seeking to understand the association between Brønsted and Lewis acid and its good performance in the conversion of glucose into HMF. The first step toward glucose to HMF conversion involves the isomerization of glucose to fructose, followed by the dehydration of fructose, resulting in HMF. The isomerization of glucose has been described as the most difficult step of the process and a Lewis acid is usually used to effectively promote the isomerization; a Brønsted or Lewis acid is then used to promote the dehydration of fructose [38,39,42–45]. Consequently, we can infer that the $NbCl_5$ acts as Lewis acid, effectively promoting the isomerization of glucose, and partially helping in the dehydration of fructose; it is the $CX4SO_3H$, however, that improves the production of HMF due to its Brønsted acidic nature.

2.3. Evaluation of Temperature and Time

Following the evaluation of the catalyst charge, we tested different reaction temperatures keeping the other reaction parameters unchanged (0.25 mmol of glucose, 10 min, water/NaCl, and MIBK (1/3 *v*/*v*)). For temperatures below 150 °C, the HMF yield decreased to 21% and 30%, respectively (Table 2, Entries 1 and 2). However, when the temperature was greater than 150 °C, the HMF yield decreased from 42% to 33% (Table 2, Entries 3 and 4).

Table 2. Evaluation of reaction temperature.



Entry	$CX4SO_3H$ (% wt)	$NbCl_5$ (% wt)	Temperature (°C)	Yield (%)
1	5.0	7.5	130	21
2	5.0	7.5	140	30
3	5.0	7.5	150	42
4 [a]	5.0	7.5	160	33

Reagents and conditions: 0.25 mmol of glucose (45 mg), water/NaCl and MIBK (1/3 *v*/*v*). [a] Formation of humin was observed.

This behavior has been reported in other studies on the dehydration of sugars to HMF. One study [46], for example, obtained an HMF yield of 51.5% in a MW glucose to HMF conversion, performed at 180 °C; however, when the temperature was increased to 190 °C, the HMF yield decreased to 40%. It is known that, although increasing the temperature promotes the dehydration of fructose to HMF, a very high temperature can lead to the formation of secondary compounds [47]. In our work, we noticed the same behavior in the formation of humin when the reaction was conducted at 160 °C.

The effect of the reaction time on the formation of HMF from glucose was evaluated by performing experiments between 5.0 and 22.5 min (Figure 2). We observed that the yield of HMF improved with the increase in the reaction time, until obtaining a maximum yield of 50% at 17.5 min of reaction (Figure 2). Further increases in the reaction time, however, resulted in a yield decrease, from 50% to 42% (Figure 2). It has been reported in the literature that long periods of reactions decrease the selectivity, leading to secondary reactions, such as humin formation and other undesirable products [48,49].

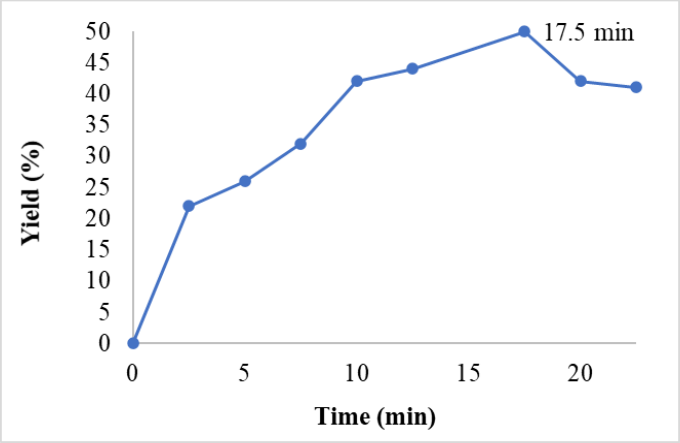
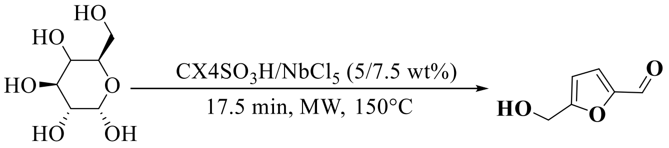


Figure 2. Evaluation of HMF yield over time. Reagents and conditions: 0.25 mmol glucose (45 mg), $CX4SO_3H/NbCl_5$ (5/7.5 wt%), MW, 150 °C, water/NaCl, and MIBK (1/3 *v*/*v*).

