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COMMUNICATION

Conversion of fructose and inulin to 5-hydroxymethylfurfural in sustainable betaine hydrochloride-based media

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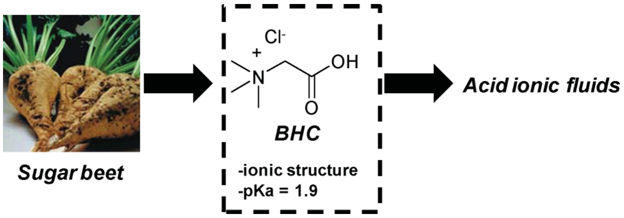
We show here that betaine hydrochloride (BHC), a co-product of the carbohydrate industry, can be used for the design of cheap and safe media capable of promoting the dehydration of fructose and inulin to HMF. In particular, in these BHC-based media, HMF was obtained with up to 84% yield, thus offering a competitive route to the traditional imidazolium-based ionic liquids.

Nowadays, many studies are dedicated to the conversion of carbohydrates to chemical platforms or transportation fuels.[1–4] Although elegant works have been reported, one should mention that these carbohydrate-based processes also generate some co-products that need to be chemically valorized in order to limit the economical and environmental impact of these bio-based processes. In this context, glycine betaine also known as *N*,*N*,*N*-trimethyl glycine, a metabolite of choline, is one of the main co-products generated by the carbohydrate industry.[5] In particular, glycine betaine represents 27 wt% of molasse derived from sugar beet[6] itself industrially produced with more than 400 million ton/year over the world.[7] It should be noted that the value of betaine rivals that of sugar contained in molasses making of this co-product a highly valuable raw material for chemistry.[8] Zwitterionic glycine betaine is also available under its acid form and called betaine hydrochloride (BHC). Although glycine betaine and BHC are cheap, biocompatible and biodegradable, valorization of BHC for the chemical industry has been scarcely investigated and betaine is nowadays mostly used for animal feeding. To date, in the field of chemistry, glycine betaine and its derivatives are essentially used as a polar heads for the synthesis of safer and more biodegradable cationic surfactants.[9,10] Clearly, new applications are nowadays strongly researched for this by-product in order to reduce the economic footprint of the sugar beet industry.

Here we wish to show that BHC can be used as a very promising derivative for the design of biorenewable solvent mixture (Scheme 1). In particular, owing to its ionic structure, its low pK_a (1.9) and its low reactivity towards alcohols, we wish to show here that BHC-based media are capable of dissolving carbohydrates such as fructose and inulin while their acid properties promote the dehydration of these carbohydrates to 5-hydroxymethylfurfural (HMF) with high yield. BHC is a solid and cannot be directly used as a solvent. In order to circumvent this problem, BHC was mixed with other renewable chemicals such as glycerol, water and choline chloride with which a liquid phase was readily obtained. These BHC-based media afford similar results than those collected in imidazolium-based ionic liquids while offering remarkable advantages such as low price and low ecological footprint. Recyclability of these media as well as extraction of HMF is also discussed.



Scheme 1 Chemical structure of BHC.

In a previous article, we have shown that 1-butyl-4-methylimidazolium chloride ([BMIM]Cl) can be partly substituted by glycerol, a renewably-sourced co-solvent, in the dehydration of fructose to HMF.[11] Although HMF was obtained with 70% yield in a mixture glycerol/[BMIM]Cl (35/65), presence of toxic and expensive [BMIM]Cl still represents a serious drawback of this process. Having these previous results in mind, we first investigated the catalytic activity of a BHC/glycerol mixture in the dehydration of fructose to HMF. Prior to catalytic experiments, reactivity of glycerol with BHC was checked. To this end, an equimolar mixture of glycerol and BHC was heated at 110 °C. Under these conditions, no esterification reaction occurred between BHC and glycerol.[12] It is noteworthy that upon prolonged reaction time, the reaction medium became slightly yellow colored suggesting a partial degradation of glycerol. Next, 2 g of fructose (40 wt%) was dissolved in 5 g of the mixture glycerol/BHC (80/20) and heated at 110 °C. Reaction progress was monitored by HPLC. Under these conditions, HMF was produced with a maximum yield of 26% after 25 min of reaction (Table 1, entry 2). With prolonged reaction time, the HMF yield gradually decreased presumably due to its reactivity with glycerol and to its acid-catalyzed degradation to humins

