Ionic Liquids: Sensitivity Enhancement in Headspace Gas Chromatography

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A relatively new application for ionic liquids, as solvents in static Headspace Gas Chromatography, is further investigated. Two ionic liquids were studied and the response towards a range of low boiling point residual solvents increased compared to when dimethyl acetamide was used as the headspace diluent. An attempt to correlate results with a suitable solvent model was made. The results highlight the potential of ionic liquids to enhance headspace sensitivity for residual solvent analysis.

Ionic liquids provide a wide spectrum of functions for chemical applications including: MALDI mass spectrometry matrices for the analysis of large biomolecules[i], 'Green solvents'[ii] and even performance additives for paint[iii]. Gas Chromatography is a relatively recent application for ionic liquids, in which novel ionic liquid stationary phases for capillary columns have been investigated[iv].

An ionic liquid can be defined as an organic salt, liquid under 100°C. Ionic liquids comprise of an organic cation, commonly based on nitrogen containing aromatic species and an anion such as Cl^-, BF_4^- or PF_6^-[v]. What makes ionic liquids so appealing for industrial applications are their physiochemical properties; these can be 'tuned' by alteration of alkyl chain length or associated anion[vi] (Figure 1). They have a wide liquid range, low thermal pressure, high viscosity, high conductivity, ability to dissolve many organic and inorganic compounds and high thermal stability[vii].

Static Headspace Gas Chromatography is a popular method for residual solvent analysis. Enhancement of headspace sensitivity is necessary because stringent guidelines exist for residual solvents in pharmaceutical products[viii].

In a previous experiment, the performance of the ionic liquid [BMIM][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate) was compared to DMSO (dimethylsulfoxide) as a diluent for high boiling point residual solvent analysis, the ionic liquid produced responses five- fold greater[ix].

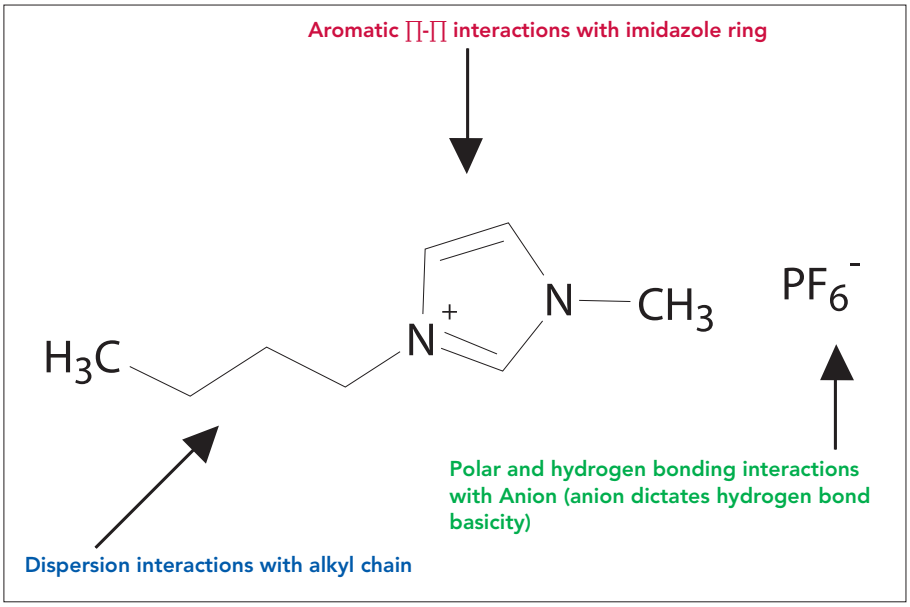

Figure 1: Illustration indicating various intermolecular interactions with ionic liquids using [BMIM][PF_6] as an example

In the following experiment the performance of two ionic liquids: [BMIM][PF_6] (1-butyl-3-methylimidazolium hexafluorophosphate) and [BMIM][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate) as static headspace solvents was determined with an aim to increase sensitivity. The sensitivity towards a range of low boiling point residual solvents was studied and the response compared to the common headspace solvent DMAC (N,N-dimethylacetamide).

Experimental

Chemicals and reagents

Analytical reagent grades of all residual solvents and ionic liquids were used and purchased from Sigma Aldrich.

