Green Chemistry

Renewable pyridinium ionic liquids from the continuous hydrothermal decarboxylation of furfural-amino acid derived pyridinium zwitterions†

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Fully renewable pyridinium ionic liquids were synthesised *via* the hydrothermal decarboxylation of pyridinium zwitterions derived from furfural and amino acids in flow. The functionality of the resulting ionic liquid (IL) can be tuned by choice of different amino acids as well as different natural carboxylic acids as the counterions. A representative member of this new class of ionic liquids was successfully used for the synthesis of ionogels and as a solvent for the Heck coupling.

The development of new methodologies for the synthesis of fine chemicals on the basis of renewable resources is a unique opportunity to increase the sustainability of modern chemistry. In recent years, lignocellulosic biomass has been identified as a promising source of building blocks and platform chemicals, including small carboxylic acids and alcohols, as well as 5-hydroxymethylfurfural and its oxidised version, furandicarboxylic acid.[1] N-heterocycles are a versatile class of molecules which find application as building blocks in the synthesis of many different types of compounds. However, the synthesis of nitrogen-containing heterocycles from lignocellulosic biomass remains elusive due to the lack of nitrogen in this resource. Complementing lignocellulose-derived molecules with other renewable N-containing precursors can sensibly increase the chemical space accessible in a sustainable manner. In this regard, amino acids have been evoked as an interesting candidate.[2]

Amino acids are a rich class of renewable amine containing compounds, which provide enantiomerically pure molecules with diverse properties, due to their different side chains. Specific amino acids can be produced by fermentation,[3] while huge amounts of protein waste, such as feathers from the

poultry industry,[4] are untapped resources to be utilised as soon as efficient separation protocols will be developed.[2]

Many nitrogen heterocycles, most notably imidazole and pyridine, can be converted into ionic liquids by quaternisation. Ionic liquids (ILs) have received a lot of attention for their application as green solvents,[5] electrolytes,[6] gas absorbents[7] and more, due to properties including very low vapour pressure and high thermal and chemical stabilities. Despite such desirable properties, widespread application of ILs is still hindered by a relatively high production cost. From a sustainability standpoint, moreover, the generation of ionic liquids on the basis of renewable resources should be addressed.

We recently reported a green synthesis of ionic liquids *via* the hydrothermal decarboxylation of imidazolium zwitterions (ImZw)[8] in which the nitrogens are obtained from amino acids and the carbons from carbohydrate-derivable synthons (Fig. 1). These compounds could be decarboxylated in superheated water in the presence of acetic acid or salt to give ionic liquids. The decarboxylation of free amino acids is still difficult and
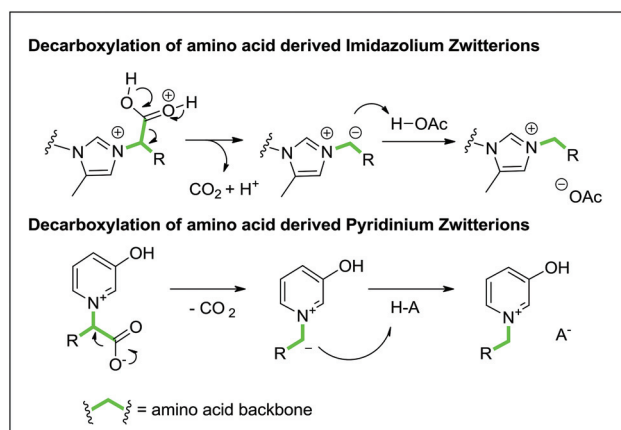

Fig. 1 Proposed decarboxylation mechanism for amino acid derived imidazolium and pyridinium zwitterions.

