Ionic Liquids:
some recent studies and what we have done

Group Meeting

9/15/11

What are ionic liquids?

- Nonmolecular salts that have melting points below 100^{o}C.
- Room Temperature Ionic Liquids (RTIL): melting point is below room temperature
- Virtually no vapor pressure (Pandey), more recently have been found to have measurable vapor pressures (Leal)
- They have a wide range of miscibility/solubility/other physical properties

Why use ionic liquids?

- They are good solvents that offer an alternative to harsh/harmful organic solvents (Pandey)
- You can tune physical properties (i.e. solubility, viscosity, miscibility, and density) with choice of anion and cation. (Pandey)
- Mostly used as solvents for various syntheses, and as catalysts. More recently also used in separations, and extractions (Pandey)
- Sometimes reusable (extraction with super critical (sc)CO_2) (Pandey)

Current Applications

- Chromatography
  - GC: Wetting ability and viscosity of bmimPF_6 and bmimCl (bmim = 1-butyl-3-methylimidazolium) good for stationary phases . Act as low polarity stationary phases for nonpolar compounds, but solutes with proton-donor groups are retained. (Pandey)
  - HPLC: RTILs added to the mobile phase have shown decreased band tailing, reduced band broadening, and improved resolution. Also functionalized silica particles of stationary phase with imidazoliumBF_4 RTILs helped separate basic compounds, i.e. basic drugs (silica particles too acidic). Drawbacks for countercurrent chromatography: high viscosity, high UV absorbance, non-volatile (difficult to detect). (Pandey)
  - CE: helps separate water-insoluble dyes in non-aqueous CE. Used RTILs to coat capillary to separate DNA and basic proteins (lysozyme, cytochrome c, trypsinogen, α-chymotrypsinogen). Suggested mechanism: association between imidazolium cations and proteins. (Pandey)

- Extraction
  - Used with crown ethers to extract aqueous metal ions (pandey)
  - Derivatized imidazolium ions for specific tasks (i.e. metal ligating groups) (pandey)
  - Liquid phase micro extraction solvents (Pandey)
  - Different types of RTILs are selective for different metal ions (Pandey)
  - Used with $scCO_2$ enhances extraction capabilities (Pandey)
  - Recovery of biofuels (Dorbritz)
- Electroanayltical: (Pandey)
  - electroytes
  - Photochemical solar cells
  - Double-layer capacitors
  - Solvents for electrodeposition of metals
- Sensing: (Pandey)
  - Sensing of organic vapors: viscosity change due to solubility of analytes. Specific to gaseous chemical and type of RTIL. Rapid response and reversibility observed.
  - Good for extreme conditions (i.e. high temperature/pressure)
  - Amperometric sensors for O_2
  - Stable solvents for ionic polymer transducers (also slower response)

- Spectrometry (Pandey)
  - Matrix for UV-MALDI: great solubilizing properties, reproducibility, and vacuum stability, however vary in ability to produce gas phase ions.
  - Matrix for MALDI: Generally fast and sensitive with little sample prep/manipulation. More homogenous distribution of analyte in matrix
  - ESI MS possible: has been used to detect ionic catalysts (ex: ruthenium catalyst)
  - Can be used with AES but viscosity decreases nebulization efficiency
  - Molecular fluorescence spectrometry: to investigate solvation processes (similar to short chain alcohols), addition of cosolvents has large effect

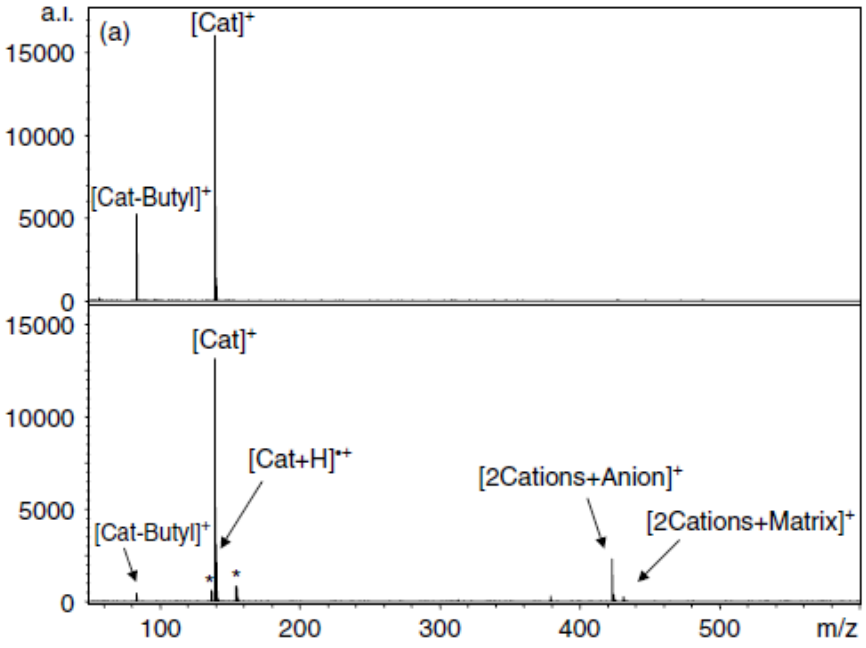
- Rocket Fuels (Jamie's ionic liquids):
  - When exposed to a strong oxidizer (such as fuming HNO_3), some dicyanamide RTILs undergo hypergolic ignition
    - FTIR studies show a fast reaction to produce unstable intermediates
  - Ionic liquids in general are appropriate fuel for ionic thrusters
  - Would allow for one main fuel to provide thrust via both chemical and ionic thrusters

Some Ionic Liquids and their Uses:

IL	Use	Specifics
1-butyl-3-methyl imidazolium (bmim)PF6	GC-SP	
	countercurrent chromatography	high viscosity is problem
	extraction (with crown ethers) of metal cations	
	extraction (with dithizone metal chelator) of heavy metals	pH dependent
	O2 sensor	wide detection range, high stability
bmimCl	GC-SP	
1-benzyl-3-methylimidazolium trifluoromethanesulfonate	GC-SP	thermal stability
1-(4-methoxyphenyl)-3-methylimidazolium trifluoromethanesulfonate	GC-SP	thermal stability
1-alkyl-3-methylimidazolium	HPLC-MP	separate catecholamines and amines
1-alkyl-3-methylimidazolium PF6	CE	separate basic proteins
	extraction	selective for Ag+
N-butylpyridinium	HPLC-MP	separate catecholamines and amines
imidazoliumBF4 RTILs	HPLC-SP	separate basic compounds
1-octyl-3-methylimidazoliumPF6	direct immersion and headspace LPME	polycyclic aromatic hydrocarbons
4-tert-octylphenol	direct immersion and headspace LPME	polycyclic aromatic hydrocarbons
4-nonylphenol	direct immersion and headspace LPME	polycyclic aromatic hydrocarbons
1-methyl-3-propylimidazolium iodide + 1-methyl-3-ethylimidazolium dicyanamide + lithium iodide	(w/ amphiphilic polypyridyl ruthenium sensitizer) solar cell	good efficiencies
tri-1-butylmethylammonium bis((trifluoromethyl)fulfonyl)imide	electrochemistry of cesium	
1-ethyl-3-methylimidazolium tetrafluoroborate	amperometric sensor for O2	
1-ethyl-3-methylimidazolium trifluoromethylsulfonate	Nafion™ transducer solvent	improved air stability
RTILs containging lithium methylsulfonyl group	sensor for ethanol	sensitive
2,5-dihydroxybenzoic acid butylamine	MALDI matrix	enzymatic reaction screening
triethylamine/α-cyano-4-hydroxycinnamic acid	MALDI matrix	"matrix free" mass spectra
n-butylpyridinium dicyanamide	potential rocket fuel	
α-cyano-4-hydroxycinnamic acid (CHCA) butylamine (CHCAB)	ESI additive	cleaner polysaccharide spectra
2,5-dihydroxybenzoic acid (DHB) butylamine (DHBB)	ESI additive	cleaner polysaccharide spectra