2.4. Evaluation of the Addition of Different Salt in Biphasic System

In order to determine how the composition of the biphasic system could affect the conversion of glucose to HMF, experiments were carried out with different salts using an organic phase MIBK (Table 3).

Table 3. Evaluation of the addition of different salt in biphasic system.



Entry	Phase		Yield (%)
	Aqueous	**Organic**	
1	NaCl	MIBK	50
2	KCl	MIBK	29
3	$CaCl_2$	MIBK	24
4	$MgCl_2$	MIBK	11
5	NaCl	-	3
6	-	MIBK	-

Reagents and conditions: 0.25 mmol glucose (45 mg), $CX4SO_3H/NbCl5$ (5/7.5 wt%), MW, 17.5 min, 150 °C, water/NaCl, and MIBK (1/3 *v*/*v*).

The effect of adding different salts to an aqueous phase was verified, and the best performance was obtained with NaCl (Table 3, Entry 1). When using KCl, $CaCl_2$, and $MgCl_2$, the yield was 29, 24, and 11%, respectively (Table 3, Entries 2–4). To verify the effect of the extracting solvent and the aqueous phase, experiments were carried out in the absence of MIBK, obtaining only 3% of HMF; whereas, without an aqueous phase, no product was detected.

The use of a biphasic system allows the reaction to be carried out in an aqueous phase and the organic solvent to act as an extractor for the product [50]. HMF is easily extracted in organic solvents that are immiscible with water. The biphasic reaction mixture is used for the continuous removal of HMF from the aqueous phase by an organic phase to prevent its side reactions (humin) [46–49,51,52].

It is known from the literature that the addition of salt, such as NaCl, KCl, $CaCl_2$, and $MgCl_2$, helps to modify the aqueous phase by modifying the partition coefficient of the system, allowing a larger fraction of a product to migrate toward the organic phase. This is called the salting-out effect, which is generated when the ions of the salts modify the intermolecular forces between the liquids in equilibrium, allowing greater immiscibility between them [53].

The lower yield observed in the presence of bivalent cations (Table 3, Entries 3 and 4) can be explained by the hydration radius size of these species. The smaller the ion's hydration radius, the greater the salting-out effect [54]. Additionally, since Ca^{2+} and Mg^{2+} have the largest hydration radium among the studied cations, their salting-out effect is smaller, and the extraction efficiency is lower [55,56].

2.5. Evaluation of Catalytic Effect of Other Lewis Acids

To demonstrate the efficiency of Lewis ($NbCl_5$) and Brønsted ($CX4SO_3H$) acids acting as a consortium, other metallic chlorides were also evaluated: $CrCl_3$, $CoCl_2$, $MnCl_2$, $AlCl_3$, $NiCl_2$, $FeCl_3$, $FeCl_2$, $ZnCl_2$, $SnCl_2$, and $CuCl_2$ (Figure 3). The highest HMF yield continued to occur when using $NbCl_5$ as the Lewis acid. However, the $AlCl_3$ and $CrCl_3$ salts presented moderate yields of 41% and 39%, respectively (Figure 3). The other Lewis acids that were evaluated showed yields between 31 and 14% (Figure 3).

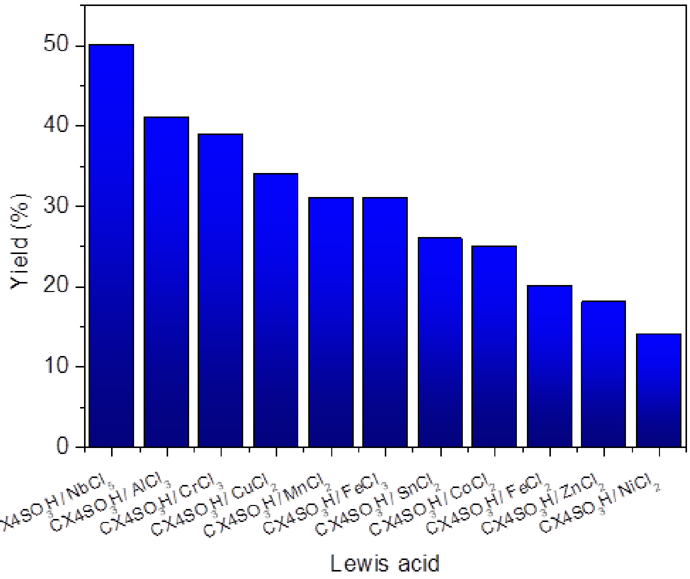


Figure 3. Evaluation of different Lewis acids. Reagents and conditions: 0.25 mmol glucose (45 mg), $CX4SO_3H/NbCl_5$ (5/7.5 wt%), MW, 150 °C, 17.5 min, water/NaCl, and MIBK (1/3 *v*/*v*).

