Electronic Supplementary Material (ESI) for Chemical Communications




# Ionic Liquids Provide Unique Opportunities for Oral Drug Delivery: Structure Optimization and In Vivo Evidence of Utility

Hywel D. Williams, Yasemin Sahbaz, Leigh Ford, Tri-Hung Nguyen, Peter J. Scammells* and Christopher J. H. Porter*

## Contents

**Table S1** The composition of self-emulsifying drug delivery systems (SEDDS) and danazol equilibrium solubility in these SEDDS (37°C. N=3, ± 1 sd).

| Name | Composition (% w/w) | Danazol solubility (mg $g^{-1}$) |
|---|---|---|
| $SEDDS_{Lipid}$ | 30% lipid (soybean oil:Maisine™ 35-1, 1:1), 60% Cremophor® EL and 10% ethanol. | 34.2 ± 0.4 |
| $SEDDS_{NTf_2}$ | 30% [hhcpy][$NTf_2$], 60% Cremophor® EL and 10% ethanol. | 34.1 ± 2.4 |
| $SEDDS_{N(CN)_2}$ | 30% [hhcpy][$N(CN)_2$], 60% Cremophor® EL and 10% ethanol. | 51.7 ± 0.6 |
| $SEDDS_{C_{10}SO_4}$ | 30% [$C_8m_\beta py$][$C_{10}SO_4$], 60% Cremophor® EL and 10% ethanol. | 52.6 ± 0.7 |
| $SEDDS_{C_{18}SO_4}$ | 30% [$C_8m_\beta py$][$C_{18}SO_4$], 60% Cremophor® EL and 10% ethanol. | 45.6 ± 2.0 |

**Table S2** Summary of the pharmacokinetic parameters for danazol after oral administration to overnight fasted rats in either lipid or ionic liquid containing SEDDS or a crystalline suspension formulation. Data is normalised to a 25 $mg.kg^{-1}$ dose. Values are expressed as means ($n \geq 4$) ± SEM.

| | $AUC_{0\text{-}8h}$ ($ng\ h\ ml^{-1}$) | $C_{max}$ ($ng\ ml^{-1}$) | $T_{max}$ (h) | Relative bioavailability (%) [a] |
|---|---|---|---|---|
| $SEDDS_{Lipid}$ | 498.3 ± 149.8 | 243.8 ± 88.5 | 1.3 ± 0.2 | 100 |
| $SEDDS_{NTf_2}$ | 96.0 ± 11.4 | 39.6 ± 9.6 | 3.3 ± 1.6 | 19.3 |
| $SEDDS_{C_{10}SO_4}$ | 154.8 ± 17.9 | 36.1 ± 3.7 | 6.5 ± 0.4 | 31.1 |
| $SEDDS_{C_{18}SO_4}$ | 485.4 ± 34.9 | 115.4 ± 10.7 | 4.6 ± 0.3 | 97.4 |
| Crystalline suspension | 112.3 ± 20.5 | 37.9 ± 10.4 | 0.8 ± 0.3 | 22.5 |

[a] Relative bioavailability (%) of the ionic liquid containing SEDDS and the crystalline formulations in comparison to the corresponding $SEDDS_{Lipid}$, expressed as the ratio of the dosage-normalized $AUC_{0\text{-}8h}$.

AUC; area under the plasma concentration-time curve. $C_{max}$; maximum plasma concentration. $T_{max}$: time to reach $C_{max}$.

**Histology of gastric and intestinal regions of the rat**

Method: At the conlusion of the pharmacokinetic study and after the collection of the last blood sample (24 h), each animal was euthanised with penobarbitone (550 mg/kg) administered via the carotid artery cannula. Immediately after euthanasia the stomach and duodenum were removed, dissected and rinsed with saline prior to being placed in a 5% v/v formaldehyde solution. The stomach from untreated (blank) rats were also taken and processed in the same manner for a control comparison. All samples were sent to Gribbles Veterinary Pathology (Clayton, Australia) where glandular and non-glandular stomach and duodenal sections underwent blinded histological examination, imaging and scoring.

Results: Figure S1 below is a representative light microscopy image (x100 magnification) of the rat non glandular stomach 24 hours after administraion $SEDDS_{lipid}$. The histological assessment concluded that the non-glandular stomach consisted of normal keratinized epithelium (red arrow) and unremarkable lamina propria (Indicated by black arrow). Additional examination of the glandular stomach and the small intestine also did not reveal any evidence of damaged epithelia. The observations of no histological damage were consistent across animals administered $SEDDS_{lipid}$.

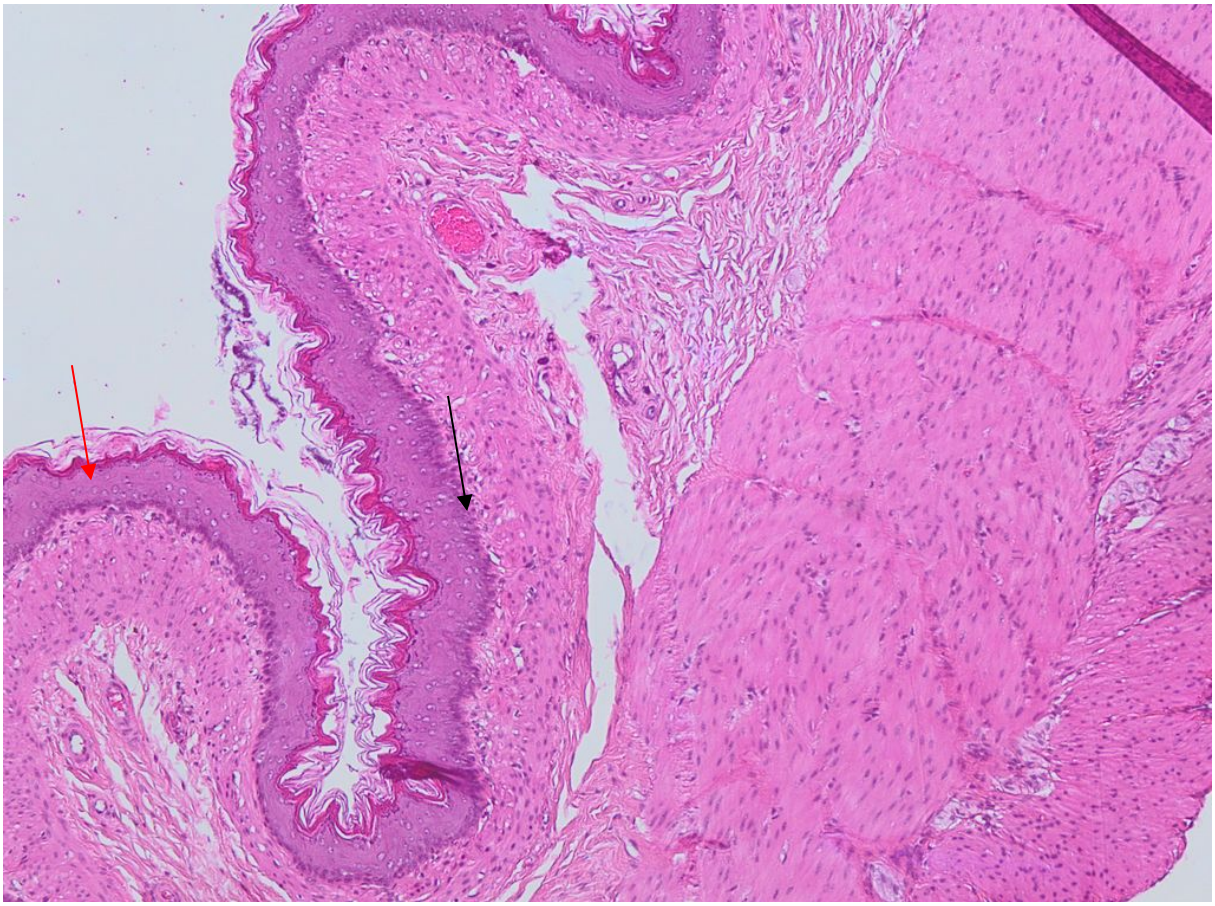


**Fig. S1** Light microscopy image of the non-glandular stomach of a rat following administration of $SEDDS_{lipid}$

For rats administered $SEDDS_{C18S04,}$ there was no evidence of toxicity in either the glandular stomach or the small intestine. Similarly, in the non-glandular stomach (Figure S2), in rats 1 and 3, the histological assessment confirmed normal keratinized epithelium (red arrow) and unremarkable lamina propria (black arrow) 24 hours after administraion $SEDDS_{C18S04.}$ In rat 2 and rat 4, in the non-glandular stomach, some evidence of irritancy was apparent. In rat 2 (Figure S2), the red arrow points to some evidence of epithelial necrosis and erosion while the black arrows point to some evidence of cell infiltration into the lamina propria. In rat 4, the red arrow points to some moderate epithelial vacuolation of non-glandular stomach and the black arrow points to some moderate inflammatory cell infiltration into lamina propria.