Ionization Methods in Mass Spectrometry

- EI and CI:
  - Initially found to be unsuccessful: low vapor pressure (Jackson)
  - Studied via APCI, EI, APTDI (atm press. Thermal desorp. Ionization) (Leal)
- FAB MS: (Jackson)
  - Characterized by a dominant peak for unbound cation and with clusters $[(AB)_nA]^+$ (Jackson)
- MALDI-MS: (Zabet)
  - DHB: dihydroxybenzoic acid
  - CCA: α-cyano-4-hydroxycinnamic acid
    - Sinapinic acid (SA)



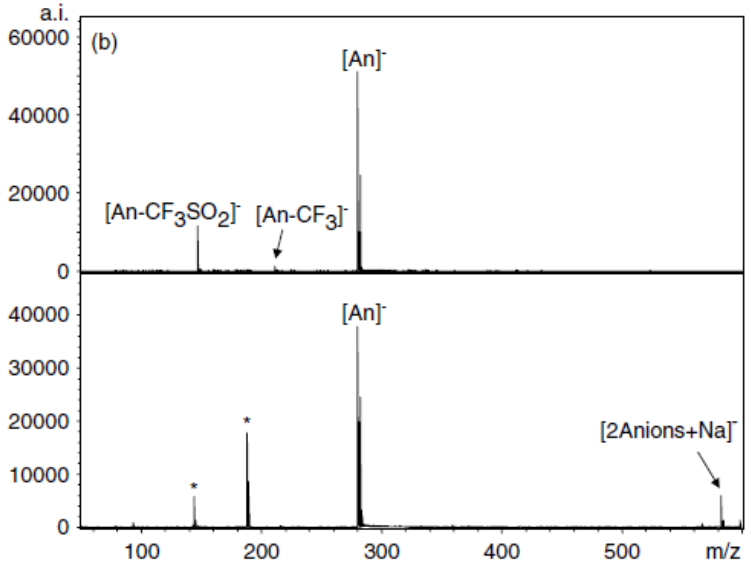


Figure 1. (a) [BMIM][PF_6] in positive ion mode measured by LDI-MS (top) and MALDI-MS (bottom) using DHB as matrix. (b) [BMIM][$(CF_3SO_2)_2N$] in negative ion mode measured by LDI-MS (top) and MALDI-MS (bottom) using CCA as matrix. $[An]^-$: signal of the ionic liquid anion. For all spectra, 200 shots were accumulated. An ionic liquid to matrix molar ratio of 1 : 10 was applied in the case of MALDI measurements. Asterisks denote peaks from DHB and CCA.

Proteins in MALDI Matrices with ILs present (Zabet)

- proteins can still be detected via MALDI with ILs present in the matrix
- Do not need to remove ILs from chromatography before analysis

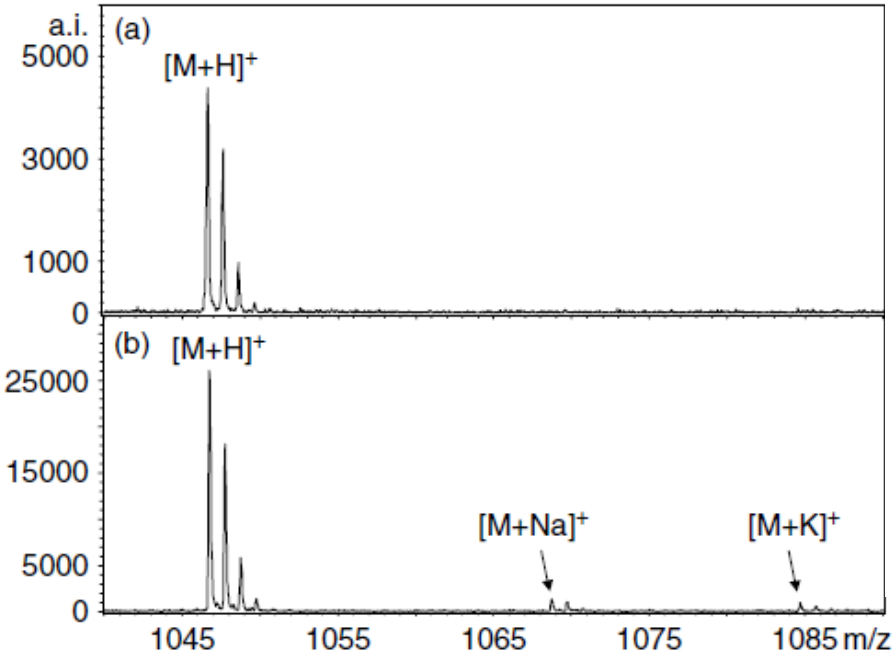


Figure 3. MALDI mass spectra of angiotensin II in CCA, (a) in the presence of [BMIM][$(CF_3SO_2)_2N$] and (b) without ionic liquid. 200 shots were accumulated in both cases.

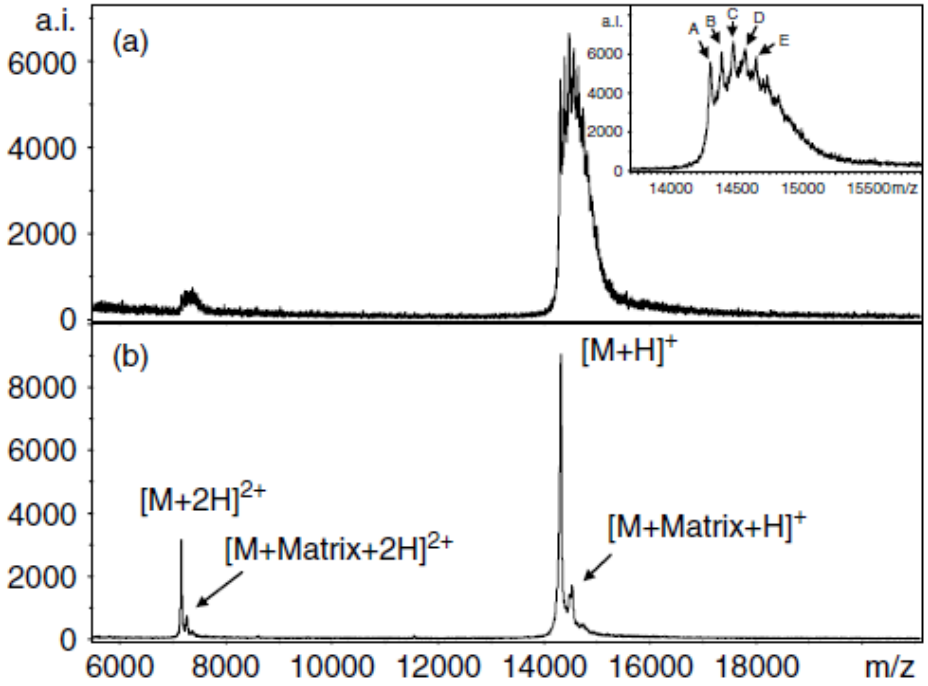


Figure 4. (a) MALDI mass spectrum of lysozyme ($M_r \approx 14\,300$) in [BMIM][BF_4] using SA as solid matrix (the inset shows a detailed view of the BF_4 adduct region: A, $[M + H]^+$; B–E, adducts of 1–4 $[BF_4]^-$ ions). An ionic liquid to matrix molar ratio of 50 000 and a matrix to analyte molar ratio of 23 000 were applied; 200 shots were accumulated. (b) MALDI mass spectrum of lysozyme in SA without ionic liquid. A matrix to analyte molar ratio of 23 000 was applied; 200 shots were accumulated.