2.6. Literature Comparison of Methods for the Conversion Glucose to HMF

In Table 4, some parameters of the methodology developed in this study, for the conversion of glucose into HMF, are compared with other studies found in the literature. References shown in Table 4 used, as a catalyst, a mixture of a Lewis and Brønsted acid (Table 4, Entries 2–4) or a bifunctional catalyst with Lewis–Brønsted acids. Viera et al. (Table 4, Entry 2) reported that the niobium catalyst acts in the formation of mannose and fructose, allowing the formation of HMF when combined with the Brønsted catalyst (HCl) in a biphasic THF/water system, using a rate of the catalyst of 1:2 wt% [7]. The biphasic THF/water system was also reported by Choudhary et al., (Table 4, Entry 3) who used chromium chloride ($CrCl_3$) as the Lewis acid and HCl as the Brønsted catalyst [57].

Table 4. Comparison of methodology developed for the conversion of glucose to HMF with data from the literature.

Entry	Organic Phase/Reaction Phase (Ratio)	Catalyst	Experimental Conditions	Yield (%)	Ref
1	MIBK/Water [a] (3:1)	CX_4SO_3H/ $NbCl_5$	T = 150 °C cat = 1/1.5 wt% time = 17.5 min	50	This work
2	THF [b]/Water (4:1)	Nb_2O_5/HCl	T = 130 °C cat = $\frac{1}{2}$ wt% time = 120 min	47	[58]
3	THF [b]/Water [a] (2:1)	$CrCl_3$/HCl	T = 140 °C cat = 3/10 wt% time = 180 min	59	[59]
4	SCB [c]/Water [a] (2:1)	$AlCl_3$/HCl	T = 170 °C cat = not reported * time = 40 min	62	[60]
5	MIBK/water [a] (6:1)	PTSA-Ca/AC	T = 180 °C cat = 1/1 time = 1440 min	57	[61]

[a] NaCl saturated solution; [b] THF: Tetrahydrofuran; and [c] SCB: 2-sec-butylphenol. * 5 mM $AlCl_3$ was added in the reaction and HCl was added until the pH of the solution was 2.5.

On the other hand, Pagán-Torres also used HCl as a Brønsted catalyst, but with $AlCl_3$ as a Lewis catalyst (3:10 catalyst ratio) and a 2-sec-butylphenol/water biphasic system. Bounoukta et al. reported a yield of 57% of HMF (Table 4, Entry 5), using the bifunctional catalyst of *p*-toluenesulfonic acid on an activated carbon surface and functionalized with activated charcoal (1:1) [60]. The catalyst ratio that they used is close to the one used in our study, 1:1.5 of $CX4SO_3H/NbCl_5$; this parameter varies greatly between published studies (Table 4). Although the reported yields are generally good, the use of THF (Table 4, Entries 2–3) as the organic phase is not recommended, since it is a problematic solvent according to the principles of green chemistry [62]. Moreover, the use of HCl as the Brønsted acid (Table 4, Entries 2–4) presents difficulties for an industrial scale production due to its corrosive qualities as a highly toxic reagent. Finally, while it is possible to use a green solvent, such as MIBK, as the organic phase for the bifunctional catalyst, its reaction time is too long (1440 min or 24 h) to be viable.

2.7. Evaluation of Other Carbohydrates to Produce HMF

Other carbohydrates, in addition to glucose, were also evaluated: sucrose, mannose, maltose, raffinose melibiose, galactose, and cellulose, the yields of which were, respectively, 50, 42, 32, 31, 19, 19, 17, and 15% (Figure 4). In general, to obtain 5-HMF directly from sugars, it is necessary that a sequence of the reaction involves catalysts for hydrolysis, isomerization of glucose to fructose, and finally, the acid-catalyzed dehydration of fructose. For example, the direct conversion of cellulose to 5-HMF using heterogeneous catalysts is difficult due to the low reactivity of cellulose and the high instability of 5-HMF [48,57,60,63,64].