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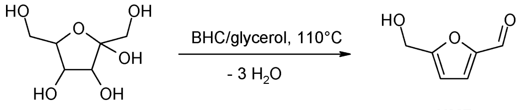
Table 1 Dehydration of fructose to HMF in a BHC/glycerol systems[a]



Fructose **HMF**

Entry	BHC (wt%)	Glycerol (wt%)	Fructose content (wt%)	HMF yield (%)[b]
1	0	100	40	0
2	20	80	40	26
3	50	50	40	33
4	80	20	40	34
5	50	50	20	51
6	50	50	10	57

[a] Reactions were performed in 5 g of a BHC/glycerol mixture. [b] Determined by HPLC.

Table 2 Dehydration of fructose to HMF in a BHC/water systems[a]

Entry	BHC (wt%)	Water (wt%)	Fructose content (wt%)	*t* (min)	HMF yield (%)[b]
1	0	100	40	60	0
2	80	20	40	60	36
3	80	20	40	120	48
4	80	20	40	180	44
5	90	10	40	180	35
6	80	20	20	120	57

[a] Reactions were performed in a biphasic system containing 5 g of a BHC/water mixture and 20 mL of MIBK. [b] Determined by HPLC.

as it was previously observed in the BMIMCl/glycerol media.[11] Note that although fructose was completely dissolved in neat glycerol, it remained unaltered confirming the effect of BHC on the dehydration of fructose (Table 1, entry 1). With the aim of limiting side reactions between glycerol and HMF, the content of BHC was first increased from 20 to 50%. As shown in Table 1, an increase of the BHC content contributed to increase the HMF yield from 26% to 33% (entries 2, 3). Note that a further increase of the BHC content from 50 to 80% did not result in an improvement of the HMF yield (entry 4) presumably because, in these conditions, BHC became sparingly soluble in the glycerol-fructose mixture.

A decrease of the fructose content from 40 wt% to 20 and 10 wt% has a clear beneficial effect on the HMF yield. As shown in Table 1, whereas HMF was produced with 33% yield starting from a BHC/glycerol (50/50) mixture containing 40 wt% of fructose, a drop of the fructose content to 20 and 10 wt% led to the production of HMF with 51 and 57% yield, respectively (entries 3, 5, 6).

Next, extraction of HMF from the BHC/glycerol mixture was explored. Inspired by our previous results, we performed the reaction in a biphasic [BHC/glycerol(50/50)]/methylisobutylketone (MIBK) system. Although we have previously reported that such approach was efficient in a biphasic [glycerol/[BMIM]Cl]/MIBK system,[11] all attempts to extract HMF from the BHC/glycerol mixture with MIBK failed since HMF was recovered with only 7% yield. Although the difficult extraction of HMF from the BHC/glycerol (50/50) mixture represents the main drawback of this process, it also clearly highlights the great ability of the BHC/glycerol medium to dissolve bio-based chemicals such as fructose and HMF. Utilization of such medium for the dissolution of biomass is now the topic of current investigations in our group.

With the aim of finding a suitable solution for the convenient extraction of HMF, other BHC-based systems were explored. In this context, dehydration of fructose to HMF was next investigated in a mixture BHC/water. In order to (1) limit the side rehydration of HMF to levulinic and formic acids and (2) evaluate the possible extraction of HMF from the BHC/water medium, all reactions were directly performed in a biphasic [BHC/water]/MIBK system. In a mixture BHC/water (80/20), we found that at least 40 wt% of fructose can be dissolved, further showing the great affinity of fructose for BHC-based medium. Interestingly, as compared to the BHC/glycerol mixture, HMF can be extracted in a larger extent from the BHC/water medium. As shown in Table 2, in a BHC/water (80/20) mixture containing 40 wt% of fructose, HMF was recovered with 48% yield at 100 °C (entry 3). This maximum yield of HMF was obtained after 120 min of reaction (entries 2–4). Analysis of the MIBK phase by HPLC revealed that the purity of the recovered HMF reached 95% further demonstrating the attractiveness of the [BHC/water]/MIBK system. As compared to other reported strategies, this is one of the highest yields of HMF obtained starting from such highly concentrated solution of fructose. It is noteworthy that an increase of the BHC content from 80 to 90% results in a drop of the HMF yield from 48 to 35% (entries 3, 5). In such conditions, BHC was not fully dissolved in water and the reaction medium became heterogeneous which may explain this lower yield obtained in the mixture BHC/water (90/10).

