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Synthesis of Imidazolium-functionalized Ionic Liquid Specialties

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Abstract

Ionic liquids (ILs) are defined as salts that are stable in the liquid state at 100°C or less. ILs have long been considered as designer solvents in preparatory chemistry because they can be made task-specific for a target application. The synthesis of imidazolium based ILs tailored with functional groups will be presented for the potential use in synthesis. There are generally two routes to synthesize ILs commonly referred to as the "conventional" Menschutkin reaction [P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram, M. Grätzel, Inorg. Chem., 35, (1996), 1168-1178.] and the "unconventional" modified Radziszewski reaction [B. Radziszewski, Ber. Dtsch. Chem. Ges., 15, (1882), 1493-1496. J. Zimmermann, B. Ondruschka, A. Stark, Org. Proc. Res. Dev., 14, (2010), 1102-1109.]. The conventional synthesis is an alkylation reaction where an amine and an alkyl halide react to form the IL cation while the halide acts as the IL anion. The unconventional synthesis is a one-pot-synthesis where five molecules react to the desired IL: formaldehyde, glyoxal, an acid and two molar equivalents of an amine. The use of the unconventional synthesis to obtain functionalized ILs was the main focus of this project. However, instead of the ILs, three internal salt derivatives of the desired ILs were surprisingly obtained with high yields (> 89%) and in high purity.

Keywords: ionic liquids, ring closing reactions, chirality

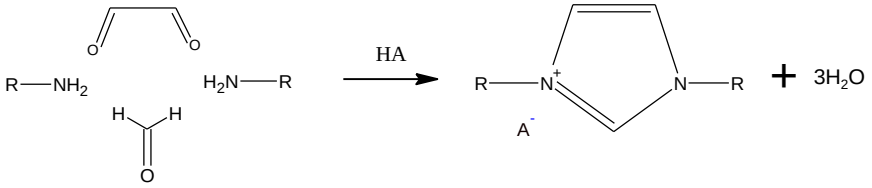
1. Introduction

Ionic liquids (ILs) are defined as salts that are stable in the liquid state at 100°C or less.[1] The variation of different cations, normally large organic ions, and different anions, usually smaller inorganic ions, allows principally for an almost unlimited possible combinations of ILs. Therefore, ILs can be made task-specific for a particular synthetic challenge or application. Although the characteristics of the IL depends on the cation and anion combination, many ILs share similar properties with respect to low vapor pressures, a wide liquid range, ability to dissolve various substrates, and low melting points. In addition, many ILs possess a high thermal and chemical stability.[2]

There are two general pathways used for the synthesis of ILs, the "conventional" Menschutkin reaction,[3] and the "unconventional" modified Radziszewski reaction.[4] For the conventional Menschutkin reaction, an amine is alkylated by an alkyl halide to form an ammonium salt, in which the halide acts as the anion. For the "unconventional" modified Radziszewski reaction, glyoxal is reacted with formaldehyde, two amines and an acid as seen in Scheme 1. The goal for this project was to explore the effectiveness of the modified Radziszewski reaction to form several cation-functionalized ILs. In particular, we aimed at using amino acids as the amine component in

order to open a pathway to include functionalities such as chiral centers in the side chains of the imidazolium cation. Chiral compounds are molecules that are not superimposable with their mirror images because they possess asymmetric carbon centers.[5] Chiral ILs as solvents may be able to direct asymmetric organic reactions to yield enantiomerically specific products acting as a chiral auxiliary.[6] As of this time, there has not been any report on relatively inexpensive preparation methods of chiral ILs.[7] Therefore, for this project the modified Radziszewski reaction was explored. The variability of the IL cation structure results from the amine groups used giving the IL its N-substituted functional groups and the acid giving the IL its anion (Scheme 1).