Sucrose showed to have the best HMF performance; since it is a dimer formed by the union of α-*D*-glucose and β-*D*-fructose through a glycosidic bond, sucrose can undergo a hydrolysis in which the carbohydrate units that make it up are separated. Additionally, it is more prone to undergo dehydration directly to HMF, since the glucose that must undergo an initial isomerization to fructose is converted into HMF [47]. On the other hand, the evaluation of cellulose is also interesting; its result was comparable with that of a more complex biomass system [65]. The 15% yield obtained from cellulose is not far from the 20% HMF obtained by one study [66] that achieved this performance using formic acid and betaine as catalysts, with 60 min of reaction at 190 °C. Another study [67] obtained a 35% yield of HMF from microcrystalline cellulose using $CrCl_3$, in addition to using ionic liquid

([EMIM]Cl) as the reaction medium. Despite being efficient in converting cellulose into HMF, ionic liquids are expensive and toxic reagents.

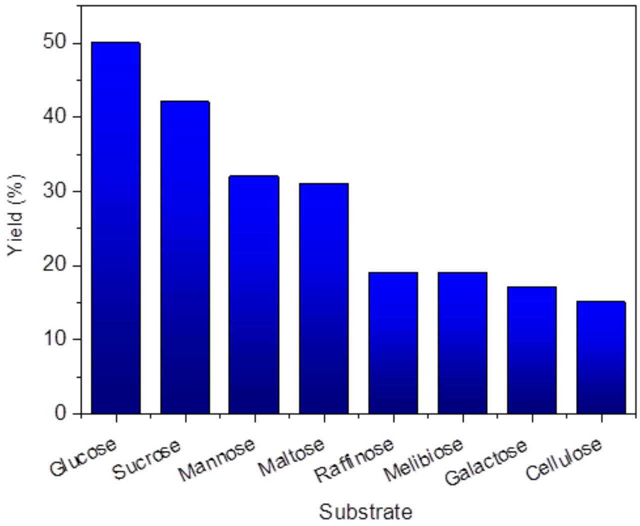


Figure 4. Evaluation of different carbohydrates.

2.8. Catalyst Recycling

The evaluation of catalyst recycling is a key-factor from a commercial and environmental point of view. Thus, if the catalyst can be used more times without decreasing its effectiveness while maintaining a constant yield of the product, less investment is needed in the purchase of reagents, and, from an environmental perspective, less chemical waste occurs [68,69].

At the end of the reaction, the system was cooled, and the organic phase was separated. The aqueous phase containing the CX4SO$_3$H/NbCl$_5$ consortium catalyst remained in the tube, and a new load of glucose and MIBK were added and used in a new reaction. In our work, it was possible to reuse the CX4SO$_3$H/NbCl$_5$ catalyst consortium up to six times while keeping the HMF yield constant. The yield decreased from 49% in the sixth cycle to 39% and 38% in the respective seventh and eighth cycles of the reuse of the system catalyst, as shown in Figure 5.

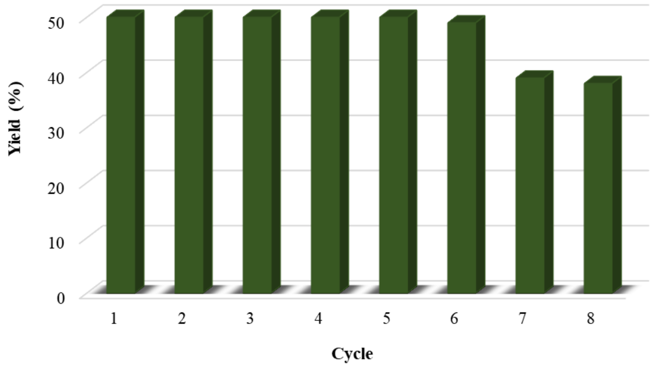
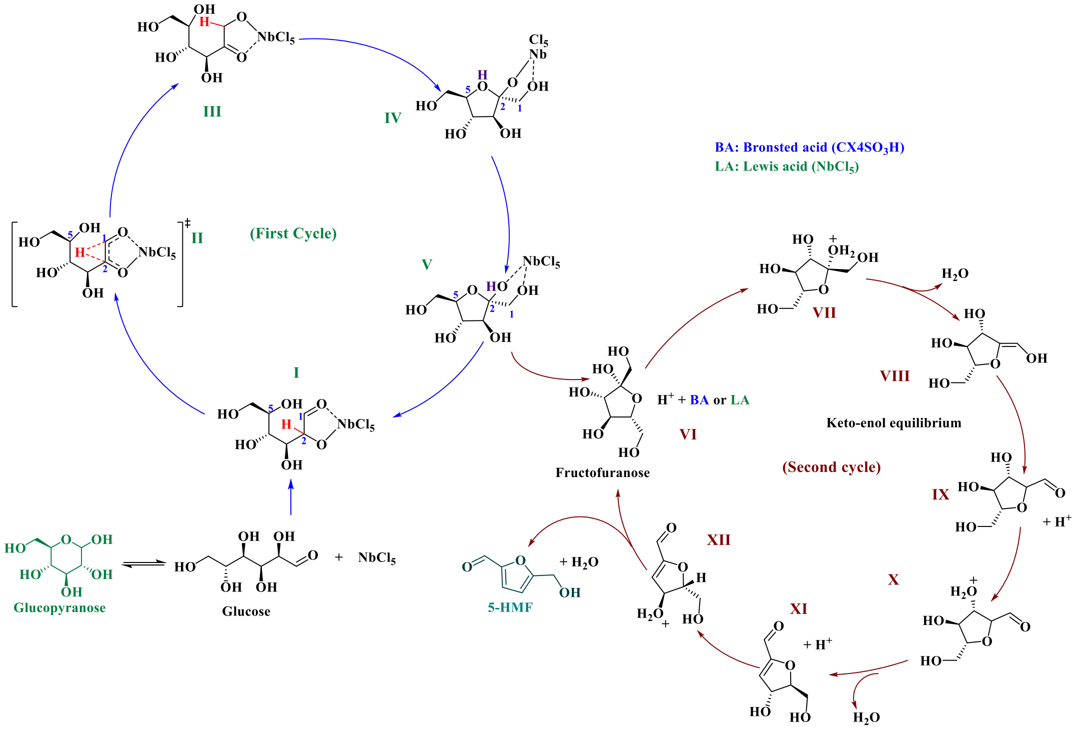


