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Extractive electrospray ionization mass spectrometry of ionic liquids†

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The growing role of ionic liquids (ILs) in industry and research is creating an urgent need for the development of analytical methods for the reliable characterization and control of the composition of the ILs. The application of mass spectrometry (MS) to the analysis of ILs is limited by the poor tolerance of classical MS methods toward samples with high salt concentrations and viscosity. Herein, extractive electrospray ionization mass spectrometry (EESI-MS) was applied to directly analyze various room temperature ILs such as 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim][PF_6]) 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]), and 1-butylpyridinium tetrafluoroborate ([BuPy][BF_4]). The EESI mass spectra of ILs diluted in methanol revealed great similarities to the mass spectra of the same samples assessed by direct infusion ESI-MS. Both cationic (C^+) and anionic (A^-) IL components could be detected with a high sensitivity from strongly diluted samples (<10^{-7} M). $[CA - H]^-$ or $[CA + H]^+$ signals were observed for certain ILs using EESI-MS, and in good agreement with their classification based on the acid–base theory. With only minor alterations to the experimental setup, analysis of the ILs could be performed without dilution, which allowed a direct observation of the IL aggregates in the gas phase at a speed of >2 samples per min. EESI-MS allows the direct analysis of ILs in a broad concentration range with a high tolerance to chemical contamination. The reported examples suggest the potential for EESI-MS to interrogate large IL assays, which is critical in both fundamental physical chemistry studies and industrial applications.

Introduction

Ionic liquids (ILs) are a class of organic salts with a low melting point, often below room temperature. Driven by their growing role in industry and research,[1,2] ILs are being produced at a continuously increasing rate. This is creating an urgent need for the development of fast analytical procedures for the reliable characterization and control of the composition of the ILs and of the processes mediated by ILs.[3] Owing to the ionic nature of ILs, mass spectrometry (MS) is a particularly attractive technique to characterize ILs requiring molecular specificity in various applications, including green chemistry, physicochemical studies, and industrial preparation of ILs. Electrospray ionization mass spectrometry (ESI-MS) has become a popular technique to characterize the chemical composition of ILs with molecular specificity,[4] but its poor tolerance toward high salt concentrations and sample viscosity limits its broader use in IL analysis. For instance, viscous ILs electrosprayed at high concentrations can rapidly accumulate in ESI transfer lines and injection needles, as well as on the surfaces of MS inlet and ion guide system. This causes serious chemical contamination and carryover effects. In addition ot ESI-MS, other soft modern ionization techniques, such as atmospheric pressure chemical ionization (APCI) and sonic spray ionization (SSI),[5–7] have also been demonstrated as suitable for investigating the properties and structures of ILs. Most recently, Hao Chen and coworkers demonstrated the direct MS analysis of ILs using probe electrospray ionization mass spectrometry.[8]

Extractive electrospray ionization mass spectrometry (EESI-MS) is a recently introduced offspring technique of ESI-MS for the direct analysis of complex mixtures.[9] In EESI-MS, the analyte solution is pneumatically nebulized toward the ionizing spray, and the generated secondary droplets give rise to gas-phase ions *via* an ESI-like mechanism.[10] The method has been shown particularly suitable for characterizing viscous samples such as ILs, and accordingly experimental protocols have been comprehensively delineated.[11] In this contribution, the application of EESI-MS toward ILs is explored further. IL samples could be analyzed both diluted in organic solvent and without dilution. The advantage of EESI-MS for the analysis of ILs is particularly obvious for concentrated IL samples, where traditional ESI-MS approaches face severe contamination problems. An appropriately designed EESI configuration, in turn, enables

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the sampling of highly-concentrated and even non-diluted ILs without any notable sample carryover and adverse effects to the performance of the MS instrument. The high tolerance of EESI-MS to concentrated IL samples should benefit the use of this method in many screening applications, *e.g.*, in the development of new IL formulations and for quality control.

