Rapid, High-Yield Fructose Dehydration to HMF in Mixtures of Water and the Non-Coordinating Ionic Liquid [bmim][OTf]

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ABSTRACT: The non-coordinating ionic liquid [bmim][OTf] is an effective and versatile solvent for the high-yield dehydration of fructose to the platform chemical HMF over short reaction times. In contrast to literature reports, which report low yields for this transformation in ionic liquids (ILs) with non-coordinating anions, this contribution reveals that the water content is an essential parameter for an efficient reaction in ILs. Achieving the optimum amount of water can increase the yield dramatically by regulating the acidity of the catalyst and partially suppressing the side reaction caused by self-condensation of HMF. Using acid catalysis in [bmim][OTf] with 3.5% water content, yields above 80% can be achieved at 100 °C in only 10 minutes, even at high (14%) fructose loading. These results suggest that [bmim][OTf] represents a superior medium for solvent extraction of HMF compared to halide-based ILs, allowing the option of isolation or further valorisation of the HMF formed.

INTRODUCTION

The depletion of oil reserves and the increase in regulation of CO_2 emissions have increased the demand for renewable chemicals that can replace oil-derived products.[1] While specific targets have been established for biofuels, little planning has been proposed for bio-derived chemicals, perhaps due to the small fraction of the total oil production used for chemical products compared to that used for transport fuel. The replacement of common oil derivatives with renewable platform chemicals is a significant challenge mainly due to the high cost of the technologies involved. In this field, sugars are seen as the most suitable feedstock for the production of a wide range of green chemicals. This sector has experienced substantial investments in research but little commercial activity. In a report submitted to the European Commission Directorate on General Energy, a consortium led by E4tech, RE-CORD and WUR[2] discussed 94 green products, including chemicals, biofuels and polymers, which were identified as accessible from sugars obtained from the pretreatment of sustainable biomass feedstocks. These products could replace the majority of all oil-derived chemicals. The sugars identified as having the potential to be converted into valuable products are glucose, fructose, galactose, xylose, arabinose, ribose, lactose, sucrose and maltose. Of the 94 products obtained from these sugars, 25 were selected as involving feasible technologies that are suitable for large scale prototype testing in a pilot plant.[2] 5-hydroxymethylfurfural (HMF) represents a promising intermediate product from sugars, capable of replacing a large variety of petrochemical derivatives, so its generation in high-yield is an important aspect in the scale up of the production of this chemical.[3] The main route to form HMF is by the dehydration of sugars,[4] and important results have been achieved for HMF production using ionic liquids.[5-9] The use of ionic liquids to produce biorenewable chemicals has illustrated many of the advantages

associated with ionic liquid media, such as their low volatility and non-flammability, even if concerns have been raised more recently over the toxicity of these solvents.[10] Deep eutectic solvents and water have also been investigated for the dehydration of fructose into HMF but improved yields are still needed.[11-13] Other research has focused on optimising heterogeneous catalysts for the dehydration reaction both involving metal catalysts[14-20] and supported ionic liquids.[21,22]

In particular, ionic liquids with halide counteranions have proved to be very efficient for the production of HMF from fructose, glucose and cellulose with both Brønsted and Lewis acid catalysts.[23-25] Due to the ability of halide-based ionic liquids to dissolve sugars and cellulose through their hydrogen bonding ability,[26] these media have proved very attractive for dehydration reactions. In many cases, superior performance is observed when compared to organic solvents and water in terms of loading, reaction time and process conditions.[27,28] In particular, chromium and tin chloride catalysts have proved extremely efficient in chloride and bromide ionic liquids.[29] While catalytic systems that use glucose as a substrate are limited, more options are reported for fructose dehydration. In an acidic ionic liquid with a coordinating anion, [bmim][HSO$_4$] / CrCl$_3$·6H$_2$O has been reported as a very efficient system to obtain a quantitative yield of HMF from fructose at high loadings (1:7 with respect to the ionic liquid).[30] Alternatively, [bmim]Br and [Hmim]Cl can dehydrate fructose in high yield with no added catalyst. Of the two systems, [Hmim]Cl proved to be more efficient, achieving 92% yield at 90 °C in 45 min while [bmim]Br required heating to 100 °C and 1 hour to obtain the same yield.[31,32] The ionic liquid [bmim]Cl can perform catalyst-free high yield dehydration (97%) under microwave irradiation at high loading,[33] however this heating methodology is not suitable for scale-up. The addition of an acid can enhance the reaction in non-protic ionic liquids. Li and co-workers managed to achieve near quantitative yields of HMF in [bmim]Cl or [bmim]Br with HCl in 10 minutes at 80 °C, while the dehydration was unsuccessful with HCl in non-halogenated and non-coordinating ionic liquids, such as [bmim][BF$_4$] and [bmim][PF$_6$], achieving less than 10% yield in 30 minutes.[34] A 52% yield was obtained in 3 hours using Amberlyst-15 in [bmim][PF$_6$] at 80 °C, with the process showing improvement (80% yield) on addition of DMSO.[35] A triphasic system based on water and the hydrophobic ionic liquid [bmim][NTf$_2$] led to 81% HMF yield in 24 hours using a vanadium phosphate catalyst.[36] However, in general, satisfactory results have not been obtained in ionic liquids with non-coordinating anions such as [BF$_4$]$^-$, [PF$_6$]$^-$, [OTf]$^-$ and [NTf$_2$]$^-$. Shi and co-workers analysed the effect of anions on the dehydration of fructose and, through a molecular dynamics study, showed that chloride anions, in contrast to triflate, tend to form a centralised structure around the fructose molecule through hydrogen bonds.[37] This finding is in agreement with others who used IR spectroscopy and molecular dynamics calculations to show that non-coordinating anions in ionic liquids, such as tetrafluoroborate, do not contribute to hydrogen bonding with the hydroxyl group of HMF.[38] While successful results have been reported for ionic liquids with chloride and bromide anions, the applicability of these reactions has always proved problematic due to the difficulties encountered in the separation of HMF from the medium.[39,40] Different approaches have been proposed for HMF recovery, such as the use of supercritical CO$_2$ or high-vacuum entrained distillation, but the feasibility of applying these techniques on a large scale is doubtful on account of the high cost associated with handling CO$_2$ or high vacuum.[41–43] Moreover, a better compromise between reaction time, heating method and catalyst loading still needs to be achieved. Some researchers have focused on the oxidation of HMF in the reaction media directly to 2,5 furandicarboxylic acid (FDCA), which can be separated by water addition,[44,45] but this reaction proved to be non-selective. A further issue is that the transition metal catalysts, which have proved to be the most selective for this oxidation[46] are deactivated in the coordinating halide-rich environment.[47] In contrast, the oxidation of alcohols is extremely efficient in non-coordinating ionic liquids with superior yields and selectivity to those reported in conventional organic solvents.[48–52] However, the dehydration of sugars to HMF in these solvents is inefficient with this poor performance being ascribed to the lack of hydrogen bonding. Therefore, an efficient chemical pathway that enhances the HMF yield from sugars in non-coordinating solvents would make the process much more attractive for both isolation of HMF and its further catalytic transformation. The absence of hydrogen bonding between the hydroxyl group of HMF and the solvent decreases the affinity of HMF for these solvents, making its extraction with organic solvents far easier, reducing the amount of extraction solvent needed. Therefore, the aim of this contribution is to focus on improving the yield of HMF in non-halogenated and non-coordinating ionic liquids, such as [bmim][OTf] (Figure), which are more suitable media for further reaction of HMF. In order to increase the yield over short reactions times, analysis was performed on a series of different reaction parameters. Water content

proved to be the most crucial parameter for solvent design as it stabilises HMF towards side reactions. This report demonstrates that the reason behind the low selectivity achieved so far in non-coordinating ionic liquids lies in the instability of HMF under acidic conditions. Water addition suppresses side reactions and stabilises the HMF, leading to high yields of HMF from the dehydration of fructose. Furthermore, this is achieved over short reaction times and with high substrate loadings, making [bmim][OTf] as efficient for this transformation as the halide-based ionic liquids reported in literature.
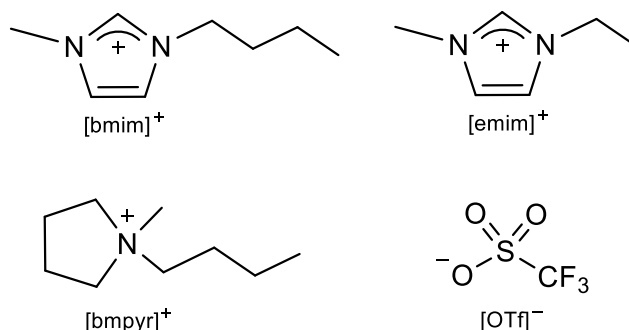
Figure 1. The cations and anions used in the ionic liquids in this contribution.

EXPERIMENTAL SECTION

Materials. Fructose, 36% hydrochloric acid, calcium hydride, phosphorus pentoxide, lithium triflate and potassium hydroxide and [emim][OTf] were purchased from Sigma Aldrich. 5-Hydroxymethylfurfural (99%, chromatography standard) was obtained from Fluorochem and purified by crystallisation at 3 °C from ethyl acetate and hexane. *N*-methylimidazole, *N*-methylpyrrolidine and chlorobutane for ionic liquid synthesis were purchased from Alfa Aesar. Methylimidazole was purified at reduced pressure (2.1 mbar. 40 °C reflux temperature) in the presence of calcium hydride. Chlorobutane was dried at atmospheric pressure over phosphorus pentoxide. Methylpyrrolidine was distilled at atmospheric pressure over KOH. Acetonitrile, ethyl acetate and hexane were purchased from VWR and further purified by distillation over calcium hydride.

Synthesis of [bmim]Cl and [bmpyr]Cl. [bmim]Cl was synthesised on a large scale (350 g). Manipulation of all chemicals was performed by cannulation under inert conditions. 1-methylimidazole (160 mL, 2 mol) was transferred to a three neck flask equipped with an air condenser followed by the addition of acetonitrile (100 mL). The mixture was heated at 60 °C under stirring and chlorobutane (230 mL, 2.2 mol, 1.1 eq) was then added dropwise using a dropping funnel. The reaction mixture was heated for 3 days at 70 °C. Complete consumption of 1-methylimidazole was confirmed by ^{1}H NMR spectroscopy. [bmim]Cl was precipitated by gradual addition of ethyl acetate at 3 °C. The resultant white crystals were washed under inert conditions with portions of ethyl acetate (2 L in total), dried under vacuum and stored in a glovebox. [bmpyr]Cl was synthesised by the same procedure using *N*-methylpyrrolidine. Data for the products were in good agreement with those reported previously.[30,53]

Synthesis of [bmim][OTf] and [bmpyr][OTf]. [bmim]Cl (30 g, 0.172 mol) was dissolved in water (100 mL) and Li[OTf] (30 g, 0.179 mol) was dissolved in water (50 mL). The lithium triflate solution was added dropwise to the chloride solution under vigorous stirring and the reaction left overnight. The product was extracted from aqueous solution using a total of 800 mL dichloromethane. The organic extracts were washed repeatedly with water (5 mL) until the silver nitrate test revealed no halide ions (5-6 washes). The organic phase was dried with magnesium sulfate and then evaporated to dryness under reduced pressure. The ionic liquid, [bmim][OTf] was further dried under reduced pressure overnight at 60 °C (final yield 96%) and handled thereafter under an inert atmosphere.

[bmpyr][OTf] was synthesised by the same procedure starting with [bmpyr]Cl. Data for the products were in good agreement with those reported previously. See Supporting Information for spectra.[54,55]

Fructose conversion to HMF. Experiments were performed in triplicate in 1.5 mL vials. A larger quantity of the IL was prepared with the desired amount of water and catalyst. This was divided into 1 g portions, which were used for each experiment. Each vial was loaded with an appropriate amount of fructose followed by the addition of the solvent to be tested in the desired fructose/solvent ratio. The vials were placed in a preheated heating block for the desired reaction time. At the end of the reaction, the reaction mixture was rapidly quenched with 1 mL of water and then further diluted 6:1 and filtered before HPLC analysis. Kinetic analysis was performed by halting the reaction by addition of water at the desired time and recording the data.

Quantification of HMF yield was performed using a Shimadzu Prominence preparative HPLC (Shimadzu, Kyoto, Japan) with refractive index (RI) and ultraviolet (UV) detectors and equipped with an Aminex HPX-87H column using 0.005 M H_2SO_4 as the mobile phase at 55 °C and flow rate of 0.6 mL/min. See Supporting Information for numerical data.

The isolation of HMF from [bmim][OTf] was performed on a larger scale, using 1 g of ionic liquid and 14% fructose loading. ^{1}H NMR analysis of the ionic liquid/water mixture after reaction showed only resonances for the IL and HMF and no precipitation was observed on water addition. Extraction with diethyl ether from the IL phase followed by solvent removal resulted in a viscous liquid (^{1}H NMR spectrum, Figure S17 in the Supporting Information). Washing with sodium carbonate solution was avoided due to the high affinity of HMF for the water phase and its instability at high pH. Instead the ionic liquid phase was neutralised to pH 7 after addition of water (20 mL). The solution was then washed with dichloromethane until the organic layer became clear (5 x 1 mL). The purified water layer was then extracted with diethyl ether (3 x 100 mL) and concentrated under vacuum to obtain a yellow liquid, which crystallised at – 4 °C to give 71% yield of HMF from fructose (Figures S18-20 in the Supporting Information). Following this procedure, the ionic liquid was extracted from the water phase mentioned above using ethyl acetate as a light brown viscous liquid. Analysis by ^{1}H NMR spectroscopy and mass spectrometry showed no degradation of the ionic liquid with only slight traces of HMF remaining in the ionic liquid phase (as evidenced by ^{1}H NMR spectroscopy).