Comparison of Various Matrices and analytes for MALDI-MS

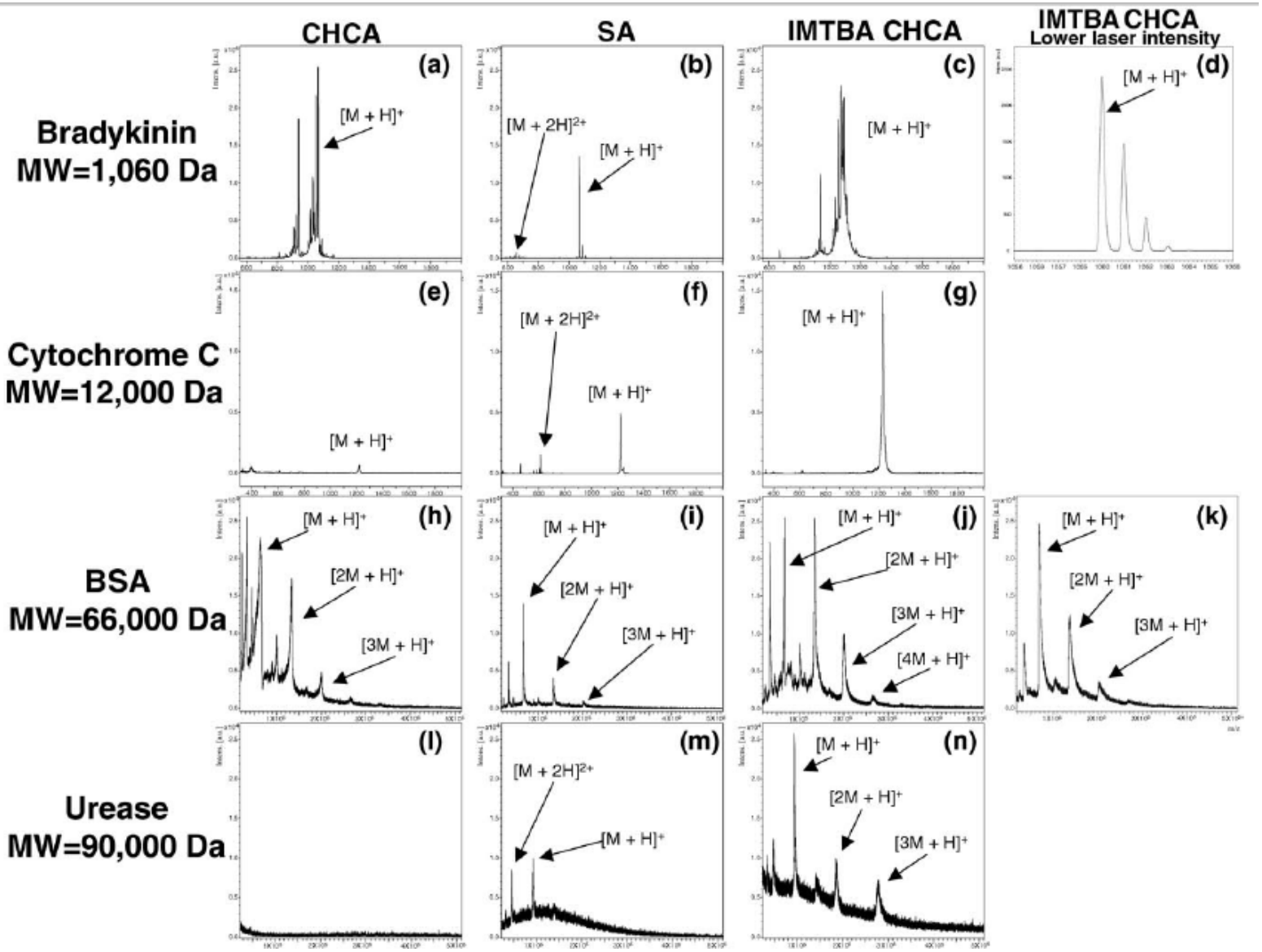


Figure 1. Comparison of solid matrices and an ILM (columns) with four different analytes (rows). CHCA, SA, and IMTBA CHCA are compared using the same laser power and analyte concentration. Analytes shown are bradykinin (MW = 1060 Da), cytochrome *c* (MW = 12,000 Da), BSA (MW = 66,000 Da), and urease (monomer MW = 90,000 Da). Peaks are labeled in the $[M + H]^+$ notation. Spectra (d) and (k) show bradykinin and BSA, respectively, at lower laser powers to show that good resolution is achieved. Spectrum (n) shows a $[3M + H]^+$ peak with a mass of 270,000 Da.

ESI-MS of ILs (Jackson)

- Undiluted IL vs. diluted IL
  - Dissolved: better signal response of dissolved "impurities," higher chemical noise
  - Undiluted: very sticky (must clean source frequently), heated curtain gas required (viscosity dependent)
- Nozzle-skimmer CID gives increased m/z 84 peak (i.e. fragment of the bmim ion)

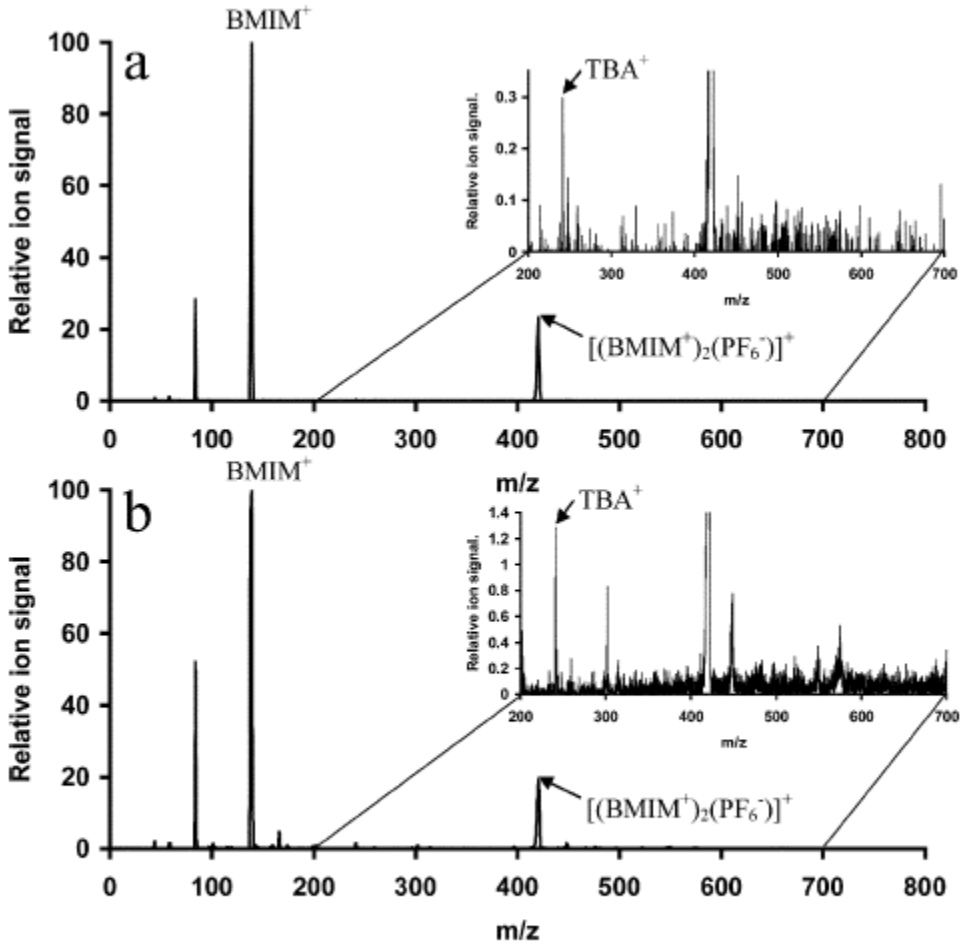


Fig. 1 ES mass spectrum of BMIM-PF_6 containing 2×10^{-4} M TBAI, a) matrix electrosprayed without dissolution, b) RTIL matrix dissolved to 2×10^{-4} in methanolic solution.

Heating effect on signal (Dyson)

- A: ~Diluted solution of IL, Cl^- is problem in purification
- B: Aggregation is more extensive, TIC fluctuates in this region depending on IL
- C: Ionic liquid decomposes—spectrum shows products of this.