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requires a high energy input in combination with catalysts. The catalysts employed for the chemical decarboxylation of amino acids generally contain conjugated carbonyl groups that react with the amino acid to form an imine,[9] as in the case of the terpenoid carvone,[10] while nature employs the cofactor pyridoxal-5-phosphate (PLP) present in decarboxylase enzymes. In the latter case, the amino acid binds to the aldehyde group of PLP forming an imine, which in this case is conjugated to the pyridinium ring of PLP. The ring works as an electron sink facilitating decarboxylation at physiological temperature via the formation of a "quinonoid" intermediate.[11]

In our previous work, we demonstrated that the imidazolium ring contained in amino acid derived zwitterions exerts a catalytic effect promoting the decarboxylation of the α-amino acid side chain. Interestingly, the β-alanine derived compound could not be decarboxylated under those conditions, suggesting that the mechanism of decarboxylation may involve the formation of an intermediate ylide species in which the developing carbanion is stabilised by the charge on the aromatic ring system.
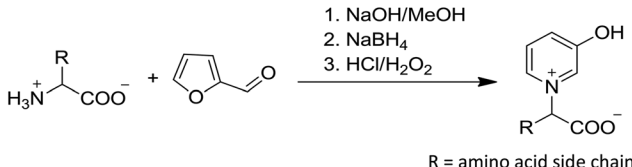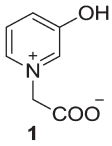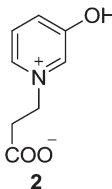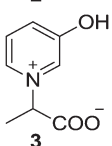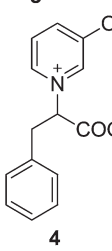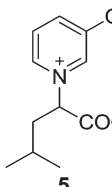
The conditions for hydrothermal decarboxylation are essentially green, since they are based on the use of water as reaction medium, do not require reagents to be used in excess and incorporate the catalytic auxiliary in the final product, bypassing the need for catalyst separation and recycling. In principle, such methodology should be applicable for other aromatic nitrogen heterocycles derived from α-amino acids, in which the ring system is in the alpha position with respect to the carboxylic group. In this way, new classes of renewable ILs with different cations could be accessed, in which the quaternary nitrogen substitution is obtained via amino acid decarboxylation rather than traditional quaternisation with alkylating agents. In this work, a group of fully renewable pyridinium ILs derived from furfural and amino acids was prepared by means of hydrothermal decarboxylation of the corresponding pyridinium zwitterions.

Furfural is one of the longer established biomass-derived chemicals. Discovered in 1821 by Doebereiner as a side product from the distillation of dead ants,[12] soon it was found that it could be produced from various crop residues via the acid-catalysed depolymerisation of hemicellulose and subsequent dehydration of xylose. Industrial production of furfural was started by the Quaker Oats company in 1921,[13] and with the development of lignocellulosic biorefineries it can be expected to be produced at high volume and lower cost in the near future.[14]

It is known that furfurylamines can be converted into 3-hydroxy-pyridines under oxidative conditions,[15] and these compounds are recognised as important intermediates in the production of fine chemicals such as pesticides and pyridostigmine type cholinergic drugs. Alapyridaine, a flavor enhancing compound which forms during the Maillard reaction between glucose and the amino acid alanine, was synthesised from 5-hydroxymethyl furfural (HMF) and alanine, following a similar synthetic route,[16] which was later extended to include other amino acids.[17] We decided to investigate the decarboxy-

lation of pyridinium zwitterions (PyrZw) derived from the reductive amination of furfural with different amino acids, followed by oxidation to the corresponding 3-pyridinol carboxylate. For this purpose we synthesised a small library of pyridinium zwitterions from different amino acids (Table 1). While the optimisation of this synthetic route (Fig. 2) was not the goal of this work, we modified the reported synthetic strategies in such a way that all reaction steps could be performed in one-pot, in order to minimise the use of quenching reagents and solvents for purification.

Table 1 Pyridinium zwitterions synthesised from amino acids and furfural

Entry	Amino acid	Product	Yield[a] [%]
1	Gly	**1**	78.0
2	β-Ala	**2**	71.9
3	Ala	**3**	93.8
4	Phe	**4**	55.4
5	Leu	**5**	100