Partition coefficient measurements. The ionic liquids (300 mg) were mixed with HMF (30 mg) and heated at 60 °C for 30 minutes to obtain a homogeneous solution and then cooled to room temperature. Diethyl ether (1 g) was added to the mixture and vigorously stirred for one hour. Aliquots from the organic phase were removed and analysed using a ThermoFischer GC ULTRA with external standard calibration. The partition coefficient was calculated using the following formula:

$$K = \frac{C_{HMF}^{organic\ phase}}{C_{HMF}^{ionic\ liquid}}$$

RESULTS AND DISCUSSION

Stability of HMF in the ionic liquid under acidic conditions

Literature studies on the mechanism of fructose dehydration appear to agree that a hydrogen bonding environment is necessary for dehydration to be achieved.[37] However, the potential for hydrogen bonding is reduced in an ionic liquid with a non-coordinating anion. To understand the behaviour of HMF in a non-coordinating environment, this study began by analysing the stability of HMF in [bmim][OTf] under acidic conditions at elevated temperatures with a range of water content. The stability of HMF has proven to be a key issue for the effective valorisation of the dehydration reaction.[56] A solvent system capable of stabilising HMF is needed to improve the yield of reaction and to avoid self-condensation of HMF over longer reaction times. Water has the potential to act as a hydrogen bond acceptor, contributing to the stabilisation to HMF. In this study, *p*-toluenesulfonic acid (PTSA) was added to the HMF in the IL at 90 °C for 10 minutes. These conditions were chosen since *p*-toluenesulfonic acid has already been

shown to be a good reagent for fructose dehydration in many different solvent systems when PTSA is used in its immobilised form (Amberlyst-15).[57-63]
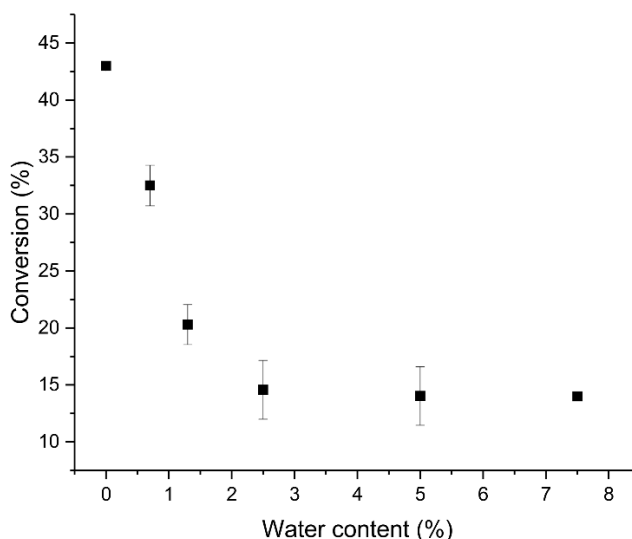

Figure 2. Degradation of HMF at 90 °C in [bmim][OTf] with a range of water content and 10% PTSA loading (with respect to HMF) and 10% HMF loading (with respect to the ionic liquid).

The data in Figure 2 appeared to confirm our hypothesis as HMF proved to be unstable in the pure ionic liquid, undergoing 43% degradation under the conditions tested. The gradual addition of water hindered the formation of side products, decreasing the decomposition to just 14%. The origin of this behaviour could be linked either to the hydrogen bonding of water with HMF or the decreasing activity of the protons on addition of increasing amounts of water. However, no trace of further hydration to formic and levulinic acids is observed, suggesting that the ionic liquid is contributing to the stability of HMF. To further investigate the role of water in the ionic liquid, a stability test was performed at 1.3% water content with HCl and H_2SO_4, which exhibit a lower pKa than PTSA. The results showed slight changes in the degree of degradation with less degradation observed for HCl (18.4 ± 0.8%) and slightly more for H_2SO_4 (23.2 ± 0.2%) compared to PTSA (20.3%). The significant difference in acidity of these Brønsted acid catalysts shows no strong correlation to the difference in degradation observed. This implies that the presence of water is not decreasing the acidity of these catalysts substantially, but has more of an effect on the stabilisation of HMF through hydrogen bonding.

Presence of intermediates

During the experiments on fructose dehydration, it was observed that HMF yield does not follow a first order relationship to the substrate, fructose, suggesting the formation of intermediates during the dehydration process. In all the conditions reported here, fructose conversion was almost complete in less than 1 minute at temperatures higher than 90 °C, while HMF yield increases over a longer reaction time (3 to 10 min). The formation of intermediates is indicated by the appearance of two peaks at 7.7 min and 8.1 min (compared to fructose at 9.3 min) in the HPLC chromatogram. By analysing the kinetics of the reaction, it was observed that HMF yield does not increase further when these two peaks were no longer present, indicating that the reaction is complete and the substrate and the intermediates have been consumed. A mechanistic study of fructose dehydration in ethanol was performed by Zhang et al[64] and the authors demonstrated that two principal intermediates were formed prior to HMF formation, according to the mechanisms depicted in Scheme 1. Their analysis was performed by *in situ* NMR spectroscopy and mass spectrometry, strongly supporting this reaction path. Due to the difficulty in quantifying the

intermediates, the rate limiting steps in the dehydration will not be discussed here. Instead, the reaction was considered complete when the intermediate peaks in the chromatogram were no longer present.
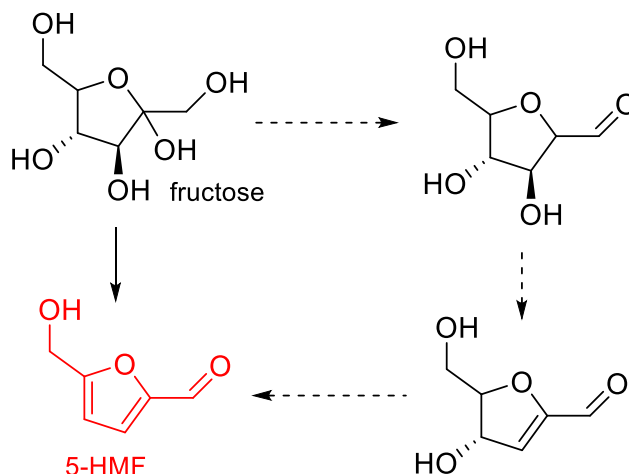
Scheme 1. Fructose dehydration scheme proposed in previous work.[45]

Selection of the acid catalyst

According to the stability test described above, it was decided to operate under conditions where the decomposition of HMF is minimised. However, the dehydration of fructose involves the generation of 3 moles of water per mole of fructose, so it was decided to operate with a lower initial water content to avoid a possible excess that could reduce the rate of reaction or lead to further undesired hydrolysis of HMF. An initial water content of 3.5% and a fructose loading of 14% was selected. Under these conditions, complete dehydration of fructose will lead to a water content of 5%. The acids, PTSA, H_2SO_4 and HCl were chosen for catalyst screening. The success of PTSA for the dehydration of HMF has already been established in different systems and HCl has been shown to be an effective catalyst in a wide variety of solvents. For example, Tuerke and co-workers obtained 82% yield at 30% fructose loading in 1 minute at 185 °C and 17 bar pressure in a microbatch reactor using HCl in a biphasic system of water/MIBK.[65] A study published in 2011 reported an 82% HMF yield in isopropanol in 1 hour at 120 °C,[66] while a near quantitative yield was obtained in [bmim]Cl at 80 °C.[34] Sulfuric acid proved to be an efficient catalyst in [bmim]Cl and DMSO, reaching over 93% yield.[34,67]

The results from the screening of different acids are shown in Figure 1. Hydrochloric acid proved to be the best acid for this purpose, reaching 74% yield in 10 minutes at 14% fructose loading. The greater acid strength can ensure complete dehydration of fructose intermediates while chloride ions can contribute to the catalysis by providing hydrogen bonding to the hydroxyl group. It was thus decided to continue the study with HCl as the catalyst.
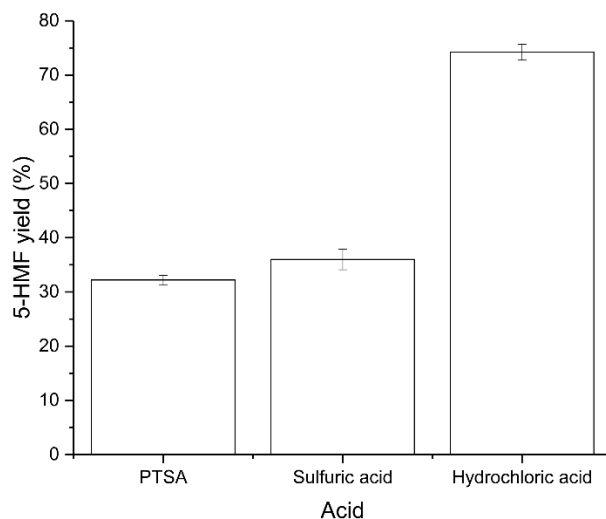
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Figure 1. Acid selection for fructose dehydration in [bmim][OTf]. Fructose loading = 14%, T = 90 °C, initial water content = 3.5%, acid catalyst loading 10%, t = 10 min.

Effect of the water content on the yield and kinetics of the reaction

In order to understand the role of water in the reaction medium, a range of water content in the ionic liquid was investigated. The results in Figure 4 clearly suggest that water has a significant effect on the yield of HMF in the reaction.
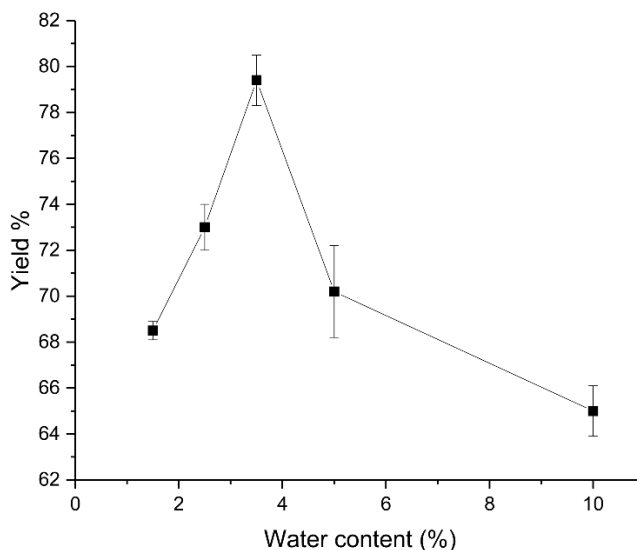

Figure 4. Effect of water content on HMF yield from fructose in [bmim][OTf], fructose loading = 10%, T = 90 °C, t = 10 min, 10 % acid catalyst loading (HCl).

Gradual addition of water led to a maximum in HMF yield (79%) at 3.5% water content, while using pure water as solvent resulted in no reaction at all, suggesting that the ionic liquid increases the activity of H^+ or enhances the hydration of the chloride anion, hindering its role in dehydration. Low water concentration led to a poor yield, which may be due to the overly aggressive activity of the H^+ ions, leading to side reactions of HMF, such as self-condensation or reaction with fructose (to produce humins). High yields are obtained at 3.5% water content, suggesting a good compromise between stabilisation and dehydration of HMF. In this medium, water plays a

different role compared to the dehydration in halogenated ionic liquids as [bmim]Cl, [bmim]Br and [Hmim]Cl,[31,32,34] where the only effect is to decrease the reaction rate. In other catalytic systems, water contamination leads to a drastic decrease in selectivity with overhydration to levulinic acid and formic acid.[68,69] In our case, the water content has a beneficial effect on the yield while an excessive amount leads to lower efficiency due to the deactivation of the protons acting as catalyst in the medium. This is further suggested by the relative amounts of water and HMF, which in the case of 3.5% water content is equivalent to 2.5 moles of water per mole of HMF.

In order to further understand the role of water content on the stability of HMF and the rate of reaction, kinetic analysis was performed at two different water contents at higher temperature (100 °C).
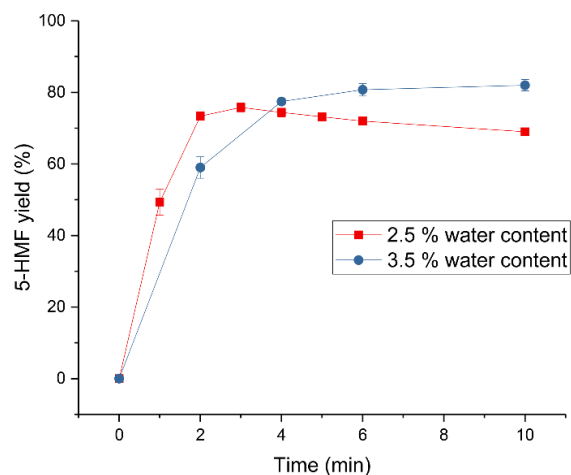
Figure 5. Effect of water content on the kinetics of HMF production from fructose in [bmim][OTf] at 100 °C, fructose loading = 10 %, catalyst loading = 10% (HCl).