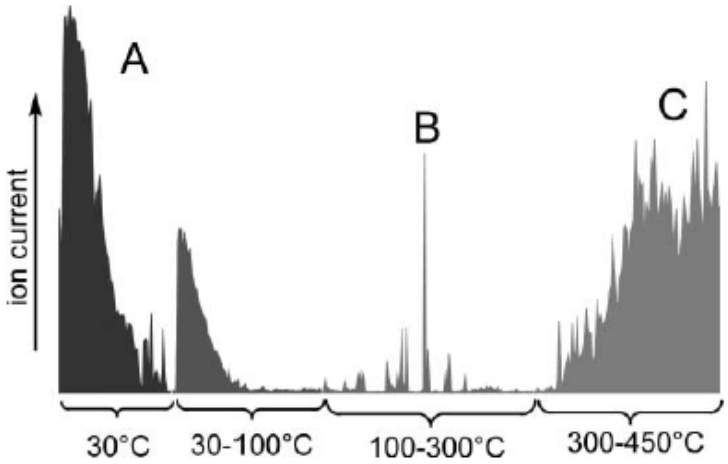


Fig. 2 Plot of ion current *vs.* time (temperature) for the direct probe analysis of neat [BuPy][BF_4]. Total acquisition time of 7 min.

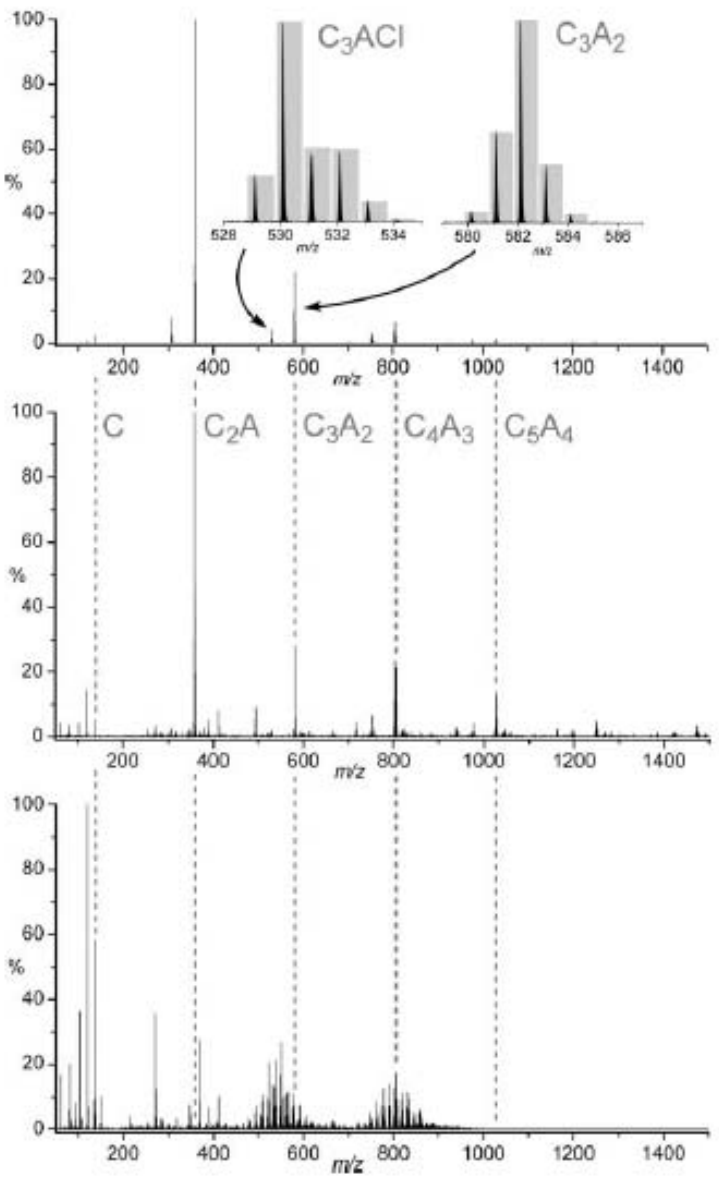


Fig. 3 Positive ion electrospray ionization mass spectra of neat [BuPy][BF_4] collected in regimes A (top), B (middle) and C (bottom).

Nature of Ionic Liquids in the Gas Phase

- Studied via EI-FTICR MS under conditions similar to IL distillation
- ILs are volatile (esp. heated)
- ILs exist as neutral ion pairs when allowed to evaporate in reduced-pressure distillation
- Large aggregates of ILs are not stable under low pressure (10^{-6}-10^{-4} Pa), high temperature (above 474K)
    - This is not the case for nESI, MALDI, and FAB
- Aprotic ILs: in gas phase ionic liquid A^+X^- exists as neutral ion pair (NIP) [AX]
- Protic ILs: in gas phase ionic liquid AH^+X^- exists as isolated neutrals A and XH

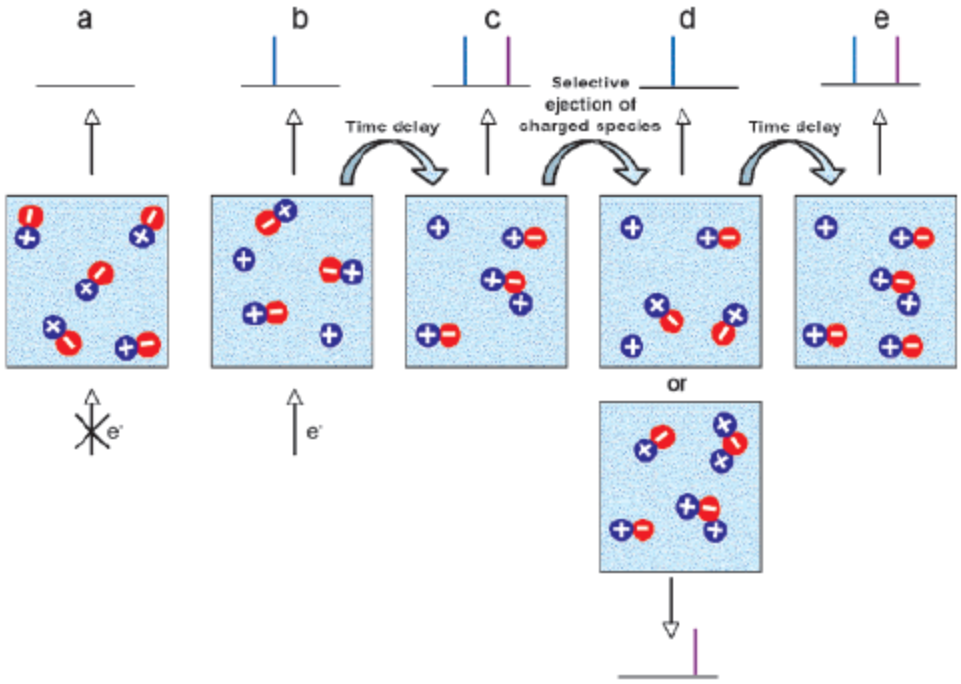


Figure 2. Schematic representation of ion−NIP reaction experiments performed in the FTICR-MS apparatus. Top and bottom: mass spectra; middle: illustration of species in the ion trap (positive mode). (a) No spectrum is observed with the electron beam turned off. (b) When recording a simple mass spectrum in the positive ion mode, the A^+ ions (in blue) formed by electron impact are immediately detected after ionization thus precluding the observation of any ion−molecule reactions; the X^- anions (in red) are neutralized at the positive cell plates and therefore not detected. (c) If a delay time is allowed before detection, the A^+ species will be trapped in the cell region during that time under cyclotron movement, and will react with the neutrals [AX] inside to produce $[A_2X]^+$ ions until reaction equilibrium is attained. A similar equilibrium involving the X^-, [AX], and $[AX_2]^-$ species is observed in the negative ion mode (not illustrated). If the $[A_2X]^+$ clusters or the A^+ ions are ejected from the cell (d) they are produced again (e) from the $A^+ + [AX] \rightarrow [A_2X]^+$ or $[A_2X]^+ \rightarrow A^+ + [AX]$

Investigating Aggregate Formation (Dorbritz)

- Methanol Dilutions:
  - Size of clusters
  - Distribution of clusters
- Larger aggregates have larger intensities in less diluted samples
- This is different from what James saw with the IL we have.