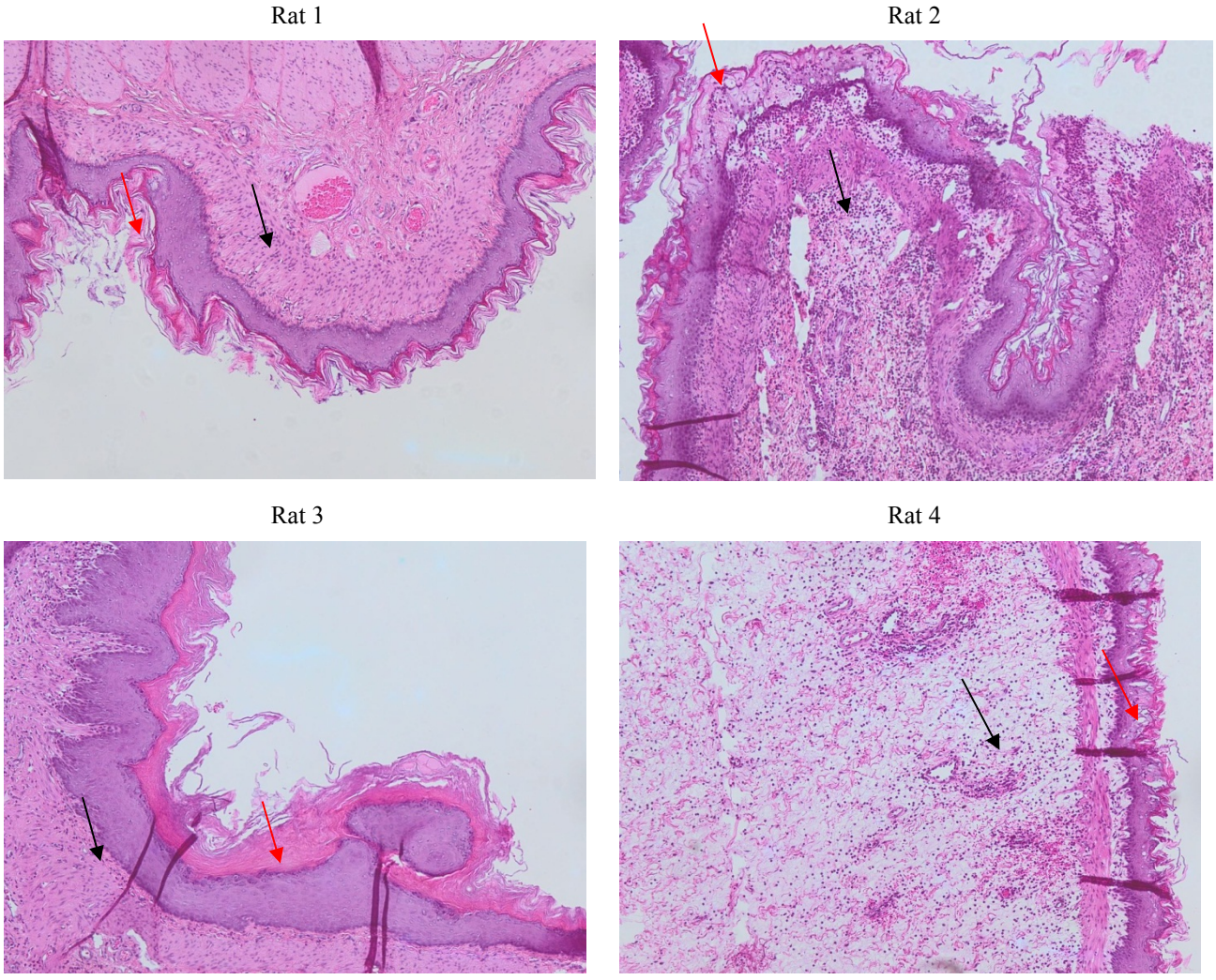



**Fig. S2** Light microscopy image of the non-glandular stomach of 4 rats that were administered $SEDDS_{C_{18}SO_4}$

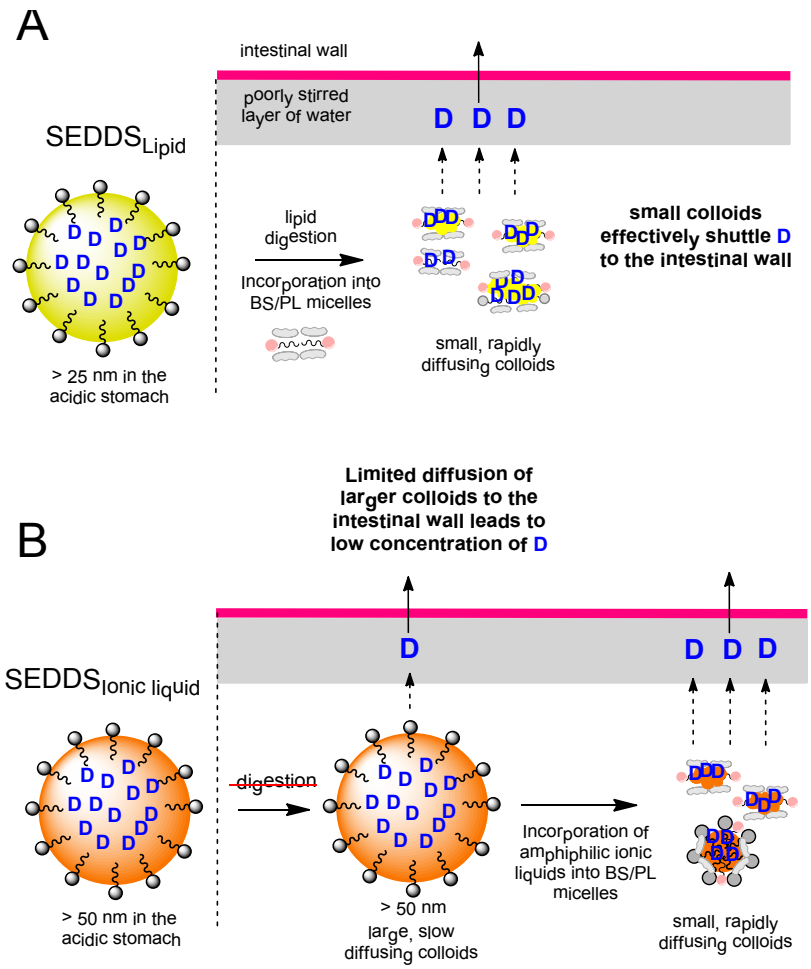



**Fig. S3** Schematic to illustrate the possible mechanisms through which typical lipid (A) and IL (B) self-emulsifying drug delivery systems present incorporated drug to the absorptive membrane in the small intestine in the presence of digestion enzymes and natural solubilisers bile salt (BS) and phospholipids (PL). D = drug molecule.

Figure S3 provides a schematic diagram to illustrate the likely mechanism of drug absorption from an IL-based SEDDS formulation in comparison to a lipid based self emulsifying drug delivery system ($SEDDS_{lipid}$). $SEDDS_{lipid}$ are rapidly digested in the small intestine under the action of pancreatic enzymes, and digestion products are solubilized in bile salt micelles (that are secreted in bile) to form mixed bile salt-lipid digestion product micelles. These small micellar structures readily diffuse across the unstirred water layer present adjacent to the absorptive membrane and promote drug (and lipid) absorption. In this way drug is able to 'hijack' the intrinsic lipid absorption pathway to the intestinal wall, where drug and digested lipids are absorbed. In contrast, SEDDS containing ILs are not digested and instead simply mix with intestinal fluids (including bile). ILsforming large colloids in intestinal fluids (e.g., $SEDDS_{NTf_2}$) are therefore likely to show drug absorption profiles that are limited by inefficient diffusion of drug to the intestinal wall. In contrast, ILs with amphiphilic properties such as the alkyl sulfate ILs interact readily with endogenous bile salt micelles to form highly dispersed colloidal particles with particles sizes that are similar to that of endogenous micellar species. These small particulates allow improved access to the absorptive surface and therefore enhanced bioavailability. The structure of the IL-based micelles, however, appears to vary and to be sufficiently different to that of lipid-BS mixed micelles to, in some cases, allow for considerably more controlled drug release and therefore sustained drug absorption.

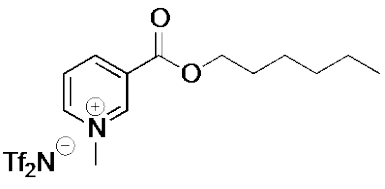
**Chemistry Experimental**

Lithium triflimide (Aldrich, 97%), potassium hexafluorophosphate (Fluka, 98%), sodium octyl sulfate (Sigma, ~95%), methyl iodide (Sigma-Aldrich, 99%), butyl iodide (Fluka ≥ 98%), ethyl bromoacetate (Merck, > 98%), toluene (Merck, GR, ≤ 0.03% $H_2O$), acetonitrile (Merck, Chromatography grade, ≤ 0.02% $H_2O$), diethyl ether (Merck, GR, ≤ 0.03% $H_2O$) were procured from the commercial supplier and used without any pre-treatment. The $^{1}H$ and $^{13}C$ NMR spectra of the purified products were recorded in $CDCl_3$ (Cambridge Isotope Laboratories Inc., 99.8% D) or DMSO $d_6$ (Cambridge Isotope Laboratories Inc., 99.9% D) on a Bruker Avance DPX 300 spectrometer at 400 and 100 MHz, respectively. High resolution mass spectra were obtained using a Waters LCT Premier XE time-of-flight mass spectrometer fitted with an electrospray (ESI) ion source and controlled with MassLynx software version 4.5. Low resolution mass spectra using electrospray ionisation (ES-MS) were obtained using a Micromass PlatformII instrument. Unless otherwise stated, cone voltage was 20 eV. Ionic liquid purity was assessed by RP-HPLC using an Agilent 6100 Series Single Quad LC/MS Agilent 1200 Series HPLC (pump: 1200 Series G1311A quaternary pump, autosampler: 1200 Series G1329A, detector: 1200 Series G1314B variable wavelength detector) fitted with a Luna C8(2) 5u 50X 4.6mm 100A column (column temperature: 30°C, injection volume: 5uL, solvent A: water plus 0.1% formic acid, solvent B: acetonitrile with 0.1% formic acid, gradient: 5-100% B over 10 min). Nicotinate esters were prepared from nicotinoyl chloride HCl salt by treating a suspension of the salt in cold (-10°C) $CH_2Cl_2$ with triethylamine and the corresponding alcohol as previously reported.[1]

**3-(Butoxycarbonyl)-1-methylpyridinium bis(trifluoromethylsulfonyl)amide:**

See Reference 2.

**3-(Hexyloxycarbonyl)-1-methylpyrdinium bis(trifluoromethylsulfonyl)amide:**

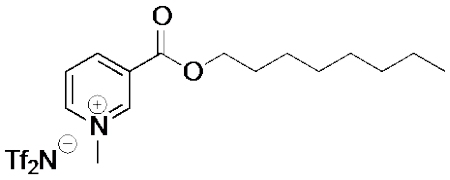



Hexyl nicotinate (466 mg, 2.25 mmol) was dissolved in 2 mL anhydrous toluene, MeI (170 μL, 2.73 mmol) was added and the resulting solution was stirred protected from light for 1 h. The mixture was then heated at 40 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with 10 mL distilled water, the organic layer was decanted and the aqueous layer was washed with a further 3 x 5 mL diethyl ether. The aqueous layer was then treated with lithium bis(trifluoromethylsulfonyl)amide (720 mg, 2.5 mmol) in 2 mL distilled water. The resulting solution was stirred at room temperature for 20 min. The reaction mixture was diluted with 10 mL $CH_2Cl_2$ the separated aqueous layer was washed with a further 3 x 10 mL

$CH_2Cl_2$ the combined organic layers were washed with 10 mL portions of cold distilled water until negative to a $AgNO_3$ precipitate test. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The ionic liquid was dried overnight at 65 $^oC$ under high vacuum. Yield 98%.

$^1H$ NMR (DMSO-$d_6$) δ 9.52 (dd, $J$ = 1.7, 1.2 Hz, 1H), 9.17 (m, 1H), 8.96 (dddd, $J$ = 8.0, 1.7, 1.3, 0.4 Hz, 1H), 8.25 (dd, $J$ = 8.0, 6.2 Hz, 1H), 4.43 (s, 3H), 4.40 (t, $J$ = 6.6 Hz, 2H), 1.71-1.79 (m, 2H), 1.39-1.45 (m, 2H), 1.31 (dq, $J$ = 7.2, 3.6 Hz, 4H), 0.88 (t, $J$ = 7.2 Hz, 3H). $^{13}C$ NMR (DMSO-$d_6$) δ 161.8, 148.9, 146.7, 144.7, 129.5, 127.9, 119.5 (q, $J_{C-F}$ = 319.8 Hz), 66.5, 48.3, 39.5, 30.9, 28.0, 25.0, 22.0, 13.9. HRMS +ve calcd 222.1489 found 222.1499, -ve calcd 279.9178 found 279.9172.

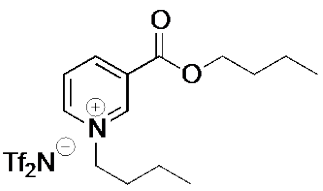
**1-Methyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**




Octyl nicotinate (465 mg, 2.00 mmol) was dissolved in 2 mL anhydrous toluene, MeI (290 μL, 4.60 mmol) was added and the resulting solution was stirred protected from light for 1 h. The mixture was then heated at 40 $^oC$ for 48 h. The reaction mixture was cooled to room temperature and diluted with 10 mL hot diethyl ether, the heterogenous mixture was sonicated for 10 min and the organic layer was carefully decanted, this was repeated a further 3 times. The resulting residue was dissolved in 5 mL anhydrous MeCN and then treated with lithium bis(trifluoromethylsulfonyl)amide (720 mg, 2.5 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo the resulting residue dissolved in 50 mL $CH_2Cl_2$ the organic solution was washed with 10 mL portions of cold distilled water until negative to a $AgNO_3$ precipitate test. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The ionic liquid was dried overnight at 65 $^oC$ under high vacuum. Yield 96%.

$^1H$ NMR (DMSO-$d_6$) δ 9.52 (td, $J$ = 1.2, 0.6 Hz, 1H), 9.16-9.18 (m, 1H), 8.95-8.97 (m, 1H), 8.23-8.26 (m, 1H), 4.43 (s, 3H), 4.40 (t, $J$ = 6.6 Hz, 2H), 1.75 (dt, $J$ = 14.5, 7.1 Hz, 2H), 1.37-1.45 (m, 2H), 1.22-1.36 (m, 8H), 0.86 (t, $J$ = 7.0 Hz, 3H). $^{13}C$ NMR (DMSO-$d_6$) δ 161.7, 148.8, 146.7, 144.7, 129.5, 127.9, 119.5 (q, $J_{C-F}$ = 320.0 Hz), 66.5, 48.3, 39.5, 31.2, 28.6, 28.6, 28.0, 25.3, 22.1, 13.9. HRMS +ve calcd 250.1802 found 250.1793; -ve calcd 279.9178 found 279.9185.

**3-(Butoxycarbonyl)-1-butylpyridinium bis(trifluoromethylsulfonyl)amide:**



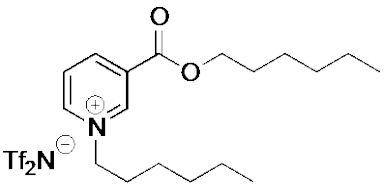

Butyl nicotinate (620 mg, 3.46 mmol) was dissolved in 5 mL anhydrous toluene, *n*-BuI (430 μL, 3.78 mmol) was added and the resulting solution was stirred protected from light for 1 h. The mixture was then heated at

reflux for 24 h. The reaction mixture was cooled to room temperature and diluted with 10 mL distilled water, the organic layer was decanted and the aqueous layer was washed with a further 3 x 5 mL diethyl ether. The aqueous layer was then treated with lithium bis(trifluoromethylsulfonyl)amide (1.09 g, 3.81 mmol) in 2 mL distilled water. The resulting solution was stirred at room temperature for 20 min. The reaction mixture was diluted with 10 mL $CH_2Cl_2$ the separated aqueous layer was washed with a further 3 x 10 mL $CH_2Cl_2$ the combined organic layers were washed with 10 mL portions of cold distilled water until negative to a $AgNO_3$ precipitate test. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The ionic liquid was dried overnight at 65 $^oC$ under high vacuum. Yield 98%.

$^1H$ NMR (DMSO-$d_6$) δ 9.60 (s, 1H), 9.28 (dt, $J$ = 6.1, 1.4 Hz, 1H), 8.98 (dt, $J$ = 8.2, 1.4 Hz, 1H), 8.26-8.29 (m, 1H), 4.71 (t, $J$ = 7.6 Hz, 2H), 4.41 (t, $J$ = 6.5, 2H), 1.91 (dt, $J$ = 15.2, 7.6 Hz, 2H), 1.75 (dt, $J$ = 14.6, 7.0 Hz, 2H), 1.37-1.50 (m, 2H), 1.32 (dq, $J$ = 15.1, 7.5 Hz, 2H), 0.93 (dt, $J$ = 9.9, 7.4 Hz, 6H). $^{13}C$ NMR (DMSO-$d_6$) δ 161.7, 147.8, 145.9, 145.0, 130.2, 128.3, 119.5 (q, $J_{C-F}$ = 321.9 Hz), 66.2, 61.0, 32.8, 30.0, 18.8, 18.5, 13.5, 13.3. HRMS +ve calcd 236.1645 found 236.1645; -ve calcd 279.9178 found 279.9181.

See also reference [4].