Standard and Sample Preparation

A stock solution was made up as follows: 500µL of the following residual solvents were added to a 50 ml volumetric flask: methanol, n-pentane, ethanol, diethyl ether, acetone, propan-2-ol, t-butanol, n-propanol, ethyl acetate, dichloromethane, chloroform, cyclo-hexane, 1,4-dioxan, 4-methyl-2-pentanone, toluene and n-butyl acetate. The diluent used was DMAC.

The samples were made up as follows: 20µL of stock solution were added to a headspace vial containing 1.98ml of diluent (DMAC, [BMIM][PF_6] and [BMIM][BF_4]). Duplicates of each diluent were prepared. The approximate concentration of each residual solvent was 500 ppm relative to a test sample concentration of 20 mg/ml. For method validation, determination of system suitability was necessary and therefore 2 ml of each system suitability solution was transferred into 6 headspace vials and made up as follows: 12µL of stock solution in 20ml of each diluent.

Instruments and Methods

A capillary gas chromatograph Agilent 6890GC with a flame ionisation detector and Agilent Technologies Model 7694 headspace analyser was used for the solvent analysis. The column used was a 6% Cyanopropylphenyl; 94% dimethylsiloxane fused silica capillary column (dimensions: 25 m x 0.15 mm internal diameter x 0.84 µm film thickness). The system was controlled via ChemStation and the data was processed using Empower.

The equilibration temperature was 85°C and equilibration time was 15 minutes with the sample shaker turned on. The transfer line and needle temperature were kept at 140 °C. The injector temperature was 180°C with an injection time of 2 minutes. Vial pressurisation was 30 seconds with 12 psi helium. The loop size was 1ml, with a fill time of 3 seconds and equilibration time of 18 seconds. The FID was kept at 250°C. The column temperature programme consisted of a starting temperature of 40°C for 2.5 minutes, rising to 50°C at 4.44°C per minute, then to 225°C at 80°C per minute. Finally the temperature was held at 225°C for 1.06 minutes. Split flow was measured manually and was 47 ml/min and the carrier gas flow was 1.2ml/minute.

Results and Discussion

The chromatogram below shows the response towards the residual solvents studied when DMAC was used as the headspace gas chromatography diluent (Figure 2).

For all low boiling point residual solvents, the response increased when an ionic liquid rather than DMAC was used as the diluent (Figure 3). The change in residual solvent peak areas was used as a measure to quantify the difference in solvent response and hence determine the change in headspace sensitivity when ionic liquids were used as HS-GC solvents instead of DMAC.

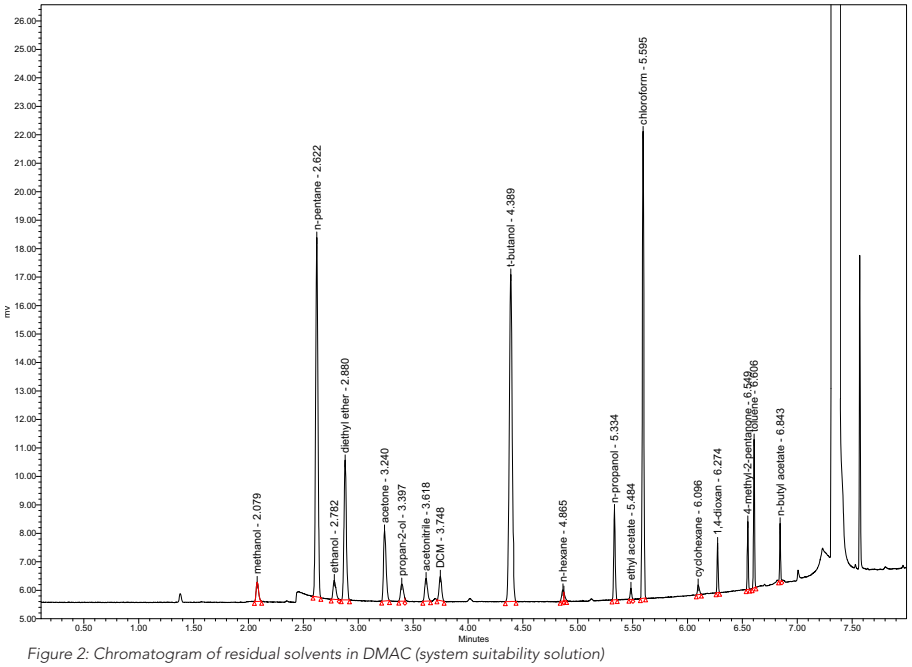

Figure 2: Chromatogram of residual solvents in DMAC (system suitability solution)