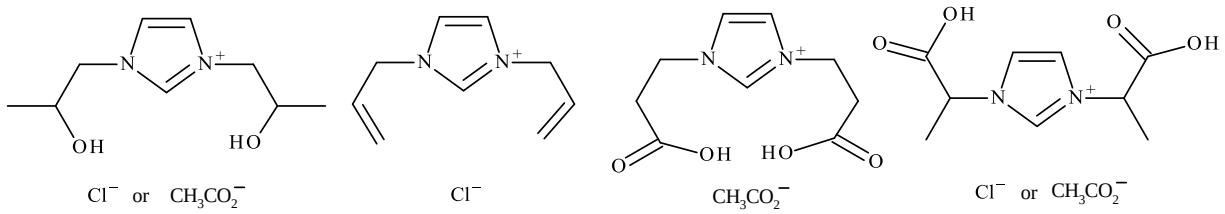
In theory, two different amines can be used in the modified Radziszewski reaction, leading to non-symmetrically substituted IL cations. However, this one-pot procedure has been shown to result in a statistical cation distribution.[8] Therefore, two molar equivalents of the same amine were used to prevent the formation of cation mixtures, and homosubstituted imidazolium cations arise. The amines used are relatively cheap (aminopropan-2-ol, allylamine, β-alanine, L-alanine) allowing for an inexpensive alternative to synthesize functionalized ILs, in particular chiral ILs.



Scheme 1: Modified Radziszewski Reaction.

2. Results and Discussions

A total of six ILs were attempted to be synthesized using the modified Radziszewski reaction (Scheme 1). As variables, either the acid (HCl, acetic acid) or the amine (aminopropan-2-ol, allylamine, β-alanine, L-alanine) was altered, aiming at the preparation of either 1,3-bis(2-hydroxypropyl)imidazolium chloride ([HOC_3 HOC_3 im]Cl), 1,3-bis(2-hydroxypropyl)imidazolium acetate ([HOC_3 HOC_3 im][OAc]), 1,3-diallylimidazolium chloride ([Allyl Allyl im]Cl), 1,3-bis(2-carboxyethyl)imidazolium acetate ([β-Ala β-Ala im][OAc]), 1,3-bis(1-carboxyethyl)imidazolium chloride ([L-Ala L-Ala im]Cl), or 1,3-bis(1-carboxyethyl)imidazolium acetate ([L-Ala L-Ala im][OAc]), Scheme 2.



Scheme 2: Cation-fuctionalized ionic liquid targets of this study.

Table 1 summarizes the results of all the IL products synthesized commenting on the relative purities confirmed by ^{1}H NMR, and other observations.

As seen in Table 1, three of the six ILs synthesized, [HOC_3 HOC_3 im]Cl, [HOC_3 HOC_3 im][OAc] and [Allyl Allyl im]Cl, were found to have insufficient purities and extensive extraction with diethyl ether did not improve the quality. Although the resulting ^{1}H NMR spectrum resonance assignments and integral heights of [HOC_3 HOC_3 im]Cl and [Allyl Allyl im]Cl show peaks that indicate that the desired products have in fact been synthesized (see Section 4.2), there were also large broad unidentified peaks in the spectra. One possible explanation for the presence of

