

IC-MS and LC-MS Determination of Ionic Liquids, Counterions, and Impurities

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INTRODUCTION

Ionic liquid commonly refers to organic salts with relatively low melting points (below 100 °C)¹ that usually consist of an organic cation or anion and a counterion, in either organic or inorganic form. Ionic liquids exhibit unique characteristics such as extremely low vapor pressure, excellent thermal stability, electrical conductivity, and high polarity. The miscibility of ionic liquids with water or organic solvents varies with side-chain lengths on the cation and with choice of anion. A wide range of applications using ionic liquids have been reported in many areas such as catalysis, organic chemistry, electrochemistry, and separation science.²⁻⁸

Analytical methods for ionic liquid characterization are challenging due to the complexity of the cationic or anionic organic ions, counterions, and ionic impurities. Ion chromatography (IC), liquid chromatography (LC), and hydrophilic interaction liquid chromatography (HILIC) have been used for ionic liquid analysis, featuring ion-exchange or reversed-phase columns.⁶⁻⁸

This study applies two analytical approaches to serve different application purposes. The LC-MS method benefits from an Acclaim[®] Trinity[™] trimode column, able to separate cations, anions, and neutral species in a single run. This approach suits qualitative, confirmative, and semi-quantitative applications. The IC-MS method applies ion-exchange separation mechanisms and provides detailed anionic profiles including anionic ionic liquids, counterions, and impurities. This second approach can be used for quality assurance, impurity analysis, and trace-level residue analysis.

INSTRUMENTATION

Liquid Chromatography

System: UltiMate[®] 3000 HPLC system
 Column: Acclaim Trinity P1 (2.1 × 100 mm, 3 μm)
 Flow Rate: 400 μL/min
 Column Temp.: 25 °C

Mobile Phases: A) CH₃CN; B) 100 mM NH₄OAc, pH 5.2; C) DI H₂O

Gradient:	Time (min)	A	B	C
	-4.0	55	5	40
	2.0	55	5	40
	10.0	60	5	35
	11.0	90	5	5
	18.0	90	5	5

Detection: MSQ Plus[™] mass spectrometer

Ion Chromatography

System: ICS-2000 Reagent-Free[™] Ion Chromatography (RFIC[™]) system

Column: IonPac[®] AS20 and AG20 (2 mm)

Flow Rate: 0.25 mL/min

Column Temp.: 35 °C

Mobile Phase: KOH gradient

Gradient:	Time (min)	Hydroxide Concentration
	-5	10 mM
	6	30 mM
	14	60 mM
	16	100 mM
	30	100 mM
	30.5	10 mM

Detection: 1st: Suppressed Conductivity

2nd: MSQ Plus mass spectrometer

Mass Spectrometry

Interface: Electrospray Ionization (ESI)

Probe Temperature: 500 °C

Nebulizer Gas: Nitrogen at 85 psi

Needle Voltage: 1.0 kV

Scan Mode: Selected Ion Monitoring (SIM)

See Tables 1A and 1B for further scan details.

Peak	Analyte	t_r /min	SIM	Scan Event	Polarity	Cone Voltage
1	Lidocaine	1.5	235	0–3	positive	55
2	1-Butyl-3-methylimidazolium	1.9	139	0–3	positive	55
3	1-Ethyl-3-methylimidazolium	2.4	111	0–3	positive	55
4	Sodium as $[\text{Na}+6(\text{CH}_3\text{CN})]^+$	3.9	269	3.0–5.3	positive	50
5	K^+	4.5	39	3.0–5.3	positive	100
6	CH_3SO_3^-	5.7	95	5.3–6.2	negative	95
7	BF_4^-	7.0	87	6.2–13.0	negative	95
8	PF_6^-	7.9	145	6.2–13.0	negative	80
9	Cl^-	9.0	35	6.2–13.0	negative	90
10	Br^-	10.0	81	6.2–13.0	negative	90
11	I^-	11.8	127	6.2–13.0	negative	90
12	Tosylate	13.6	171	13.0–15.0	negative	70
13	Docusate	16.9	421	15.0–18.0	negative	80