As observed above, a decrease of the fructose content from 40 to 20 wt% led to an increase of the HMF yield from 48 to 57% (entries 3, 6).

Taken together, these results show that the mixture BHC/water (80/20) is more convenient than the BHC/glycerol (50/50) medium for the dehydration of fructose to HMF. Main advantage of the BHC/water system stems from the possible and selective extraction of HMF with MIBK allowing (1) a convenient and selective recovery of HMF and (2) to limit the reactivity of HMF with water.

With the aim of further improving the yield of HMF, we next investigated the dehydration of fructose to HMF in a mixture BHC/Choline chloride (ChCl). ChCl has recently attracted considerable attentions as a reaction medium mainly because of its low price, biodegradability and its ability to form deep eutectic solvents in combination hydrogen bond donors such as urea[13] or carboxylic acid.[14] Note that if ChCl can be extracted from biomass, one should also comment that ChCl available on the market is still synthesized from fossil carbon.

Although ChCl is also known to create low-melting mixtures with different carbohydrates (including fructose),[15] formation of a liquid phase from BHC, ChCl and fructose was difficult to obtain. Indeed, from a mixture BHC/ChCl (90/10) containing 40 wt% of fructose, no transparent liquid phase was observed after 15 min of stirring at 110 °C. Note that liquefaction of the reaction medium was observed at 110 °C only upon addition of a small amount of water. Hence, we decided to use a ChCl/BHC/H_2O system with a mass ratio of 10/1/2. It should be noted that all attempts to increase the BHC content failed

Table 3 dehydration of fructose to HMF in a ChCl/BHC systems[a]

Entry	BHC (wt%)	Fructose content (wt%)	*t* (min)	HMF yield (%)
1	10	40	120	50
2	5	40	120	65
3	3.3	40	170	63
4[b]	5	40	120	62
5[c]	5	40	120	75
6[d]	5	40	240	24
7	5	80	315	48
8	5	120	375	37
9	5	20	60	76
10	5	10	60	81
11[e]	5	2	120	66
12[e]	5	10	60	84
13[f]	5	15[g]	60	52

[a] Reactions were performed in 6.5 g of a ChCl/BHC/H_2O mixture. [b] Reaction performed at 130 °C. [c] Reaction performed at 90 °C. [d] Reaction performed at 70 °C. [e] In a biphasic [ChCl/BHC]/MIBK system. [f] Starting from inulin. [g] Inulin.

since in this case no formation of liquid phase was observed. Therefore, in the following experiments, BHC was used in a catalytic amount (30 mol% *vs.* fructose). In a typical procedure, 2 g of fructose (40 wt%) was heated at 110 °C in 6.5 g of a ChCl/BHC/H_2O mixture. In these experiments, the amount of BHC was always maintained lower than 10 wt%. Results are presented in Table 3.

In the mixture ChCl/BHC/H_2O (10/1/2, *i.e.* 30 mol% of BHC *vs.* fructose), HMF was obtained with a maximum yield of 50% after 2 h of reaction (entry 1). When the amount of BHC was decreased from 10 to 5 wt%, the yield of HMF was unexpectedly improved from 50% to 65% after 2 h of reaction (entries 1, 2). This result was ascribed to the initial lower viscosity of the reaction medium. Indeed, using 10 wt% of BHC the system is highly viscous and the reaction may be initially strongly limited by diffusion problems.[15] It should be noted that effect of the reaction viscosity on the reaction rate only impacts the initial stage of the reaction. Indeed, as we previously reported in a mixture glycerol/[BMIM]Cl,[10] the viscosity of the system rapidly dropped after only few minutes of reaction due to the release of water caused by the dehydration of fructose. Therefore, no correlation between the reaction viscosity and reaction rate has been clearly established. Similar conclusions can be also drawn for the BHC/glycerol and BHC/water systems. When, the amount of BHC was further decreased from 5 to 3.3 wt%, the reaction time was then logically increased from 120 min to 170 min while the yield of HMF remained similar (63%) (entries 2, 3). This result shows that below 5 wt% of BHC the system is no longer limited by diffusion problems and BHC normally acts as a homogeneous catalyst.

As researched, in the ChCl/BHC/H_2O (10/0.5/2) mixture, HMF was produced with higher yield (65%) than in BHC/glycerol (33%) and BHC/water (48%) mixtures due to the very low reactivity of HMF with ChCl.

