Synthesis and Characterization of Novel Nopyl-Derived Phosphonium Ionic Liquids

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Abstract

A series of novel nopyl-derived chiral phosphonium ionic liquids have been successfully synthesised and characterised. Analysis of each novel ionic liquid was conducted in order to confirm structure, purity and thermal stability.

Key Words

Ionic liquid; phosphonium; chiral; nopyl-derivative

Introduction

The use of ionic liquids (ILs) as both reagents and solvents has seen significant interest in recent years and has been the subject of a recent review.[1] ILs offer a number of advantages in comparison with conventional organic solvents, advantages including: chemical and thermal stability,[2] no measurable vapour pressure,[3] low-combustibility[4] and catalytic ability.[5] Moreover, studies of the involvement of ILs in catalytic transformations have demonstrated their ability to exert unique thermodynamic and kinetic effects within a reaction system, with some ILs increasing the efficiency and selectivity of known transformations in comparison with the same transformations conducted in conventional solvents.[5] As such, the use of ILs as alternative media for organic chemistry, as well as other applications such as chemical separations, analytical chemistry amongst others is increasing.[1]

Chiral ionic liquids (CILs), where chirality is built into the IL itself, have facilitated chiral induction in a range of chemical transformations.[6] The use of CILs as a medium for asymmetric synthesis is one example of their many uses – others include chiral separation of racemates,[7] stereoselective polymerizations[8] and gas chromatography.[9]

The preparation of CILs has historically proven difficult, but their potential utility across a range of applications has driven the development of more reliable and reproducible syntheses.[1] CILs are typically synthesised from chiral building blocks from a natural chiral pool (e.g. amino acids, amines, amino alcohols and alkaloids etc.)[10] or *via* asymmetric synthesis, depending on the component of the IL that contains the chiral centre.[11] As CILs have two components (the cation and anion), there are three possible combinations for introducing chirality, which can be classified as: chiral cation, chiral anion, and [chiral cation + chiral anion] diastereomeric salt.

One of the most widely investigated classes of ILs is the imidazolium anion family which has found wide-spread utility since their initial development in 1982.[12,13] Although widely applied, including use in asymmetric synthesis, they can sometimes display undesirable behaviour, being unstable under harsh conditions and having relatively high decomposition rates with each reaction cycle.[14] Phosphonium salt ILs offer advantages over their imidazolium counterparts as they generally show greater thermal stability (due to a lack of the acidic hydrogen found on imidazolium variants) and as such, show less decomposition per reaction cycle.[15,16] The relative stability of phosphonium ionic liquids (PILs) makes them an attractive alternative for numerous synthetic applications, and yet they remain under-explored.

The core component of PILs is the phosphonium cation, containing phosphorous bonded to four substituents. This phosphonium cation is associated with a counter anion and these salts can be represented by the generic formula $[PR_1R_2R_3R_4][X]$. There are two main strategies to include chirality at the phosphonium cation; the chirality can be at the phosphorus centre $[PR_1R_2R_3R_4]^+ [X]^-$ (where R_1,R_2,R_3,R_4 are not equivalent), or can be located on one or more of the phosphorous-bound substituents, see Figure 1.

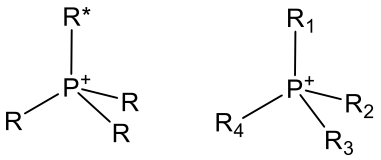


Figure 1: Chirality residing on substituent (left) and inherent chirality due to inequivalent substituents (right)

Chiral PILs (CPILs) with chirality located on a phosphorous-bound substituent offer several advantages over chiral phosphorus centres - phosphines such as Ph_3P, *n*-Bu_3P, *i*-Bu_3P, *n*-Oct_3P, which are low cost and commercially available, can be used, avoiding the need to selectively substitute four separate alkyl groups at the phosphorus centre, a potentially complicated and costly process.

The synthesis of tetraalkylphosphonium ILs [R*PR_3][X] would proceed *via* nucleophilic substitution an appropriate electrophile by a tertiary phosphine. Derivatives of (*R*)-nopol (Figure 2) have previously been utilized as the electrophile - these studies have shown that this low-cost terpineol, available as a single enantiomer, can be incorporated into imidazolium ILs with the leaving group, which will form the counter anion, being easily manipulated.[17] (*R*)-Nopol has also demonstrated an ability to interact stereospecifically with (*S*)-α-pinene when incorporated into a chiral membrane, which gives promise for its potential application in asymmetric synthesis when utilised in an ionic liquid.[18] With the above in mind, and the knowledge that there are no previous reports of the synthesis of phosphonium ionic liquids derived from (*R*)-nopol, and as such we report herein the synthesis and characterisation of 16 novel nopyl-derived PILs.