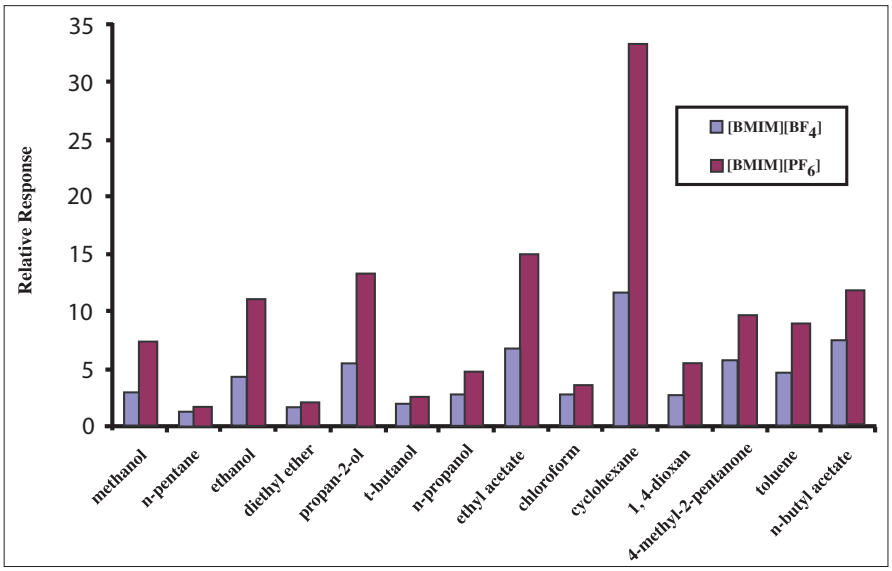

Figure 3: Relative responses of residual solvents in [BMIM][BF_4] and [BMIM][PF_6] compared to DMAC. Note that acetone, acetonitrile and dichloromethane were not included because of interference with the solvent peak of [BMIM][BF_4]

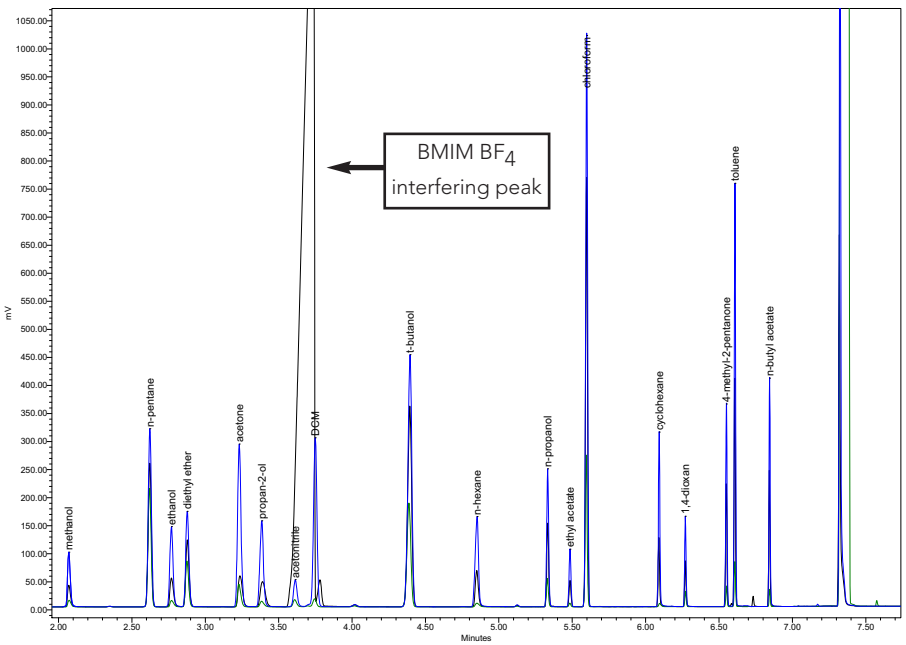

Figure 4: Overlay of chromatograms for the external standard solution in DMAC (green) [BMIM][PF_6] (blue) and [BMIM][BF_4] (black)