Experimental section

2.1 Reagents

The following ionic liquids (purity = 99%) were purchased from Shanghai Cheng Jie Chemical Co. LTD. (Shanghai, China): 1-ethyl-3-methylimidazolium hydrogen sulfate [Emim][HSO_4], 1-butyl-3-methylimidazolium hexafluorophosphate [Bmim][PF_6], 1-aminoethyl-3-methylimidazolium hexafluorophosphate [AEmim][PF_6], 1-butylpyridinium tetrafluoroborate [BuPy][BF_4], 1-hexyl-3-methylimidazolium chloride [Hmim][Cl], 1-octyl-3-methylimidazolium tetrafluoroborate [Omim][BF_4], 1-ethyl-3-methylimidazolium tetrafluoroborate [Emim][BF_4], 1-propyl-3-methylimidazolium iodide [Pmim][I], 1-butyl-3-methylimidazolium hydrogen sulfate [Bmim][HSO_4], 1-butyl-3-methylimidazolium acetate [Bmim][Ac], 1-butyl-3-methylimidazolium tetrachloroaluminate [Bmim][$AlCl_4$], 1-butyl-3-methylimidazolium nitrate [Bmim][NO_3], and 1-butyl-3-methylimidazolium chloride [Bmim][Cl]. HPLC grade methanol was purchased from ROE Scientific, Inc. (Newark, USA). Water was purified and deionized in house to Milli-Q grade. For MS analysis, the ILs were diluted in methanol.

2.2 Extractive electrospray ionization (EESI)

In this study, we employed close variations of two earlier described EESI interfaces.[9,12] An IL solution was sampled either from the neutral sprayer (Fig. 1a) or directly from the tip of a plastic pipette placed in front of the neutral sprayer (Fig. 1b). For the EESI-MS analysis of diluted IL solutions (Fig. 1a), a pure methanol–water mixture (1 : 1) and the IL sample were infused *via* identical fused-silica capillaries (ID 100 μm, OD 190 μm) at a flow rate of 5 μL min^{-1} using a conventional pumping system (PHD ULTRA™ CP, Harvard Apparatus, Holliston, MA, USA). An ionizing voltage was applied to the syringe (ThermoFisher Scientific, Waltham, MA, USA) needle, varying from 0 to +3.5 kV in positive polarity (EESI(+)) and from 0 to −3.5 kV in the negative polarity (EESI(−)). The nebulizer nitrogen gas flow was optimized by regulating the pressure in the tank. Under optimized experimental conditions, nitrogen for both sprayers was supplied at a pressure 1 MPa *via* stainless steel capillaries (ID 250 μm, OD 1590 μm). The gas flow rate was not measured. The ionizing sprayer was located *ca.* 3 cm away from the inlet of the MS instrument at 60°.

Neutral sprayer was *ca.* 1 cm away from the inlet, roughly orthogonal to the axis of the instrument (Fig. 1a). Unlike highly diluted solutions, non-diluted ILs were analyzed directly from the tip of a plastic pipette placed in front of the neutral sprayer, as shown in Fig. 1b. In this case, 1 : 1 methanol–water mixture was used in both charged and neutral EESI channels. IL

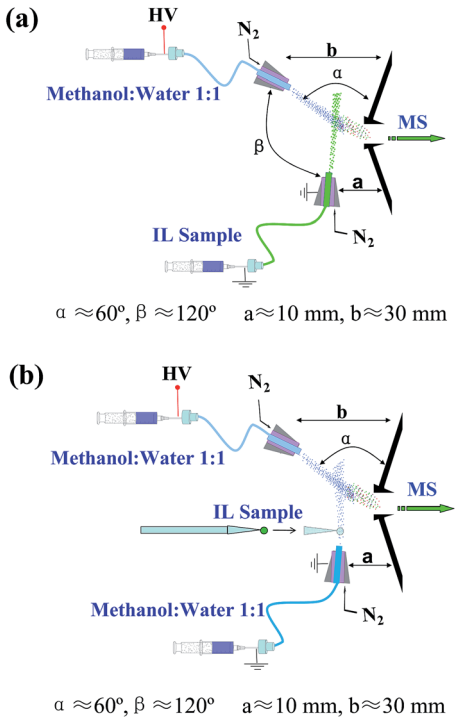

Fig. 1 Experimental configurations for the EESI-MS analysis of diluted (a) and non-diluted (b) ionic liquids.

sampling was achieved by dipping the clean pipette tip into the IL aliquot.

The use of pneumatically controlled nebulization in our experiments allowed a high stability of both the ionizing and sample sprays, regardless of the distance to MS inlet, voltage and solution flow rate. Moreover, pneumatic control prevented the charged droplets from neutralizing on the neutral sprayer. Finally, pneumatic nebulization enabled the use of lower ionizing voltages than in conventional ESI (*e.g.*, 500 V), which minimized the possibility of atmospheric discharge, the accumulation of static charge and health risks. In the course of the current study, we did not observe any discharge in the ionization area. No MS signal was observed when the solvent flow to the charged emitter was stopped; thus, the possibility of inductive ESI occurring from extractive capillary could be ruled out.