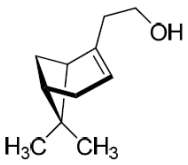
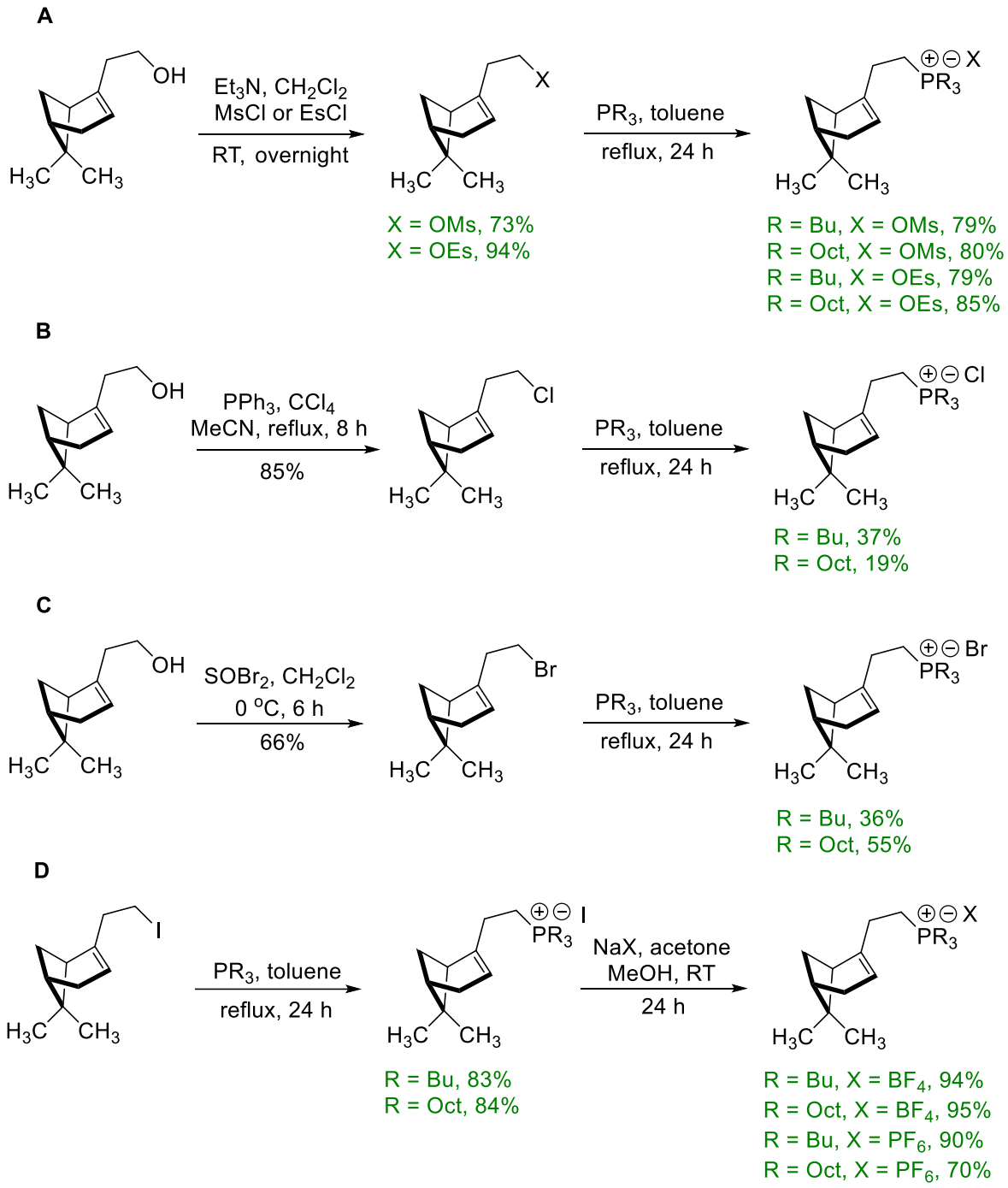