The data in Figure 5 suggest that the water content contributes to both the stability of HMF and the kinetics of reaction. At 2.5% water content, the reaction was complete after 3 minutes, reaching a maximum of 76% followed by a gradual decrease in HMF yield of 6% by 10 minutes. In contrast, at 3.5% water content, the reaction achieves a steady state at 82% HMF yield. This trend suggests that water contributes to an increase in the yield of reaction by stabilising HMF towards self-condensation side reactions. Compared to the previous results (Figure), the yield at 3.5% water content was improved, suggesting that the yield was limited by some intermediates that did not undergo complete dehydration. In contrast, at lower water content, the instability of HMF in the system decreases the yield by the 10 minute time point, reaching a maximum of 75%. From these observations, it can be seen that the contribution of water is distinct from studies in which it exerts a favourable catalytic effect as proton bridge for the dehydration of glucose in DMSO/water mixtures,[70,71] or as a contaminant that leads to side reactions.[72] A consistent reduction in yield can be observed due to the side reaction between fructose and HMF (or the intermediates formed) and this mainly occurs in the initial stages, when the fructose and the intermediates are present in high concentration. This is supported by the following investigations on fructose loading.

Effect of fructose loading

The next step in the study was to analyse the effect of fructose loading on the HMF yield (Figure 6). This revealed that the yield of HMF seemed to be affected significantly by the substrate loading. At 90 °C, the yield decreases from 86% under very dilute conditions (2% fructose loading) to 72% at 14% loading. The decrease in yield can be traced to secondary reactions that arise from the instability of HMF and the reaction of HMF with fructose. To analyse this phenomenon, a kinetic study was conducted at 14% and 10% loading to determine whether an optimum set of conditions would emerge (Figure 6). At 90 °C, it was observed that even at 14% loading and 3.5% water content, HMF does not undergo any significant decomposition, reaching a plateau (the yield decreases by only 2% from 8 to 10 minutes). At 10% fructose loading, the HMF yield increases to 82% in 10 minutes, showing a

trend of increasing yield. The decrease in rate can be attributed to the increase in the amount of water in the reaction mixture, which lowers the activity of the protons present. The fact that the yield of HMF does not increase beyond 8 minutes at 14% fructose loading, in contrast to the slight yield increase with 10% loading, suggests that the kinetics of the side reactions are more rapid in the former case. Moreover, the plateau observed suggests that HMF is stable under these operating conditions, indicating that the major loss in yield is actually due to the reaction of HMF with fructose or the intermediates.
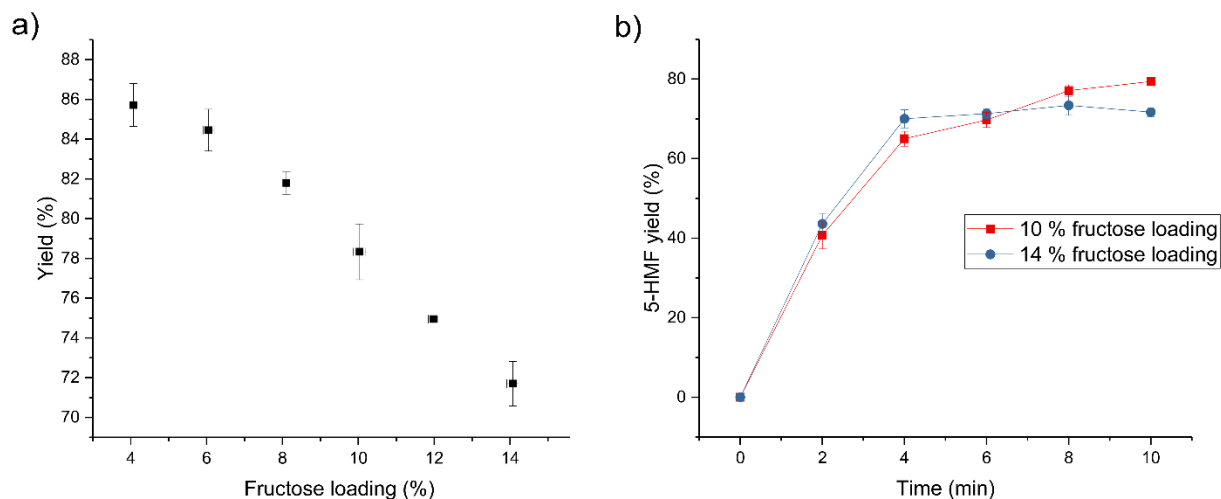
Figure 6. a) The HMF yield from fructose in [bmim][OTf], at different fructose loadings and b) kinetic analysis of the same reaction at two fructose loadings (right). Reaction conditions: T = 90 °C, 3.5% water content, t = 10 min, 10% HCl loading.

Effect of temperature

This can lead to the rate of reaction being increased remarkably but it can also favour side reactions. The optimisation for temperature was performed at 10% fructose loading, as shown in Figure 7.
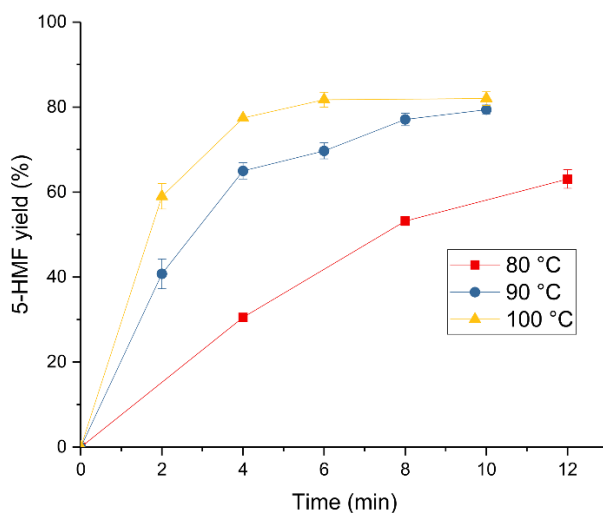
Figure 7. Effect of temperature on HMF yield from fructose in [bmim][OTf], 10% fructose loading, 10% HCl loading, 3.5% water content.

At 100 °C, the HMF yield reaches a steady state after 6 min at 81% with slight improvements compared to the result at 90 °C (79%), indicating that, at the lower temperature, the reaction is still limited by the dehydration of the intermediates. At 80 °C, it was observed that the reaction is limited not only by the conversion of intermediates but also by fructose dehydration. Higher temperatures were not analysed so as to avoid loss of water from the reaction mixture. According to these results, 100 °C is the optimal temperature for the reaction.

In order to improve the economics of the process, a kinetic analysis was carried out at 14% fructose loading at 100 °C (Figure 8). By increasing the temperature, it was possible to improve the yield from 72% to 81%, making the dehydration at high concentration a more feasible process from a techno-economic viewpoint.
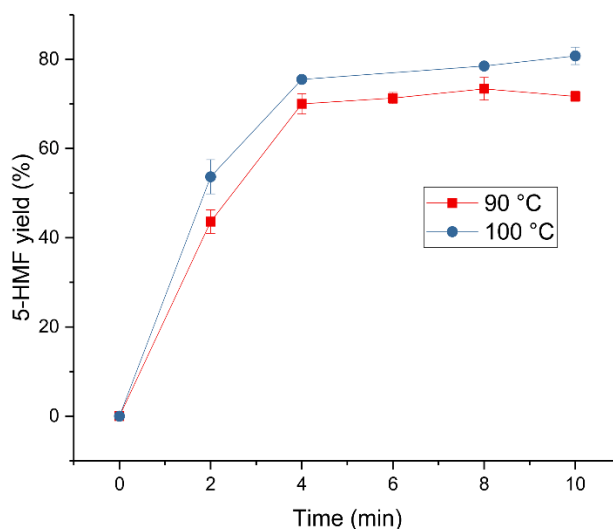
Figure 8. Kinetic analysis of the dehydration of fructose to HMF in [bmim][OTf] at two different temperatures and 14% fructose loading, 10% HCl loading, 3.5% water content.

Effect of the cation

According to a previous study,[64] the cation plays an important role in the dehydration of fructose at low temperature through the coordination between the protons of the cations and the hydroxyl groups of fructose. This effect was investigated by changing the cation of the ionic liquid solvent. The pyrrolidinium ionic liquid, [bmpyr][OTf], has a lower hydrogen donating ability compared to the imidazolium cation, according to their Kamlet-Taft parameters.[73] However, the results reported in Table 1 show no significant effect of the cation on HMF yield, suggesting that no interactions arise with the fructose molecule at higher temperatures.

Table 1. Effect of the cation on HMF yield from fructose in different ILs. Reaction conditions: 14% fructose loading, T = 100 °C, t = 10 min, 10% HCl loading, 3.5% water content.

Ionic Liquid	HMF yield (%)
[bmim][OTf]	80.8 ± 2.0
[emim][OTf]	77.4 ± 0.7
[bmpyr][OTf]	80.1 ± 0.5

Dehydration from glucose to HMF

Glucose represents a valuable feedstock for HMF synthesis since it is considerably cheaper than fructose. The dehydration of this sugar in [bmim][OTf] with HCl proved to be completely unselective, mainly due to the very low

solubility of glucose in [bmim][OTf] and the incompatibility of the Brønsted acid catalyst with the substrate. In order to improve the yield, CrCl$_3$·6H$_2$O was used as the catalyst and the solvent composition was modified with [bmim]Cl, thus increasing the solubility of glucose. Figure 9 shows the yield at different [bmim]Cl concentrations after 30 min at 10% glucose loading and 10 mol% catalyst loading. It can be seen that a minimum proportion of 10% [bmim]Cl is required to maintain the yield of HMF above 50%. In order to improve the yield, the solvent composition was varied while maintaining a 3.5% water content, but an improvement in yield of only 5% was achieved. While water can improve the dehydration of fructose in non-coordinating ionic liquids, the same is not true for glucose.
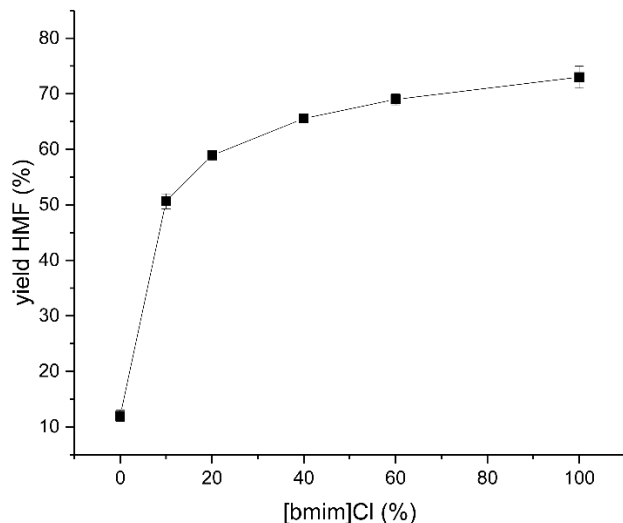
Figure 9. Glucose dehydration to HMF at 120 °C in [bmim][OTf]/[bmim]Cl mixtures using CrCl$_3$·6H$_2$O (10 mol% loading with 10% glucose loading.

Extraction of HMF from the ionic liquid

While there are many reports of catalysis in non-coordinating ionic liquids, the ability to isolate HMF from media such as [bmim][OTf] is also an important factor in the use of these systems. This is facilitated by the lack of hydrogen bonding between the hydroxyl group and the solvent, favouring the partitioning of HMF towards the extracting solvent. In order to analyse the effect of a coordinating environment on the partition coefficient, the extraction of HMF by diethyl ether was performed from mixtures with varying proportions of [bmim]Cl. Figure 10 shows a remarkably negative impact of chloride anions on the partition coefficient, even at low concentrations. This illustrates the impracticality of extracting HMF from chloride-based ionic liquid media. In contrast, in the absence of chloride anions, the partition coefficient increases by an order of magnitude, facilitating the extraction into the organic phase.
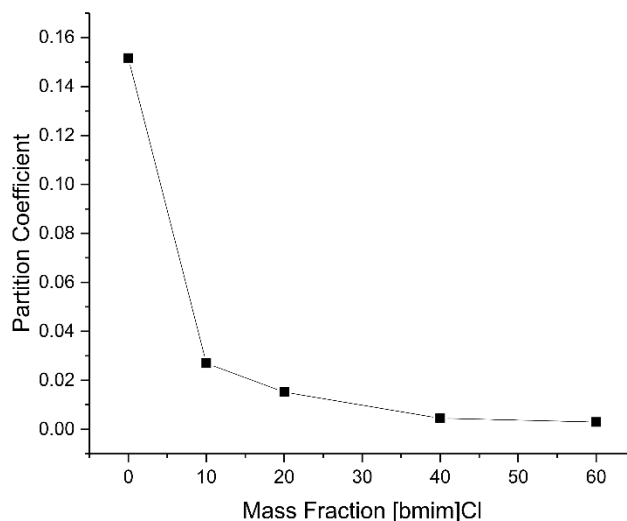
Figure 10. Partition coefficient of HMF in diethyl ether and ionic liquid mixtures with different chloride concentrations.