Reaction conditions: (1) 1 eq. amino acid, 1 eq. NaOH, 1 eq. furfural, 60 °C, 30 min, (2) 1.05 eq. NaBH$_4$, MeOH, 0 °C, 1 h, (3) 3 M HCl, 2 eq. H$_2$O$_2$, 100 °C, 30 min. [a] Yield determined by NMR using 2-methyl imidazole as an internal standard.
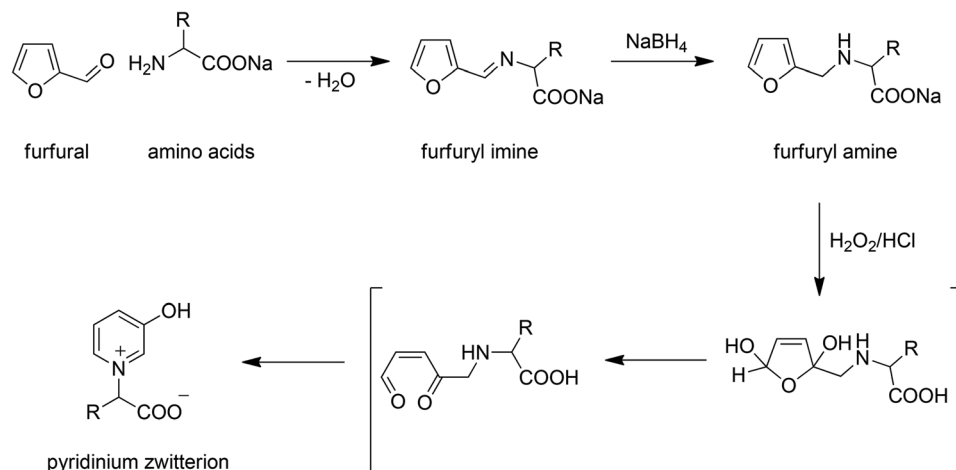
Fig. 2 Synthetic route for the pyridinium zwitterions from furfural and amino acids.

Briefly, in this one-pot synthesis the sodium salt of the amino acid was formed by reaction with NaOH, followed by addition of furfural, to generate the corresponding furfurylimine (after solvent removal). The imine was reduced to the furfurylamine using sodium borohydride and then converted to the pyridinium zwitterion by oxidation with hydrogen peroxide in HCl (Fig. 2). The reduction step can be optimised for a more sustainable protocol, for example by using a heterogeneous metal catalyst and hydrogen gas. The selective reduction of furfurylimines and related compounds is currently being investigated in our group, but was out of the scope of the current work. Using the method described above, a small library of pyridinium zwitterions could be produced, in which the polarity of each compound is modulated by the different amino acid side chains.

Employing our continuous hydrothermal decarboxylation strategy, all PyrZw derived from alpha amino acids were decarboxylated affording the desired pyridinium IL in high yields. Results are shown in Table 2. Interestingly, the optimum temperature for this reaction was found to be around 250 °C, ca. 50 °C lower than for the imidazolium compounds reported earlier. This is probably the result of a larger stabilising effect of the pyridinium ring compared to the imidazolium one, combined with the fact that a single decarboxylation event has to occur to generate the product, unlike in the case of imidazolium zwitterions. As in the case of ImZw, the reactions could be completed within remarkably short times (4 min) and the beta-alanine derived compound **2** did not form the decarboxylated product, indicating again that the ring stabilisation is effective only for α-substituted carboxylic groups as described in Fig. 1.

In this work we focused on hydrophobic amino acids to generate ionic liquids with the typical alkyl chains, as well as the aromatic phenylalanine. In fact, all hydrophobic amino acid derived compounds gave high yields, whereas the glycine-derived compound **6** formed in a slightly lower yield of 68.8%. The decarboxylated compounds were analysed by DSC and all showed glass transition temperatures (T_gs) below room temperature, with the T_g decreasing for increasing alkyl chain length, in the case of acetate counterion. The T_g for the phenylalanine derived compound **8** was the highest at −7.6 °C among all acetates.

In our previous work we demonstrated the decarboxylation of different compounds using acetic acid, or alternatively NaCl as another source of counterion. Here we wanted to expand on the use of different acids as counterions. Leucine-derived pyridinium **5** was chosen for these experiments due to the fact that its acetate salt has the lowest T_g and, due to the longest alkyl chain, it can be expected to be characterised by the lowest viscosity also in presence of different counterions. In theory, the decarboxylation method should be compatible with any medium strength acid that does not corrode the reactor coil at the used temperatures or degrades the PyrZw. To demonstrate the scope of this method we chose two non-toxic carboxylic acids which are available from biomass, namely L-lactic acid and succinic acid. For lactic acid and succinic acid the reaction conditions were optimal using stoichiometric amounts of PyrZw and acid. The results are shown in entries 5 and 6 of Table 2.