**1-Hexyl-3-(hexyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**

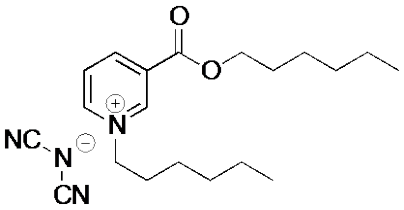



Hexyl nicotinate (315 mg, 1.52 mmol) was dissolved in 2 mL anhydrous toluene, 1-bromohexane (255 μL, 1.82 mmol), NaI (228 mg, 1.52 mmol) was added and the resulting solution was stirred protected from light for 1 h. The mixture was then heated to reflux for 72 h. The reaction mixture was cooled to room temperature and diluted with 10 mL hot petroleum spirits, the mixture was sonicated and the organic phase was decanted, this was repeated twice. The resulting residue was dissolved in 10 mL anhydrous $CH_2Cl_2$ and treated with lithium bis(trifluoromethylsulfonyl)amide (483 mg, 1.68 mmol). The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered, the precipitate washed with portions of anhydrous $CH_2Cl_2$, the combined organic filtrates were washed with 10 mL portions of cold distilled water until negative to a $AgNO_3$ precipitate test. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The ionic liquid was dried overnight at 65 $^oC$ under high vacuum. Yield 95%.

$^1H$ NMR (DMSO-$d_6$) δ 9.60 (s, 1H), 9.28 (dt, $J$ = 6.1, 1.3 Hz, 1H), 8.98 (dt, $J$ = 8.3, 1.5 Hz, 1H), 8.28 (dd, $J$ = 8.0, 6.3 Hz, 1H), 4.70 (t, $J$ = 7.5 Hz, 2H), 4.40 (t, $J$ = 6.6 Hz, 2H), 1.92 (quin, $J$ = 7.1 Hz, 2H), 1.76 (dt, $J$ = 14.6, 7.1 Hz, 2H), 1.28-1.46 (m, 12H), 0.85-0.90 (m, 6H). $^{13}C$ NMR (DMSO-

$d_6$) δ 161.7, 147.8, 145.9, 145.03, 130.1, 128.4, 119.5 (q, $J_{C\text{-}F}$ = 321.9 Hz), 66.5, 61.2, 30.9, 30.6, 28.0, 25.2, 25.0, 25.0, 22.0, 13.9, 13.8. HRMS +ve calcd 292.2271 found 292.2280 –ve calcd 279.9178 found 279.9186.

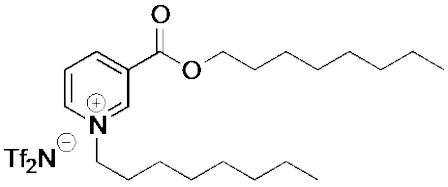
**1-Hexyl-3-(hexyloxycarbonyl)pyridinium dicyanamide:**



Hexyl nicotinate (315 mg, 1.52 mmol) was dissolved in 2 mL anhydrous toluene, 1-bromohexane (255 μL, 1.82 mmol), NaI (228 mg, 1.52 mmol) was added and the resulting solution was stirred protected from light for 1h. The mixture was then heated to reflux for 72 h. The reaction mixture was cooled to rt and diluted with 10 mL hot petroleum spirits, the mixture was sonicated and the organic phase was decanted, this was repeated twice. The residue was dissolved in anhydrous MeOH, with an treated with freshly prepared $AgN(CN)_2$ (1.68 mmol) ($AgNO_3$ and $NaN(CN)_2$ in distilled water at 40°C for 1 h, then high vacuum for 2 h with stirring overnight, the resulting suspension was filtered, the filtrate was concentrated *in vacuo* and then taken up in 5 mL anhydrous $CH_2Cl_2$ and cooled to -20 °C overnight, the resulting suspension was filtered and the organic solution concentrated in vacuo to give the desired IL, which was dried overnight at 65 °C under high vacuum. Yield 92%.

$^1$H NMR (DMSO-$d_6$) δ 9.60 (s, 1H), 9.28 (dt, *J* 6.1, 1.1 Hz, 1H), 8.98 (dt, *J* = 8.1, 1.4 Hz, 1H), 8.28 (dd, *J* = 8.1, 6.1 Hz, 1H), 4.70 (t, *J* = 7.6 Hz, 2H), 4.40 (t, *J* = 6.6 Hz, 2H), 1.92 (quin, *J* = 7.1 Hz, 2H), 1.75 (quin, *J* = 7.3 Hz, 2H), 1.42 (quin, *J* = 7.3 Hz, 2H), 1.31 (dd, *J* = 8.5, 4.6 Hz, 10H), 0.86-0.90 (m, 6H). $^{13}$C NMR (DMSO-$d_6$) δ 161.7, 147.8, 145.9, 145.0, 130.1, 128.4, 119.1, 66.5, 61.2, 30.9, 30.8, 30.6, 28.0, 25.0, 24.9, 22.0, 21.8, 13.9, 13.8. HRMS +ve calcd 292.2271, found 292.2282.

**1-Octyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**

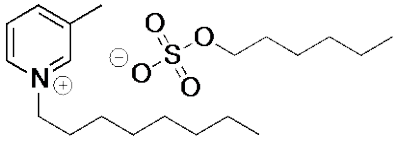


To a suspension of nicotinic acid (0.62 g, 5.0 mmol), potassium carbonate (0.76 g, 5.5 mmol) in 5 mL of anhydrous MeCN was added 1-bromooctane (3.65 mL, 21.1 mmol). The resulting solution was stirred at room temperature for 2 h, then heated to gentle reflux for 4 days. The reaction mixture was filtered, washing with $CHCl_3$, the organic solution was concentrated in vacuo to give a residue which was shaken with 3 x 30 mL portions of 4 : 1 petroleum spirits : diethyl ether to give a brown solid. The solid was dissolved in 10 mL anhydrous $CH_2Cl_2$ and treated with lithium bis(trifluoromethylsulfonyl)amide (1.58 g, 5.5 mmol) and stirred overnight at room temperature. The resulting solution was extracted with 3 x 30

mL cold distilled water, the third water portion was negative to a $AgNO_3$ precipitate test. The organic solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*, the ionic liquid was dried overnight at 65 $^oC$ under high vacuum. Yield 85%.

$^1H$ NMR (400 MHz, DMSO-$d_6$) δ 9.59 (s, 1H), 9.27 (d, $J$ = 6.1 Hz, 1H), 8.97 (d, $J$ = 8.1 Hz, 1H), 8.26-8.29 (m, 1H), 4.69 (t, $J$ = 7.5 Hz, 2H), 4.39 (t, $J$ = 6.6 Hz, 2H), 1.92 (quin, $J$ = 6.8 Hz, 2H), 1.72-1.79 (m, 2H), 1.42 (dt, $J$ = 14.8 and 7.3 Hz, 2H), 1.21-1.33 (m, 18H), 0.84-0.87 (m, 6H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 161.7, 147.8, 145.9, 145.0, 130.1, 128.4, 119.5 (q, $J_{C-F}$ = 321.9 Hz), 66.4, 61.2, 31.2, 31.1, 30.8, 28.6, 28.6, 28.4, 28.4, 28.0, 25.4, 25.3, 22.1, 22.0, 13.8, 13.8. HRMS +ve calcd 348.2897 found 348.2897, -ve calcd 279.9178 found 279.9185.

**1-Methyl-3-octylpyridinium hexyl sulfate:**



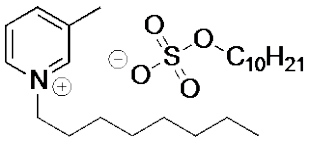
The precursors, hexylsulfate ammonium salt and 1-octyl-3-methylpyridinium bromide were initially synthesized according to a modified literature procedure.[1] A mixture of 1-hexanol (5.11 g, 50 mmol) and sulfamic acid (4.86 g, 50 mmol) was heated at 110 °C for 24 h in a moisture guarded assembly. The resulting mixture was allowed to cool to room temperature. The solidified product was crushed and stirred in hexane (300 mL) for 1 h. After the filtration of hexane, the compound was washed with hexane (3 x 50 mL) and dried under reduced pressure. The crude product was stirred in $CH_2Cl_2$ (100 mL) for 1 h and precipitated with hexane (500 mL), filtered and washed with hexane (3 x 50 mL). The salt was finally dried under reduced pressure to give pure target product, hexyl sulfate ammonium salt. Yield 83%.

A mixture of 3-methylpyridine (15.52 g, 166.7 mmol) and 1-bromooctane (38.62 g, 199.9 mmol) in toluene (200 mL) was stirred for 1 h at rt under nitrogen before being heated at 110 °C overnight. The completion of reaction was marked by the separation of ionic liquid. The reaction was cooled to rt and the toluene was decanted. The IL was mixed with fresh toluene (200 mL) and left in the fridge overnight, which resulted in formation of white solid, 1-octyl-3-methylpyridinium bromide. The toluene was decanted and the product was washed with diethyl ether (4 x 200 mL). Yield 97%.

1-Octyl-3-methyl pyridinium bromide (1.43 g, 5.0 mmol) was dissolved in water (20 mL) and a solution of hexylsulfate ammonium salt (1.0 g, 5.0 mmol) in water (20 mL) was added. The solution was stirred at rt for 10 min, before being extracted with $CH_2Cl_2$ (3 x 20 mL). The combined extracts were washed with distilled water (3 x 20) until a negative $AgNO_3$ test was obtained. The organic layer was dried (anhydrous $MgSO_4$), filtered and evaporated to afford the desired product. The ionic liquid was dried overnight at 60 $^oC$ under high vacuum. Yield 94%.

$^{1}$H NMR (DMSO-$d_6$) δ 8.99 (s, 1H), 8.91 (d, $J$ = 6.0 Hz, 1H), 8.44 (d, $J$ = 8.0 Hz, 1H), 8.05 (dd, $J$ = 8.0, 6.0 Hz, 1H), 4.53 (t, $J$ = 7.4 Hz, 2H), 3.67 (t, $J$ = 6.6 Hz, 2H), 2.50 (s, 3H), 1.91 (quin, $J$ = 7.4 Hz, 2H), 1.47 (quin, $J$ = 6.6 Hz, 2H), 1.34-1.17 (br s, 16H), 0.86 (2 x t, 6H). $^{13}$C NMR (DMSO-$d_6$) δ 145.7, 144.4, 142.0, 138.8, 127.3, 65.6, 60.5, 31.2, 31.0, 30.8, 29.1, 28.5, 28.4, 25.5, 25.2, 22.1, 22.0, 17.7, 13.8, 13.7. HRMS +ve calcd 206.1903 found 206.1906 –ve calcd 181.0540 found 181.0537.

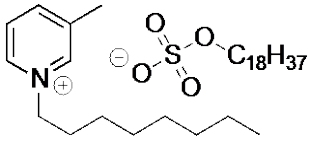
**1-Methyl-3-octylpyridinium decyl sulfate:**



Decylsulfate ammonium salt was synthesised using the same procedure used to prepare hexylsulfate ammonium salt. Yield 77%. 1-Octyl-3-methyl pyridinium bromide (8.61 g, 30.07 mmol) was dissolved in water (100 mL) and a solution of decylsulfate ammonium salt (7.68 g, 30.07 mmol) in water (100 mL) was added. This solution was stirred for 10 min before being extracted with $CH_2Cl_2$ (3 x 100 mL). The combined extracts were washed with distilled water (3 x 100 mL) until a negative $AgNO_3$ test was obtained. The organic layer was dried (anhydrous $MgSO_4$), filtered and evaporated to afford the desired product. The ionic liquid was dried overnight at 60 $^{o}$C under high vacuum. Yield 97%.

$^{1}$H NMR (DMSO-$d_6$) δ 9.02 (s, 1H), 8.93 (d, $J$ = 6.0 Hz, 1H), 8.45 (d, $J$ = 8.0 Hz, 1H), 8.05 (dd, $J$ = 8.0, 6.0 Hz, 1H), 4.55 (t, $J$ = 7.4 Hz, 2H), 3.68 (t, $J$ = 6.7 Hz, 2H) 2.50 (s, 3H), 1.91 (quin, $J$ = 7.4 Hz, 2H), 1.47 (quin, $J$ = 6.7 Hz, 2H), 1.33-1.14 (br s, 24H), 0.85 (2 x t, 6H), $^{13}$C NMR (DMSO-$d_6$) δ 145.7, 144.2, 142.0, 138.8, 127.3, 65.4, 60.6, 31.3, 31.1, 30.7, 29.1, 29.0, 29.0, 28.8, 28.7, 28.4, 28.4, 25.5, 25.4, 22.1, 22.0, 17.8, 13.9, 13.9. HRMS +ve calcd 206.1903 found 206.1910 –ve calcd 237.1166 found 237.1163.