By exploiting this feature, the isolation of HMF from this solvent was performed on a larger scale, using 1 g of ionic liquid and 14% fructose loading, giving 71% isolated yield of HMF (Figures S18-20 in the Supporting Information). The ionic liquid was extracted from the water phase using ethyl acetate as a light brown viscous liquid. Analysis by ^{1}H NMR spectroscopy and mass spectrometry showed no degradation of the ionic liquid (Figure S21-23 in the Supporting Information).

CONCLUSIONS

As far as we are aware, the results presented here represent the highest yields yet reported for the rapid dehydration of fructose in non-coordinating ionic liquids. It was demonstrated that high HMF yields (>80%) could be obtained at high fructose loading (14%) in a short reaction time (<10 min) making this reaction system very competitive. This is despite the widespread belief that non-coordinating ionic liquids are unsuitable reaction media for this transformation compared to halide-based ionic liquids (e.g. [bmim]Cl). We have shown that the water content is a key parameter for efficient dehydration, providing stability to the HMF product. The analysis presented here shows that the dehydration of fructose to HMF in non-coordinating ionic liquids is compromised by the instability of HMF in the (pure) ionic liquid under acidic conditions. However, this behaviour can be suppressed by regulating the amount of water present, stabilizing HMF towards self-condensation. By harnessing this approach we were able to achieve efficient dehydration without significant loss in yield due to the reaction of fructose with HMF in the initial stages. The overall reaction appears to be partially limited by the intermediates generated and their successful conversion to the desired HMF product. By increasing the temperature, it was possible to improve the yield of reaction by dehydrating all the intermediates present. Further research is underway in order to optimise the water content in the system and increase the fructose loading still further.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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For ToC use:

Rapid, High-Yield Fructose Dehydration to HMF in Mixtures of Water and the Non-Coordinating Ionic Liquid [bmim][OTf]

Amir Al Ghatta, James D. E. T. Wilton Ely* and Jason P. Hallett*
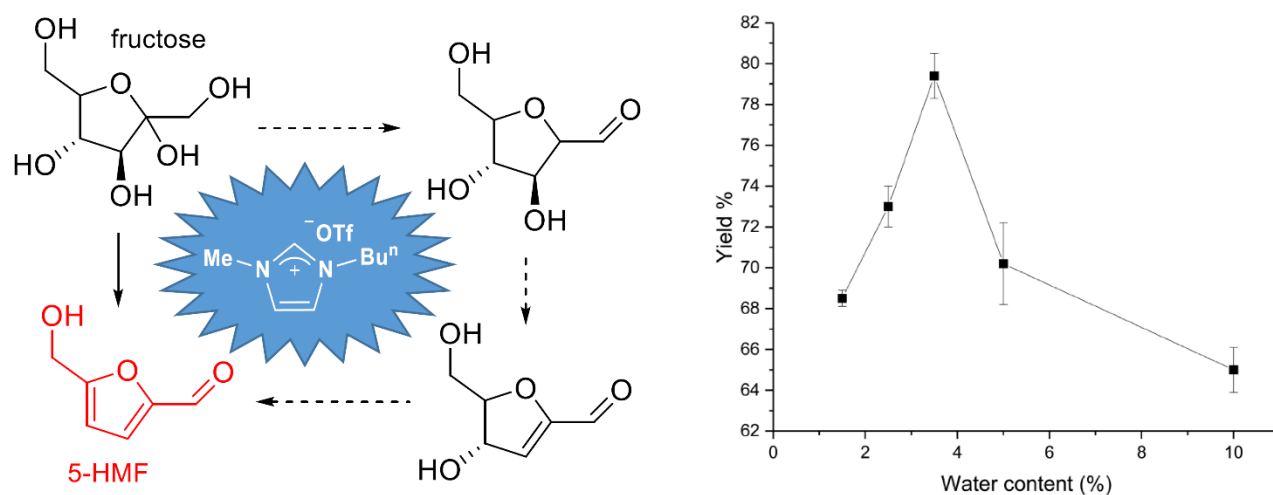
In contrast to literature reports, the non-coordinating ionic liquid [bmim][OTf] is an effective and versatile solvent for the high-yield dehydration of fructose to the platform chemical HMF over short reaction times. The study reveals that water content is an essential parameter and that judicious addition of water can increase the yield dramatically.

Rapid, High-Yield Fructose Dehydration to HMF in Mixtures of Water and the Non-Coordinating Ionic Liquid [bmim][OTf]

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S1. Ionic Liquid Characterisation: NMR spectra

Nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker 400 MHz spectrometers using deuterated DMSO as solvent. Mass spectrometry was performed using a Synapt G2 instrument (in positive mode).

S1.1 NMR spectra of [bmim]Cl
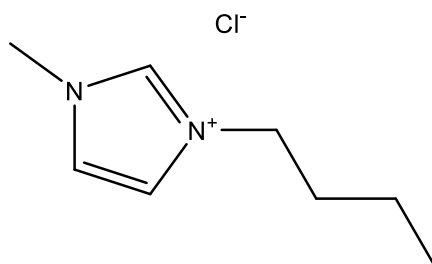
Figure S1. Structure of [bmim]Cl.
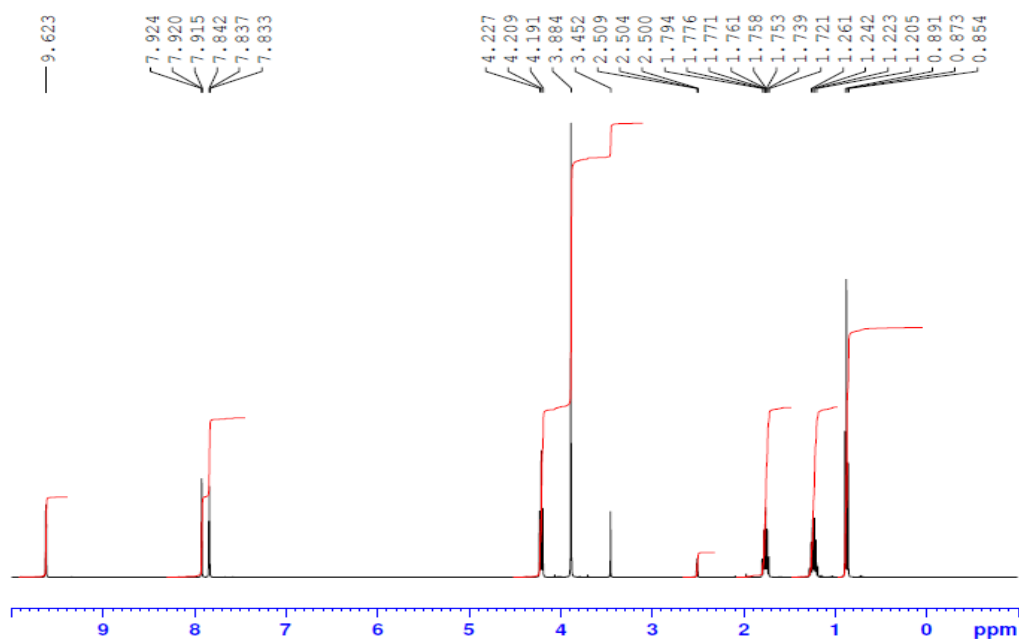
Figure S2. ^1H NMR spectrum of [bmim]Cl in deuterated DMSO.

^1H NMR (DMSO-d_6): δ 9.62 (s, 1H, N_2CH), 7.92, 7.84 (m x 2, 2 x 1H, 2 x N-CH), 4.20 (t, 2H, N-C$\underline{H}_2$-CH$_2$, J_{HH} = 7.2 Hz), 3.88 (s, 3H, N-CH$_3$), 1.77, 1.24 (m x 2, 2 x 2H, N-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH$_3$), 0.87 (t, 3H, -CH$_2$-C$\underline{H}_3$, J_{HH} = 7.3 Hz) ppm.
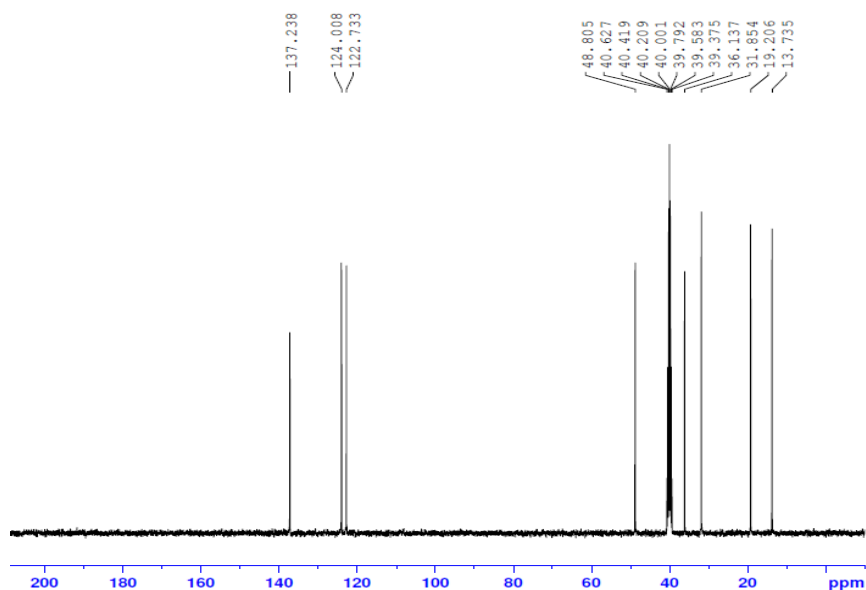
Figure S3. $^{13}C\{^1H\}$ NMR spectrum of [bmim]Cl in deuterated DMSO.

$^{13}C\{^1H\}$ NMR (DMSO-d$_6$): δ 137.2 (N$_2$-CH), 124.1, 122.7 (2 x N-CH), 48.8 (N-C̲H$_2$-CH$_2$-CH$_2$-CH$_3$), 36.14 (NCH$_3$), 31.8 (NCH$_2$C̲H$_2$CH$_2$CH$_3$), 19.2 (NCH$_2$-CH$_2$-C̲H$_2$-CH$_3$), 13.7 (N-(CH$_2$)$_2$-CH$_2$-C̲H$_3$) ppm.

  The characterisation data for [bmim]Cl were in good agreement with those reported in the literature.[S1]
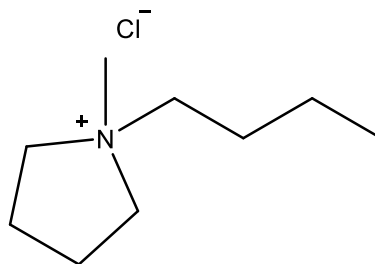
S1.2 NMR spectra of [bmpyr]Cl

Figure S4. Structure of [bmpyr]Cl.
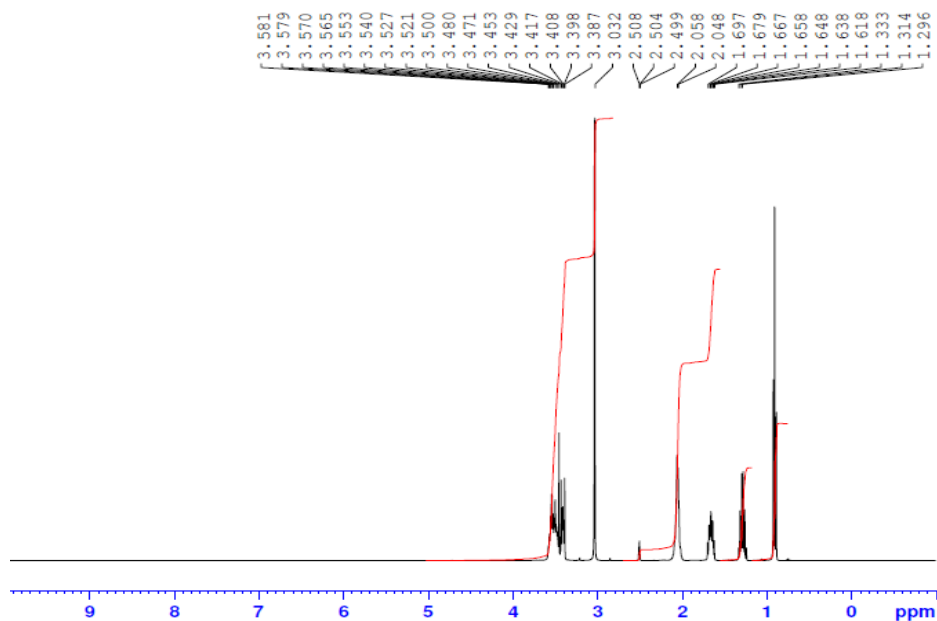
Figure S5. ^1H NMR spectrum of [bmpyr]Cl in deuterated DMSO.