Also with these acids the decarboxylation yields were very high. DSC analysis showed slightly higher T_gs compared to the corresponding acetate IL, probably due to increased hydrogen bonding of the anions. Therefore, all in all the hydrothermal decarboxylation strategy could be successfully transferred to renewable pyridinium zwitterions and extended to other acids as the source of counterions.

Noteworthily, the price of the ILs synthesised in this way is quite competitive. Simply using the prices for the reagents (furfural, amino acids, NaBH₄, etc.) from the Sigma Aldrich catalogue, we calculated the price for IL **9** to come to around £ 1000 per kg. With the optimisation of the reduction reaction and the availability of cheaper amino acids the price is expected to be much lower in the future. The purity of the ILs generated by this method is generally ≥97% (see ESI†). This is well within the range of commercially available pyridinium ILs, which range from 97% (Sigma) to 99% from specialist suppliers.

Table 2 Pyridinium ionic liquids synthesised *via* hydrothermal decarboxylation of zwitterions

R = amino acid side chain

Entry	Product	Yield[a] [%]	T_g [°C]
1	**6**	68.8	−13.0
2	**7**	91.0	−18.9
3	**8**	81.0	−7.6
4	**9**	80.7	−32.0
5	**10**	84.0	−6.0
6	**11**	82.4	−11.7

Reaction conditions: entries 1, 2 and 4: 0.1 M pyridinium zwitterion in water, 2 eq. HOAc, 250 °C, 120 bar, 4 min residence time, entry 3: 0.05 M, 4 eq. HOAc, 50 : 50 H_2O : EtOH, 200 °C, 100 bar, 4 min. Entries 5 and 6: 1 eq. acid, 250 °C, 120 bar, 4 min. [a] Isolated yield reported as the average of two reactions.

At this stage, we decided to illustrate the usefulness of our new sustainable ILs as a test case for the production of iono-gels (IGs). This rather new class of multifunctional hybrid materials is based on the incorporation of an IL into a polymeric or inorganic matrix. The resulting IG combines the properties of the IL such as catalytic activity, electrochemical addressability and color change upon action of external stimuli, with the properties of the matrix, such as mechanical properties for example. As a result, IGs have been used or suggested for a wide variety of applications.[18] Recently, the electrospinning of ionogels has also attracted increasing attention due to the fact that electrospinning provides a fairly simple way to achieve surface modification.[19]

The preparation of IGs requires moderate to large quantities of ILs to be available. In order to challenge the robustness of our methodology for the production of sustainable pyridinium ILs, production of **9** was scaled up by injecting a solution of **5** (0.09 M) into the microreactor running continuously for 420 min, which produced 6.8 g of compound. Then, **9** was employed in combination with poly(methyl methacrylate) (PMMA) for ionogel production *via* solution casting using acetone as the solvent.

Fig. 3A shows the full IR spectrum of an ionogel along with the spectrum of the PMMA used as the matrix. Spectra of pure PMMA show a strong band at 1730 cm^{-1} from the PMMA carbonyl group. The bands at 2950, 2925, 1434, 1238, 958, 838, and 746 cm^{-1} are assigned to aliphatic C–H vibrations. The bands at 1270, 1140, and 983 cm^{-1} are assigned to C–O–C stretching vibrations of PMMA. The IR spectrum of the ionogel is dominated by the absorption bands of the PMMA matrix. The fact that this band does not shift when the IL is incorporated into the PMMA matrix suggests that the interaction between the IL and the PMMA is either rather weak or does not primarily occur through interaction *via* the PMMA carbonyl groups. This is consistent with previous literature.[20,21]

DSC curves only show one glass transition at *ca.* 80–82 °C, in agreement with earlier work based on traditional ILs[20] (Fig. 3C). The T_g is lower than the T_g of the pure PMMA at *ca.* 103 °C, but is much higher than the T_g of IL **9** at −32 °C. This indicates that the mixing between the IL and the PMMA is homogeneous, as otherwise two glass transitions would have been observed (IL and PMMA).

