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Ionic liquids: Solutions for Electrospray Ionization Mass Spectrometry

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Ionic liquids pose challenges and provide solutions for electrospray ionization mass spectrometry (ESI-MS). Being inherently charged, they are themselves easy to characterize in both positive- and negative-ion mode by ESI-MS, but the challenge arises when using the IL as a solvent – how does one then identify the dissolved species? ILs can also be used to solve problems in ESI-MS, most notably removing the restriction that only polar solvents can support the electrospray ionization process.

Introduction

The huge growth witnessed in the field of ionic liquids over that last few years has been facilitated by new synthetic routes to ionic liquids, new ionic liquids with tailored physical and chemical properties, and an increasing scope

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of potential applications (1). Notably, with the discovery of the air and moisture stable imidazolium based ionic liquids (2) the field has seen incredible growth, especially, but not exclusively, in the use of ionic liquids as alternative reaction media (3). For example, ionic liquids are under investigation in energy research as electrolytes in solar cells and batteries, in materials science, in analytical and separation processes and elsewhere (4).

All the applied aspects of ionic liquid research are strongly facilitated by the development of analytical, spectroscopic and theoretical methods to probe their fundamental properties. In this respect an increasing body of papers devoted to these topics have been published. In turn, these studies have actually led to new applications of ionic liquids, such as matrices for matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) (5) – and an example of such a case concerning electrospray ionization (ESI) mass spectrometry is described herein.

Electrospray ionization mass spectrometry

ESI is a well-established method for the generation of gas-phase ions from solution for subsequent analysis by mass spectrometry (6). The technique gained rapid prominence for its ability to analyze high molecular weight, polar biomolecules as multiply-charged ions (7). It has also found favour among chemists interested in characterizing small molecules, in metabolomics, proteomics, trace analysis and quantification. ESI essentially involves pumping a solution through a charged (3-5 kV) stainless steel capillary into the atmospheric pressure source region. Under these conditions, the solution separates at the tip into a fine spray of charged droplets, from which the solvent is evaporated by a counterflow of warm nitrogen gas. The charge density on the droplets increases to the point that the droplet begins to divide, either by Coulomb explosion (in which the droplet splits into roughly equal parts) or by ion evaporation (in which individual solvated ions depart from the surface of the droplet). The ions are ultimately completely desolvated, and are transferred through a series of differentially pumped chambers into the mass analyzer, where the ions are separated by m/z in entirely conventional fashion. The description of ESI as a “soft” ionization technique comes from the fact that little energy is imparted to the ion in the process of transferring it from solution to gas phase, so minimal fragmentation occurs and spectra are dominated by intact ions.

Ionic liquids in ESI-MS

For relatively concentrated solutions of ionic compounds, including ionic liquids, it is entirely plausible that a small droplet contains a single net positive

(the same applies to negative ions) charge along with a number of paired cations and anions. A net double charge is unfavoured, as charge repulsion will break the droplet apart. A net surplus of one cation generates a series of aggregated ions of the type $[\{\text{cation}\}_{n+1}\{\text{anion}\}_n]^+$, and spectra of ionic liquids at all but the lowest concentrations contain exactly these series. Interestingly, this phenomenon means spectra in both ionization modes can readily characterize both cation and anion by molecular weight, since the difference in m/z between each ion in the series is equal to the mass of cation plus anion, and the first m/z value provides the mass of the cation (or anion, if in the negative ion mode). Figure 1 illustrates a typical ESI mass spectrum of an ionic liquid, in this case [bmim][BF₄]. The aggregates $[\{\text{cation}\}_{n+1}\{\text{anion}\}_n]^+$ can be clearly observed, and in this case, the presence of chloride ions in addition to the tetrafluoroborate ions can be detected, as an additional series of ions, $[\{\text{bmim}\}_{n+1}\{\text{BF}_4\}_{n-1}\{\text{Cl}\}]^+$. ESI-MS is therefore a rapid method not only for characterization of ILs, but is also capable of giving an indication of impurities that are *ionic* in nature. ESI-MS can not, of course, reveal the presence of neutral molecules, including solvent.