Figure 5. Evaluation of system catalyst and aqueous phase recycle. Reagents and conditions: 0.25 mmol glucose (45 mg), CX4SO$_3$H/NbCl$_5$ (5/7.5 wt%), MW, 150 °C, 17.5 min, water/NaCl, and MIBK (1/3 v/v).

2.9. Reaction Mechanism

The mechanism of glucose for fructose isomerization is still a matter of debate. There are two mechanistic proposals for the key step of the isomerization of glucose to fructose: one proceeding via a 1,2-enediol intermediate [59,70–73] and an intramolecular hydride shift from C-2 to C-1 [11,57,74–76] (Scheme 1). A study with isotopic labeling using D_2O was performed under the same optimized conditions (0.25 mmol glucose (45 mg), 150 °C, 17.5 min, water/NaCl, and MIBK (1/3 *v*/*v*) for $NbCl_5$ (7.5 wt%), $CX4SO_3H$ (5 wt%), and $CX4SO_3H/NbCl_5$ (5/7.5 wt%), except for the solvent (H_2O was replaced by D_2O).



Scheme 1. Mechanistic proposal for the conversion of glucose to HMF. The first catalytic cycle is based on the reference [75].

Analysis of the mass spectrum (GC-MS) showed that there was no incorporation of deuterium atoms into the HMF structure for none of the catalytic systems evaluated: $NbCl_5$, $CX4SO_3H$, and $CX4SO_3H/NbCl_5$. Since D_2O was used as the solvent, we propose a mechanistic step of the isomerization of glucose to fructose through simultaneously activating the carbonyl group at the C-1 position and the hydroxyl group at the C-2 position on glucose (intermediate **I**, Scheme 1) proceeding an intramolecular hydride shift from C-2 to C -1 catalyzed by $NbCl_5$ (state transition **II** and intermediate **III**, Scheme 1). Then, cyclization occurs through the attack of the hydroxyl on the carbonyl (intermediates **IV** and **V**, Scheme 1). The subsequent dehydration of fructose occurs with the $CX4SO_3H/NbCl_5$ consortium with protonation of the hydroxyl bound to the anomeric carbon of fructofuranose, followed by the loss of a water molecule and the formation of the enol (intermediate **VIII**, Scheme 1). The enol that is in tautomeric equilibrium with the keto (aldehyde) form (intermediate **IX**, Scheme 1). From the aldehyde, there is the protonation of a second hydroxyl, followed by the loss of a water molecule, leading to the formation of an α,β-unsaturated aldehyde (intermediate **X**, Scheme 1). Finally, the protonation of the secondary hydroxyl (intermediate **XI**, Scheme 1) followed by the loss of a water molecule leads to the formation of the aromatic ring of the HMF.