^1H NMR (DMSO-d_6): 3.58-3.39 (m, 6H, 2,5-pyrrole-CH_2 and N-C$\underline{H}_2$-CH_2-CH_2-CH_3), 3.03 (s, 3H, N-CH_3), 2.02-2.05 (m, 2 x 2H, 3,4-pyrrole-CH_2), 1.65 (m, 2H, NCH$_2$C$\underline{H}_2$CH$_2$CH$_3$, J_{HH} = 7.2 Hz), 1.2 (m, 2H, NCH$_2$CH$_2$C$\underline{H}_2$CH$_3$, J_{HH} = 7.3 Hz), 0.86 (t, 3H, N-CH_2-CH_2-CH_2-C$\underline{H}_3$, J_{HH} = 7.3 Hz) ppm.
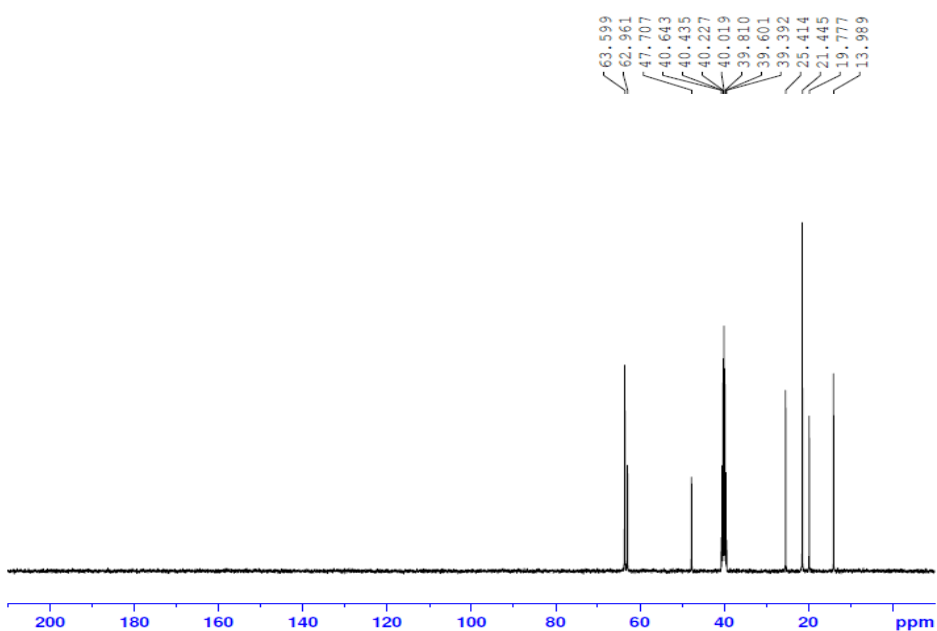
Figure S6. $^{13}C\{^1H\}$ NMR spectrum of [bmpyr]Cl in deuterated DMSO.

$^{13}C\{^1H\}$ NMR (DMSO-d_6): 63.7 (s, N-C$\underline{H}_2$-CH_2-), 63.0 (s, 2,5-pyrrole-CH_2), 47.6 (s, NCH_3), 25.4 (s, 3,4-pyrrole-CH_2), 21.4 (s, N-CH_2-C$\underline{H}_2$-CH_2-CH_3), 19.8 (s, N-$(CH_2)_2$-C$\underline{H}_2$-CH_3), 14.0 (s, N-$(CH_2)_3$-C$\underline{H}_3$) ppm.

The characterisation data for [bmpyr]Cl were in good agreement with those reported in the literature.[S2]
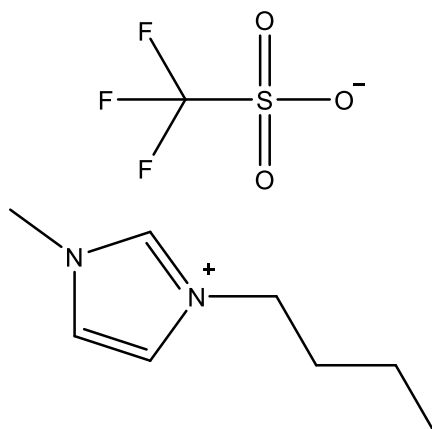
4

S1.3 NMR spectra of [bmim]OTf
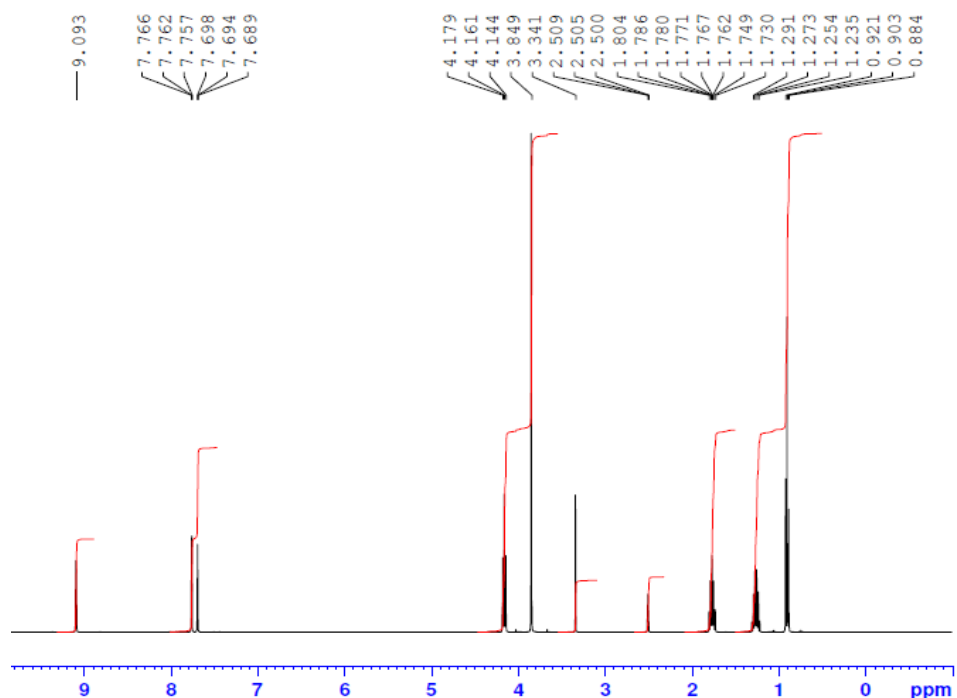

Figure 7. Structure of [bmim]OTf.

Figure S8. ^{1}H NMR spectrum of [bmim]OTf in deuterated DMSO.

^{1}H NMR (DMSO-d$_6$): δ 9.08 (s, 1H, N$_2$CH), 7.76-7.69- (m x 2, 2 x 1H, 2 x N-CH), 4.17 (t, 2H, N-C$\underline{H}_2$-CH$_2$, J_{HH} = 7.2 Hz), 3.85 (s, 3H, N-CH$_3$), 1.77- 1.26 (m x 2, 2 x 2H,N-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH$_3$), 0.9 (t, 3H, -CH$_2$-C$\underline{H}_3$, J_{HH} = 7.4 Hz) ppm.
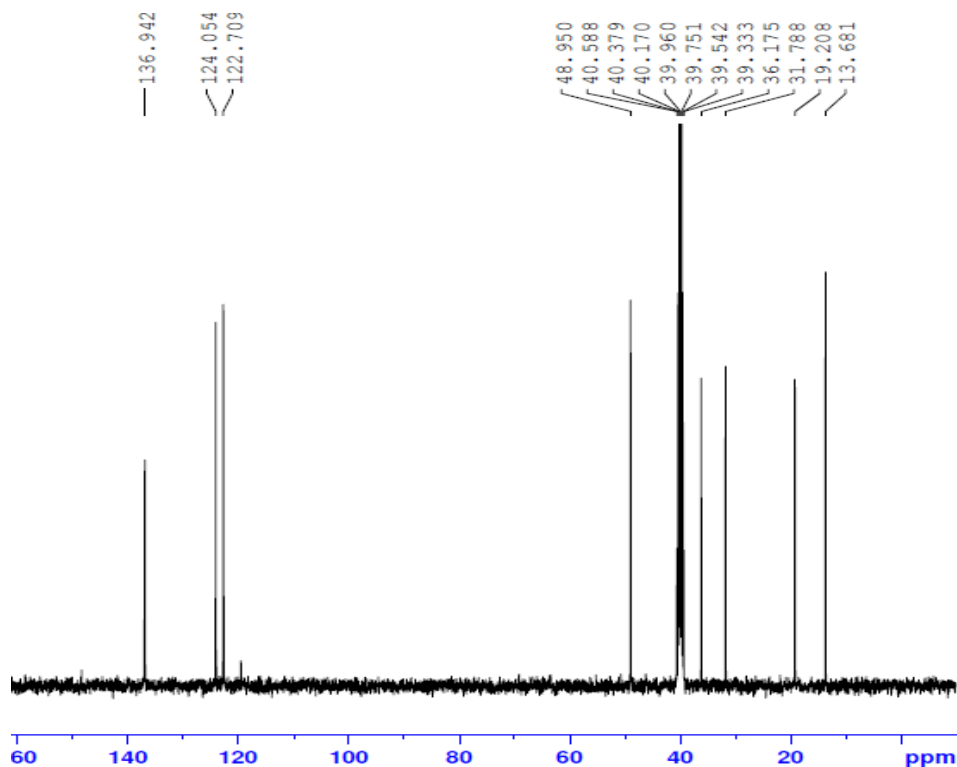
Figure S9. $^{13}C\{^1H\}$ NMR spectrum of [bmim]OTf in deuterated DMSO.

$^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 137.7 (N$_2$-CH), 123.6-122.4 (2 x N-CH),119.2 (CF$_3$), 49.1 (N-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 35.8 (NCH$_3$), 32.0 (NCH$_2$CH$_2$CH$_2$CH$_3$), 19.0 (NCH$_2$-CH$_2$-CH$_2$-CH$_3$), 13.8 (N-(CH$_2$)$_2$-CH$_2$-CH$_3$) ppm.

The characterisation data for [bmim]OTf were in good agreement with those reported in the literature.[S3]
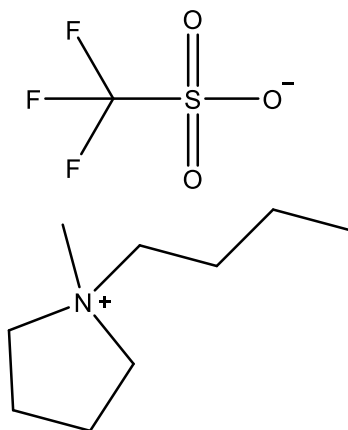

S1.4 NMR spectra of [bmpyr]OTf

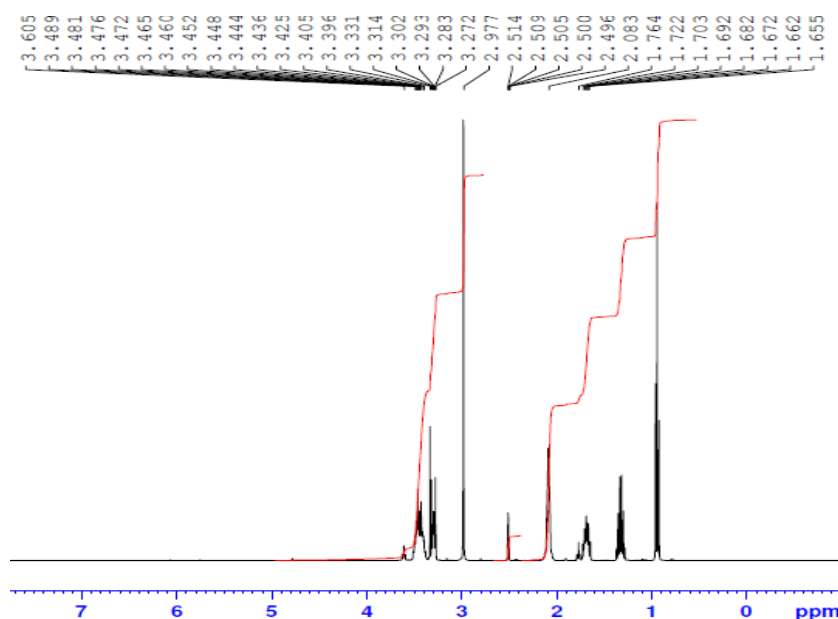*Figure S10. Structure of [bmpyr]OTf.*

Figure S11. ^1H NMR spectrum of [bmpyr]OTf in deuterated DMSO.

^1H NMR (DMSO-d_6): 3.51-3.26 (m, 6H, 2,5-pyrrole-CH_2 and N-C$\underline{H}_2$-CH_2-CH_2-CH_3), 2.98 (s, 3H, N-CH_3), 2.02-2.08 (m, 2 x 2H, 3,4-pyrrole-CH_2), 1.68 (m, 2H, NCH$_2$C$\underline{H}_2$CH$_2$CH$_3$, J_{HH} = 7.2 Hz), 1.32 (m, 2H, NCH$_2$CH$_2$C$\underline{H}_2$CH$_3$, J_{HH} = 7.3 Hz), 0.94 (t, 3H, N-CH_2-CH_2-CH_2-C$\underline{H}_3$, J_{HH} = 7.3 Hz) ppm.