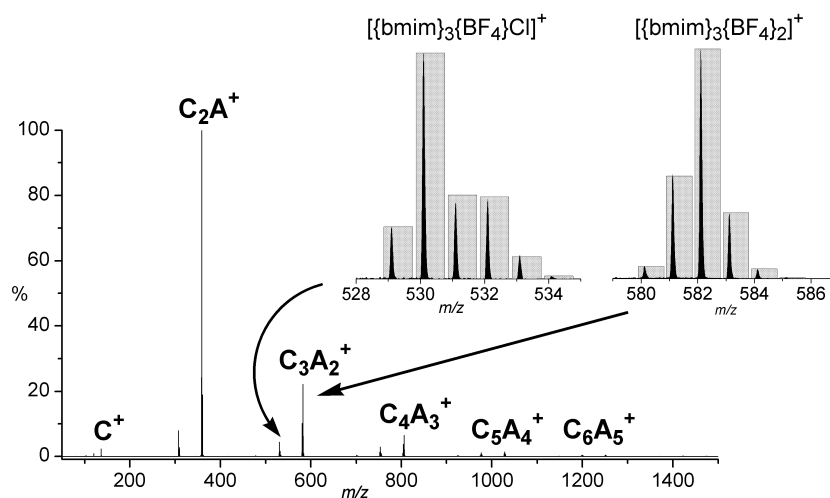


Figure 1. Positive-ion ESI-MS spectrum of the benchmark ionic liquid [bmim][BF₄], contaminated with chloride. The inset spectra are expansions of the isotope patterns (black line is experimental, histogram is calculated) of two of the aggregated ions, one with Cl⁻ and one with BF₄⁻ only. The combination of m/z and isotope pattern identifies the ions unambiguously. (Modified from reference 13. Copyright Royal Society of Chemistry.)

ESI-MS has also identified anion decomposition reactions of [bmim][PF₆], with [PF₄O]⁻ and [PF₂O₂]⁻ ions being observed from the hydrolysis of [PF₆]⁻ (8). The presence of the oxygen-containing ions could be correlated to the water content of the IL, and provided similar results to a Karl-Fischer titration.

The relative strength of anion-cation interaction in various ILs has been probed using ESI-MS/MS, and “magic numbers” observed for some aggregates (9). By selecting the mixed aggregate species [C¹⋯Br⋯C²]⁺ in the positive ion mode and [X¹⋯bmim⋯X²]⁻ in the negative ion mode and subjecting them to fragmentation via collision-induced dissociation, a qualitative order of interaction strength can be established (10).

Characterisation of IL solutes

Ionic liquids are currently undergoing extensive study as media for catalyst immobilisation in multiphasic catalysis. A diverse array of transformations are under investigation employing modified homogeneous catalysts (11). Although a wide range of catalysts and reactions have been screened across a range of ILs, a limited amount of *in situ* spectroscopic information regarding the fate of the catalyst is available. Extraction of the catalyst after reaction is difficult or impossible (at least for catalysts that do not easily leach), hampering post-reaction analysis by spectroscopic techniques. It has become apparent that often the optimum catalysts that operate in ionic liquids are those that are themselves ionic, with the charge either located on the metal centre or on a ligand. Such species lend themselves well to ESI-MS analysis (12), but since the solvent is also ionic and present in vast excess, swamping of the compound of interest and saturation of the detector makes analysis seem, at first glance, to be highly problematic. The question becomes whether or not the technique is sensitive enough to detect the trace quantities of ionic catalyst in the presence of large quantities of the IL solvent. The answer, fortunately, is yes, although the ionic liquid/ionic catalyst mixture must be diluted in a molecular solvent to enable the analysis to proceed (13). The degree of dilution can be very high, and needs to be, since pure ionic liquids (usually) have a concentration of >1 mol L⁻¹. ESI-MS, in comparison, routinely characterizes analytes at the micromolar level and is capable of much lower detection limits; indeed, one of the challenges in analyzing ionic compounds by ESI-MS is to ensure that dilution is sufficient that lingering contamination of the source does not occur. For the type of analysis described here, a balance has to be struck between appropriate dilution and successful detection of the dissolved catalyst. The range has been tested on the ionic liquid active catalyst [Ru(η⁶-*p*-cymene)(η²-triphos)Cl][PF₆] (1), dissolved in the ionic liquid [C₄mim][PF₆] at 0.1 mmol L⁻¹. The catalyst solution was diluted in methanol to concentrations of 10, 1, 0.1, 0.01 and 0.001 mmol L⁻¹.