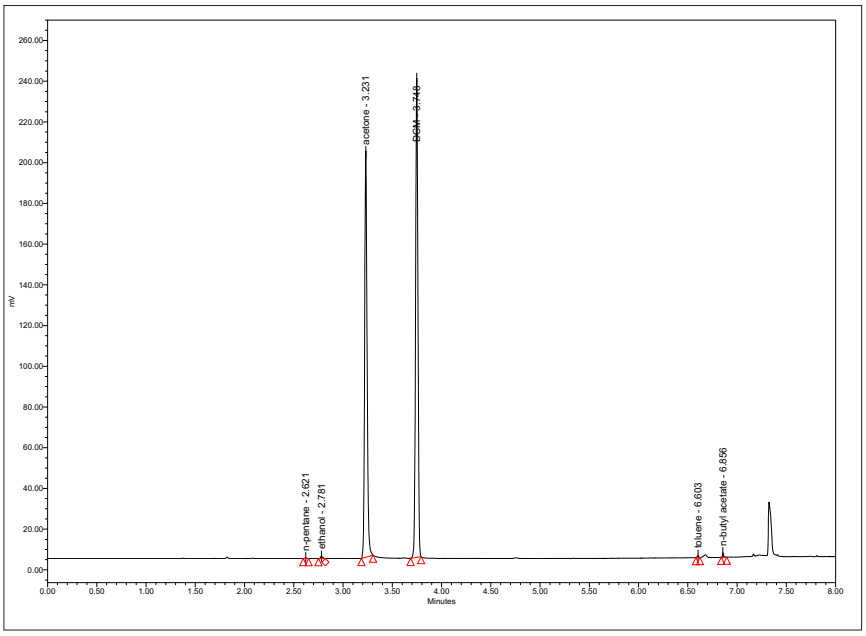

Figure 5: Chromatogram of [BMIM][PF_6]; showing residual solvent impurities.

In all cases the residual solvents response in [BMIM][PF_6] was superior to [BMIM][BF_4]. The response of cyclohexane has been increased almost 33 fold when compared to its DMAC response.

As can be seen in the chromatogram below, no peak relating to [BMIM][PF_6] is observed during the run (Figure 4). However, the chromatogram of blank showed two large peaks corresponding to the retention time of dichloromethane, acetone and two smaller peaks corresponding to low levels of toluene and n-butyl acetate (Figure 5) were also present. Therefore this solvent would not suitable for residual solvent analysis of the aforementioned solvents since significant levels of these volatile organic compounds are already present in the ionic liquid. [BMIM][BF_4] has an interfering peak (Figure 4) making quantification of acetone and acetonitrile difficult.

The difference in behaviour between ionic solvents may be explained by their difference in hydrogen bond basicity. [BMIM][PF_6] has a lower hydrogen bond bascity (1.579 at 70°C) than [BMIM][BF_4] (1.967°C)[10]. Due to the unique functionality of the ionic liquids their intermolecular interactions are numerous and complex (Figure 1). The main solute solvent interactions involve: hydrogen bonding, dispersion and polar interactions. Several linear free energy relationships have been proposed to account for the nature of the intermolecular interactions, the most recent being the Abraham solvent parameter model[x].

The decrease in partition coefficient of the residual solvents in the ionic liquids may account for the observed increase in response. The aim of the sample matrix is to lower the partition coefficient of the analyte (i.e. increase the analyte activity coefficient so that a greater concentration can be sampled in the headspace). Thus ionic liquids have lowered the residual solvent's partition coefficient and hence greater sensitivity has been achieved.

The relative responses of the analytes in [BMIM][PF_6] may additionally be understood by the Hansen solubility parameters when classified according to functional group (Table 1). Hansen solubility parameters were developed by Charles Hansen as a way of predicting if one material will dissolve in another. They are based on the idea that like dissolves like, with three descriptors being used to define the energy of a molecule;

- δ_d - The energy from dispersion bonds between molecules
- δ_p - The energy from dipolar intermolecular force between molecules
- δ_h - The energy from hydrogen bonds between molecules.

(Note: Δ δX = (δX(solute) /δX(DMAC)) - ((δX(solute) /δX[BMIM][PF_6])

Solute	Δ δD	Δ δP	Δ δH	Boiling Point/°C	rel. response
Propan-2-ol	0.19	0.17	0.10	82	13
Ethanol	0.19	0.25	0.12	78.3	11
Methanol	0.18	0.35	0.14	64.7	7.1
n-Propanol	0.19	0.20	0.11	97	4.6
t-Butanol	0.19	0.17	0.10	99	2.3

Table 2: to illustrate difference in Hansen solubility Parameters from DMAC to [BMIM][PF_6]

For the purposes of this experiment, the relative response is equal to the peak area of the solute in ionic liquid divided by the peak area of the solute in DMAC.