Peak	Analyte	Formula	t_r /min	SIM	Scan Event	Cone Voltage
1	Fluoride	$[\text{F}+\text{HF}]^-$	4.4	39.0	3.5–7.2	25
2	Acetate	CH_3COO^-	5.0	59.1	3.5–7.2	50
3	Methanesulfonate	CH_3SO_3^-	5.3	95.0	3.5–7.2	60
4	Butanesulfonate	$\text{CH}_3(\text{CH}_2)_3\text{SO}_3^-$	6.0	137.2	3.5–7.2	60
5	Chloride	Cl^-	6.5	35.0	3.5–7.2	80
6	Trifluoroacetate	CF_3COO^-	7.9	113.1	7.2–9.5	30
7	Bromide	Br^-	9.0	78.9	8.5–9.5	100
8	Nitrate	NO_3^-	9.9	62.0	9.5–11.4	75
9	Sulfate	HSO_4^-	10.7	97.1	9.5–11.4	50
10	Tosylate	$\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3^-$	12.0	171.0	11.4–12.8	60
11	Tetraborate	BF_4^-	13.4	87.0	12.8–15.1	50
12	Triflate	CF_3SO_3^-	13.8	149.1	12.8–15.1	60
13	Phosphate	H_2PO_4^-	14.3	97.1	12.8–15.1	50
14	Iodide	I^-	15.7	127.0	15.1–17.6	90
15	Thiocyanate	SCN^-	19.4	58.0	17.6–22.6	50
16	Perchlorate	ClO_4^-	20.5	99.0	17.6–22.6	80
17	Hexafluorophosphate	PF_6^-	27.7	145.1	22.6–30.5	80

RESULTS

Choice of Analytical Methodology for Different Application Purposes

Due to the variety of applications using ionic liquids, different analytical methodologies are desired to meet different analytical goals. For example, pharmaceutical formulations using ionic liquids as active ingredients need analytical methods to determine those ingredients and counterions at high concentrations with high throughput; ideally, this means a single injection with simultaneous analysis. Other applications using high-purity ionic liquids or ionic liquids as synthetic solvents require analytical methods to determine trace-levels of impurities and the efficacy of the impurity removal process.

An LC-MS method was developed for high-throughput simultaneous determination of cationic, neutral, and anionic analytes. The Acclaim Trinity column was selected for the separation, because it features reversed phase, anion-exchange, and cation-exchange retention mechanisms.

The IC-MS method was developed to achieve low detection levels for anionic analytes, including anionic counterion and impurity profiles. Ion chromatography was the method of choice for quantification purposes due to the significantly improved sensitivity for anionic species observed with IC-MS over the LC-MS method. This observation can be explained by comparing the eluents entering the MS detector. For IC-MS methods, the suppressed eluent is virtually only analytes in deionized water. This keeps the electrospray current at a very low level, enabling efficient ionization and detection of the analytes in the ESI process. In contrast, for the LC-MS method, analytes are eluted in a mobile phase of higher ionic strength (5 mM total acetate) where analytes are detected with much less efficacy.

LC-MS for Simultaneous Determination of Ionic Liquids, Counterions, and Impurities

Previously reported LC-MS methods used reversed-phase columns to analyze organic cations or anions, and ion-exchange columns to analyze inorganic counterions and impurities such as tetrafluoroborate (BF_4^-), methanesulfonate (CH_3SO_3^-), hexafluorophosphate (PF_6^-), chloride (Cl^-), bromide (Br^-), and iodide (I^-). In this study, attempting to retain and resolve ionic liquids, counterions, and inorganic ions simultaneously, a trimode column was selected featuring reversed-phase retention and cationic/anionic-exchange retention mechanisms. Chromatographic behaviors of ionic organics were affected by mobile phase strength (including percentage of organic solvent in the mobile phase and the buffer concentration/ionic strength), buffer pH, and operating temperature. In this study, chromatography was optimized to simultaneously separate imidazolium and lidocaine cationic species, inorganic cations (sodium and potassium), inorganic anionic counterions (CH_3SO_3^- , BF_4^- , PF_6^- , Cl^- , Br^- , I^-) and anionic species (tosylate and docusate).

As shown in Figure 1, 13 analytes were eluted in groups from a Trinity P1 analytical column in the following elution order: organic cations, inorganic cations, inorganic anions, and organic anions.