2.3 Mass spectrometry

Mass spectrometric detection was carried out using an LTQ ion trap mass spectrometer (ThermoFisher, San Jose, CA, USA) at standard instrument settings. The capillary temperature was set at 150 °C. Mass spectra were collected in a *m*/*z* range of 50–2000. In CID mode, the collision energy was 15–30%, and the isolation window was 1.4 u.

Results and discussion

Fig. 2a–d shows the EESI mass spectra of [Bmim][PF_6] and [BuPy][BF_4] diluted in methanol to the concentration of *ca.*

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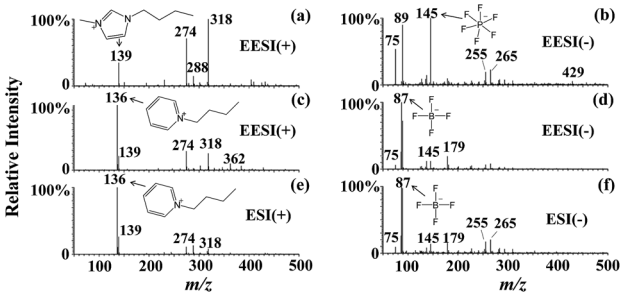

Fig. 2 (a and b) EESI(+) and EESI(−) mass spectra of [Bmim][PF_6] in methanol (3×10^{-8} M) obtained using the experimental setup in Fig. 1a; (c and d) EESI(+) and EESI(−) mass spectra of [BuPy][BF_4] in methanol (4×10^{-8} M) obtained using the experimental setup in Fig. 1a; (e and f) direct-infusion ESI(+) and ESI(−) mass spectra of [BuPy][BF_4] in methanol (4×10^{-8} M).

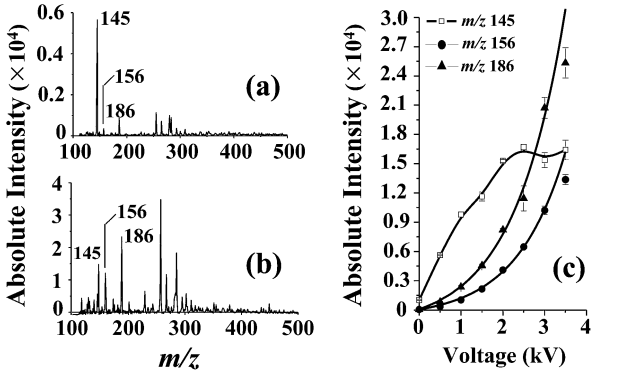

Fig. 3 (a and b) EESI(−) mass spectra of [Bmim][PF_6] in methanol (3×10^{-8} M) at 0.5 kV (a) and 3.5 kV (b) voltage; (c) voltage dependence of MS intensity for PF_6^- (*m/z* 145) and two IL-unrelated signals in the spectrum with close *m/z* values (*m/z* 156 and *m/z* 186). These data were obtained using the experimental setup in Fig. 1a. The signal intensities are plotted in the LTQ-MS instrument units. To guide the eye, the data points in the voltage dependence for the signal intensity of *m/z* 145 are connected with the curve line, and the data points for *m/z* 156 and *m/z* 186 are fitted with exponentials.

3×10^{-8} M and 4×10^{-8} M within the linear range of detection (Fig. S-1†). Characteristic signals were detected corresponding to the IL cation (C^+) in EESI(+) ($Bmim^+$ at *m/z* 139; $BuPy^+$ at *m/z* 136) and IL anion (A^-) in EESI(−) (PF_6^- at *m/z* 145; BF_4^- at *m/z* 87). For [BuPy][BF_4], a weak signal (*m/z* 429) corresponding to a CA_2^- cluster was also observed in EESI(−) (Fig. 2b). The rest of the peaks in the spectra, such as *m/z* 274, *m/z* 288, *m/z* 318 in EESI(+) and *m/z* 75, *m/z* 89, *m/z* 179, *m/z* 255, *m/z* 265 in EESI(−), were also observed by EESI-MS of pure methanol solution, and therefore were IL-unrelated. The limit of detection (LOD) for the free cations of imidazolium ILs in EESI-MS was found to be *ca.* 50 pM. A reference direct-infusion ESI-MS analysis of the same IL solutions produced very similar mass spectra (Fig. 2e and f). This similarity reflects the mechanistic kinship of ion formation from charged droplets in ESI and EESI.[10] The LOD for imidazolium cations in ESI-MS was found to be *ca.* 3 pM, which is about one order of magnitude lower than in EESI-MS. The lower sensitivity of EESI compared to ESI is general for a broad class of analytes, because the charge transfer to analyte molecules by the droplet extraction in EESI is less efficient than direct charging in classical ESI. The prevalence of C^+ and A^- signals over higher-order $[C_{n+1}A_n]^+$ and $[C_nA_{n+1}]^-$ clusters in both ESI and EESI indicates the high degree of ion separation in solution. However, earlier conductivity measurements for Bmim ILs, such as [Bmim][PF_6] and [Bmim][BF_4], suggest enhanced ionic association induced by methanol and other organic solvents.[13] To account for this apparent contradiction, we propose that IL aggregates in organic solvents are mostly neutral, *i.e.* $[C_nA_n]$, and they are therefore more difficult to ionize compared to free ions and charged clusters. Alternatively, the aggregates may simply be too large for MS detection.