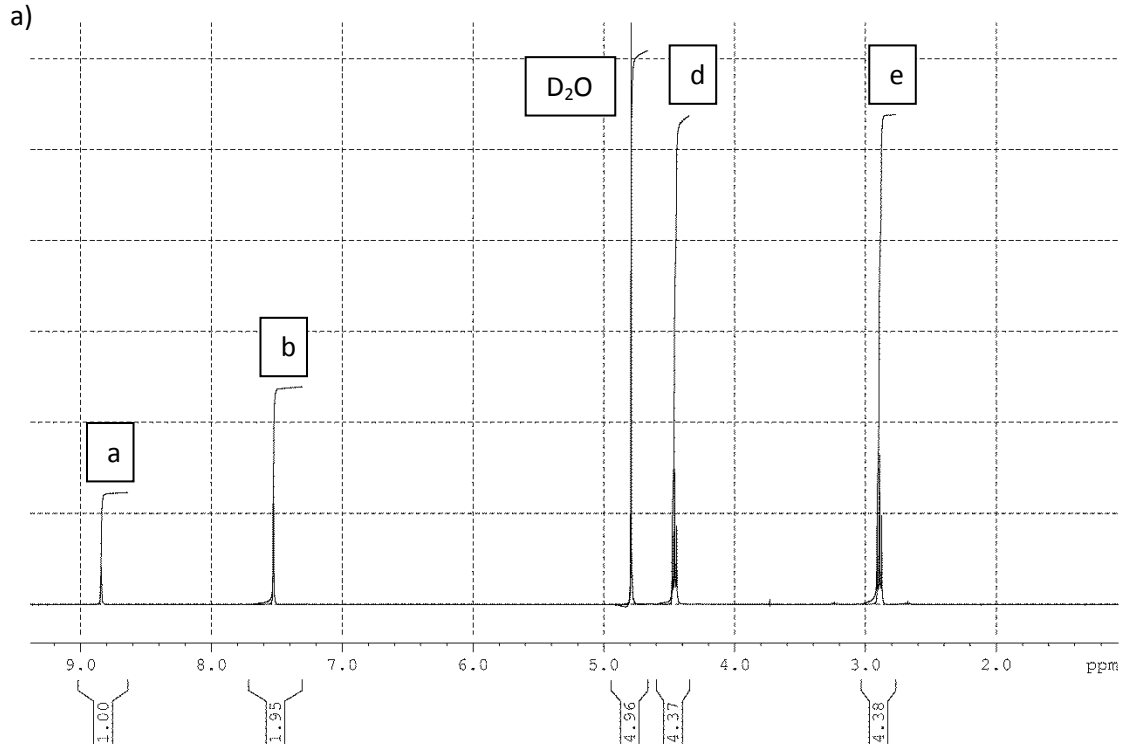
impurities is the decomposition of the product due to the strong acid (HCl) in these reactions. Due to the amount of impurities, the samples were disposed of and no further tests were performed on either [HOC_3 HOC_3 im]Cl or [Allyl Allyl im]Cl. The preparation of the [HOC_3 HOC_3 im] cation was attempted again using the weaker acid, acetic acid. The peak assignments (see Section 4.2) and integral heights of ^{1}H NMR spectrum of [HOC_3 HOC_3 im][OAc] show that the desired product has in fact been synthesized. However, again the purity was insufficient, and the sample hence disposed of.

Table 1: Results of the modified Radziszewski Reaction Aiming at Cation-functionalized ILs

Ionic Liquid [a]	Yield (g)	Yield (%)[b]	Observations and Comments
[HOC_3 HOC_3 im]Cl	21.5	98	Solid. Product formed (^{1}H NMR), but insufficient purity
[HOC_3 HOC_3 im][OAc]	24.5	99	Solid. Product formed (^{1}H NMR), but insufficient purity
[Allyl Allyl im]Cl	12.1	71	Viscous liquid. Product formed (^{1}H NMR), but insufficient purity
[β-Ala β-Ala im][OAc]	18.7	89	Solid. Betaine structure identified (^{1}H, ^{13}C NMR, titration), pure
[L-Ala L-Ala im][OAc][c]	20.8	96	Solid. Betaine structure identified (^{1}H, ^{13}C NMR, titration), pure
[L-Ala L-Ala im]Cl [c]	24.2	120	Solid. Betaine structure identified (^{1}H, ^{13}C NMR, titration), pure

[a] Ionic liquid aimed for in the synthesis. [b]The percent yields are given for the betaine structure where applicable, see Section 2. [c] Minor traces of unreacted L-alanine visible at 4.0 and 1.4 ppm (^{1}H NMR).