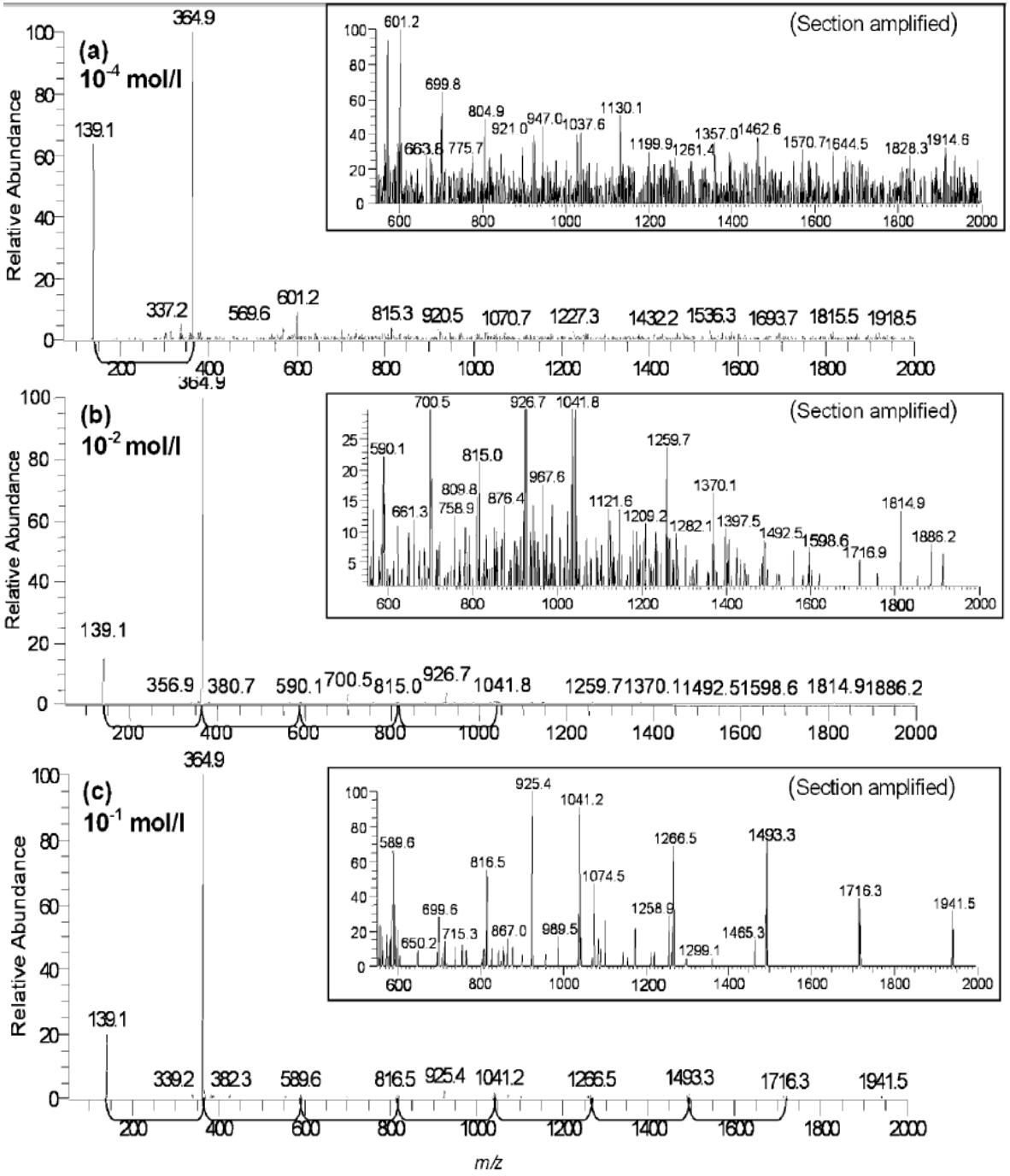


Figure 3. Spectra of [BMIM][BF_4] solutions in methanol, (**a**) 10^{-4} mol/L, (**b**) 10^{-2} mol/L, (**c**) 10^{-1} mol/L (positive mode).

Type of Solvent (Dorbritz)

- The single anion is also present (although not visible in spectra)
- Solvents with smaller $E_T(30)$ give larger aggregates
  - $E_T(30)$ = solvent polarity parameters

Solvent	$E_T(30)$[11] [kcal/mol]
Water	63.1
Methanol	55.4
2-Propanol	48.4
Ethyl acetate	38.1

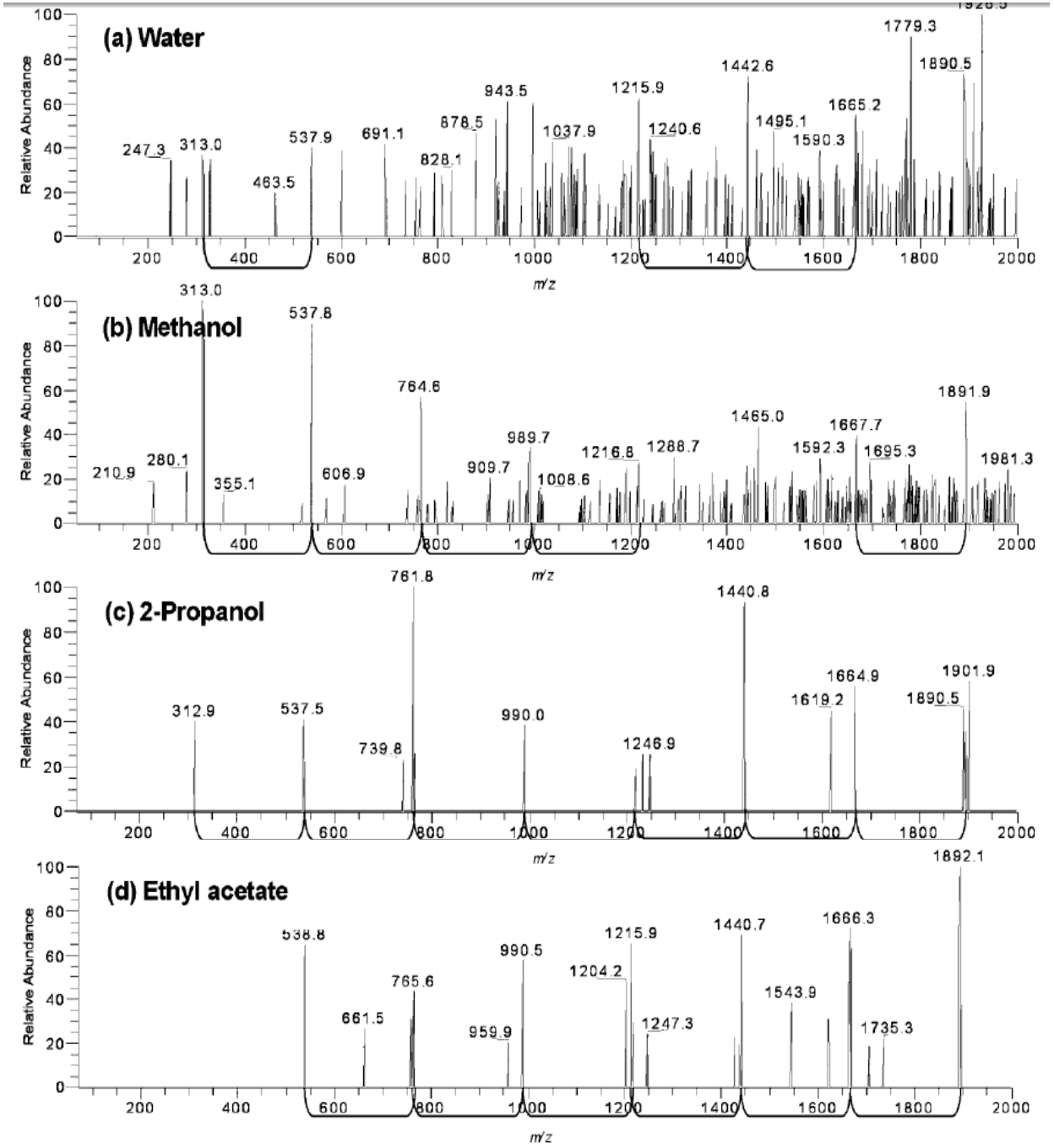
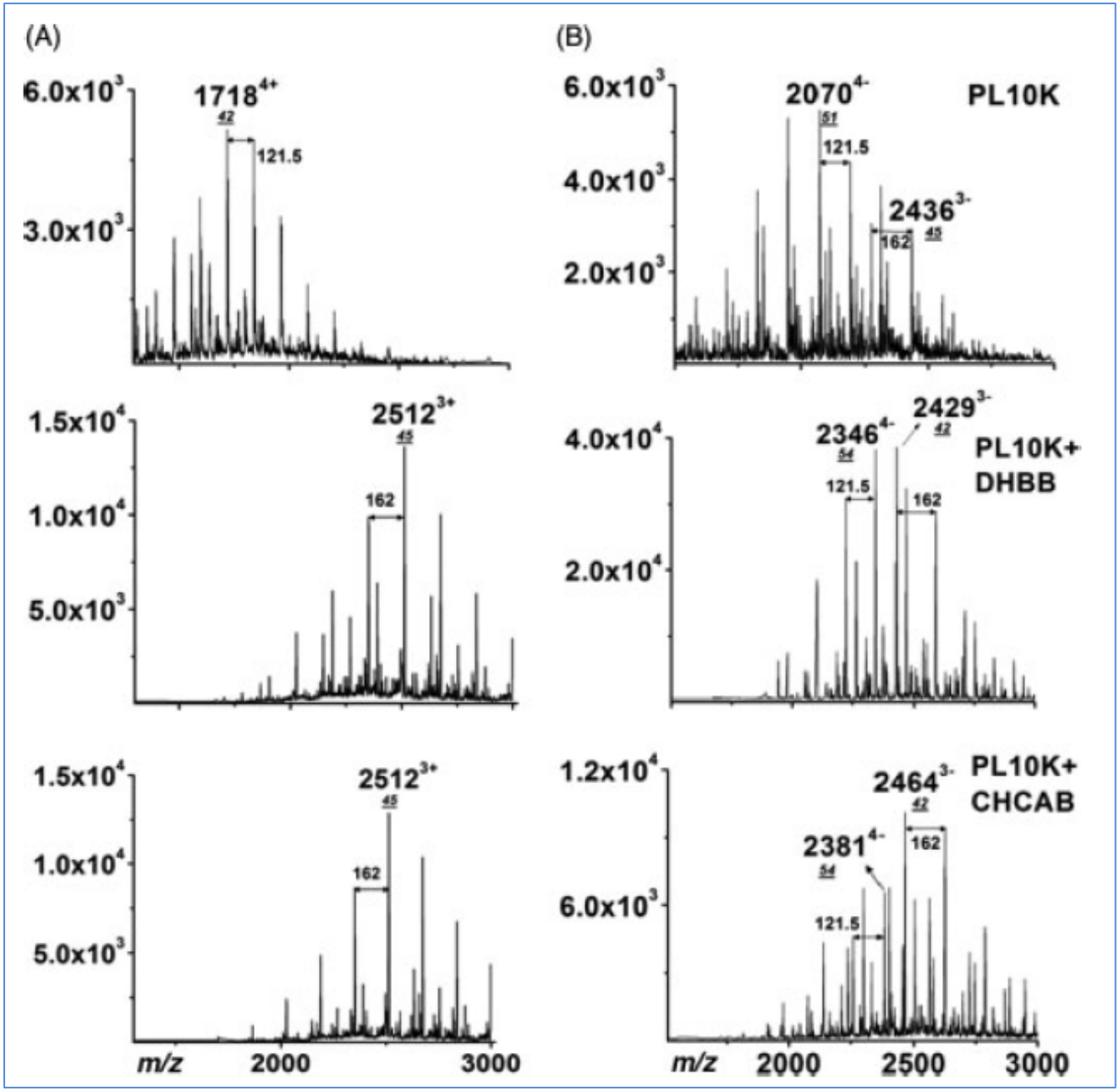