3. Materials and Methods

3.1. Materials

$Nb_2O_5{\cdot}nH_2O$ (NbO), $NbOPO_4{\cdot}nH_2O$ (NbP), and HNb_3O_8 were supplied by Companhia Brasileira de Metalurgia e Mineração (CBMM, Araxá, Minas GeraisBrazil). The niobium pentachloride ($NbCl_5$) and the standard HMF were purchased from Sigma-Aldrich (Saint

Louis, United States), as well as all other materials and reagents that were necessary for the development of this work.

3.2. Synthesis of $CX4SO_3H$

The $CX4SO_3H$ was synthesized according to the procedures reported in the literature [77–79].

3.3. General Procedure for Conversion of Glucose into HMF

In a Pyrex® glass tube suitable for microwave, the following were added: 0.25 mmol glucose (45 mg), 5.0 wt% of $CX4SO_3H$, 7.5 wt% of niobium chloride ($NbCl_5$), 1.0 mL of aqueous solution saturated with NaCl, and 3.0 mL of MIBK. After sealing the tube, this mixture was taken to a MW reactor (CEM Discovery), where it was heated to 150 °C under magnetic stirring for 17.5 min. At the end of the experiment, the mixture was cooled at room temperature and the organic phase was separated and dried over anhydrous sodium sulphate to remove residual water; the mixture was subsequently filtered and transferred to a 5.0 mL volumetric flask, which had its volume checked with methanol. From this solution, an aliquot of 100 µL was removed and transferred to another 5.0 mL volumetric flask. Finally, from this solution, an aliquot of 397 µL was removed into a vial, along with a 603 µL aliquot of methanol. The sample was analyzed by ultra-high-performance liquid chromatography (UHPLC).

3.4. Quantification of HMF by UHPLC

The chromatograms were obtained by UHPLC employing a Thermo Scientific Accela LC liquid chromatograph (diode array detector (DAD), autoinjector, and Accela pump) (Thermo Fischer Scientific, Austin, TX, USA). The column used for separation was a Hypersil GOLD reverse phase (50 × 2.1 mm, 1.9 µm particle size, and 175 Å pore) (Thermo Fischer Scientific, Austin, TX, USA). The mobile phase consisted of water and methanol (1:1), and elution was carried out in isocratic mode for two minutes. The applied amount was 200 $\mu L\ min^{-1}$ and the injection volume was 1 µL (partial loop), with a temperature of 25 °C for the injector and column. The peak of HMF was detected at a wavelength of 280 nm.

HMF was quantified based on the external calibration technique. Standard solutions were prepared in methanol, with HMF at concentrations of 2–50 $mg\ L^{-1}$ and injected into the UHPLC system. The calibration curve ($R^2 = 0.9960$) was obtained in relation to the area of each HMF standard. The HMF yield (%) was calculated based on a calibration curve.

3.5. Catalyst Recycling

The recycling of system catalysts was conducted using a model reaction employing 0.25 mmol glucose (45 mg), 5.0 wt% $CX4SO_3H$, 7.5 wt% $NbCl_5$, 1.0 mL saturated aqueous solution for NaCl, and 3.0 mL of MIBK. This mixture was heated to 150 °C for 17.5 min. At the end of this period, the system was cooled and the organic phase was separated. To the aqueous phase that stood in the tube, a new 0.25 mmol glucose load (45 mg) and MIBK (3.0 mL) were added, which were subjected to the reaction conditions. The recycling procedure was repeated another seven times.

4. Conclusions

In this study, we presented an efficient route to convert glucose into HMF with a high 50% yield using the consortium catalysts $NbCl_5$ and $CX4SO_3H$ in an MW reactor. The reaction conditions optimized result was $CX4SO_3H/NbCl_5$ (5 wt%/7.5 wt%) as a consortium catalyst, using water/NaCl and MIBK (1:3 *v*/*v*) at 150 °C for a 17.5-minute reaction time. This catalyst system showed excellent recyclability, with its catalytic activity maintained for six cycles. Thus, the glucose isomerization is due to the Lewis acid ($NbCl_5$), followed by the fructose dehydration to HMF, which is due to $CX4SO_3H/NbCl_5$. The application of this consortium catalytic system is attractive, environmentally friendly, and cost-effective for the conversion of biomass into higher value-added products. Finally, isotopic labeling experiments suggested a mechanism for the glucose isomerization for fructose reactions involving an intramolecular hydride shift from C-2 to C-1 since the incorporation of a deuterium atom was not observed; the proposed mechanism was validated using mass spectrometry.

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