Our data suggest that the highest quality of IL detection by EESI-MS, as well as by pneumatically assisted ESI, in both ion modes is achieved at a moderate ionization voltage of *ca.* 0.5–1 kV. Fig. 3 shows two EESI(−) mass spectra of [Bmim][PF_6] in methanol (*ca.* 3×10^{-8} M) generated at 0.5 kV (Fig. 3a) and 3.5 kV (Fig. 3b). While the first spectrum displays PF_6^- (*m/z* 145) as the most abundant peak, the second spectrum is dominated by IL-nonrelated signals and has a higher background base level, perhaps due to the much higher ESI current. Fig. 3c compares the voltage dependence of the PF_6^- peak intensity to two other signals in the spectra with close *m/z* values (*m/z* 156 and *m/z* 186). These two signals may originate from the chemicals in the spraying solution as well as from the chemicals in the air ionized *via* the EESI mechanism. Interestingly, rather different voltage profiles can be seen, which may reflect different ionization mechanisms for the corresponding analytes. For example, PF_6^- could be detected at the zero ESI voltage, because some charge separation occurs even in the neutral spray.[6] As the voltage is increased, the ESI ion current rapidly grows, mainly due to the increased amount of solvent ions in the charged droplets. This allows a more efficient ionization of the analytes based on proton transfer, which may account for the exponential growth in the *m/z* 156 and *m/z* 186 signals. In contrast, the PF_6^- signal is levelled off at >2 kV, probably because the extraction efficiency of PF_6^- ions has reached 100%.

Surprisingly, for some ILs we were able to detect protonated CA clusters in EESI(+) and for some ILs deprotonated CA clusters in EESI(−). The intensity of these signals was usually much lower compared to the intensity of C^+ and A^-, but the MS/MS analysis clearly suggests, at least for some ILs, the occurrence of a CA pair in the gas phase (Fig. S-2†). Overall, a good correlation was found between the observation of the CA clusters and the acid–base properties of the corresponding ILs: highly basic ILs yielded protonated clusters and less basic ILs yielded deprotonated clusters (Table S-1†). However, neither a protonated nor deprotonated CA signal could be detected from highly acidic ILs. The occurrence of contact [Bmim][I] pairs in solution is suggested by earlier studies[14] and that the binding strength of the C^+A^- association should be particularly high in organic solvents such as methanol.[13] In ESI-MS, intact noncovalent complexes such as CA can be ionized *via* proton transfer without disintegration, and the stoichiometry of the IL

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complexes observed in the gas phase often corresponds to their organization in solution.[4] We therefore cautiously propose that the CA complexes detected by EESI-MS may reflect the occurrence of IL contact pairs in solution.

Despite the low concentration of ILs in our experiments ($<10^{-7}$ M), carryover effects could not be fully avoided. For example, the mass spectra of [BuPy][BF_4] analyzed after [Bmim][PF_6] revealed the presence of both $Bmim^+$ (Fig. 2c, *m/z* 139) and PF_6^- (Fig. 2d, *m/z* 145), even when 1 mL volume of methanol, water or acetonitrile (four full 250 mL syringes) was passed through the neutral EESI channel in between the runs. A tedious cleaning procedure, including sonication of the syringe parts and connector ferrules, was required in order to fully dispose of contamination and avoid spectral cross-interference. We attribute the observed carryover effects to the high viscosity of ILs and their high affinity to microporous surfaces. In the reference direct-infusion ESI-MS experiments, contamination of the MS inlet and ion optics was observed in addition to contamination of the transfer lines. This resulted in stronger carryover effects.