**1-Methyl-3-octylpyridinium octadecyl sulfate:**

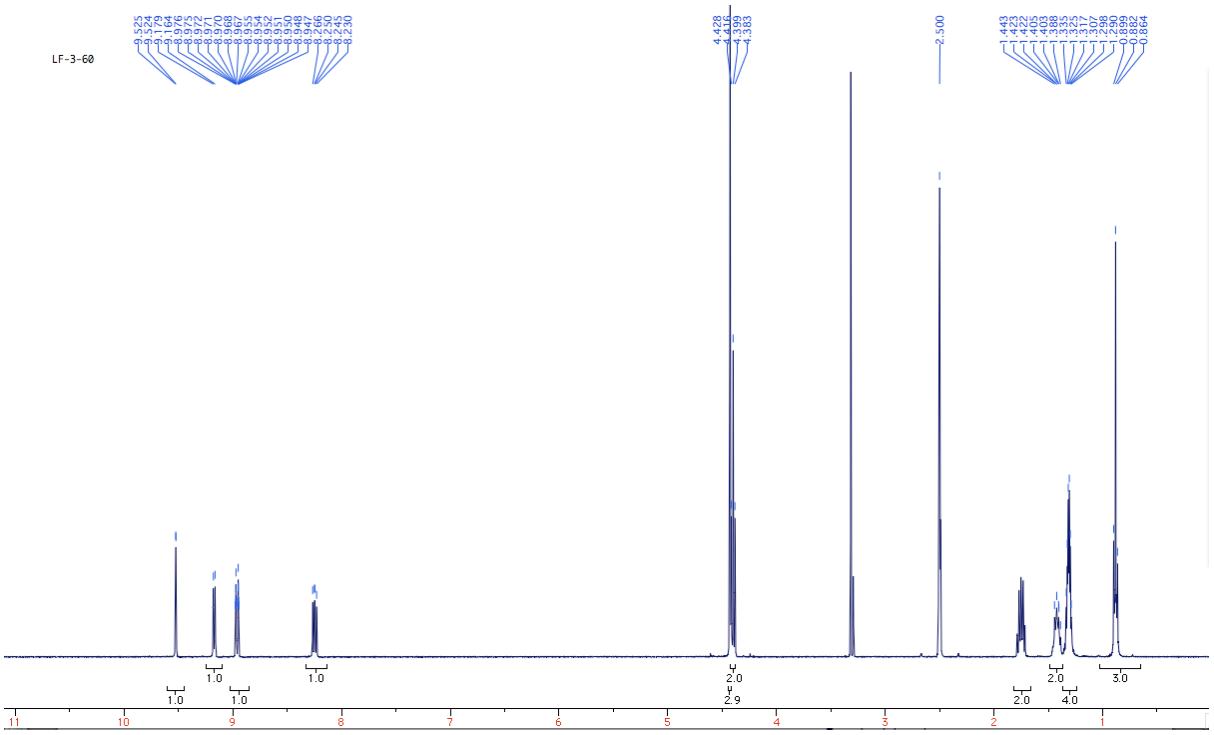


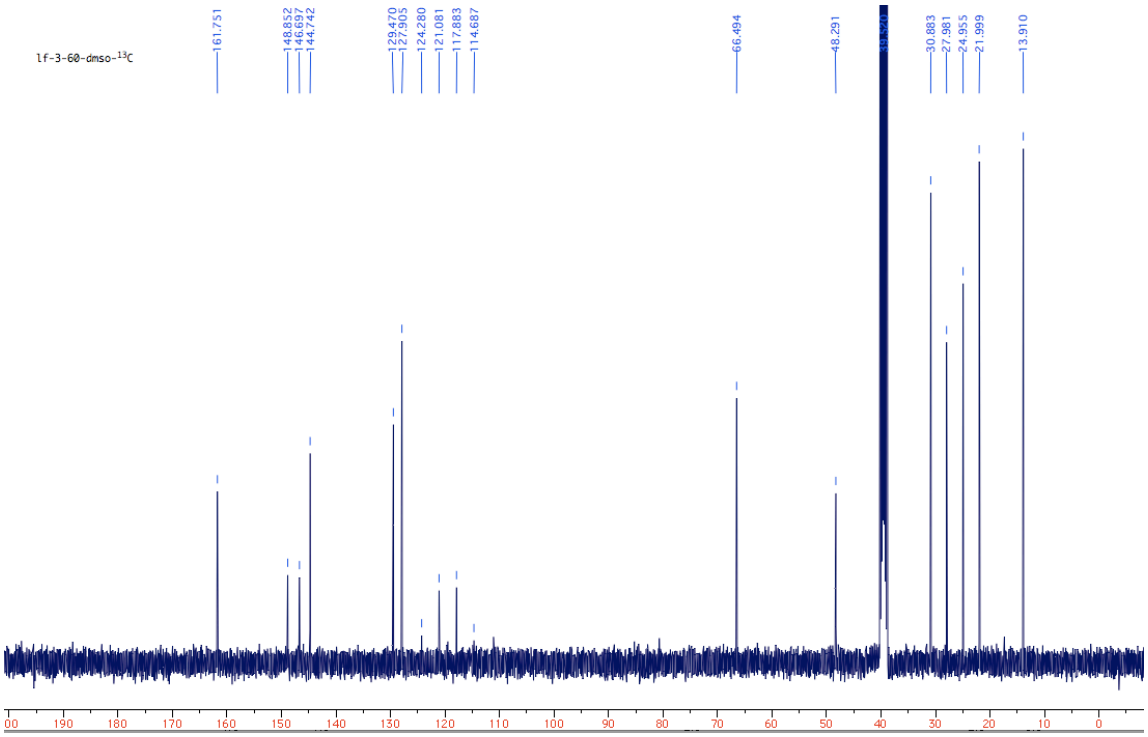
Octadecylsulfate ammonium salt was synthesised using the same procedure used to prepare hexylsulfate ammonium salt. Yield 80%. 1-Octyl-3-methylpyridinium bromide (12.95 g, 45.25 mmol) was dissolved in water (100 mL) and a solution of octadecyl sulfate ammonium salt (16.63 g, 45.25 mmol) in water (100 mL) was added. This solution was stirred for 10 min before being extracted with $CH_2Cl_2$ (3 x 100 mL). The combined extracts were washed with distilled water (3 x 100) until a negative $AgNO_3$ test was obtained. The organic layer was dried (anhydrous $MgSO_4$), filtered and evaporated to afford the target product. The ionic liquid was dried overnight at 60 $^{o}$C under high vacuum. Yield 96%.

$^{1}$H NMR (DMSO-$d_6$) δ 9.03 (s, 1H), 8.94 (d, *J* = 5.9 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 8.0, 5.9 Hz, 1H), 4.55 (t, *J* = 7.4 Hz, 2H), 3.68 (t, *J* = 6.6 Hz, 2H) 2.50 (s, 3H), 1.91 (quin, *J* = 7.4 Hz, 2H), 1.46 (quin, *J* = 6.6 Hz, 2H), 1.35-1.14 (br s, 40H), 0.85 (2 x t, 6H), $^{13}$C NMR (DMSO-$d_6$) δ 145.7, 144.3, 142.0, 138.8, 127.4, 65.5, 60.6, 31.4, 31.2, 30.8, 29.2, 29.2, 29.1, 29.0, 28.8, 28.6, 28.5, 25.6, 25.5, 22.2, 22.1, 17.8, 13.8 13.7. HRMS +ve calcd 206.1903 found 206.1909 –ve calcd 349.2418 found 349.2435.

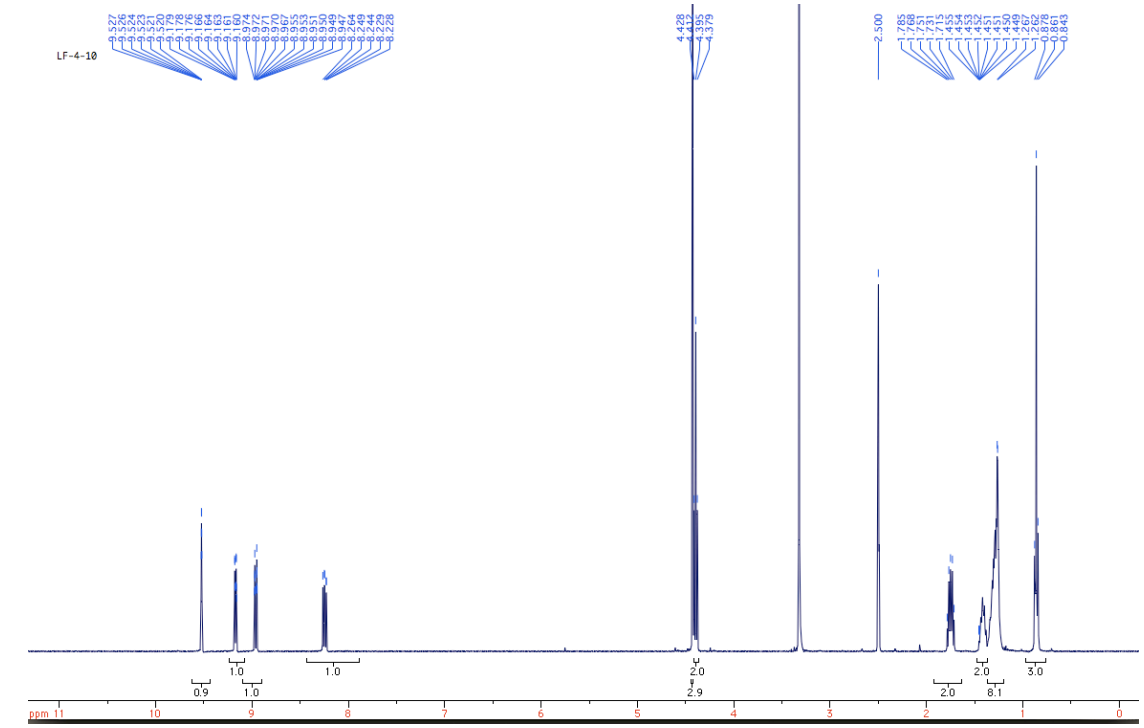
## NMR Spectra

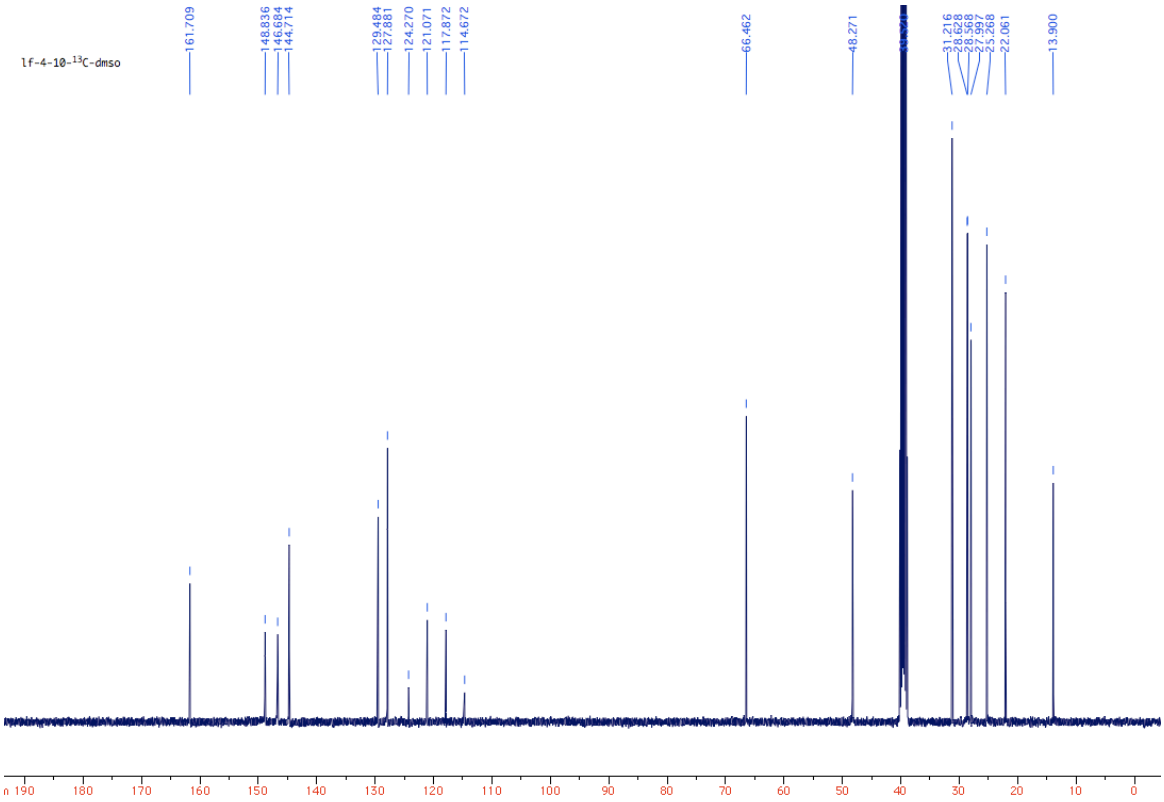
### 3-(Hexyloxycarbonyl)-1-methylpyrdinium bis(trifluoromethylsulfonyl)amide:



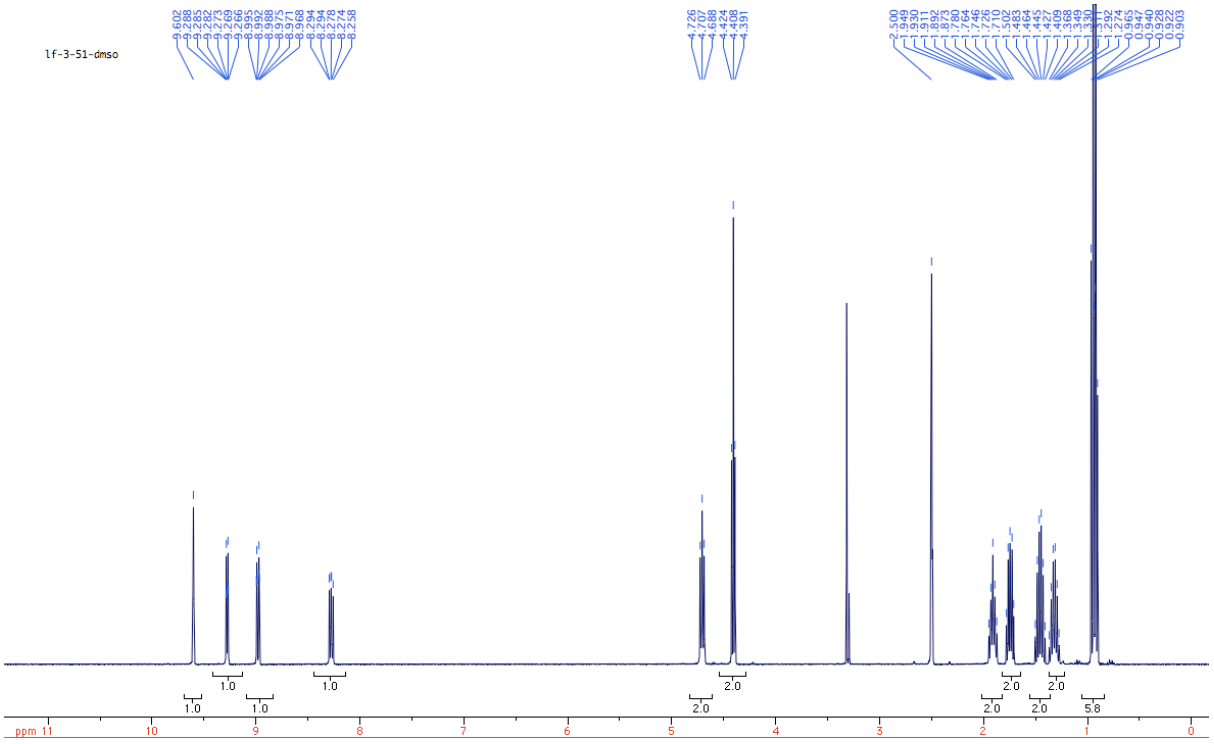



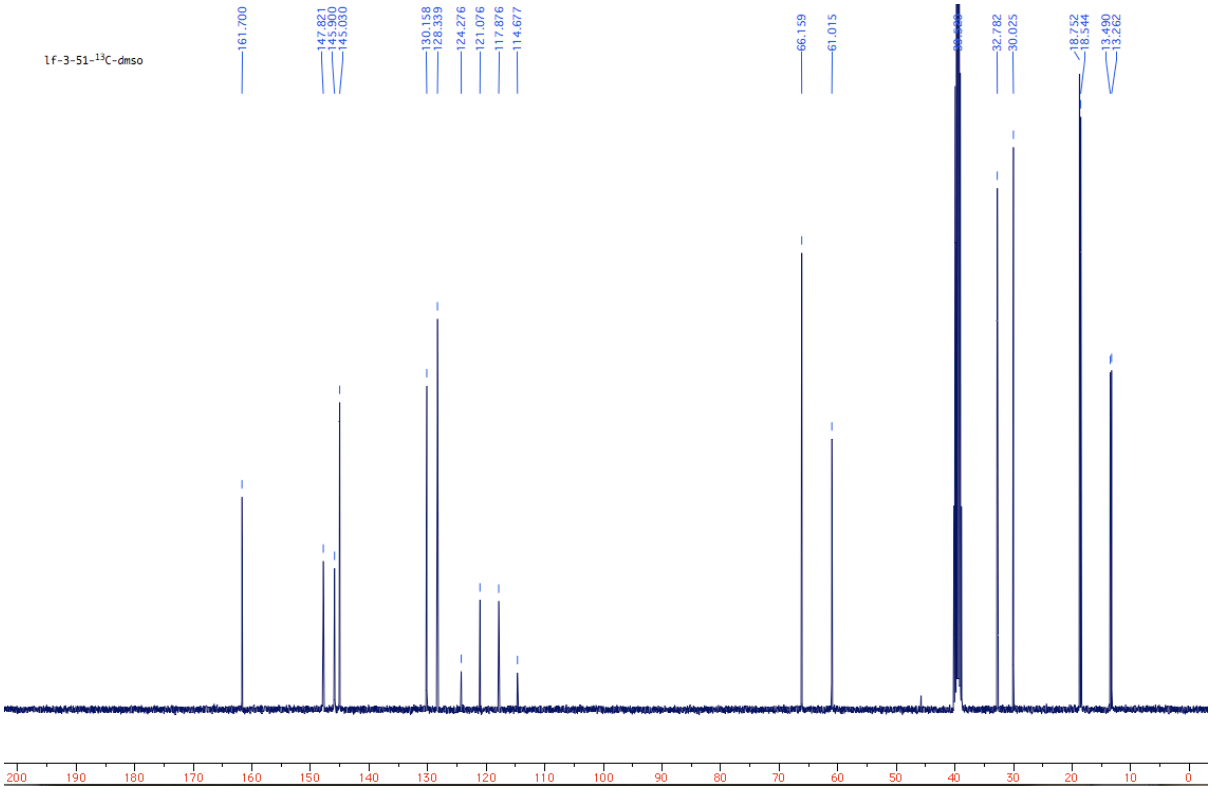
**1-Methyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**



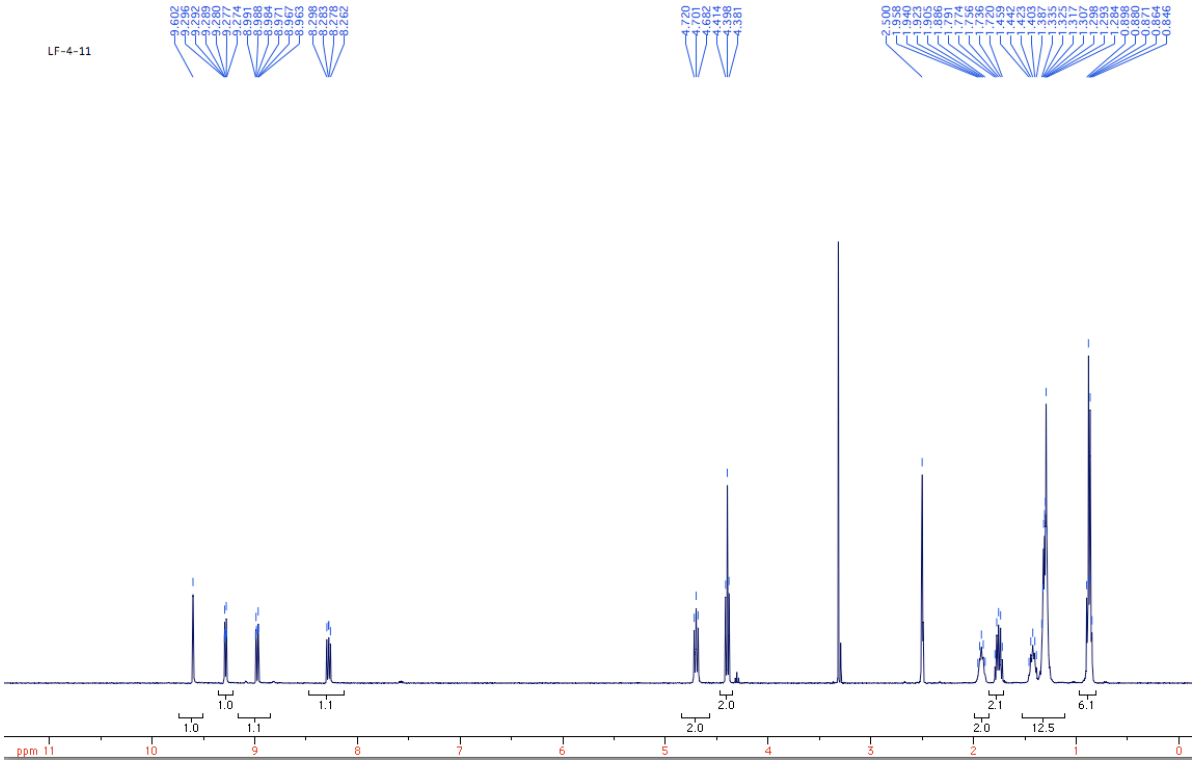



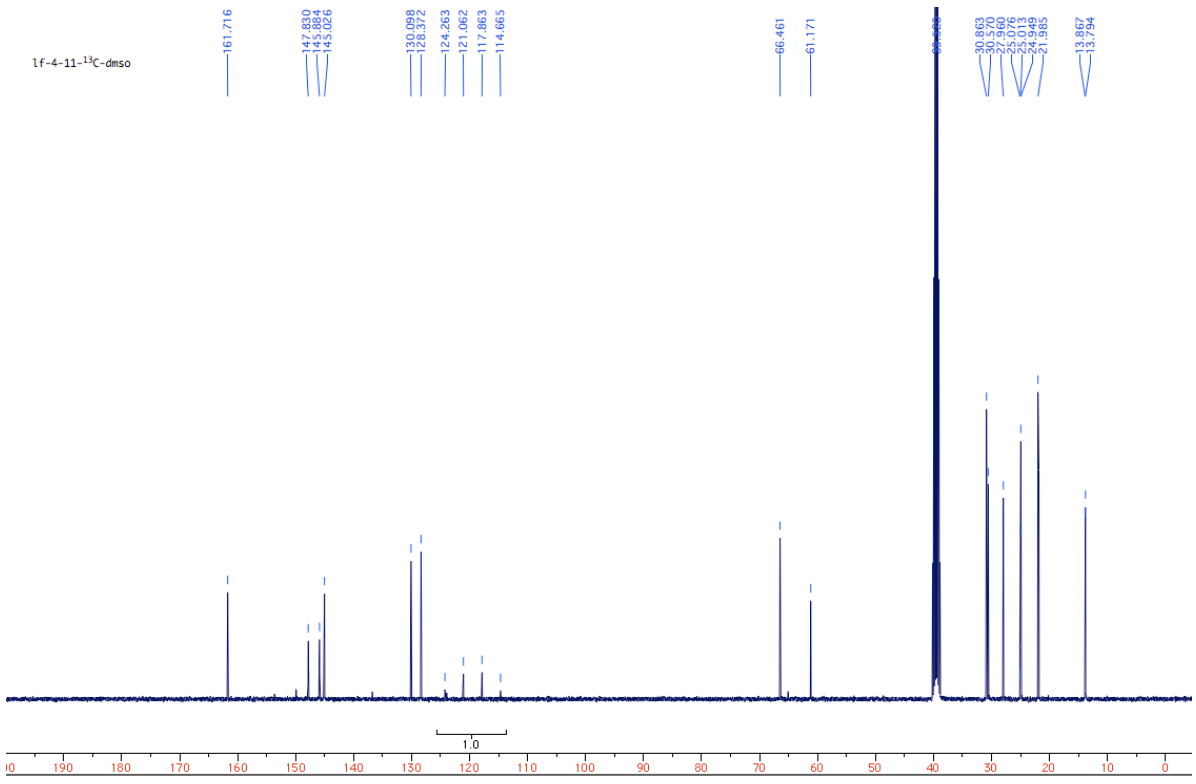
**3-(Butoxycarbonyl)-1-butylpyridinium bis(trifluoromethylsulfonyl)amide:**