For the three amino acid-derived ILs, the analysis of both the ^{1}H and ^{13}C NMR spectra show peak assignments and integral heights that are consistent with the cations of the desired ILs [β-Ala β-Ala im][OAc], [L-Ala L-Ala im]Cl and [L-Ala L-Ala im][OAc] (Figures 1-2). However, in both of the acetate-based ILs, the signal corresponding to the acetate ion at 2.05 ppm in the ^{1}H spectrum is not present (Figures 1 and 2). The ^{1}H NMR spectrum obtained in the synthesis of [L-Ala L-Ala im]Cl is principally the same as that obtained from the synthesis of [L-Ala L-Ala im][OAc] (see Section 4.2).



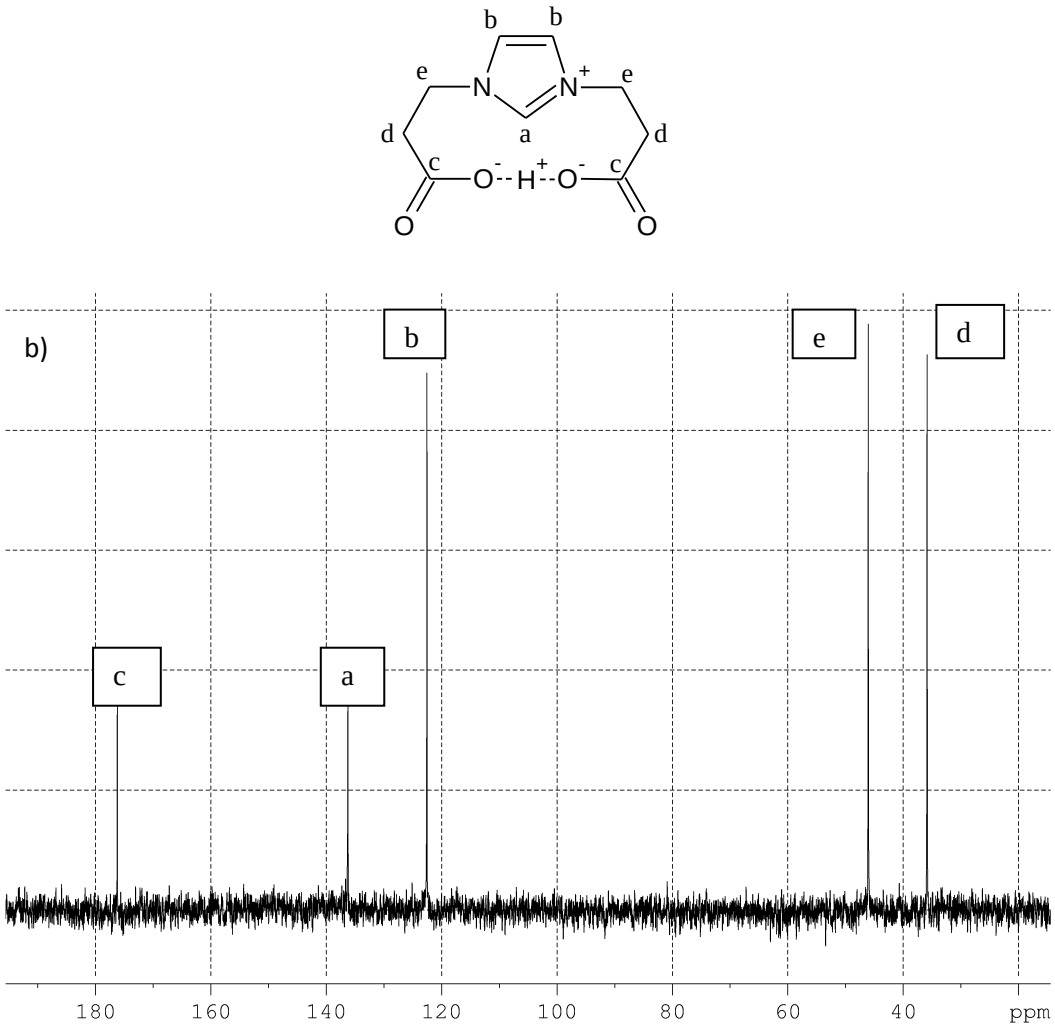


Figure 1: NMR spectra and spectral assignment of the hydrogen 1,3-bis(2-carboxyethyl)imidazolium betaine structure, abbreviated [β-Ala β-Ala im] betaine, obtained in D_2O: a) ^{1}H NMR, b) ^{13}C NMR.