To avoid the possibility of chemical contamination in the transfer lines during the analysis of ILs, we also implemented a modified version of the original EESI setup, as shown in Fig. 1b. The modified version bears similarity to the earlier introduced platform for the EESI-MS analysis of perfumes.[12] With the aid of neutral desorption, a small drop of IL sample is aerosolized from the tip of a plastic pipette toward the charging spray for EESI ionization and subsequent MS detection. Compared to the original EESI configuration (Fig. 1a) and classical direct-infusion ESI-MS, the 'droplet' version (Fig. 1b) allows higher throughput of screening (>2 samples per min *vs.* ~1 sample per 5 min), without the need to interrupt solvent infusion and reload the analyzed samples into a syringe (Fig. S-3†), but has *ca.* 2 orders of magnitude lower sensitivity, probably because of the larger size of the primary droplets. The sampling of a liquid drop directly from a pipette tip is similar to probe electrospray ionization (PESI), in which an analyte solution is electrosprayed from the tip of a sharp probe.[15] However, the use of disposable and non-expensive plastic tips makes the analysis more convenient and prevents the possibility of sample carryover effects. Moreover, because the primary neutral aerosol in 'droplet' EESI is off-axis to the mass spectrometer (Fig. 1b), the flux of neutral IL droplets into the MS interface is minimized.

The high tolerance of the modified EESI approach to chemical contamination allows the analysis of concentrated or even non-diluted samples. Ionic components in non-diluted ILs are not isolated from each other by solvent. As a result, large ionic clusters can be observed and studied in the gas phase.[13,16–18] Fig. 4a shows the EESI(+) mass spectrum of pure undiluted [BuPy][BF_4]. Unlike the diluted sample (Fig. 2c), a series of equidistant peaks separated by 223 u can be clearly observed in the spectrum from the non-diluted [BuPy][BF_4]. This series corresponds to $[C_{n+1}A_n]^+$ clusters and spans the entire mass range. The signal intensity decreases exponentially from C^+ to $[C_9A_8]^+$. The same type of clusters was observed in the EESI(+) mass spectrum of non-diluted [Bmim][BF_4]. However, the intensity of signals within the series did not decrease monotonously, but rather displayed a local maximum at C_5A_4 (Fig. 4b). The local intensity maximum at C_5A_4 in imidazolium ILs was also documented earlier by ESI-MS.[19] Theoretical calculations suggest that "magic numbers" in the mass spectra of ILs reflect the most stable intrinsic configurations.[20]

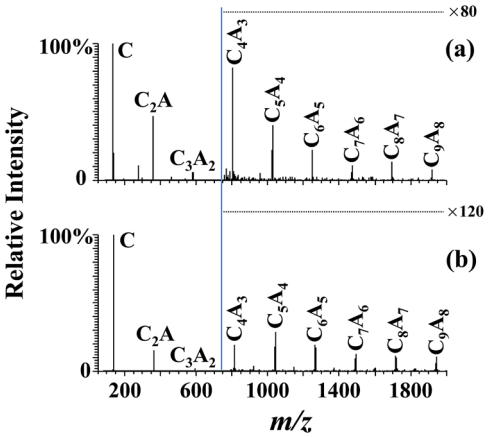

Fig. 4 EESI-MS analysis of non-diluted ILs by the experimental setup in Fig. 1b: (a) [BuPy][BF_4], (b) [Bmim][BF_4]. The vertical blue line separates the left side of the spectra normalized to the signal intensity of C^+ from the accordingly zoomed area on the right.

Conclusions

In conclusion, the application of EESI ionization to the MS analysis of ionic liquids has been demonstrated. The mechanistic kinship of EESI to the conventionally used ESI approach accounts for a similar performance, although with some important distinct features. Compared to ESI-MS, EESI-MS allows higher rapidity and throughput of the analysis, but also with simple operation and minimal matrix effects. Remarkably, unlike the majority of conventional MS approaches, including ESI-MS, the suitability of EESI-MS for the analysis of ILs increases at higher sample concentrations. Because ionic compounds have a high MS visibility, concentrated ILs can be analyzed using a sampling interface with lower chemical sensitivity but with an enhanced tolerance to chemical contamination. As a result, ILs can be analyzed in a broad concentration range from sub-ppb to non-diluted samples. Reported examples suggest the potential of EESI-MS to interrogate large IL assays, which is critical in both fundamental physical chemistry studies and industrial applications.

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