In terms of application potential, ionogels have been proposed for many different fields. Among others, surface modification – by way of the different chemical composition of the ILs available today – is interesting for many areas such as medicine, engineering, or construction. We have thus evaluated the wetting of our ionogel. Indeed, the addition of IL **9** to the PMMA lowers the static contact angle by *ca.* 20°. In principle, proper selection of the IL, whose polarity can be now tuned by changing the amino acid, will enable the formation of surfaces with a tailored wetting behaviour from quite hydrophilic to rather hydrophobic. Such surfaces are interesting for microfluidic applications, where controlled wetting and dewetting is in some cases necessary to ensure proper function of the device. The potential of the ILs prepared in this study for controlled surface modification will be explored in more detail in forthcoming work.
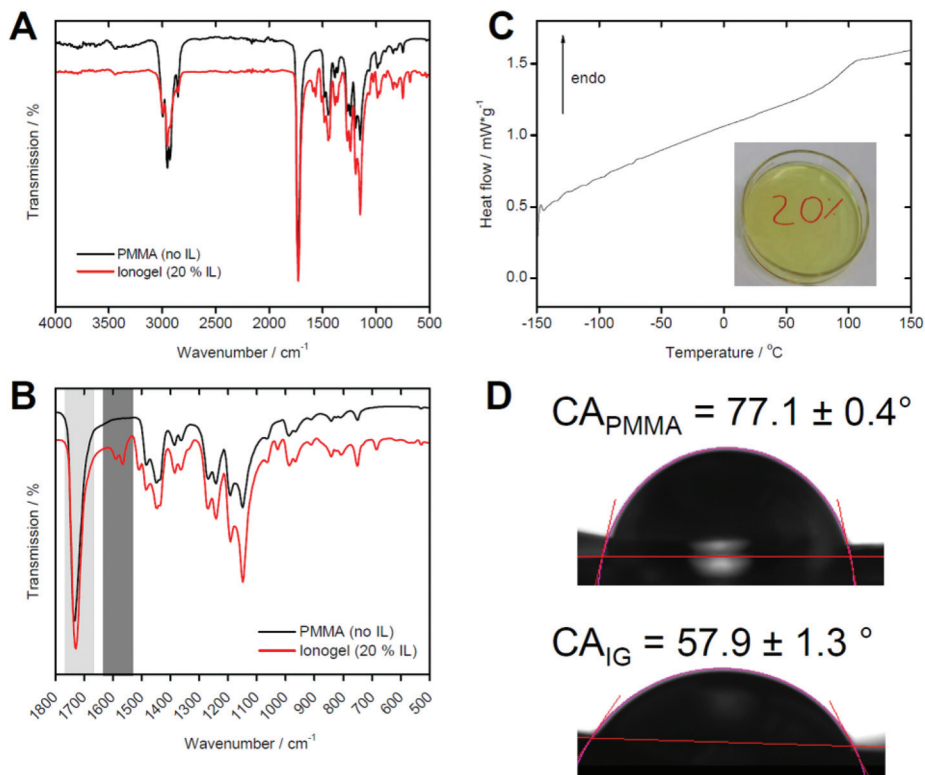
Fig. 3 (A) Full IR spectrum of the PMMA matrix and an ionogel with 20% of IL. (B) Magnified view of the low wavenumber region. (C) DSC curve of the ionogel. Inset is a photograph of the ionogel. (D) Photographs of a water droplet on the pure PMMA (CA$_{PMMA}$) and the ionogel (CA$_{IG}$) showing the different contact angles.

Besides the preparation of gels, we also employed a representative IL as a solvent for the Heck coupling between iodobenzene and methyl acrylate. Hydrophobic pyridinium ILs have been previously reported as efficient solvents for Pd catalysed reactions,[22] due to their stabilising effects on metal nanoparticles (NPs). This obviates the need for elaborate metal complexes and, instead, simple Pd salts can be used. For the Heck coupling, a batch of compound **9** was produced, followed by anion metathesis with LiTFSI. A standard Heck coupling was performed using Pd(OAc)$_2$ as the catalyst (see ESI†). The desired product could be isolated in 98% yield after 3 hours. No precipitate of Pd black was visible after the reaction, indicating the stabilisation of Pd by the IL. The in depth evaluation of this system as medium for cross coupling reaction will be the object of future studies.