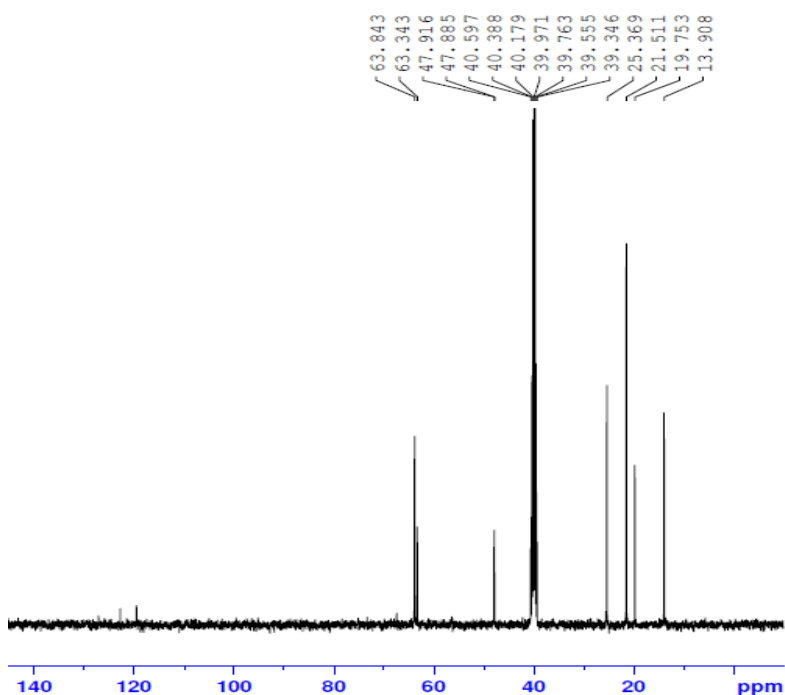*Figure S12. ^{13}C NMR spectrum of [bmpyr]OTf in deuterated DMSO.*

$^{13}C\{^1H\}$ NMR (DMSO-d_6): 119.4 (s,CF_3),63.9 (s, N-$\underline{C}H_2$-CH_2-), 63.3 (s, 2,5-pyrrole-CH_2), 47.8 (s, NCH_3), 25.2 (s, 3,4-pyrrole-CH_2), 21.5 (s, N-CH_2-$\underline{C}H_2$-CH_2-CH_3), 19.7 (s, N-$(CH_2)_2$-$\underline{C}H_2$-CH_3), 14.1 (s, N-$(CH_2)_3$-$\underline{C}H_3$) ppm.

The characterisation data for [bmpyr][OTf] were in good agreement with those reported in the literature.[S4]

S2. Ionic liquid characterisation: Mass spectra
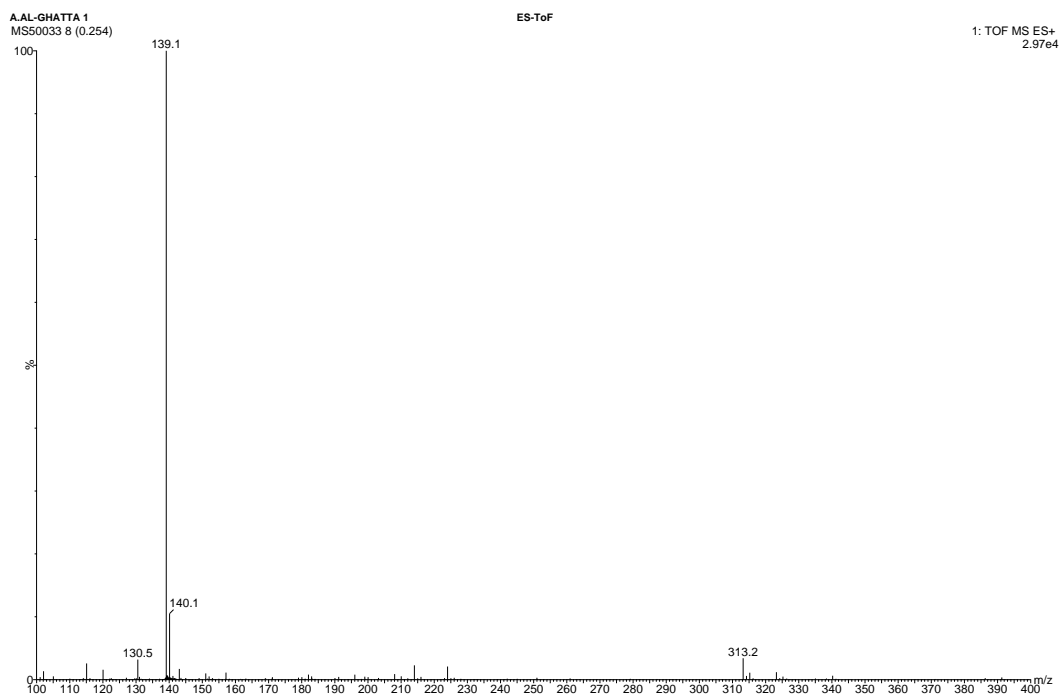
Figure S13. Mass spectrum of [bmim]Cl.
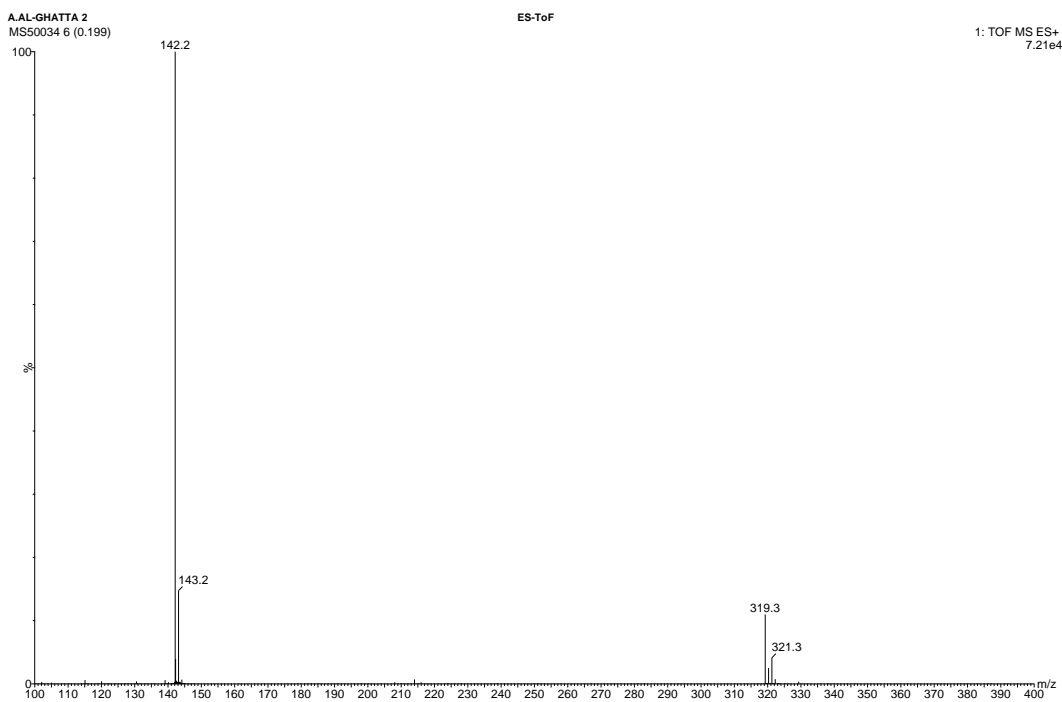
Figure S14. Mass spectrum of [bmpyr]Cl.

ES-ToF

1: TOF MS ES+
4.54e4

100

139.1

%

140.1

143.1

0
100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400   m/z
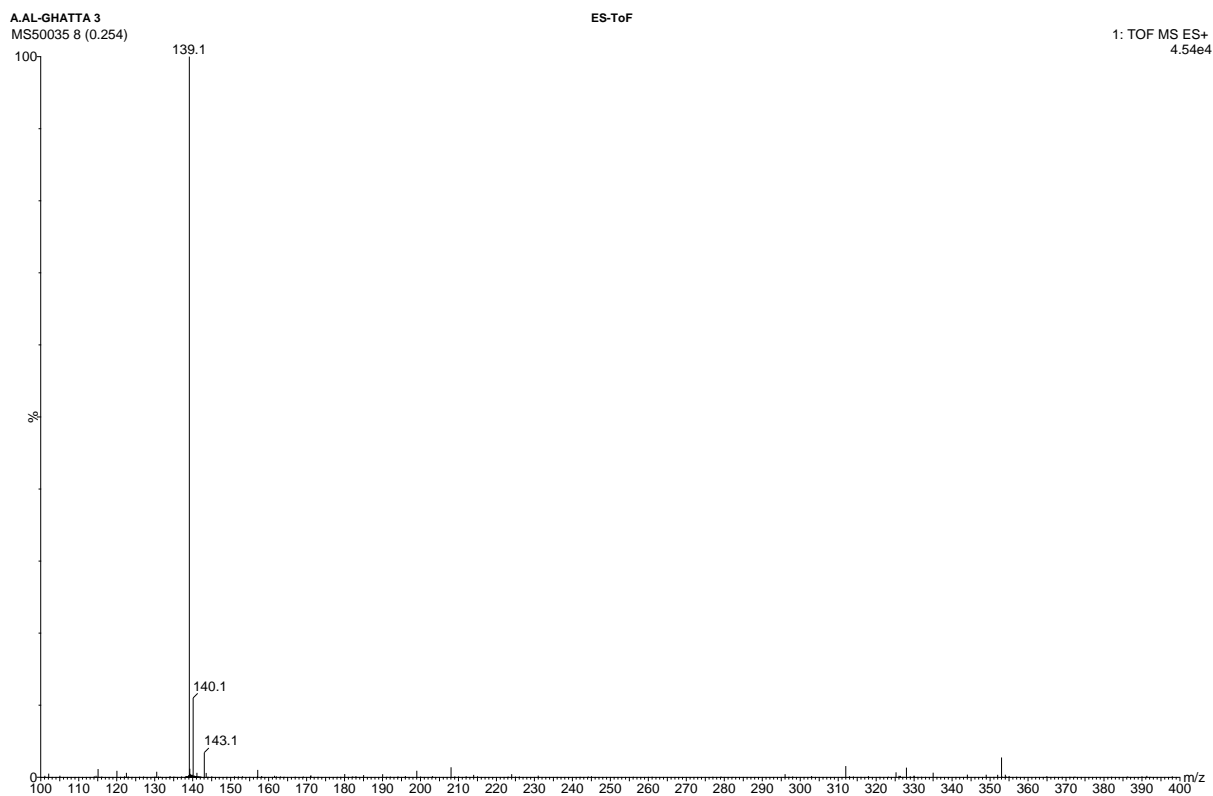
Figure S15. Mass spectrum of [bmim]OTf.

ES-ToF

1: TOF MS ES+
1.04e5

100

142.2

%

143.2

0
100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400   m/z
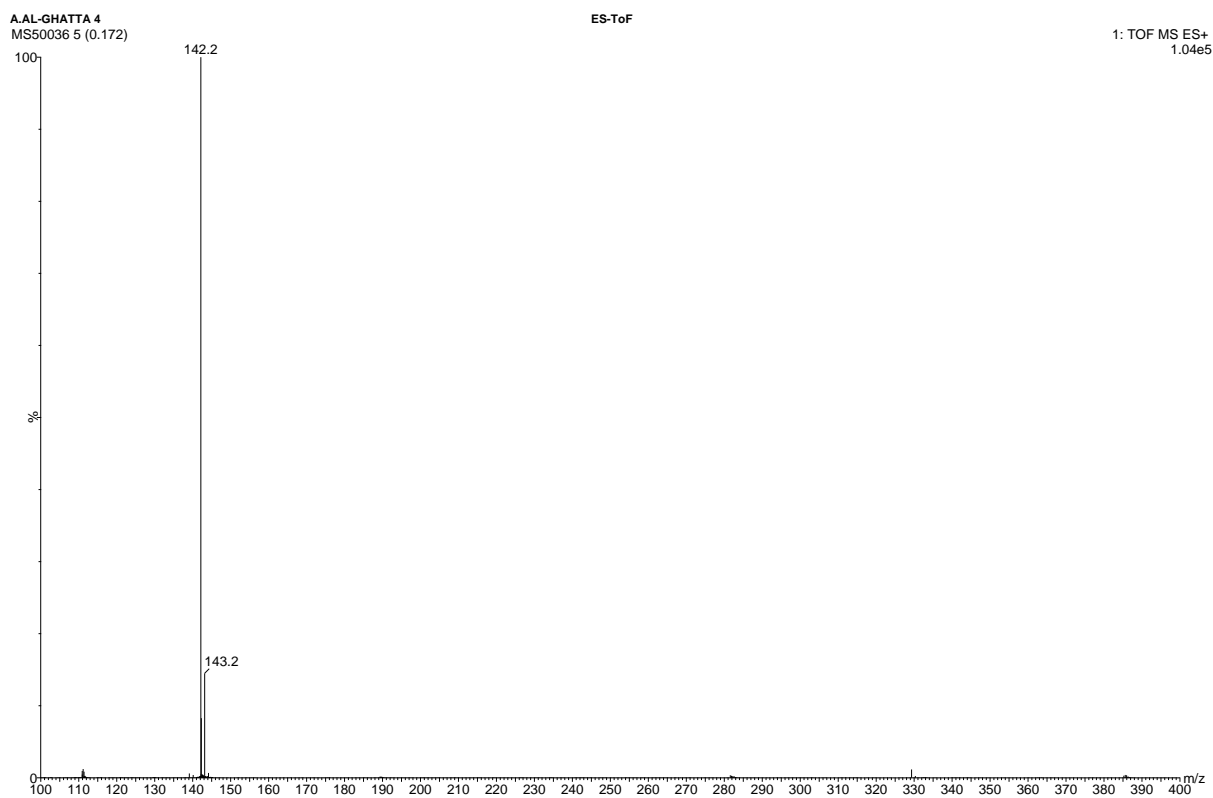
Figure S16. Mass spectrum of [bmpyr]OTf.