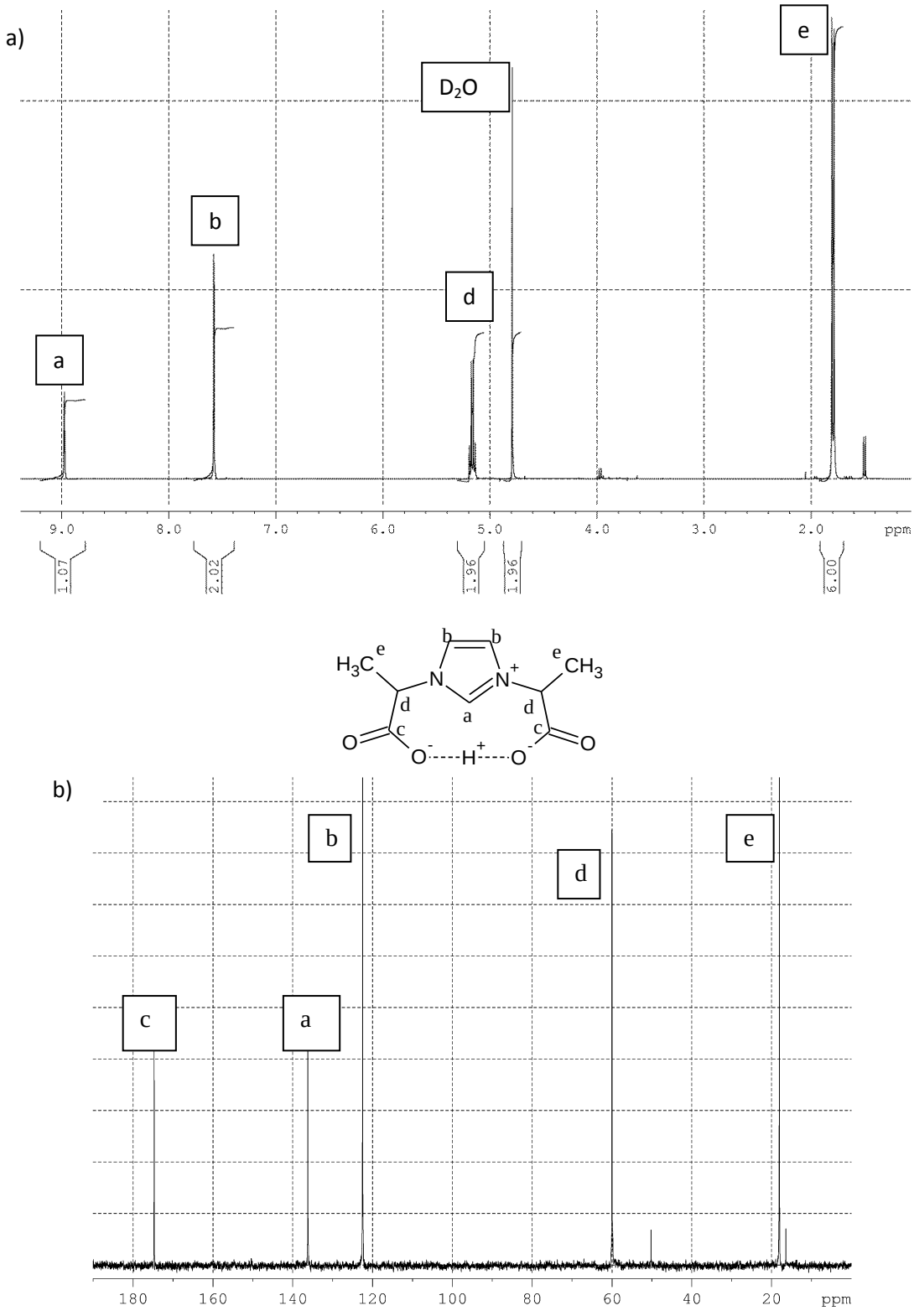
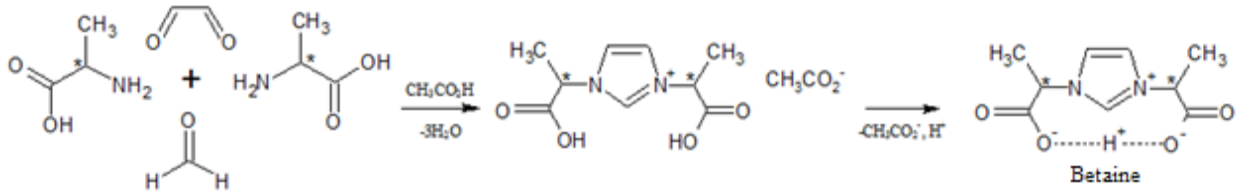