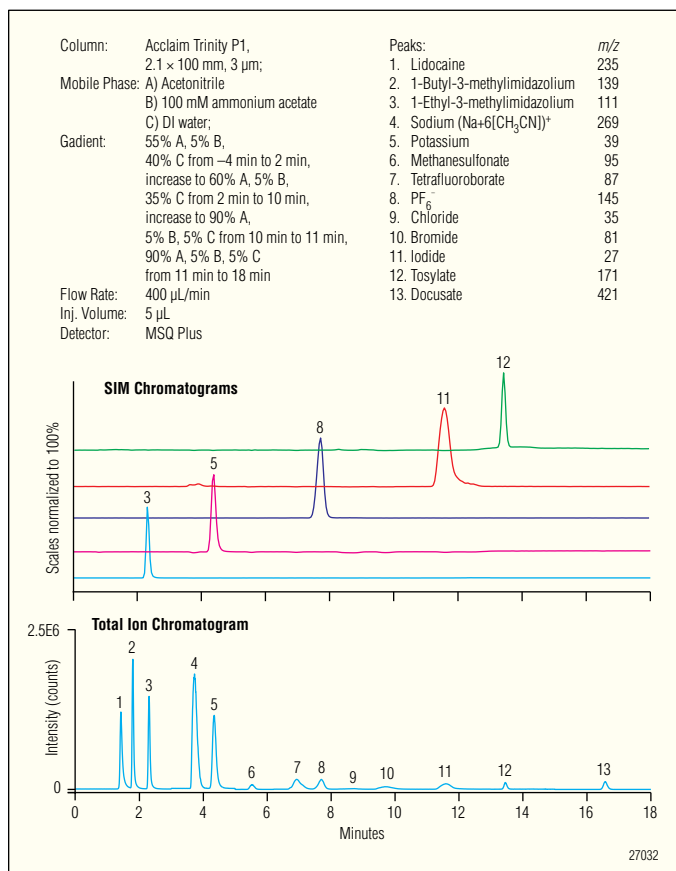


Figure 1. LC-MS for simultaneous analysis of ionic liquids, counterions, and impurities.

When used in a confirmative analysis mode, this LC-MS method can detect sub-ppb levels of major ionic liquid analytes (lidocaine, 1-butyl-3-methylimidazolium, 1-ethyl-3-methylimidazolium, PF₆⁻, docusate), sub-ppm levels of halogen impurities (Cl⁻, Br⁻, I⁻), and ppb levels of cationic counterions (sodium and potassium).

IC-MS Determination of Anionic Ionic Liquid Profiles

As previously mentioned, the IC-MS method provided better sensitivity for anionic species, and better suited the purpose of low-level quantification of anionic profiles. This IC-MS method focused on the quantitative determination of anionic impurity profiles in ionic liquids, including not only halogen anions such as fluoride (F⁻), but also additional commonly encountered anions: acetate (CH₃COO⁻), butanesulfonate (CH₃(CH₂)₃COO⁻), trifluoroacetate (TFA, CF₃COO⁻), nitrate (NO₃⁻), sulfate (detected as HSO₄⁻), triflate (CF₃SO₃⁻), phosphate (detected as H₂PO₄⁻), thiocyanate (SCN⁻), and perchlorate (ClO₄⁻). A multistep gradient (details described in experimental section) was applied to chromatographically separate all analytes, shown in Figure 2.

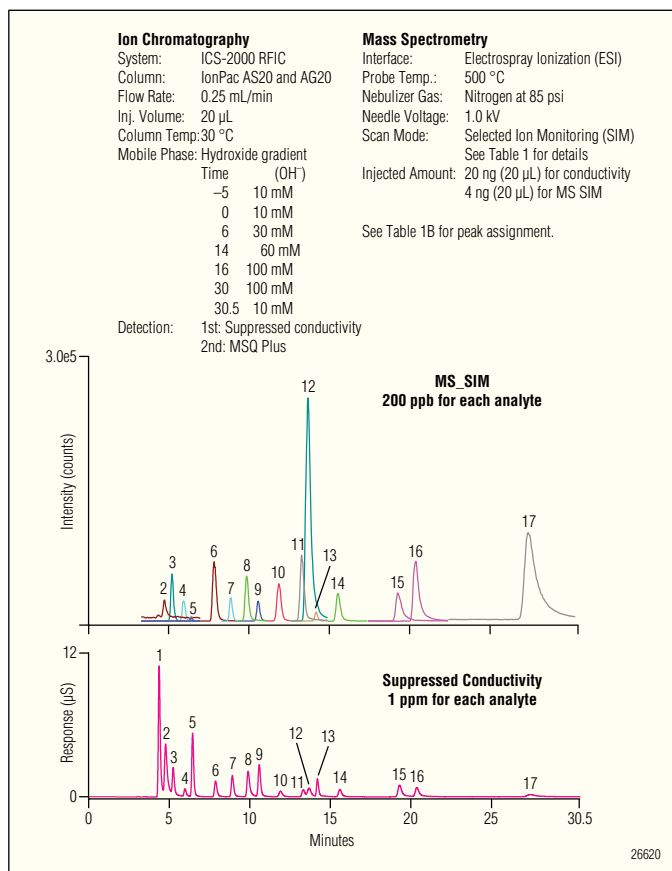


Figure 2. Suppressed conductivity and MS SIM chromatograms for ionic liquids and anions.