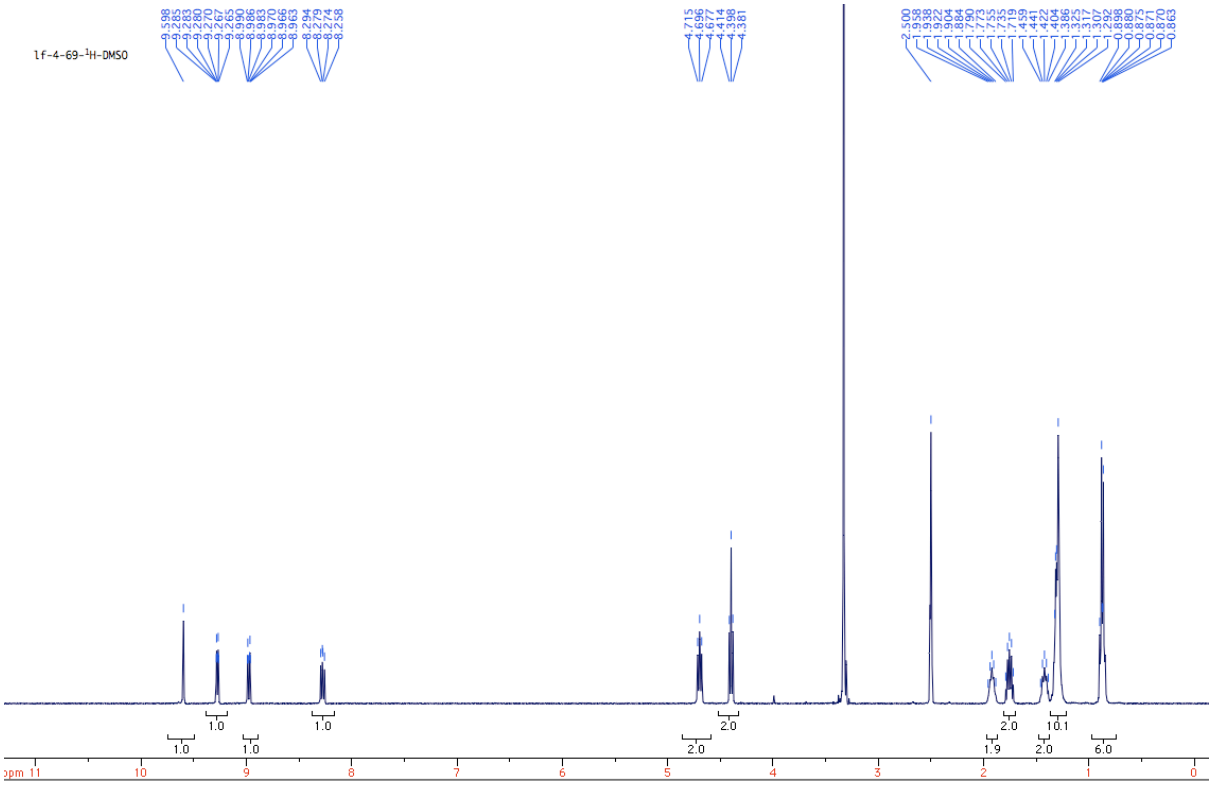



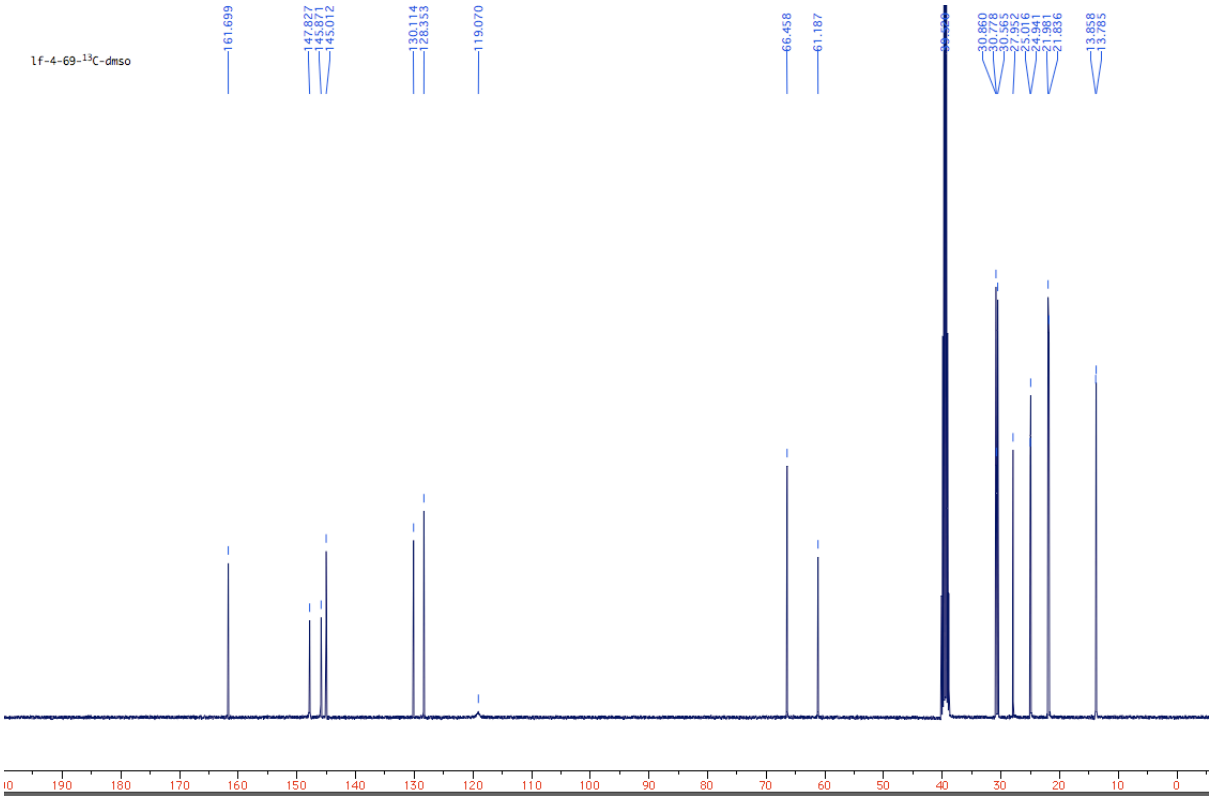
**1-Hexyl-3-(hexyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**



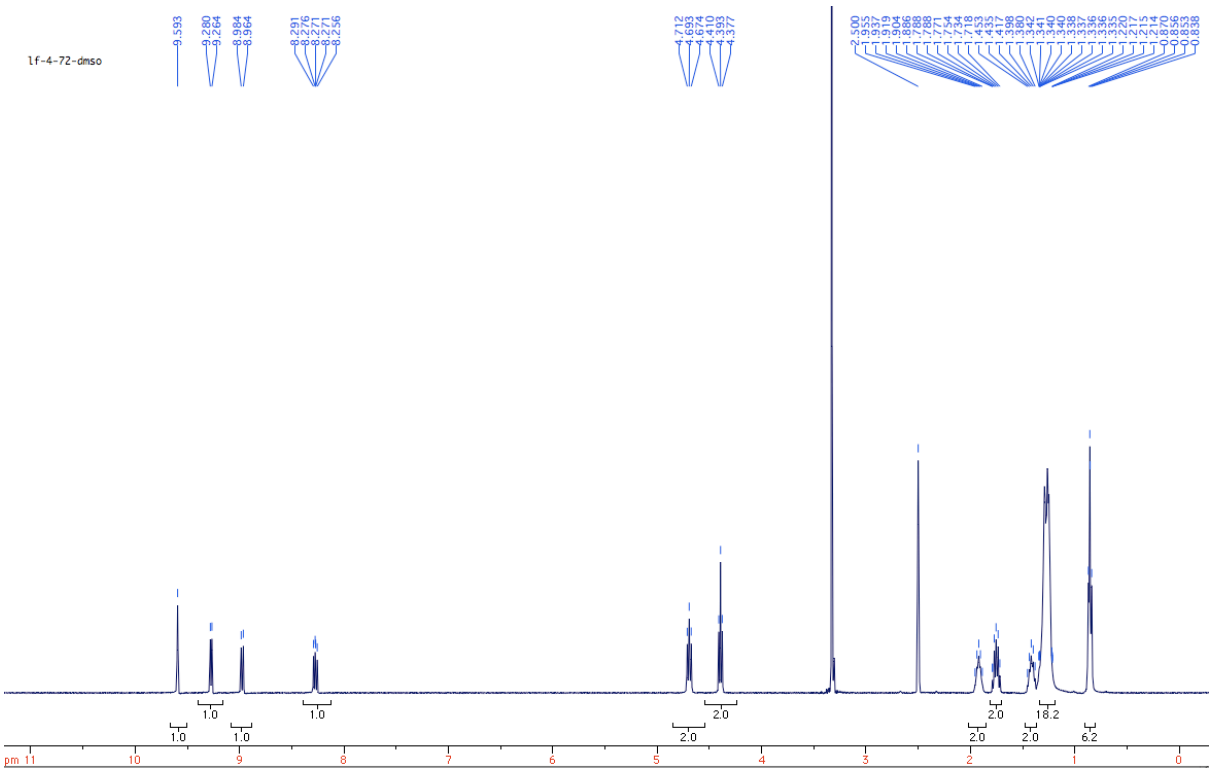



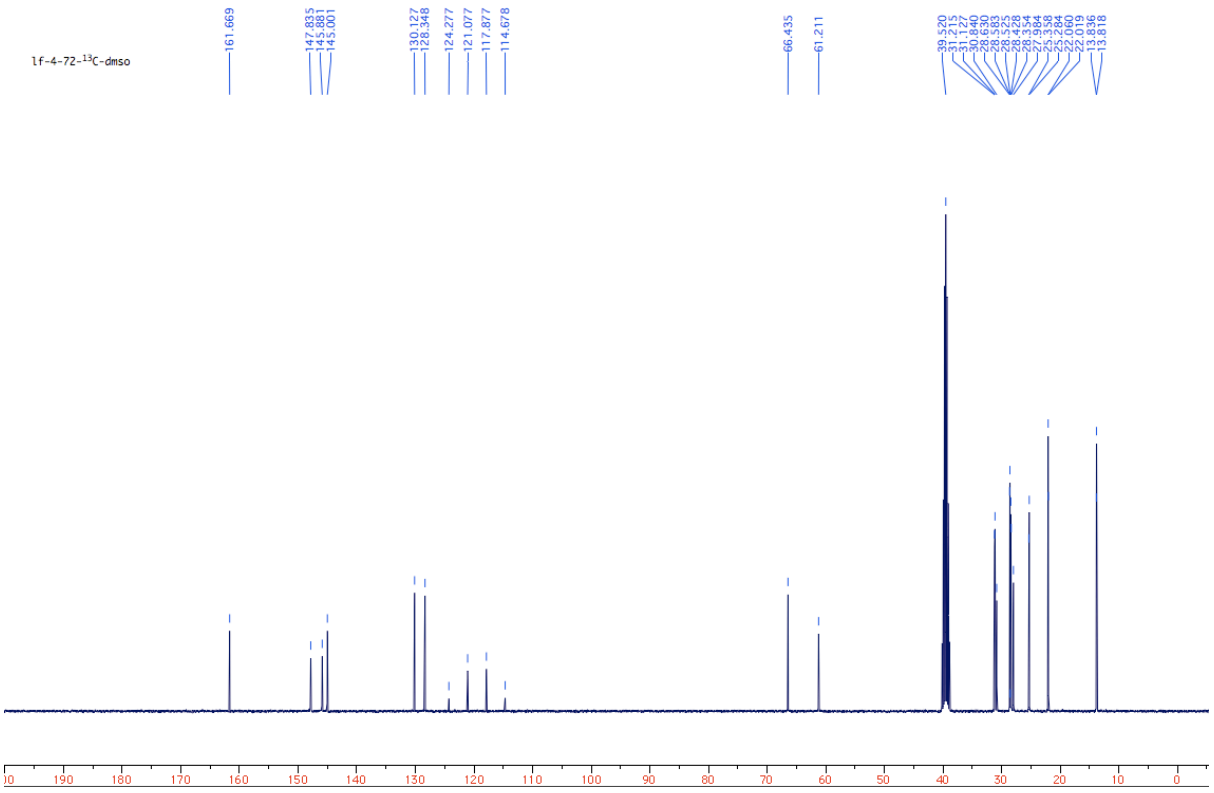
**1-Hexyl-3-(hexyloxycarbonyl)pyridinium dicyanamide:**