Figure 4. Spectra of 0.1 M [BMIM][BF_4] solutions in (**a**) water, (**b**) methanol, (**c**) 2-propanol, (**d**) ethyl acetate (negative mode).

IL assisted ESI of polysaccharides (Chang)

- PL6K (10 pmol/uL) in 50:50 H_2O:CAN; IL added in middle and bottom (100 pmol/uL)
- PL6K (5900 Da): 6 maltotriose units
- With the addition of the ionic liquids DHBB and CHCAB to polysaccharides in ESI:
  - better S/N
  - Greater signal intensities
  - Simpler spectra for polysaccharides (usually only one type of charge)
  - Enhanced detection sensitivities (fmoles/µL)



IL affects on folding of small peptides (Huang)

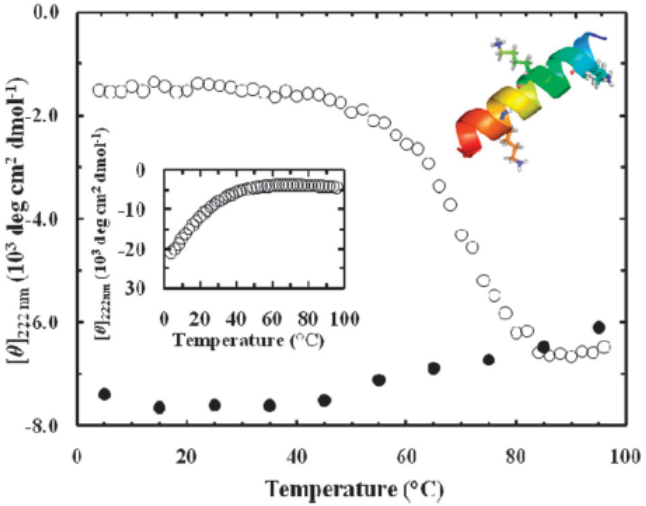


Fig. 1 Mean residue ellipticity of AKA_2 in $[C_4mpy][Tf_2N]$ at 222 nm as a function of temperature. Open circles represent data from a heating experiment and closed circles are data for subsequent cooling. The insets show the temperature-dependent ellipticity of AKA_2 in aqueous solution and the structure of an ideal helix generated from the AKA_2 sequence with Lys sidechains shown.

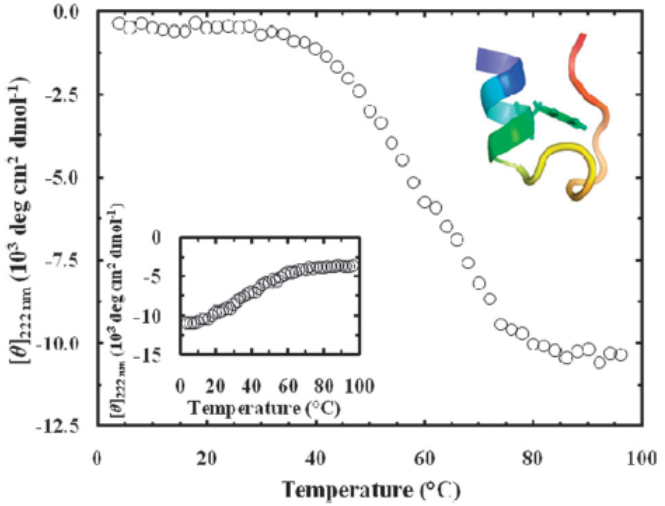


Fig. 2 Mean residue ellipticity of Trp-cage in $[C_4mpy][Tf_2N]$ at 222 nm as a function of temperature. The insets show the temperature-dependent ellipticity of Trp-cage in 20 mM phosphate buffer and the NMR structure of Trp-cage (1L2Y) with Trp-6 shown.[10]

- Used circular dichroism spectroscopy used to learn about the secondary structures of small peptides
- IL used: 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([C4mpy]-[Tf2N])
- Peptides:
- a-helix AKA2 and Trp-cage: heat-induced structure formation persisting into higher temperatures
- Monellin: IL stabilized structure (no heat induced folding)
- b-hairpin Trpzip4: IL destabilized structure