Method Performance for Quantification

Because this IC-MS method was developed primarily for quantification purposes, method performance was evaluated with respect to calibration range, precision, and detection limits. The evaluation results are summarized in Table 2.

Table 2. Calibration, Range, and Method Detection Limits (MDL)							
Peak	Analyte	Calibration Range (ppb)		Fitting	r ²	%RSD ^b	MDL ^c
1	Fluoride ^a	100	1000	Linear	0.997	9.35	29.39
2	Acetate ^a	50	1000	Linear	0.999	NC ^d	NC ^d
3	Methanesulfonate	5	1000	Quadratic	0.999	5.40	3.39
4	Butanesulfonate	5	1000	Linear	0.999	3.90	2.62
5	Chloride	2	1000	Quadratic	0.996	5.55	3.49
6	Trifluoroacetate	5	1000	Cubic	1.000	1.72	1.16
7	Bromide	2	1000	Cubic	0.997	2.95	1.85
8	Nitrate	2	1000	Cubic	0.994	2.86	1.80
9	Sulfate	5	1000	Quadratic	0.998	9.75	6.13
10	Tosylate	5	1000	Quadratic	0.999	1.55	1.04
11	Tetraborate	5	1000	Cubic	1.000	4.99	3.36
12	Triflate	5	1000	Cubic	0.998	2.11	1.42
13	Phosphate	5	1000	Quadratic	1.000	4.99	3.36
14	Iodide	5	1000	Cubic	1.000	4.42	2.78
15	Thiocyanate	5	1000	Cubic	1.000	1.69	1.06
16	Perchlorate	5	1000	Cubic	0.999	4.54	2.85
17	Hexafluorophosphate	5	1000	Quadratic	0.998	4.76	2.99

^aData obtained from previous experiments

^b%RSD calculated based on experiments with n > 5

^cMDL calculated by $MDL = S \times t_{(99\%, n > 5)}$

^dNC not calculated

Calibration curve and range were evaluated against a set of calibration standards from 2 to 1000 ppb at 8 levels. Good coefficients of determination were achieved for each analyte with r² > 0.99 from the lowest calibration standard with S/N > 10 to 1000 ppb.

Method detection limits (MDL) were statistically calculated by the equation $MDL = S \times t_{(99\%, n > 5)}$, where S is the standard deviation and t is the Student's t at 99% confidence interval (n > 5). MDLs were achieved at low ppb levels for each analyte, ranging from 1.04 ppb (tosylate) to 6.13 ppb (sulfate).

Analysis of Commercial Ionic Liquids

The two methods described here were used for the analysis of several commercial ionic liquids. Neat chemicals were dissolved in DI water at 2 mg/mL, and injected directly for IC-MS analysis. For LC-MS analysis, the standard solutions were first diluted to 1 μM and injected for analysis. Figure 3 shows the LC-MS chromatograms for four ionic liquids and counterions. Figure 4 shows the conductivity and MS SIM traces of 1-butyl-3-methylimidazolium/PF₆⁻ and detected anions by IC-MS. Table 3 summarizes the quantification results for the detected anions.