The corresponding concentration of catalyst was 4 orders of magnitude lower in each case, i.e. 1000, 100, 10, 1 and 0.1 pmol L⁻¹. The spectrum collected at the highest concentration is depicted in Figure 2. Despite the overwhelming dominance of ionic liquid species (the cation itself and cation/anion aggregates), the presence of the catalyst can easily be detected. Even at the lowest concentrations used, the catalyst was still detectable.

The issue of overlap between IL aggregate ions and species of interest is potentially a problem, but one that may be overcome readily by making a slight change to either the cation or the anion of the IL; thus changing the *m/z* intervals at which the IL aggregates appear and removing the overlap problem.

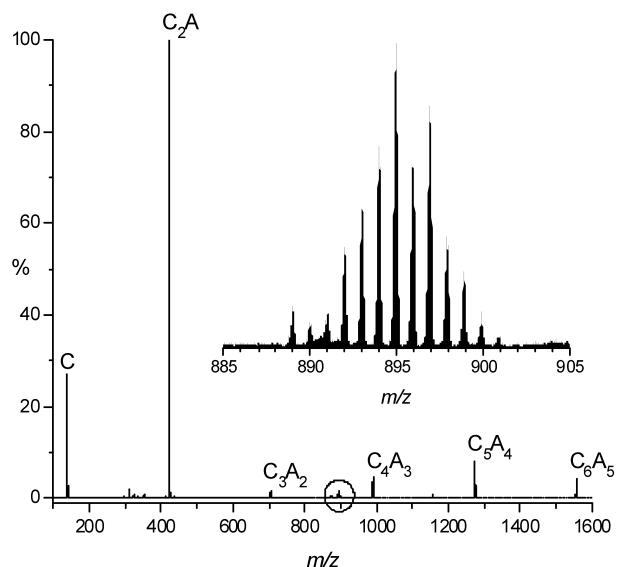


Figure 2. The positive ion ESI mass spectrum of $[Ru(\eta^6\text{-p-cymene})(\eta^2\text{-triphos})Cl][PF_6]$ in the ionic liquid $[C_4\text{mim}][PF_6]$, diluted in methanol to a concentration of 1000 pmol L⁻¹. “C” corresponds to the cation, “A” to the anion, so “C₅A₄” is the aggregated ion $\{[C_4\text{mim}]_5[PF_6]_4\}^+$. The circled peak and enlarged isotope pattern correspond to $[Ru(\eta^6\text{-p-cymene})(\eta^2\text{-triphos})Cl]^+$. (Reproduced from reference 13. Copyright Royal Society of Chemistry.)

It has been pointed out that a potential problem with the ESI-MS approach is the need to dilute the catalyst solution with a polar (nonionic) solvent. This alters the medium and may, under some circumstances, cause the species in solution to change (14). This perceived weakness attracted attention from Jackson and Duckworth (15), who showed that in fact it perhaps was possible to analyze ILs

directly, without dilution, using ESI-MS. An experiment in which ILs were infused directly into the source (desolvation gas heated to 250°C) allowed spectra to be collected that showed not only IL aggregates but also tetraalkylammonium ions dissolved in the IL. Such an approach has advantages, especially for reactive ILs such as chloroaluminate salts, but has some practical deficiencies: injecting such a high concentration of ionic material into the instrument inevitably leads to serious contamination issues requiring thorough cleaning of the source after each experiment.

Seeking ways to mitigate this disadvantage, we evaluated two alternative experimental methods: the first used a hanging drop of IL mounted on the charged capillary (a modification of Shiea's direct probe method) (16), and the second, nanospray from a preloaded microcapillary, both drastically reducing the amount of IL entering the instrument. The first method provided interesting results, because ion generation could be monitored over time as the temperature of the desolvation gas was increased. Ion production proved to be copious upon applying a high voltage to the capillary (the normal operating mode of ESI-MS), then tapered to zero, and could be recovered only upon heating the desolvation gas. Further, sporadic bursts of ion production were observed, and at very high desolvation temperatures (>300 °C), the ion current became high and steady. These three regimes of ion production **A**, **B**, and **C** (see ion chromatogram in Figure 3) were attributed as follows. Regime **A** represents residual molecular solvent departing from the droplet, taking with it small quantities of ions in a process reminiscent of conventional ESI. Once the residual solvent (or water, etc.) is exhausted, ion production nearly shuts down, but some ions and ion aggregates are able to periodically evaporate directly from the drop of heated IL (regime **B**). Finally, at very high temperature (regime **C**), the IL begins to decompose and a wide range of ions is observed in the mass spectrum.