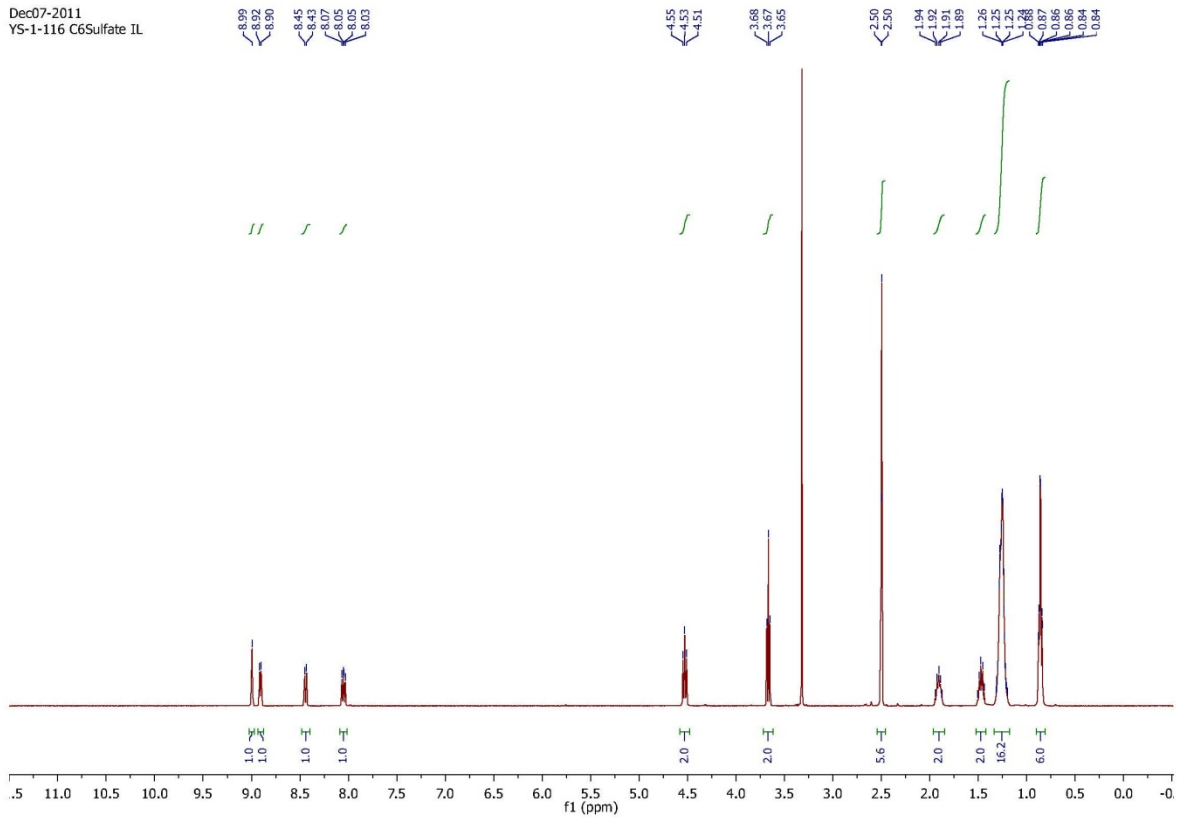



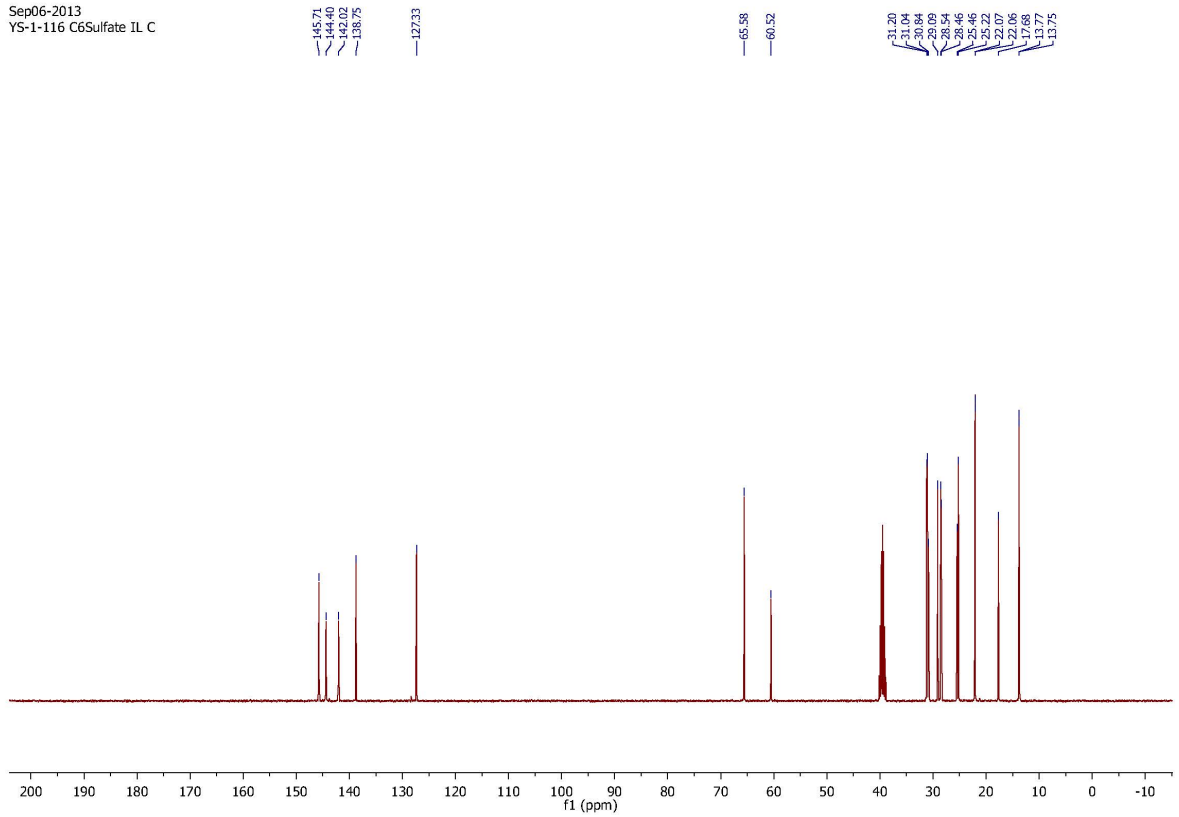
**1-Octyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide:**



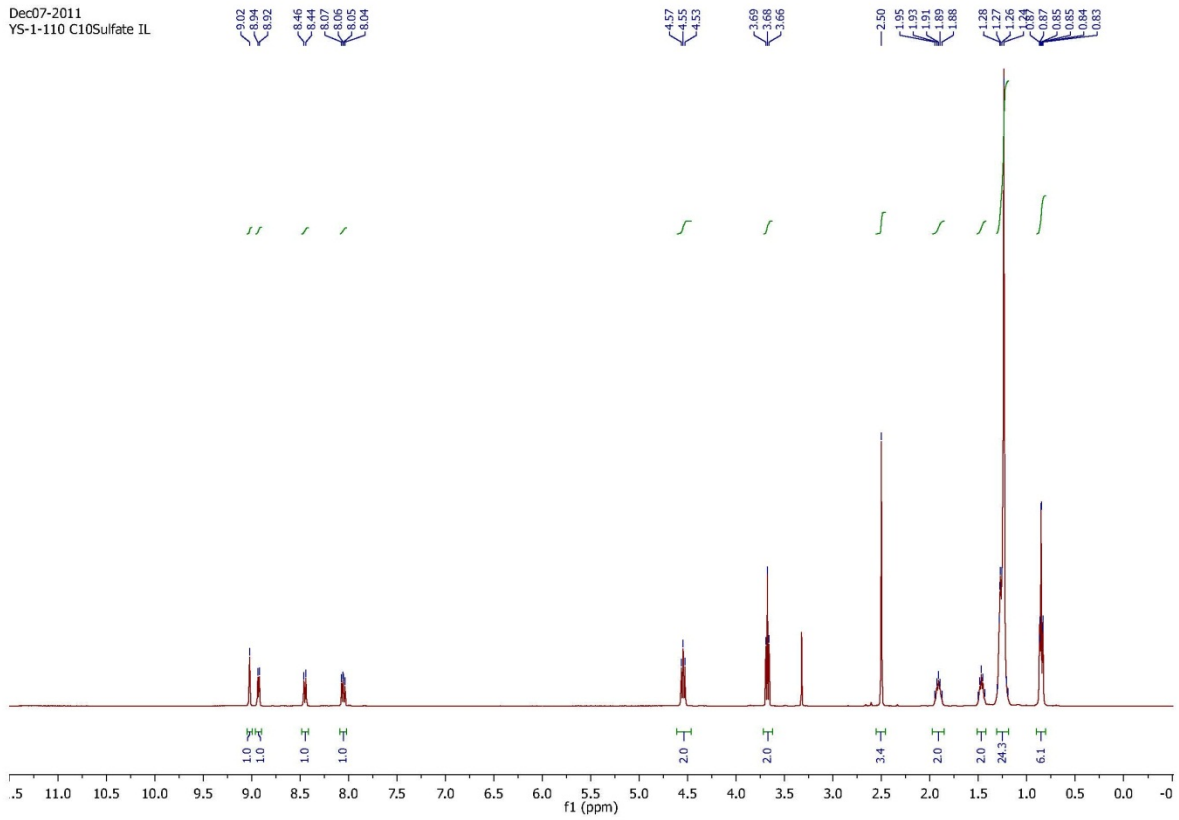



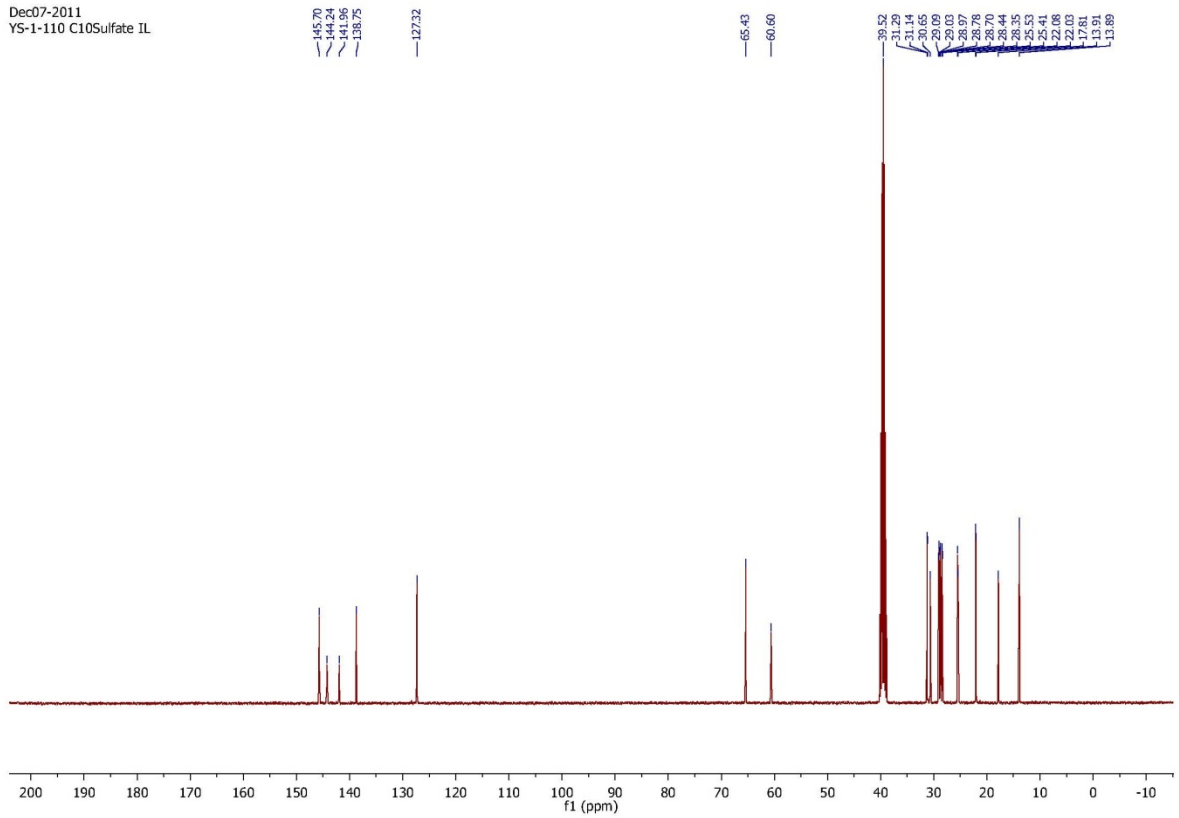
## 1-Octyl-3-methylpyridinium hexylsulfate:



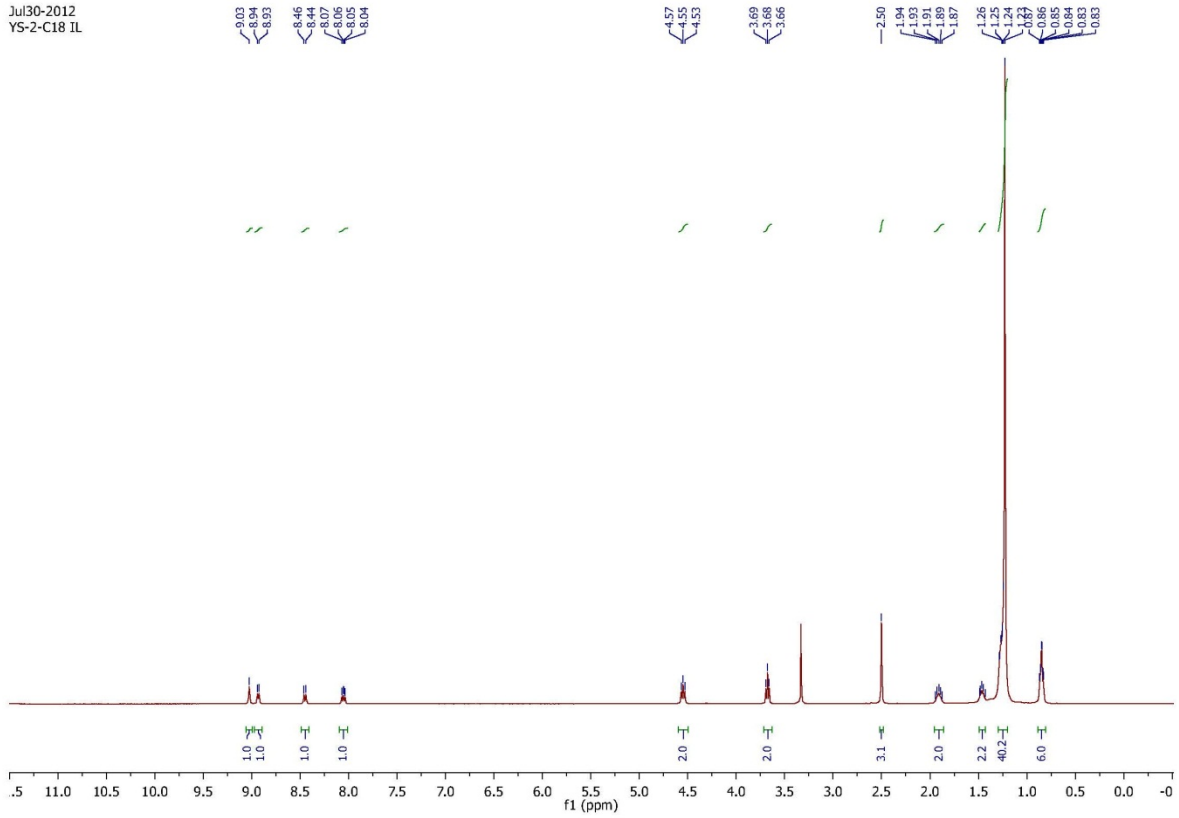



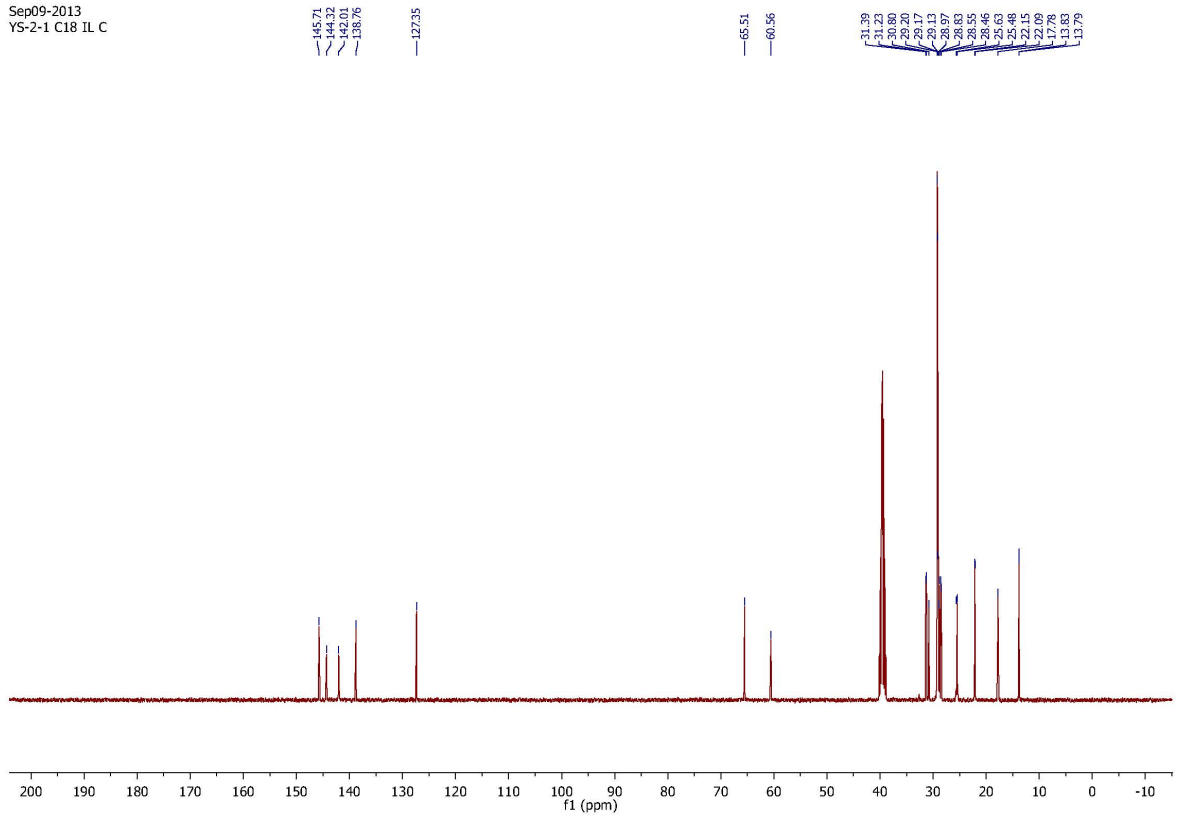
**1-Octyl-3-methylpyridinium decylsulfate:**



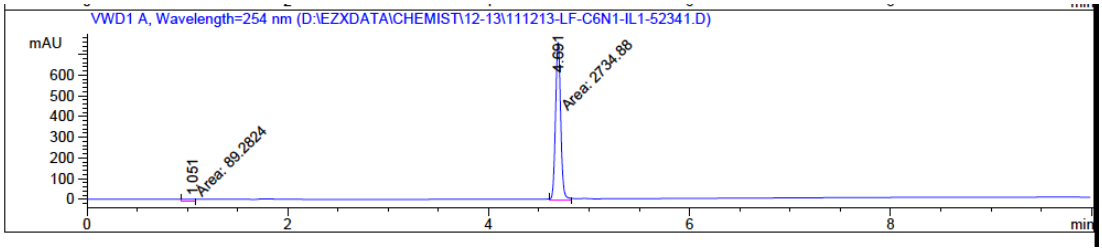
**1-Octyl-3-methylpyridinium octadecylsulfate:**



## HPLC Data

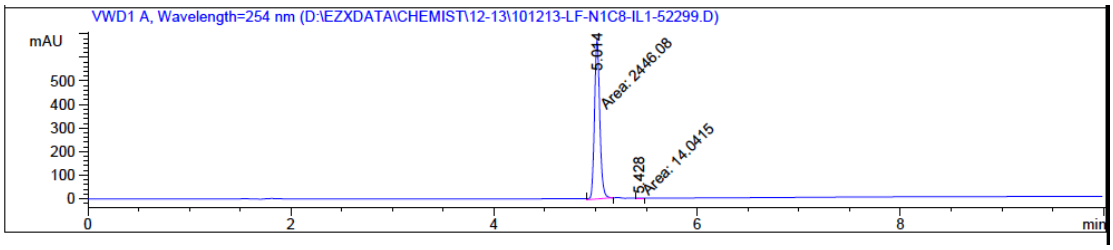
### 3-(Hexyloxycarbonyl)-1-methylpyrdinium bis(trifluoromethylsulfonyl)amide




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 1.051 | MM | 0.1385 | 89.28242 | 10.74156 | 3.1614 |
| 2 | 4.691 | MM | 0.0595 | 2734.87866 | 766.50745 | 96.8386 |
| Totals : | | | | 2824.16108 | 777.24901 | |

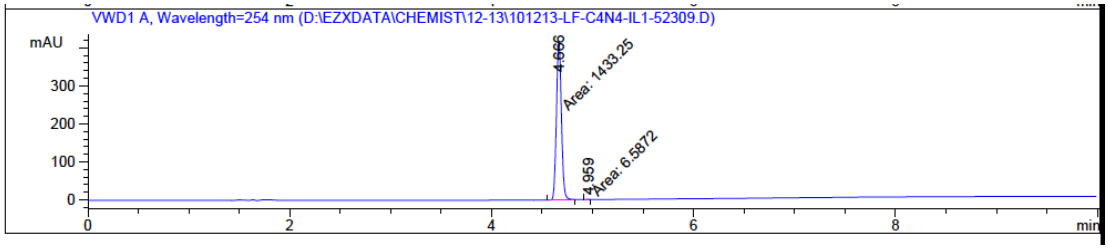
### 1-Methyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.014 | MM | 0.0605 | 2446.08032 | 673.54529 | 99.4292 |
| 2 | 5.428 | MM | 0.0743 | 14.04152 | 3.15108 | 0.5708 |
| Totals : | | | | 2460.12185 | 676.69637 | |

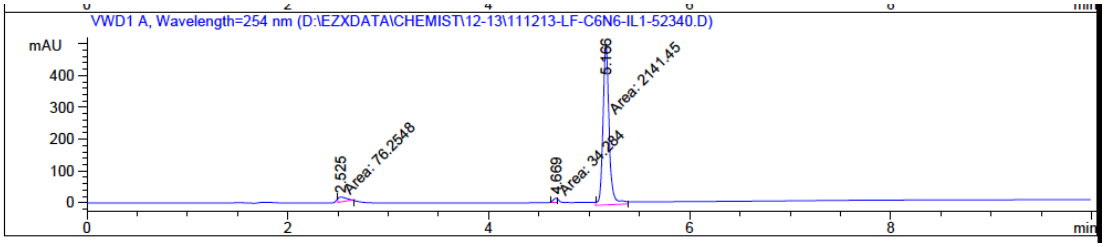
### 3-(Butoxycarbonyl)-1-butylpyridinium bis(trifluoromethylsulfonyl)amide




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.666 | MM | 0.0572 | 1433.25354 | 417.60999 | 99.5425 |
| 2 | 4.959 | MM | 0.0585 | 6.58720 | 1.87700 | 0.4575 |
| Totals : | | | | 1439.84074 | 419.48699 | |

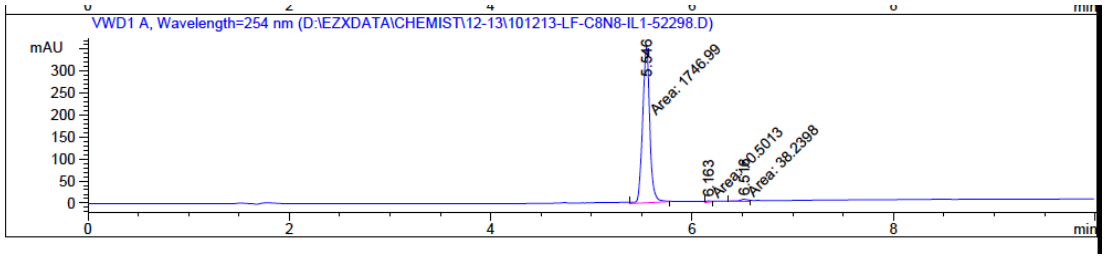
## 1-Hexyl-3-(hexyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 2.525 | MM | 0.0818 | 76.25480 | 15.54382 | 3.3861 |
| 2 | 4.669 | MM | 0.0424 | 34.28400 | 13.48918 | 1.5224 |
| 3 | 5.166 | MM | 0.0710 | 2141.45459 | 502.70697 | 95.0915 |
| Totals : | | | | 2251.99339 | 531.73997 | |

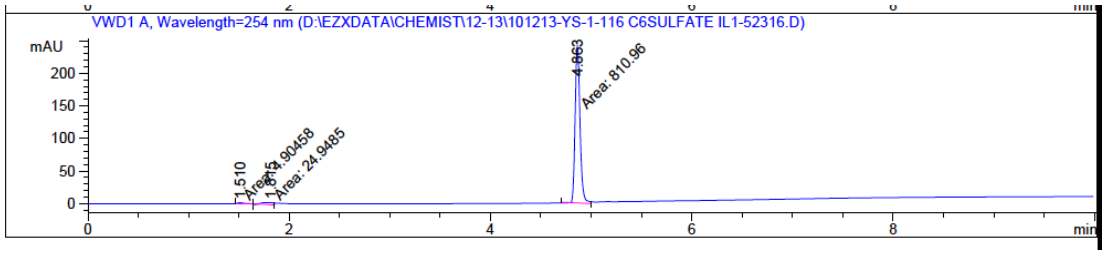
## 1-Octyl-3-(octyloxycarbonyl)pyridinium bis(trifluoromethylsulfonyl)amide




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.546 | MM | 0.0820 | 1746.98718 | 355.13049 | 97.2857 |
| 2 | 6.163 | MM | 0.0558 | 10.50129 | 2.80537 | 0.5848 |
| 3 | 6.516 | MM | 0.1201 | 38.23985 | 5.30825 | 2.1295 |
| Totals : | | | | 1795.72832 | 363.24411 | |

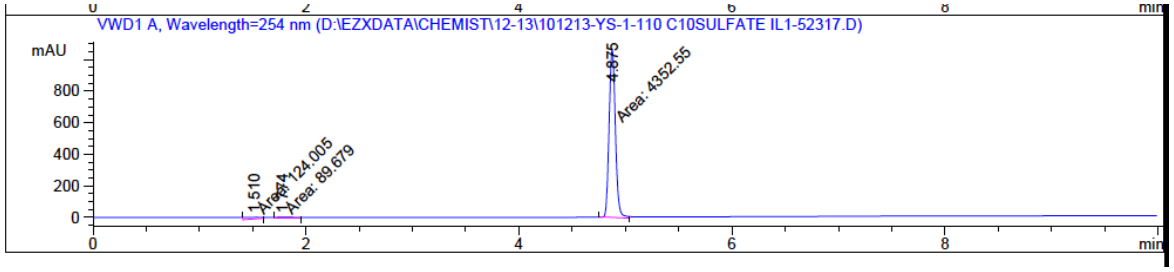
## 1-Methyl-3-octylpyridinium hexyl sulfate




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 1.510 | MM | 0.0595 | 4.90458 | 1.37443 | 0.5833 |
| 2 | 1.815 | MM | 0.1286 | 24.94847 | 3.23271 | 2.9672 |
| 3 | 4.863 | MM | 0.0562 | 810.96033 | 240.55383 | 96.4495 |
| Totals : | | | | 840.81338 | 245.16098 | |

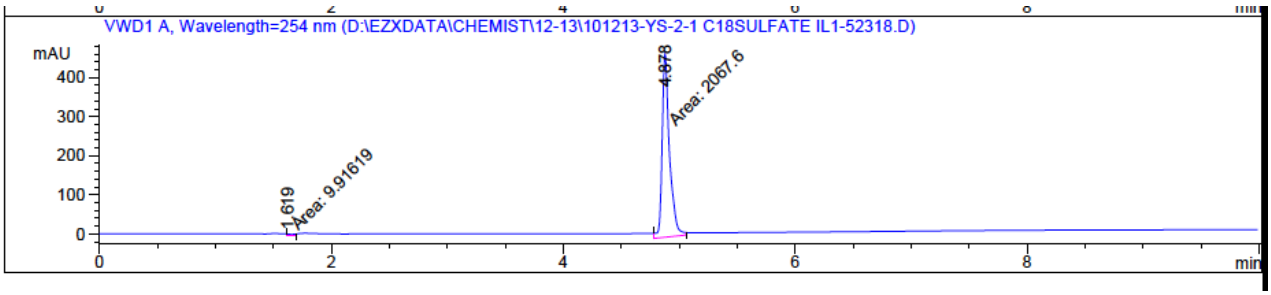
## 1-Methyl-3-octylpyridinium decyl sulfate




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 1.510 | MM | 0.1418 | 124.00526 | 11.35557 | 2.7157 |
| 2 | 1.774 | MM | 0.2238 | 89.67902 | 6.67872 | 1.9640 |
| 3 | 4.875 | MM | 0.0682 | 4352.54883 | 1063.32397 | 95.3203 |
| Totals : | | | | 4566.23311 | 1081.35826 | |

## 1-Methyl-3-octylpyridinium octadecyl sulfate




Signal 3: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 1.619 | MM | 0.0571 | 9.91619 | 2.89270 | 0.4773 |
| 2 | 4.878 | MM | 0.0733 | 2067.59888 | 470.38647 | 99.5227 |
| Totals : | | | | 2077.51507 | 473.27918 | |

**References**

1. J. R. Harjani, R. D. Singer, M. T. Garciac, P. J. Scammells, *Green Chem.* **2009**, *11*, 83-90.

2. J. R. Harjani, R. D. Singer, M. T. Garcia, P. J. Scammells, *Green Chem.* **2008**, *10*, 436-438.