Next, influence of the reaction temperature was investigated. At 130 °C, the maximum yield of HMF was unchanged (62%, entry 4). Conversely, a drop of the temperature from 110 °C to 90 °C resulted in a slight increase of the maximum yield of HMF from 65% to 75% (entry 5). This higher yield observed at 90 °C was partly due to the higher stability of HMF at this temperature. For instance, when neat HMF was heated in ChCl/BHC/H_2O (10/0.5/2), only 4 mol% of HMF was degraded after 120 min of reaction at 90 °C *vs.* 10 mol% and 13 mol% at 110 °C and 130 °C, respectively. Note that a further decrease of the temperature from 90 °C to 70 °C unfortunately dropped the reaction rate to an unacceptable level since HMF was produced with only 24% yield after 240 min of reaction (entry 6).

In agreement with previous existing reports, the efficiency of the ChCl/BHC/H_2O (10/0.5/2) mixture is also strongly dependent on the fructose content. As shown in Table 3, an increase of the fructose content from 40 wt% to 80 and 120 wt% resulted in a gradual drop of the HMF yield from 65% to 48% and 37%, respectively, due to the dominant acid-catalyzed degradation of HMF to soluble and insoluble humins (entries 2, 7, 8). Conversely, a decrease of the fructose content from 40 wt% to 20 and 10 wt% logically resulted in an improvement of the HMF yield from 65% up to 81% (entries 2, 9, 10).

As in the case of the BHC/water medium, ChCl and BHC are not soluble in MIBK. Therefore, we explored the possibility to carry out the reaction in a biphasic [ChCl/BHC/H_2O]/MIBK system with the aim of continuously extracting HMF from the catalytic phase. To this end, reactions were first performed at 110 °C starting from 40 wt% of fructose dissolved in a mixture ChCl/BHC/H_2O (10/0.5/2). Interestingly, in the presence of MIBK, HMF can be selectively extracted and HMF was recovered with 66% yield (entry 11). Thanks to the very low solubility of ChCl and BHC in MIBK, HMF was obtained with a purity higher than 95% (determined by HPLC). ^{1}H NMR also confirmed the high purity of recovered HMF (Fig. 1). To our delight, when the fructose content was dropped from 40 wt% to 10 wt%, HMF was recovered with a yield as high as 84% (entry 12), thus offering competitive results with those commonly obtained in imidazolium-based ionic liquids.

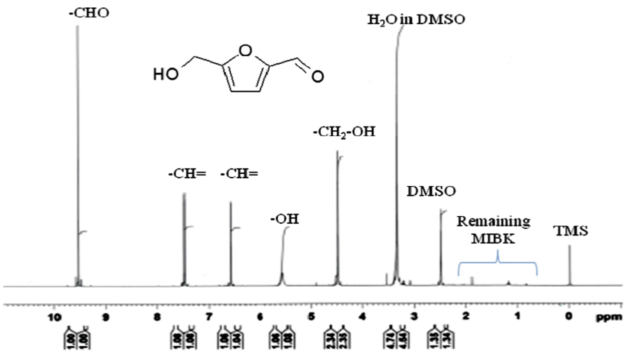


Fig. 1 ^{1}H NMR spectra (300 MHz, 25 °C, DMSO-d6) of HMF recovered with MIBK from ChCl/BHC/H_2O (10/0.5/2) containing 40 wt% of fructose.

Considering that HMF can be conveniently and selectively extracted from the ChCl/BHC/H_2O mixture with MIBK, recyclability of the reaction medium was investigated. Recycling experiments were performed at 100 °C using a fructose content of 40 wt% which is, in our views, a good compromise between the yield of HMF and the concentration of fructose. For recycling experiments, the vessel was partly opened in order to continuously remove water. Note that such a reactor configuration also led also to a slight evaporation of MIBK (boiling point = 118 °C) which can be then further separated from water by liquid phase decantation. At the end of the first catalytic cycle, 40 wt% of fructose was directly reloaded to the recovered ChCl/BHC mixture (no water was added) and the reaction was heated for another 2 h at 100 °C. As shown in Fig. 2, the ChCl/BHC mixture can be successfully reused at least 7 times without appreciable loss of yield further demonstrating the effectiveness of BHC-based medium for the synthesis of HMF. It should be mentioned, however, that after 7 cycles, the HMF yields started to decrease due to the unavoidable accumulation of black materials (presumably humins) in the ChCl/H_2O/BHC medium.