Figure 2: NMR spectra and spectral assignment of the hydrogen 1,3-bis(1-carboxyethyl)imidazolium betaine structure obtained from the reaction using acetic acid, abbreviated [L-Ala L-Ala im] betaine, obtained in D_2O: a) ^{1}H NMR, b) ^{13}C NMR.

Given the missing acetate ion peak, and the lack of impurities in the ^{1}H NMR and ^{13}C NMR spectra, it was hypothesized that not the desired ILs, but the corresponding betaine structures (internal salts) have been formed (Scheme 3). Due to the low solubility in other solvents, deuterium oxide was used as the solvent for ^{1}H NMR analysis, which explains why the proton shared between the carboxylic acid functional groups of the betaine structure are not observed due to the chemical exchange with the solvent. Since one proton is shared between two carboxylic acid groups in the betaine structure one might possibly observe two peaks near 180 ppm one for a carbonate and the other for the carboxylic acid ^{13}C NMR spectra. However, the intra-molecular exchange of the acidic proton or the intermolecular exchange of the proton with the D_2O solvent appears to be fast on the NMR time scale and only one resonance is observed the carbon spectra of Figures 1-2.



Scheme 3: Betaine formation of [L-Ala L-Ala im] betaine; the asterisk represents the chiral centers.

The possible betaine formation is discussed in detail in the following focusing as an example on the synthesis of 1,3-bis(1-carboxyethyl)imidazolium acetate. As specifically shown in Scheme 3, two molar equivalents of the chiral amine L-alanine were reacted with glyoxal, formaldehyde, and acetic acid in a one-pot reaction. The final drying of the material was achieved by heating under vacuum (80°C, 12 h, 7-8 mbar), during which acetic acid has been removed, together with remaining other volatiles. In the resulting betaine structure, the remaining proton is then shared between the two functional $-COO^-$ groups. In analogy, HCl and acetic acid are removed during the drying process from [L-Ala L-Ala im]Cl and [β-Ala β-Ala im][OAc], respectively. The resulting betaine structures are abbreviated herein as [L-Ala L-Ala im] betaine and [β-Ala β-Ala im] betaine for hydrogen 1,3-di(1-carboxyethyl)imidazolium and hydrogen 1,3-di(2-carboxyethyl)imidazolium inner salt, respectively.