The nanospray studies confirmed the importance of the presence of molecular solvent to the success of the ESI-MS experiment. The spectra of [Ru(η^6 -*p*-cymene)-(η^2 -triphos)Cl][PF₆] in [bmim][PF₆], [bmim][PF₆]/MeOH (1:1) and MeOH recorded under identical conditions are compared in Figure 4, illustrating the benefit of dilution. The presence of a molecular solvent results in a much higher ion current leading to a vast improvement in signal-to-noise ratio and hence detection limit.

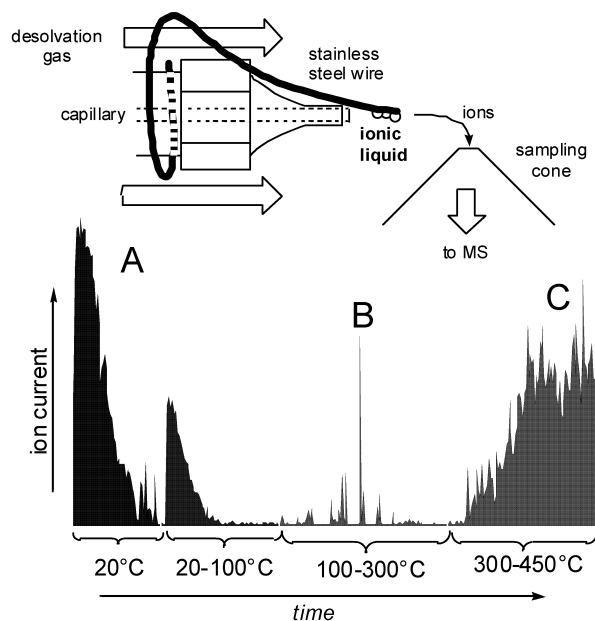


Figure 3. Top: Suspension of ionic liquid in the path of desolvation gas to enable direct probe analysis. Bottom: plot of ion current vs. time (temperature) for the direct probe analysis of neat [BuPy][BF₄]. Total acquisition time of seven minutes. (Modified from reference 13. Copyright Royal Society of Chemistry.)

It therefore seems highly probable that at least some molecular solvent is required to obtain satisfactory data from species dissolved in ILs. Directly infusing ILs may contain enough water or other solvent contamination for the purpose (assuming the IL has not been scrupulously dried), but has the downside of resulting in considerable contamination of the source. As such, the most reliable method is to dilute the IL with molecular solvent. The next section demonstrates just how wide a choice chemists have; essentially, the very presence of an IL facilitates the ESI process to the extent that practically any volatile solvent will do, regardless of its polarity. If it is suspected that catalyst speciation is being perturbed by the molecular solvent, this aspect can be investigated by choosing different diluents.

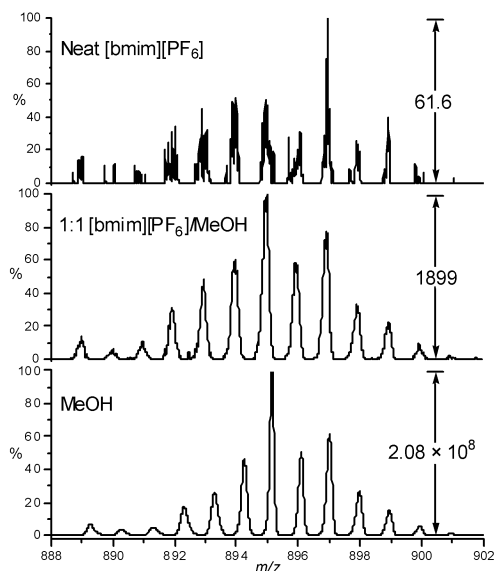


Figure 4. The positive-ion nanospray mass spectra of $[\text{Ru}(\eta^6\text{-p-cymene})-(\eta^2\text{-triphos})\text{Cl}][\text{PF}_6]$ in (top) neat $[\text{bmim}][\text{PF}_6]$, 1 mM; (middle) $[\text{bmim}][\text{PF}_6]$ -methanol 1:1, 0.5 mM; (bottom) neat MeOH, 0.5 mM. Acquisition time 5 min per spectrum. Absolute intensity (ion count) is indicated to the right of each spectrum. (Modified from reference 13. Copyright Royal Society of Chemistry.)