(Note: Δ δX = (δX(solute) /δX(DMAC)) - ((δX(solute) /δX[BMIM][PF_6])

Solute	Δ δD	Δ δP	Δ δH	rel. response
Pentane	0.17	0	0	1.5
Cyclohexane	0.2	0	0	33

Table 1: Difference in Hansen solubility parameters from DMAC to [BMIM][PF_6]

The first functional group to be considered are the alkanes. In order of relative response: cyclohexane > pentane. The dispersion interaction difference between DMAC and ionic liquid is greater for cyclohexane (Δ δD = 0.2) than pentane (Table 1). Thus dispersion forces may be the dominant interaction for the alkanes. However, the response of only 2 alkanes cannot be used as reliable indication of a trend for the entire homologous series and thus further work should be undertaken to correlate response with dispersion interaction difference.

However, there is no clear trend for alcohols. The strength of all three interaction parameters need to be taken into account to describe for the difference in relative response (Table 2). The solute which displays the largest change in relative response is propan-2-ol (13), however there is no difference in δH (Δ δH = 0.1) compared to the t-butanol which has a smallest change in relative response (2.3). It is worth noting that the solvent boiling points may have an effect on the observed response. The equilibration temperature is 85°C and thus under these conditions we can assume that the analytes are fully vapourised. However, t-butanol and n-propanol have higher boiling points, 99°C and 97°C respectively and therefore may only be partially vapourised in the headspace, and consequently t-butanol and n-propanol may have low relative responses because only low concentrations of solvents are present in the headspace, thus the difference between DMAC and [BMIM][PF_6] is too small for an accurate comparison to be made.

Reproducibility

The peak area %RSD peak area for each volatile organic impurity needed to be less than 10% and the retention time %RSD for each volatile organic impurity needed to be less than 1% as per the regulatory requirement.

The reproducibility criteria for %RSD peak

area were satisfied for all analytes when DMAC was used as headspace solvent (Table 3). For the ionic liquid [BMIM][BF_4], dichloromethane (%RSD = 88.53), acetonitrile (%RSD = 100.08), and n-butyl acetate (%RSD = 16.7) do not satisfy the method requirements. This is due to the interfering peak in the solvent which prevents quantification of these residual solvents.

The validation criteria for %RSD retention time (not shown) was satisfied for all analytes with the exception of dichloromethane in the ionic liquid [BMIM][BF_4] (%RSD = 1.36). This has been explained due to a significant amount of this residual solvent in the ionic liquid itself, which leads to inconsistent results.

Components	DMAC	[BMIM][BF_4]	[BMIM][PF_6]
Methanol	1.59	2.68	5.49
n-pentane	0.86	6.05	6.23
ethanol	2.45	4.1	4.21
diethyl ether	0.65	4.07	6.6
acetone	0.46	1.33	0.82
propan-2-ol	8.57	3.52	6.98
acetonitrite	1.94	100.08	5.94
dichloromethane	1.21	88.53	0.78
t-butanol	0.76	5.4	7.32
n-propanol	1.19	3.11	5.59
ethyl acetate	1.06	2.52	6.23
chloroform	0.85	4.88	7.54
cyclohexane	6.46	2.13	7.89
1, 4-dioxan	1.56	2.76	6.84
4-methyl-2-pentanone	2.31	3.43	6.25
toluene	4.18	3.35	5.14
n-butyl acetate	2.67	16.7	5.92

Table 3: Results to show the reproducibility of the different headspace solvents determined by %RSD peak area.

Conclusion

The performance of ionic liquids for headspace GC solvents was assessed and has provided invaluable insight into the enhancement of sensitivity towards residual solvents.

In all cases, ionic liquids increased the response towards the residual solvents in comparison to DMAC. The relative response of the analytes in the ionic solvents was partially explained by a combination linear free energy models, however, some trends were not fully accounted for.

Significant volatile organic impurities were present in [BMIM][PF_6] and therefore this ionic liquid was shown to be unsuitable for the determination of acetone and dichloromethane. [BMIM][BF_4] had a large endogenous interfering peak which co-eluted with the acetonitrile, dichloromethane and acetone peaks making the determination of these solvents impossible.

In conclusion, ionic liquids have shown promise as solvents in static headspace Gas Chromatography for low boiling point residual solvent analysis. The enhancement of headspace sensitivity by ionic liquids could be further exploited to achieve low limits of quantification for residual solvents and the potential to use smaller quantities of the active pharmaceutical ingredient.

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