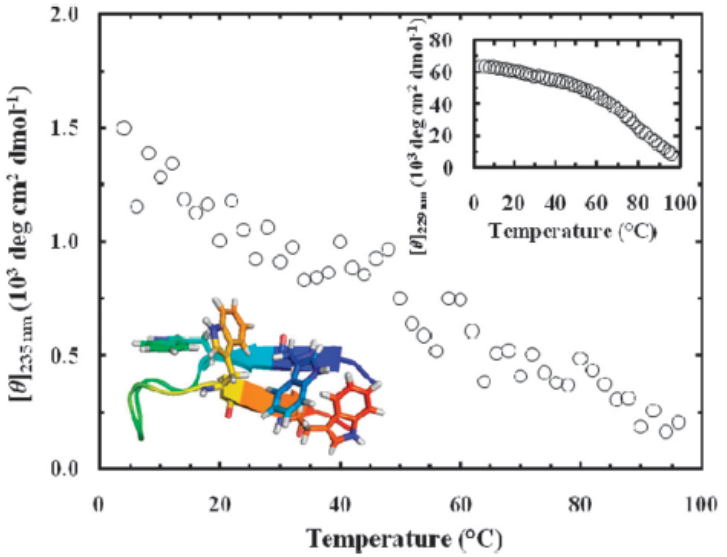


Fig. 3 Mean residue ellipticity of Trpzip4 in $[C_4mpy][Tf_2N]$ at 235 nm as a function of temperature. The insets show the temperature-dependent ellipticity of Trpzip4 in 20 mM phosphate buffer collected at 229 nm and the NMR structure of Trpzip4 (1LE3) with Trp residues shown.[11]

Magic Numbers and H-Bond Strengths in IL Clusters (Gozzo/Eberlin)

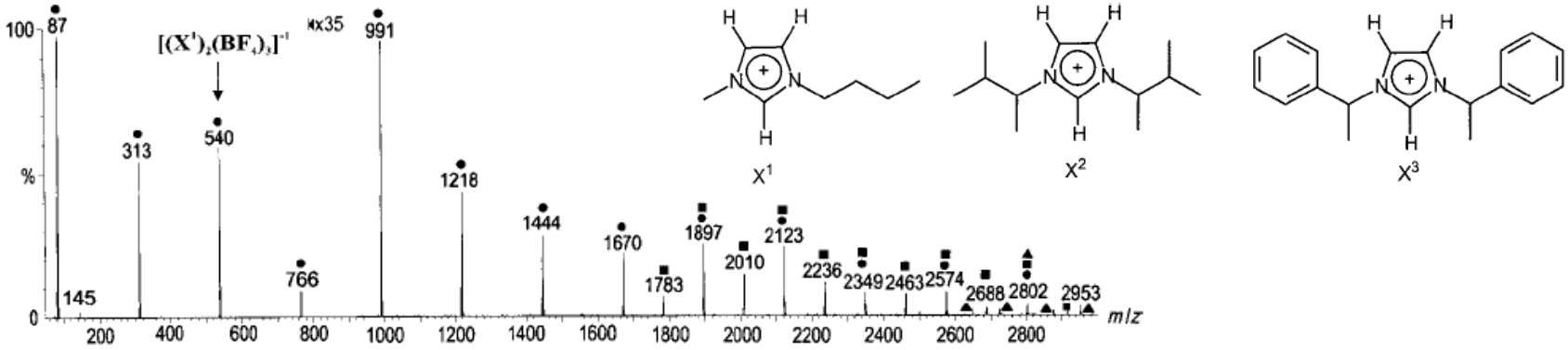


Figure 1. ESI-MS mass spectrum in the negative ion mode of an acetonitrile solution of X^1BF_4. Note the series of singly negatively charged gaseous $[(X^1)_n(BF_4)_{n+1}]^-$ supramolecules of m/z 313, 540, 766, 991, etc. ($\Delta m/z$ 226 for ^{11}B). The intensity scale has been increased from m/z 900 to show more clearly the series of doubly charged supramolecules $[(X^1)_n(BF_4)_{n+2}]^{-2}$ (n=13–25) of m/z 1783, 1897, 2010, etc. ($\Delta m/z$ 113 for ^{11}B), and the triply charged ones $[(X^1)_n(BF_4)_{n+3}]^{-3}$ (n=34–39) of m/z 2648, 2723, 2799, 2802, etc. ($\Delta m/z$ 75.3 for ^{11}B). The "magic" number supramolecule $[(X^1)_2(BF_4)_3]^{-1}$ is indicated. ●: singly, ■: doubly, ▲: triply charged.

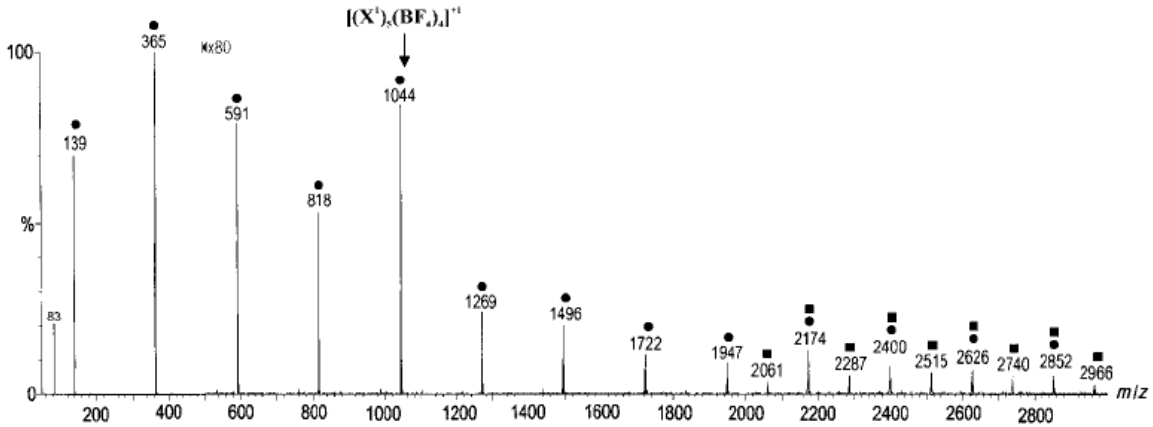
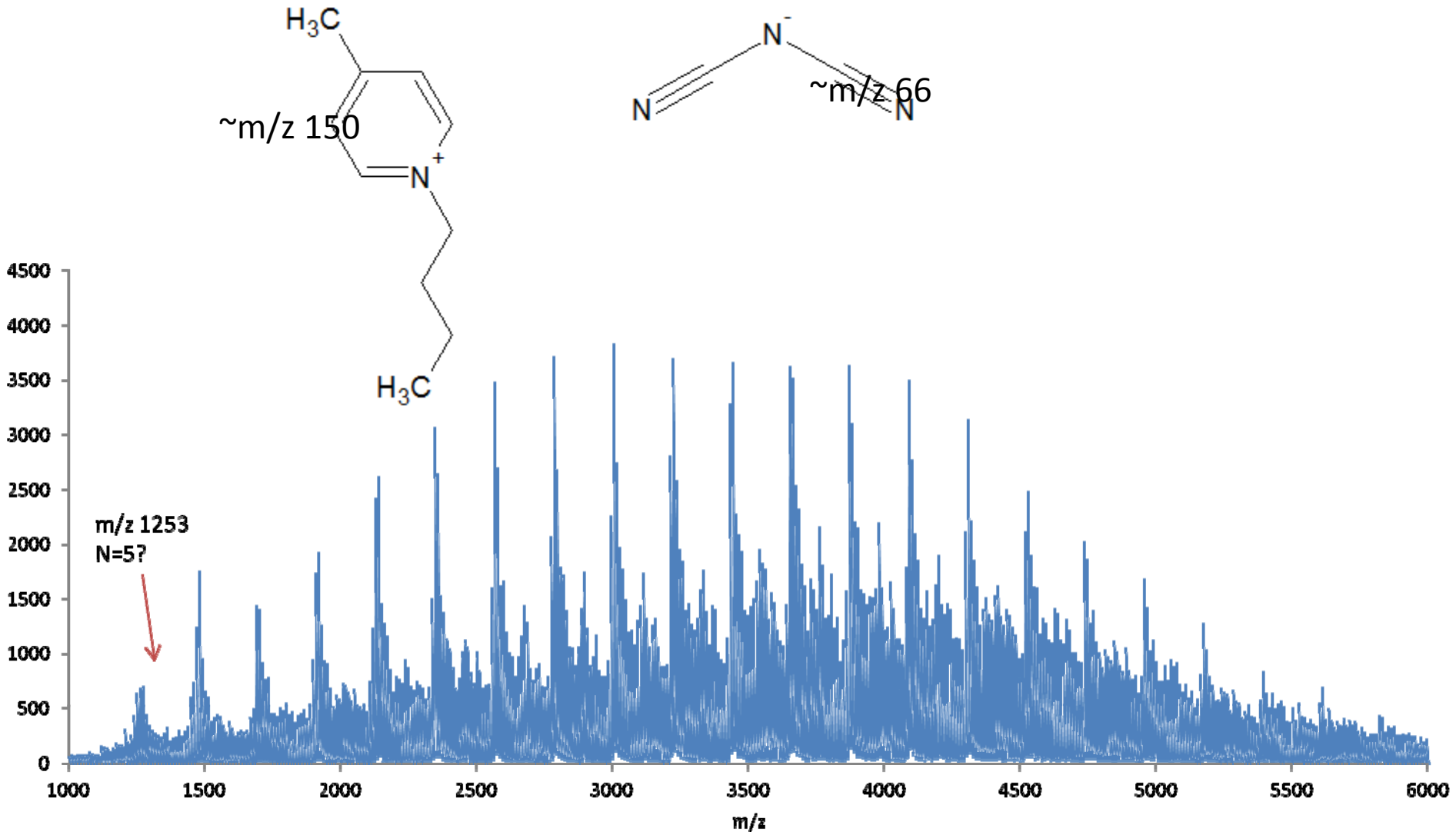