In conclusion, we described a new methodology for the generation of substituted pyridinium ILs *via* the continuous hydrothermal decarboxylation of pyridinium zwitterions, which are in turn generated *via* the condensation of amino acids and furfural. Since the starting materials employed for the synthesis are entirely based on renewable resources and the employed decarboxylation strategy is essentially based on the use of water, the method reported represents a convenient solution for the green and sustainable preparation of pyridinium based ILs. The method shows a relatively broad scope, as different amino acids can be employed with good results,

offering a convenient possibility to tune the polarity of the final molecule. In addition, the obtained compounds are characterised by properties which are equivalent to the ones of analogous ILs obtained on the basis of non-renewable resources, as demonstrated in the preparation of ionogels and the use as solvent for the Heck coupling. Finally, it is worth mentioning that all pyridinium ILs introduced in this work present a phenolic functionality that may be exploited for further derivatisation and may influence their general redox properties as well as the acid–base behaviour, which will be the object of future studies.

References

1 D. Esposito and M. Antonietti, *Chem. Soc. Rev.*, 2015, DOI: 10.1039/C4CS00368C.

2 C. O. Tuck, E. Pérez, I. T. Horváth, R. a. Sheldon and M. Poliakoff, *Science*, 2012, **337**, 695–699.

3 W. Leuchtenberger, K. Huthmacher and K. Drauz, *Appl. Microbiol. Biotechnol.*, 2005, **69**, 1–8.

4 P. G. Dalev, *Bioresour. Technol.*, 1994, **48**, 265–267.

5 T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2084.

6 M. Galiński, A. Lewandowski and I. Stępniak, *Electrochim. Acta*, 2006, **51**, 5567–5580.

7 N. M. Yunus, M. I. A. Mutalib, Z. Man, M. A. Bustam and T. Murugesan, *Chem. Eng. J.*, 2012, **189–190**, 94–100.

8 S. Kirchhecker, M. Antonietti and D. Esposito, *Green Chem.*, 2014, **16**, 3705–3709.

9 Z. Xiang, *J. Mol. Struct.*, 2013, **1049**, 149–156.

10 R. W. Morrison and D. M. Jackson, *US pat.*, 20140275569, University of Georgia Research Foundation, Inc., USA, 2014.

11 M. D. Toney, *Arch. Biochem. Biophys.*, 2005, **433**, 279–287.

12 J. W. Döbereiner, *Ann. der Pharm.*, 1832, **3**, 141–146.

13 H. J. Brownlee and C. S. Miner, *Ind. Eng. Chem.*, 1948, **40**, 201–204.

14 C. M. Cai, T. Zhang, R. Kumar and C. E. Wyman, *J. Chem. Technol. Biotechnol.*, 2014, **89**, 2–10.

15 C. Müller, V. Diehl and F. W. Lichtenthaler, *Tetrahedron*, 1998, **54**, 10703–10712.

16 R. Villard, F. Robert, I. Blank, G. Bernardinelli, T. Soldno and T. Hofmann, *J. Agric. Food Chem.*, 2003, **51**, 4040–4045.

17 T. Soldo and T. Hofmann, *J. Agric. Food Chem.*, 2005, **53**, 9165–9171.

18 J. Le Bideau, L. Viau and A. Vioux, *Chem. Soc. Rev.*, 2011, **40**, 907–925.

19 A. Taubert, *Eur. J. Inorg. Chem.*, 2015, **2015**, 1148–1159.

20 M. A. B. H. Susan, T. Kaneko, A. Noda and M. Watanabe, *J. Am. Chem. Soc.*, 2005, **127**, 4976–4983.

21 Z.-L. Xie, A. Jelicic, F.-P. Wang, P. Rabu, A. Friedrich, S. Beuermann and A. Taubert, *J. Mater. Chem.*, 2010, **20**, 9543–9549.

22 M. H. G. Prechtl, J. D. Scholten and J. Dupont, *Molecules*, 2010, **15**, 3441–3461.