S3. HMF isolation and characterisation of used ionic liquid.
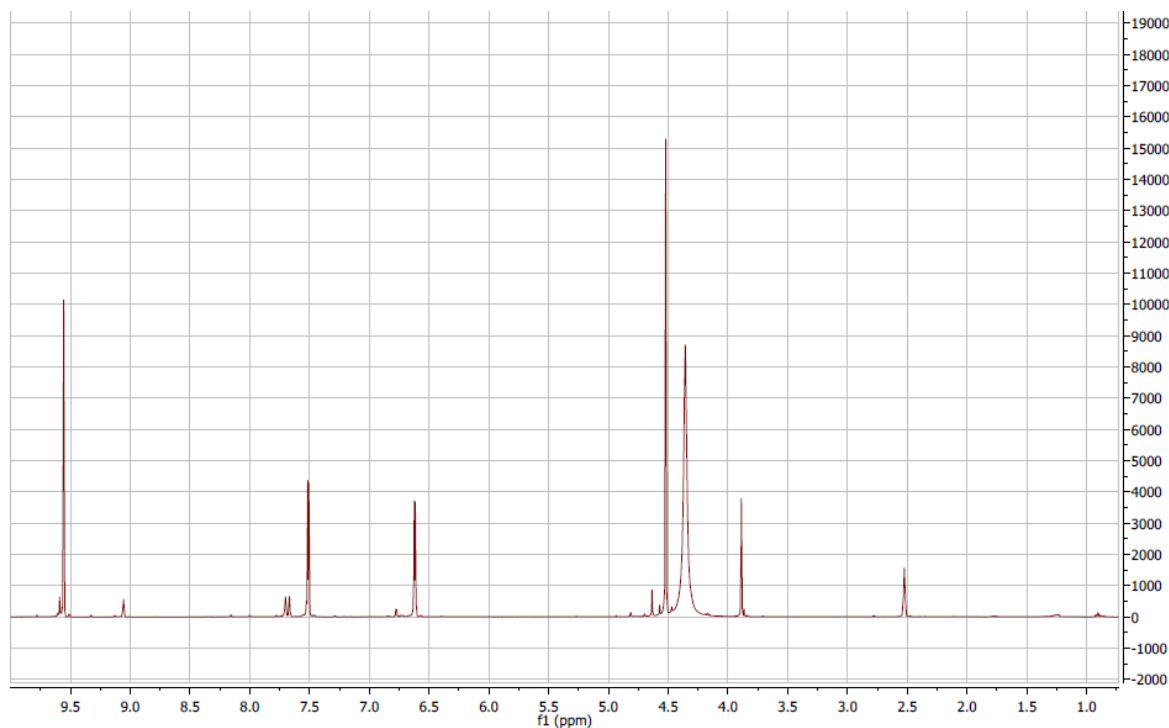
Figure S17. ^{1}H NMR spectrum of crude HMF product prior to washing with DCM.
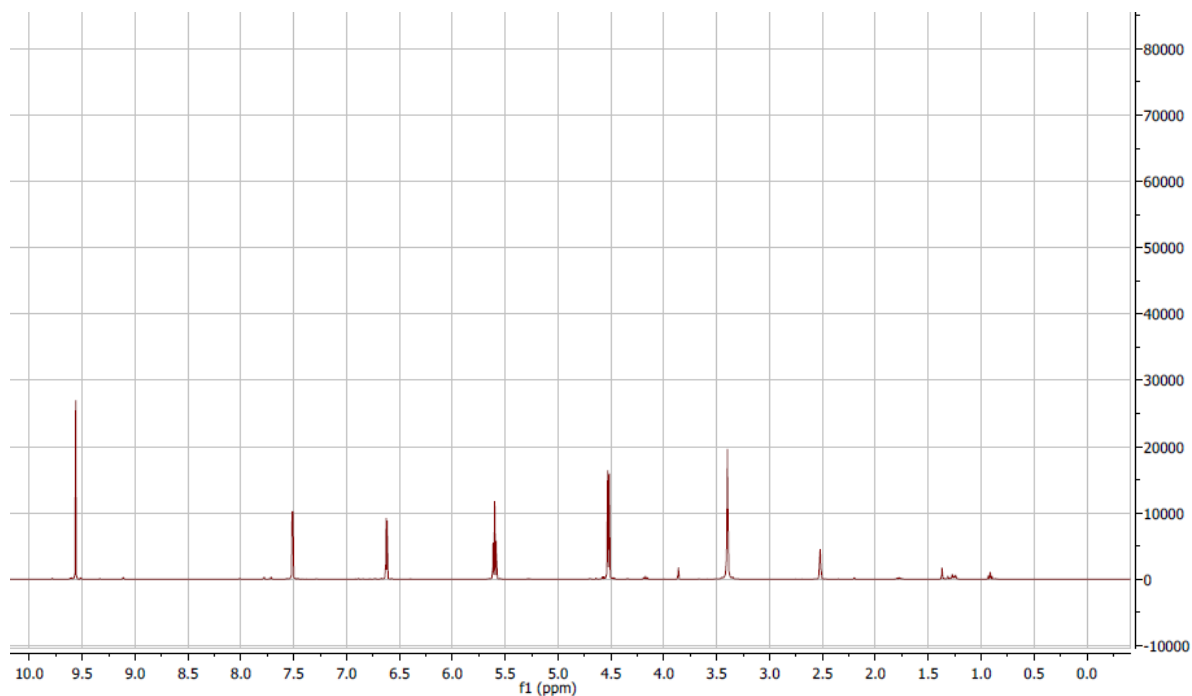
Figure S18. ^{1}H NMR spectrum of the purified HMF after DCM washing.
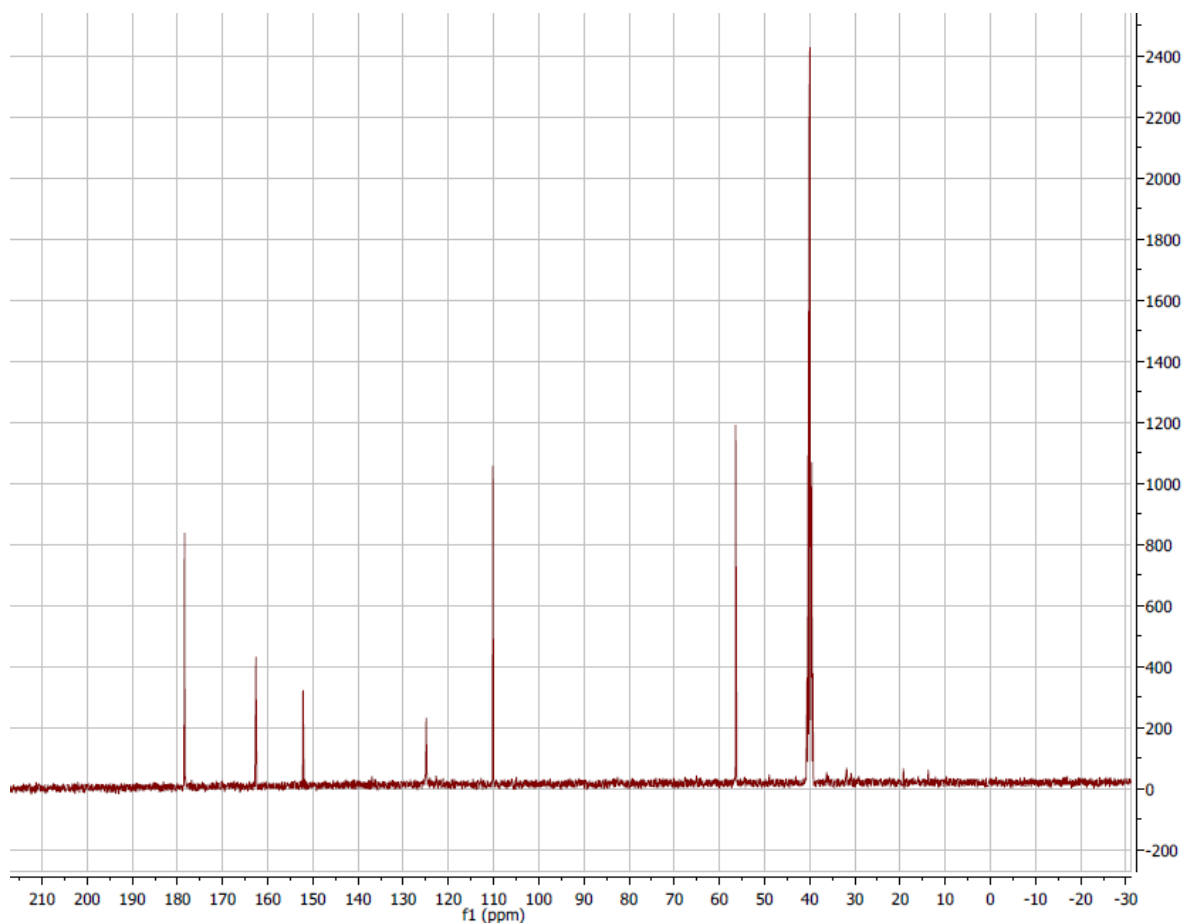
Figure S19. $^{13}C\{^{1}H\}$ NMR spectrum of the purified HMF after DCM washing.

^{1}H NMR (DMSO-d$_6$): 9.56 (s, 1H, O=C<u>H</u>), 7.51 (d, 1H, H-furan), 6.62 (s, 1h, H-furan), 5.60 (t, 1H, CH$_2$-O<u>H</u>), 4.52 (d, CH$_2$-O<u>H</u>) ppm.

$^{13}C\{^{1}H\}$ NMR (DMSO-d$_6$): δ 178 (s, O=C<u>H</u>), 161,151 (s, O-<u>C</u>-C furan),123,110 (s, C-furan), 57 (C-<u>C</u>-OH) ppm.
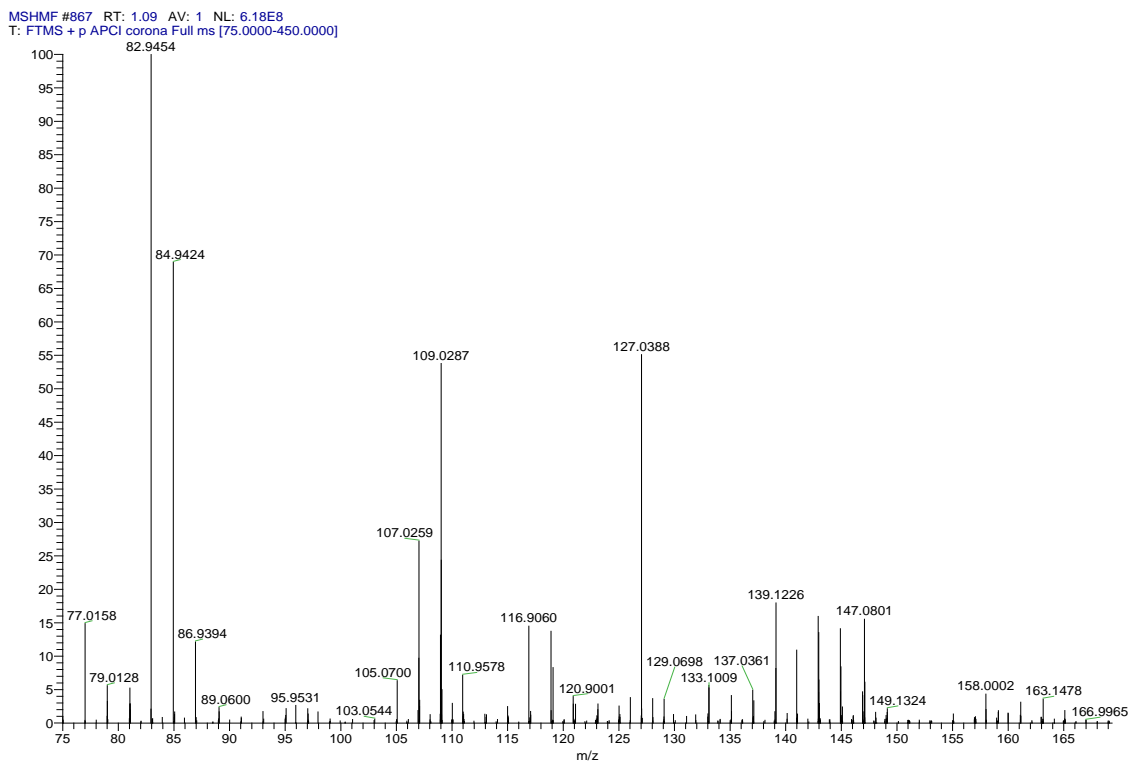
Figure S20. Mass spectrum of isolated HMF.