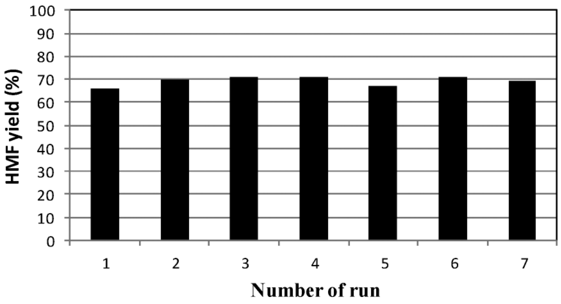


Fig. 2 Recycling of the ChCl/BHC system.

Finally, in a last set of experiments, we investigated the capability of the ChCl/BHC/H_2O system to directly promote the conversion of inulin to HMF. Inulin is a biopolymer of fructose. Inulin used in this work is commercially available and was extracted from chicory roots. The degree of polymerization of inulin is 46 and the water content is 15 wt%. Remarkably inulin is also soluble in the ChCl/BHC mixture further demonstrating the efficiency of such medium for solubilizing carbohydrates. Reaction was performed at 100 °C in a biphasic [ChCl/BHC/H_2O]/MIBK system and starting from 15 wt% of inulin. As described above, the ChCl/BHC/H_2O mass ratio was initially 10/0.5/2. Here, initial addition of water not only helps to solubilize chemicals but also to induce the hydrolysis of inulin to fructose. Interestingly, under these conditions, HMF was produced with 52% yield confirming that the ChCl/BHC/H_2O is also capable of promoting the tandem hydrolysis/dehydration of inulin to HMF (Table 3, entry 13). As observed in other media, no reaction took place from glucose in the ChCl/BHC/H_2O system. This result is in accordance with the current literature suggesting that dehydration of glucose to HMF required the *in situ* isomerization of glucose to fructose as a pre-requisite step. Note that dehydration of glucose to HMF (40% yield) in the ChCl/BHC/H_2O medium required the assistance of 10 mol% of $AlCl_3$ which is known to promote the isomerization of glucose to fructose.

In conclusion, we report here that BHC, a co-product of the sugar beet industry, can be employed in combination with glycerol or water or ChCl as a cheap and sustainable acid media for the dehydration of fructose and inulin to HMF. These BHC-based media affords similar yields (up to 84%) than those commonly obtained in traditional imidazolium-based ILs while offering notable economical and environmental advantages. Except for the BHC/glycerol mixture, HMF can be conveniently extracted from the BHC/water and ChCl/BHC/H_2O media by liquid–liquid phase extraction allowing (1) isolation of HMF with a purity higher than 95% and (2) the recycling of the ChCl/BHC medium.

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Experimental

Analytical methods

Yields of HMF were determined by external calibration at 25 °C using a HPLC equipped with a nucleosil 100–5 C18 column (250 × 4.6 mm), a Shimadzu LC-20AT pump, a Shimadzu RID-10A detector and using a mixture acetonitrile/water (10 : 90) as mobile phase (0.8 mL min^{-1}). Fructose was quantified by external calibration at 25 °C using a HPLC equipped with a Varian NH_2-column, a Varian Prostar RID detector, Varian Prostar pumps (model 210) and a mixture acetonitrile/water (90 : 10) as mobile phase (0.8 mL min^{-1}).

General procedure for the dehydration of fructose to HMF

Fructose was dissolved in 5 g of a mixture BHC/glycerol or BHC/water or BHC/ChCl/H_2O. Then the mixture was heated under air at 110 °C (or 100 °C in the case of water). During the reaction, HMF was continuously extracted with 20 mL of MIBK. The MIBK phase containing HMF was then separated from the BHC-based medium by simple phase decantation. Then, MIBK was removed under vacuum affording HMF as a dark brown chemical. Because the extraction with MIBK is highly selective to HMF, the distilled MIBK could be recycled for other extraction cycles.

Recycling experiments

Recycling experiments were performed in the ChCl : BHC : H_2O mixture (10 : 0.5 : 2) using a fructose content of 40 wt% (related to the weight of ChCl + BHC). After the first extraction of HMF with MIBK, fructose was directly reloaded to the recovered BHC/ChCl mixture. No water was added. The reaction was then heated again at 110 °C for 2h. Similar procedure was repeated up to the 7th cycle.

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