ESI-MS of non-polar solvents

Our efforts to use ESI-MS to probe ILs and solutes in ILs led us to investigate the range of diluting molecular solvents that might be used. ILs themselves have a huge range of solvation properties, ranging from miscibility in all proportions with water to miscibility with entirely non-polar solvents such as hexane or carbon tetrachloride. Insofar as ESI-MS is concerned, the IL must be at least slightly soluble in the diluting molecular solvent, immediately restricting the range of solvents that can be employed. Furthermore, ESI-MS is most amenable to polar solvents such as water, methanol and acetonitrile, and it is widely accepted that non-polar solvents such as hydrocarbons are essentially “off-limits” to the technique. It is less clear from the literature why this should be the case, but one possibility is that because ESI-MS is essentially an electrochemical process – the same number of ions are discharged at the

capillary as are generated in the source – and non-polar solvents may inhibit this process due to high resistance (17). In electrochemistry, the problem is dealt with in a straightforward way: a supporting electrolyte is added (18). ILs themselves are, of course, electrolytes, so an obvious experiment suggested itself: add a lipophilic IL to a non-polar solvent to examine its effect on the ESI-MS process (Figure 5) (19). We were encouraged in this approach by the fact that ILs had been successfully characterized from benzene using ESI-MS (20).

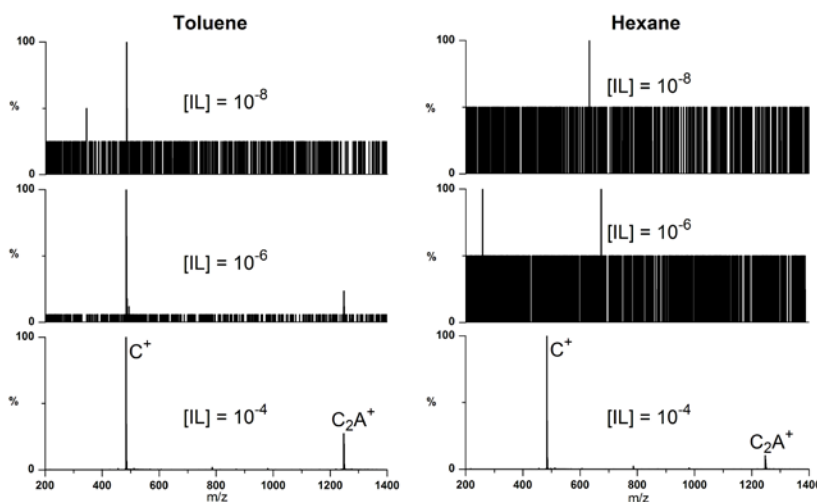


Figure 5. (left) $[P(C_6H_{13})_3(C_{14}H_{29})][NTf_2]$ in toluene and (right) $[P(C_6H_{13})_3(C_{14}H_{29})][NTf_2]$ in hexane. Reasonable quality spectra are obtained at different threshold concentrations for the two solvents. For toluene, approximately $10^{-6} \text{ mol L}^{-1}$ $[P(C_6H_{13})_3(C_{14}H_{29})][NTf_2]$ is required, whereas $10^{-5} \text{ mol L}^{-1}$ of the same IL is needed for hexane.

From Figure 5 it can be seen that the approach works quite satisfactorily using the lipophilic IL $[P(C_6H_{13})_3(C_{14}H_{29})][NTf_2]$, facilitating the collection of good quality data under quite conventional conditions (cone voltage, temperature, desolvation gas flow, etc.) for toluene and hexane. In the case of non-polar hexane, the highest concentration is required, approximately $10^{-5} \text{ mol L}^{-1}$, or preferably, $10^{-4} \text{ mol L}^{-1}$. Because the IL has a relatively high molecular weight, the higher concentration corresponds to about 0.1 mg ml^{-1} , high by MS standards but sufficiently low that source contamination is not a disabling problem. For more polar solvents such as, diethyl ether, fluorobenzene and dichloromethane good spectra of the IL could be collected down to the detection

limits of the instrument and there appears to be no minimum concentration of IL required for a stable spray.