Figure 2. ESI-MS mass spectrum in the positive ion mode of an acetonitrile solution of X^1BF_4. Note the series of singly positively charged $[(X^1)_{n+1}(BF_4)_n]^+$ supramolecules of m/z 365, 591, 818, 1044, etc. ($\Delta m/z$ 226 for ^{11}B). The intensity scale has been increased from m/z 500 to show more clearly the series of doubly charged species $[(X^1)_{n+2}(BF_4)_n]^{+2}$ (n=15–26) of m/z 2061, 2174, 2287, etc. ($\Delta m/z$ 113 for ^{11}B). The "magic" number supramolecule $[(X^1)_5(BF_4)_4]^{+1}$ is indicated. ●: singly, ■: doubly charged.

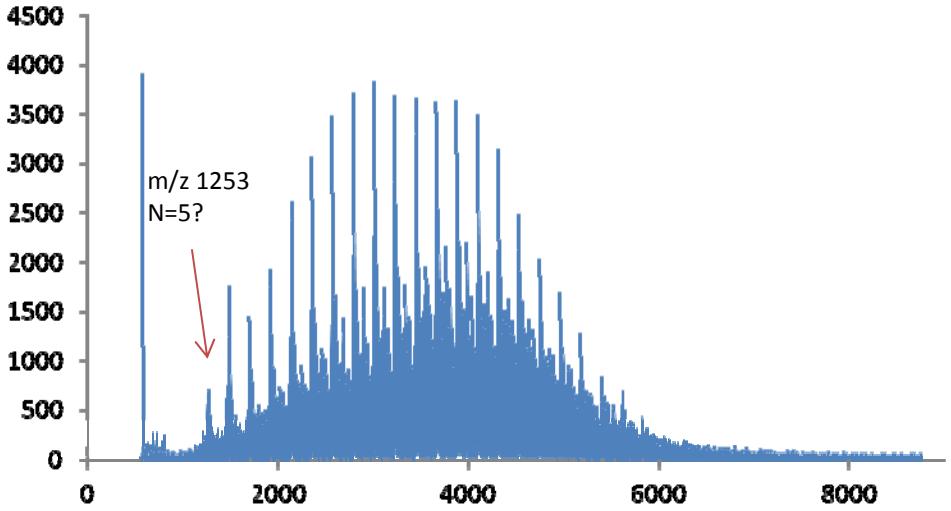
- Used the Cooks Kinetic Method to determine H-bond strength in clusters
- Investigating the "magic numbers": found $[(X^1)_5A_4]$+ most stable except for when A=InCl4

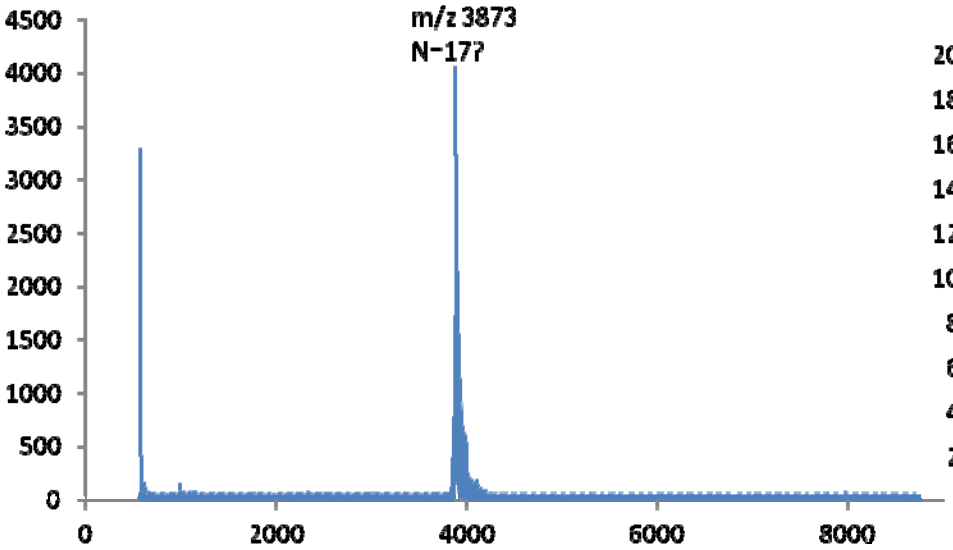
+nESA of Jamie's IL: n-butyl-3-methylpyridinium dicyanamide
(mass: 216 Da)

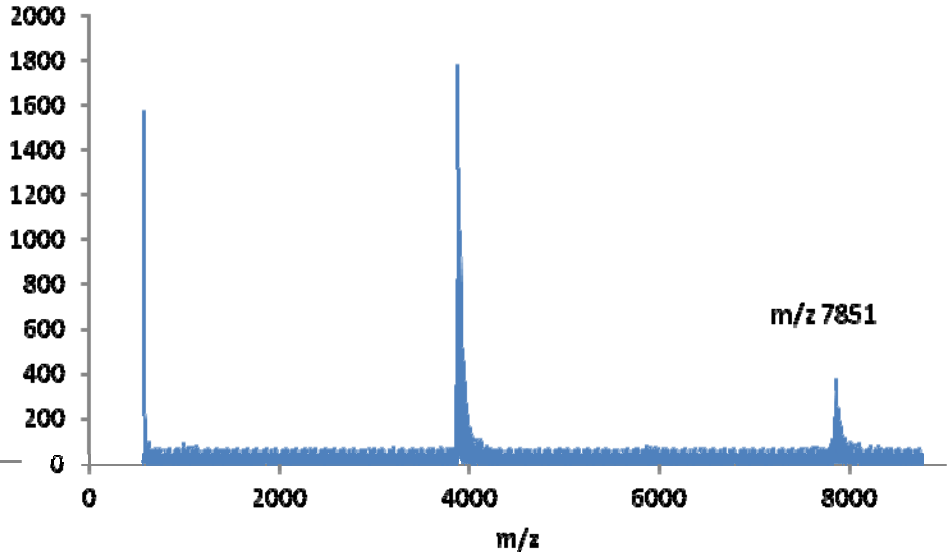


Jamie's Ionic Liquids

- N-butyl-3-methylpyridinium dicyanamide
- Diluted:10% IL in 50:50 H_2O:MeOH
- +nESI
- Bottom left: isolated n=17?
- Bottom right: isolated n=? Reaction with butyl iodide (GD= I^- m/z 127))







What Can We Do?

- Ionic Liquids with proteins/peptides in ESI/nESI?
  - 2 papers report using ILs in extracting/denaturation/separation of membrane proteins (Tao, Sun)
  - In both cases ILs were removed before MS analysis

- Looking at ILs as surfactants (in relation to Anastasia's Leak-in)?

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