To further confirm the presence of these betaine structures, a series of acid-base titrations were performed. An aqueous betaine solution was titrated with an aqueous NaOH solution of equal molarity using phenolphthalein as the indicator as described in Section 4.3. If the product was the expected [L-Ala L-Ala im] betaine (Scheme 3, or [β-Ala β-Ala im] betaine by analogy), only one molar equivalent of NaOH would be needed to neutralize the single proton shared between the carboxylate groups of the betaine structure, whereas it would take two molar equivalents of the sodium hydroxide to neutralize both of the carboxylic acid functional groups of the ionic liquids [β-Ala β-Ala im][OAc], [L-Ala L-Ala im]Cl or [L-Ala L-Ala im][OAc] (Scheme 2). Indeed, it was found that one equivalent of sodium hydroxide was needed to neutralize the product, confirming the betaine structure. More precisely, the relative difference of the titrated molarity from the calculated molarity based was found to be 0.4%, -0.2% and 22.4% for [β-Ala β-Ala im] betaine, [L-Ala L-Ala im] betaine (from the reaction with acetic acid) and [L-Ala L-Ala im] betaine (from the reaction with HCl). The higher acid content determined from the titration of [L-Ala L-Ala im] betaine from the reaction with HCl explains also the over-stoichiometric yield, i.e. not all HCl has been removed in vacuo (see Table 1).

Although the betaine structures synthesized were not the desired ILs, the betaine structures do contain the desired functionalities, in particular the asymmetric carbon centers of L-alanine. It is straightforward to revert the internal salt back to an IL by adding an equivalent of the acid. It is also possible to choose any IL anion at this stage by adding different acids to the betaine structure.

3. Conclusion

The modified Radzizewski-reaction was successful used to synthesize six functionalized ILs. However, 1,3-bis(2-hydroxypropyl)imidazolium chloride and –acetate, and 1,3-diallylimidazolium chloride were of very poor purity, and extensive extraction with diethyl ether did not improve the purity sufficiently. On the other hand, the derivatives of β- and L-alanine had clean-looking ^{1}H and ^{13}C NMR spectra. Closer inspection of the spectra and subsequent titration experiments with NaOH revealed that in fact, not a di-carboxylic acid-derivatized imidazolium cation was

formed, but that an internal salt (betaine) formed, i.e. formally one carboxylate and one carboxylic acid moiety is present on the functional groups, and no anion. Recalculation of the yield based on the betaine structure showed that the reaction proceeded very efficiently. In the case of using acetic acid, quantitative removal of acetic acid was achieved in vacuo. This aspect can be beneficially exploited to generate cation-functionalized ionic liquids with a variety of anions by simple back-titration with any acid.

4. Methodology

NMR spectra were recorded on either a VARIAN MERCURY plus 400 NMR spectrometer, at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The program Topspin was used to process the measured data. The deuterated solvents DMSO-d_6 (for [HOC_3 HOC_3 im]Cl) and deuterium oxide (for [HOC_3 HOC_3 im][OAc], [Allyl Allyl im]Cl, [β-Ala β-Ala im][OAc], [L-Ala L-Ala im][OAc] and [L-Ala L-Ala im]Cl) were utilized as internal reference. The spectra were taken at the Institute of Analytical Chemistry, University of Leipzig.

4.1. General Synthesis Protocol

A solution containing the acid and formaldehyde was placed in a separatory funnel and added drop-wise to a three-necked round bottom flask containing the amine and a magnetic stirrer, placed in an ice-bath as the reaction is exothermic. For detailed amounts of the reactants, see Table 2. After 0.5-1 hour of stirring, the glyoxal solution was added drop-wise to the stirred contents of the flask. The clear and homogeneous solution was stirred for 4 hours in an ice-bath, then over night at room temperature. The yellow-brown solution was extracted with diethyl ether (10x50 ml). Water was removed from the aqueous phase using a rotary evaporator. Traces of volatiles were further removed using a vacuum line (80°C, 12 hours, 7-8 mbar) to give the product in the yield indicated in Table 1.