Investigation of other ILs showed that the same enabling behavior. Careful choice of cation and anion could almost completely shut down the appearance of aggregate ions in the mass spectrum: the combination of a $[P(C_6H_{13})_3(C_{14}H_{29})]^+$ cation with a $[B(C_6H_3\{CF_3\}_2)_4]^-$ anion (a large, non-coordinating, lipophilic counterion) resulted in almost complete suppression of the aggregate ions $[C_2A]^+$ and $[CA_2]^-$ (present at <0.5 % of the base peak).

Provided a stable spray is obtained, any other soluble species can come along for the ride. So the circumstance in which a charged compound is only stable in a non-polar solvent is no longer a barrier to a successful analysis; addition of an IL enables ESI-MS detection of the IL and anything else present. Figure 6 demonstrates this approach; addition of a lipophilic IL to a small amount of a rhodium catalyst in cyclohexane results in a spectrum that is dominated by the IL and aggregates thereof, but the catalyst is visible and good quality data can be obtained on this species.

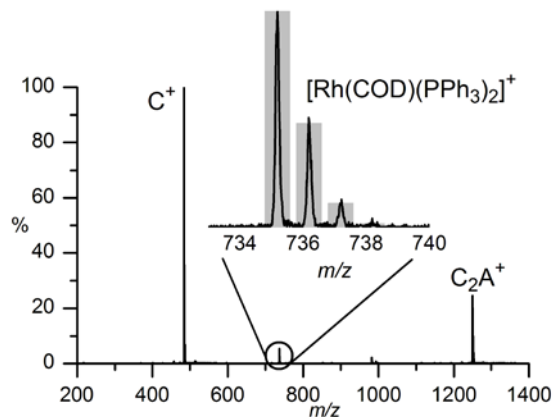


Figure 6. Facilitation of the ESI process in non-polar solvents by the presence of a lipophilic IL also enable the ready detection of analytes dissolved in the IL.

Here, high quality positive-ion ESI-MS data has been obtained on $[Rh(COD)(PPh_3)_2]^+$ dissolved in $[P(C_6H_{13})_3(C_{14}H_{29})][NTf_2]$ and diluted in cyclohexane. Inset: expansion of isotope pattern match for the analyte.

The addition of the IL has some other, less immediately obvious but still useful benefits. Firstly, the IL aggregates make excellent calibrants for obtaining accurate mass determinations. Secondly, in circumstances where the ionic compound of interest is not especially soluble in the non-polar solvent, addition of a lipophilic IL serves to dissolve the insoluble material, presumably through

counterion exchange. An example of this behavior is shown in Figure 7, where the hexane-insoluble $[\text{HNEt}_3][\text{HFe}_3(\text{CO})_{11}]$ is dissolved rapidly upon addition of a small amount of IL.

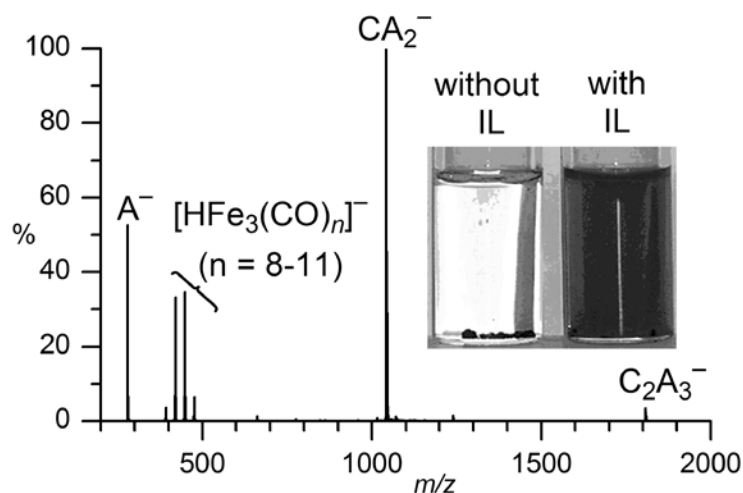


Figure 7. Negative ion ESI-MS of $[\text{HNEt}_3][\text{HFe}_3(\text{CO})_{11}]$ in hexane, with 10^{-4} mol L^{-1} of $[\text{P}(\text{C}_6\text{H}_{13})_3(\text{C}_{14}\text{H}_{29})][\text{NTf}_2]$ added. Inset shows how the salt is insoluble in hexane prior to the addition of the IL.

Conclusions

ILs and ESI-MS

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