The data in the mass spectrum above agree well with those reported in literature.[S5,S6]
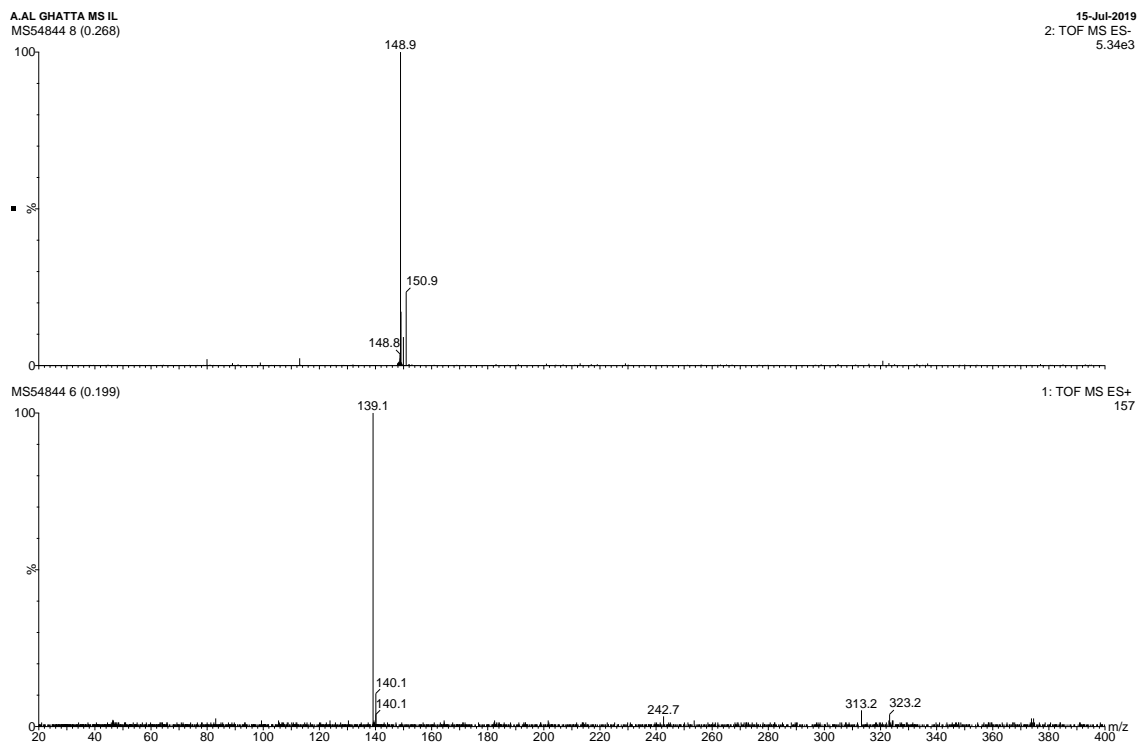
Figure S21. Mass spectra of used [bmim][OTf] in negative (above), positive (below) mode.
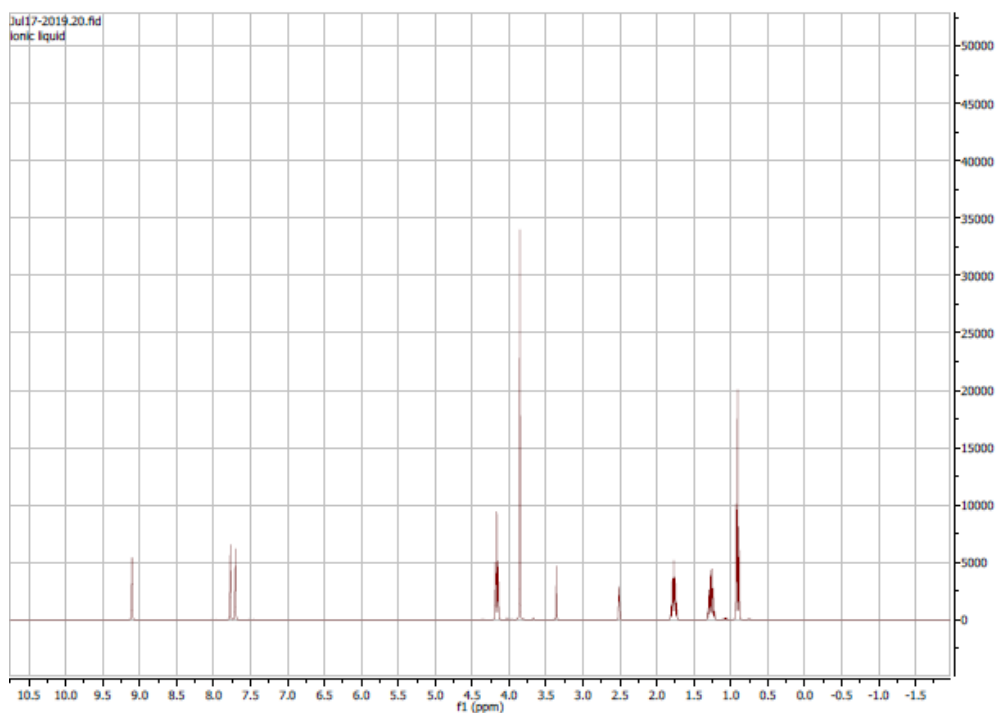
Figure S22. ¹H NMR spectrum of used [bmim][OTf].
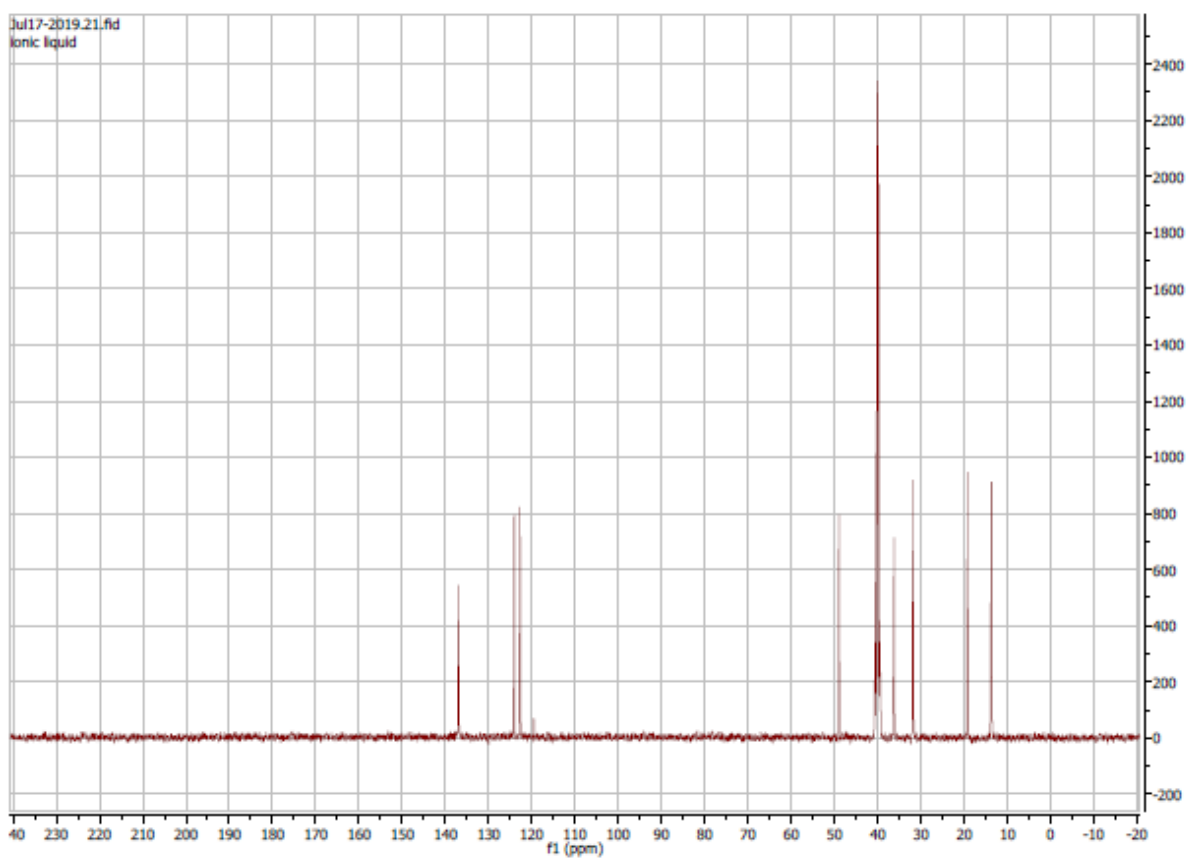
Figure S23. ¹³C{¹H} NMR spectrum of used [bmim][OTf].

S4. Numerical data

S4.1. Degradation of HMF at different water content

Table S1. Degradation of HMF at 90 °C in [bmim]OTf with different water content in 10 mol% p-toluenesulfonic acid (PTSA) loading (with respect to HMF) and 10% HMF loading (with respect to the ionic liquid).

| Water content (%)	Yield of HMF (%)	Standard deviation
0	43.3	0.1
0.73	32.5	1.8
1.32	20.3	1.8
2.50	14.6	2.6
5.00	14.0	2.6
7.50	14.0	0.0

S4.2. Data on acid selection

Table S2. Acid selection for fructose dehydration in [bmim]OTf. Fructose loading 14%, temperature 90 °C, initial water content 3.5%, acid catalyst loading 10 mol%, 10 min.

Acid	HMF yield (%)	Standard deviation
p-Toluenesulfonic acid (PTSA)	32.2	0.9
Sulfuric Acid	35.9	1.9
Hydrochloric Acid	71.7	1.1

S4.3 Effect of the water content on the yield of reaction

Table S3. Effect of water content on HMF yield from fructose in [bmim][OTf], fructose loading = 10%, T = 90 °C, t = 10 min. 10 % acid catalyst loading (HCl)

Time (min)	Yield of HMF (%)	Standard deviation
1.5	68.5	0.4
2.5	73	1
3.5	79.4	1.1
5	70.2	2
10	65	1.1
100	0	0

S4.4. Effect of the water content on the kinetic of the reaction

Table S4. Effect of water content on fructose dehydration to HMF in [bmim]OTf. Reaction conditions: T = 100 °C, fructose loading 10%, HCl catalyst 10 mol%, water content 2.5%

Time (min)	Yield of HMF (%)	Standard deviation
0	0	0
1	49.3	3.7
2	73.4	1.2
3	75.8	1.2
4	74.4	1.2
5	73.2	0.2
6	72.0	0.4
10	69.0	0.0

Table S5. Fructose dehydration to HMF in [bmim]OTf as a function of time. Reaction conditions: 100 °C, fructose loading 10%, HCl catalyst loading 10 mol%, water content 3.5%.

Time (min)	Yield of HMF (%)	Standard Deviation
0	0	0
2	59.0	3.0
4	77.5	0.1
6	80.8	1.8
10	82.0	1.6

S4.5. Effect of fructose loading and kinetic data

Table S6. Yield of HMF in [bmim]OTf at different fructose loadings, T = 90 °C, 3.5% water content, HCl acid catalyst loading 10 mol%, t = 10 min.

Fructose loading (%)	Standard deviation	Yield of HMF (%)	Standard deviation
4.1	0.1	85.7	1.1
6.1	0.2	84.5	1.1
8.1	0.0	84.5	1.1
10.0	0.2	78.3	1.4
12.0	0.1	75.0	0.1
14.1	0.2	71.7	1.1

Table S7. Yield of HMF from fructose in in [bmim]OTf against time, 90 °C, 3.5% water content, 10% fructose loading, HCl catalyst loading 10 mol%.

Time	Yield HMF (%)	Standard Deviation
0	0	0
2	40.8	3.5
4	65.0	1.9
6	69.7	1.9
8	77.1	1.5
10	79.4	1.1

Table S8. Yield of HMF from fructose in in [bmim]OTf against time. Reaction conditions: T = 90 °C, 3.5% water content, 14% fructose loading, HCl 10 mol% catalyst loading.

Time	Yield of HMF	Standard Deviation
0	0	0
2	43.6	2.6
4	70.0	2.3
6	71.3	1.3
8	73.4	2.5
10	71.7	1.1

Table S9. Fructose dehydration to HMF in [bmim]OTf. Reaction conditions: T = 80 °C, 3.5% water content, 14% fructose loading, 10 mol% HCl catalyst loading.

Time	Yield HMF	Standard Deviation
0	0	0
4	30.5	0.6
8	53.2	1.1
12	63.1	2.2

Table S10. Fructose dehydration to HMF in [bmim]OTf. Reaction conditions: T = 100 °C, 3.5% water content, 10% fructose loading, 10 mol% HCl catalyst loading.

Time	Yield of HMF	Standard Deviation
0	0	0
2	59.0	3.0
4	77.5	0.1
6	81.8	1.8
10	82.0	1.6

Table S11. Fructose dehydration to HMF in [bmim]OTf. Reaction conditions: T = 100 °C, 3.5% water content, 14% fructose loading, 10 mol% HCl catalyst loading.

Time	Yield HMF	Standard Deviation
0	0	0
2	53.7	3.8
4	75.5	0.4
6	78.5	0.7
10	80.8	2.0

Table S12 Glucose dehydration to HMF in [bmim][OTf]/ [bmim]Cl mixture using $CrCl_3 6H_2O$ (10 % loading), 10 % glucose loading, 120 °C

[bmim]Cl content	Yield HMF	Standard Deviation
0	12.0	1.1
10	50.7	1.4
20	58.9	0.5
40	65.6	0.6
60	69.0	1.0
100	73.0	2.0

Table S13 Partition coefficient HMF in diethyl ether and ionic liquid mixture.

[bmim]Cl concentration (%)	K
0	0.15
10	2.7×10^{-2}
20	1.5×10^{-2}
40	0.45×10^{-2}
60	0.3×10^{-2}

S5. References

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