Table 2: Reaction conditions used for the modified Radziszewski Reaction Aiming at Cation-functionalized ILs

Ionic liquid [a]	**Acid**			**Formaldehyde**[c]		**Amine**			**Glyoxal**[d]	
	Type	n (mol)	m (g)	n (mol)	m (g)	Type	n (mol)	m (g)	n (mol)	m (g)
[HOC_3 HOC_3 im]Cl	HCl[b]	0.1172	11.704	0.0999	8.109	Aminopropan-2-ol	0.2009	15.088	0.1018	14.775
[HOC_3 HOC_3 im][OAc]	HOAc	0.1208	7.251	0.1024	8.311	Aminopropan-2-ol	0.2043	15.347	0.1018	14.774
[Allyl Allyl im]Cl	HCl[b]	0.1195	11.930	0.0998	8.098	Allylamine	0.2000	11.419	0.1009	14.644
[β-Ala β-Ala im][OAc]	HOAc	0.1206	7.239	0.1015	8.237	β-Alanine	0.1984	17.680	0.1008	14.629
[L-Ala L-Ala im][OAc]	HOAc	0.1187	7.125	0.1056	8.575	L-Alanine	0.2036	18.142	0.1017	14.757
[L-Ala L-Ala im]Cl	HCl[b]	0.1225	12.068	0.1032	8.378	L-Alanine	0.2019	17.986	0.1000	14.510

[a] Ionic liquid aimed for in the synthesis. [b] 36.5% aqueous solution. [c] 37% aqueous solution. [d] 40% aqueous solution.

4.2 NMR Spectra

[HOC_3 HOC_3 im]Cl: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.08 (1H, s), 7.69 (2H, s), 4.20 (4H, d), 3.95-3.80 (2H, m), 1.07 (6H, d). (Spectrum not shown).

[HOC_3 HOC_3 im][OAc]: ^{1}H NMR (400MHz, D_2O) δ 8.64 (1H, s), 7.35 (2H, s), 4.64 (4H, d), 3.95 (2H, m), 1.71 (3H, s), 1.04 (6H,d). (Spectrum not shown).

[Allyl Allyl im]Cl: ^{1}H NMR (400MHz, D_2O) δ 8.97 (1H, s), 7.63 (2H, s), 6.12 (2H, m), 5.47 (4H, m), 4.92 (4H, d). (Spectrum not shown).

[β-Ala β-Ala im] (betaine): ^{1}H NMR (400MHz, D_2O) δ 8.84 (1H, s), 7.52 (2H, s), 4.46 (4H, t), 2.89 (4H, t) see Figure 1a). ^{13}C NMR (400MHz, D_2O) δ 178, 138, 122, 45, 38 see Figure 1b).

[L-Ala L-Ala im] (betaine) from reaction with acetic acid: ^{1}H NMR (400MHz, D_2O) δ 8.97 (1H, s), 7.58 (2H, s), 5.16 (2H, quart), 1.80 (6H, d) see Figure 2a). ^{13}C NMR (400MHz, D_2O) δ 175, 138, 122, 60, 19 see Figure 2b).

[L-Ala L-Ala im] (betaine) from reaction with HCl: ^{1}H NMR (400MHz, D_2O) δ 8.85 (1H, s), 7.45 (2H, s), 5.03 (2H, quart), 1.67 (6H, d). (Spectrum not shown).

4.3. Acid-Base Titration Of The Betaines

Acid-base titrations were performed using the resulting products from the [ß-Ala ß-Ala im][OAc], [L-Ala L-Ala im][OAc], and[L-Ala L-Ala im]Cl synthesis reactions respectively. The molar solutions of the ILs were prepared based on the molar mass of the corresponding betaine structures. Each product was dissolved in distilled water in a 50mL volumetric flask to prepare a 0.1M solution (theoretically, if 100% pure). A 10mL portion of this solution was transferred to an Erlenmeyer flask, and titrated with NaOH (0.0997 M) against phenolphthalein using a 25mL burette. Titrations were performed in triplicate.

5. Acknowledgements

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