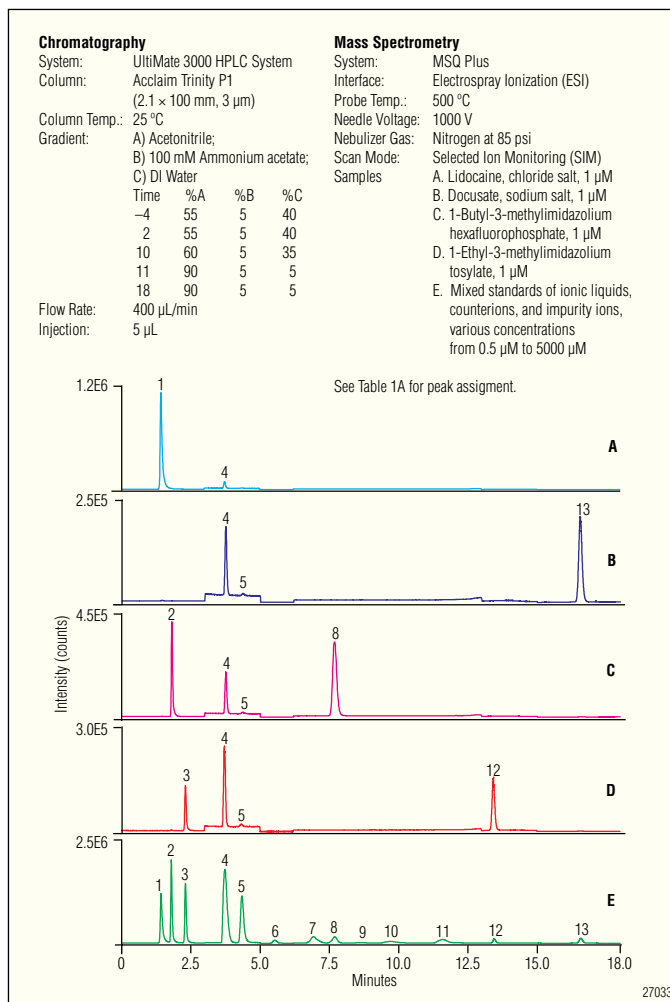


Figure 3. LC-MS analysis of commercial ionic liquids. The Total Ion Chromatogram (TIC) shown in Trace E is the sum of 13 SIM scans.

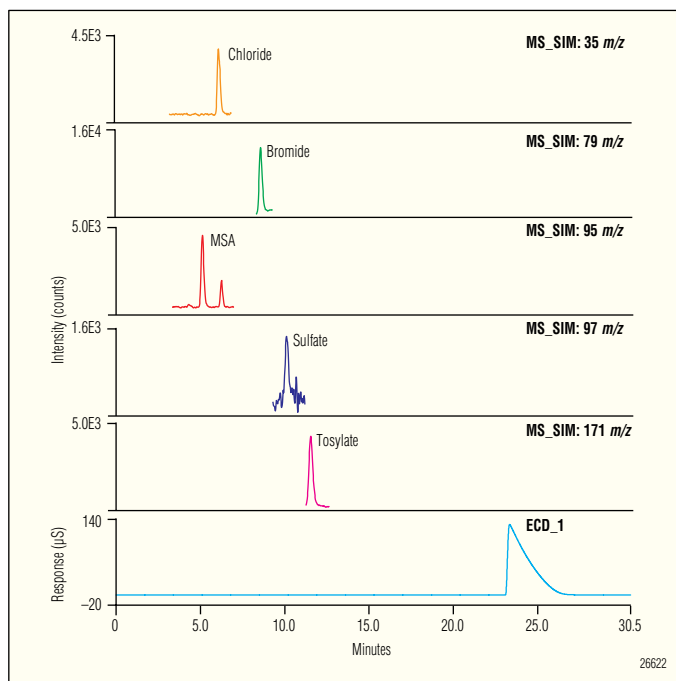


Figure 4. PF_6^- and impurity anions by IC-MS and conductivity.

Table 3. Quantification of Anions in Commercial Ionic Liquids			
Analyte	Lidocaine/HCl	1-Butyl-3-methyl-imidazolium/ PF_6^-	1-Ethyl-3-methyl-imidazolium/Tosylate
Acetate	25.99	ND	ND
Methanesulfonate	ND	BRL	ND
Chloride	—	12.55	13.23
Bromide	7.7	7.69	3.41
Nitrate	BRL	BRL	BRL
Sulfate	BRL	BRL	5.65
Tosylate	BRL	BRL	—
Hexafluorophosphate	BRL	—	14.08

CONCLUSION

- This study describes two approaches for analysis of ionic liquids: an LC-MS method for ionic liquid quantification and confirmative analysis for counterions and impurities, and an IC-MS method for low level quantification of anionic ionic liquids and anionic species, including counterions and impurities.
- Using the LC-MS method, major ionic liquid analytes can be analyzed at sub-ppb levels with the confirmation of major cation impurities: sodium and potassium.
- Using the IC-MS method, quantification at low-ppb levels was achieved for diluted solutions (low-ppm level in original sample) with good coefficients of determinations ($r^2 > 0.99$). Three commercially available ionic liquid samples were analyzed by this method, with the common impurities of chloride and bromide quantified at ppm levels. Acetate, sulfate, and hexafluorophosphate were also discovered in some samples.

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