Figure 2: (1*R*)-(-)-Nopol

Results and Discussion

Novel nopyl-PILs were prepared as shown in Scheme 1 A-D. Depending on the desired counter anion, the alcohol on (*R*)-nopol was converted to the appropriate precursor functional group. In order to synthesise the mesylate or esylate ILs, (*R*)-nopol was reacted with either mesyl chloride or esyl chloride respectively, followed by treatment with the appropriate trialkyl phosphine, producing the target ILs in good yields (79-85%, Scheme 1A). Phosphonium chlorides were synthesised by an initial Appel reaction to convert the alcohol to the alkyl chloride, followed by nucleophilic substitution with the corresponding phosphine (Scheme 1B). Bromides were synthesised by treatment of the alcohol with $SOBr_2$ followed by displacement with a phosphine to produce these ILs in up to 55% yield (Scheme 1C). The approach to tetrafluoroborate and hexafluorophosphate ILs was slightly different – an initial reaction of the iodo-nopol derivative was reacted with the appropriate alkyl phosphine to give the intermediates approximately 84% yield, followed by successful ion exchange with sodium tetrafluoroborate or hexafluorophosphate salts to form the desired ILs in excellent yield (70-95%, Scheme 1D).



Scheme 1. **A-D** Synthesis of nopyl-phosphonium ionic liquids

Characterisation and Stability Studies

IL	R	X	Yield (%)	Form at 25 °C	δ_p	δ_F	P-C stretch / cm^{-1}	Anion stretch / cm^{-1}	Measured mass	Calculated mass
1	Bu	Cl	37	oil	34.17	-	1463	-	387.2968	387.2955
2	Oct	Cl	19	oil	33.75	-	1464	-	555.4787	555.4763
3	Bu	Br	36	oil	33.95	-	1465	-	431.2456	431.2450
4	Oct	Br	55	oil	33.87	-	1465	-	599.4244	599.4238
5	Bu	I	83	oil	33.87	-	1466	-	479.2311	479.2298
6	Oct	I	84	oil	33.68	-	1467	-	647.4211	647.4176
7	Bu	OTs	91	oil	33.95	-	1470	1131 (S=O)	523.3403	523.3369
8	Oct	OTs	71	oil	33.84	-	1470	1131 (S=O)	691.5238	691.5247
9	Bu	OMs	79	oil	34.02	-	1464	1125 (S=O)	447.3077	447.3056

10	Oct	OMs	80	oil	33.86	-	1465	1123 (S=O)	615.4921	615.4934
11	Bu	OEs	79	oil	34.04	-	1464	1124 (S=O)	461.3255	461.3213
12	Oct	OEs	85	oil	33.89	-	1465	1123 (S=O)	629.5125	629.5091
13	Bu	PF_6	90	wax	34.00	–71.92	1465	849 (P–F)	-	-
14	Oct	PF_6	70	wax	33.94	–71.73	1466	848 (P–F)	627.4737	627.4751
15	Bu	BF_4	94	oil	34.06	–150	1464	1227 (B–F)	439.3245	439.3240
16	Oct	BF_4	95	oil	33.87	–150	1465	1226 (B–F)	607.5155	607.5164

Table 1: Collated physical data for the new ionic liquids.

Form, ^{31}P and ^{19}F NMR

Most of the nopyl PILs are oils at room temperature, with the exception of the PF_6^- salts, which are waxes, and as such can potentially be used as solvents for processes requiring elevated reaction temperatures.

^{31}P NMR spectroscopy was employed to monitor the quaternarization of the tertiary phosphine as formation of the phosphonium salt was a key diagnostic indicator for successful synthesis; the ^{31}P NMR resonances of the starting alkyl and aryl phosphines typically displayed a single peak between -30 ppm and -5 ppm, with the quaternary phosphonium salts appearing at around +34 ppm. The presence of a single peak in the ^{31}P NMR spectra of the newly synthesised compounds showed that the liquids contained phosphonium ions only. New ILs containing fluorine counterions, clear fluorine resonances could be seen by ^{19}F NMR spectroscopy, and so confirmed that ionic exchange had successfully occurred.

^{1}H and ^{13}C NMR Spectroscopy

The ^{1}H and ^{13}C NMR data detailed in the supporting information fully agree with the structures of each synthesised IL.

Infrared Spectroscopy

Analysis of the IR spectra of all PILs (Table 1) showed characteristic strong absorption bands for P—C bond stretching at approximately 1460 cm^{-1}. The phosphonium liquids containing mesyl and esyl anions showed the appropriate S=O stretch at approximately 1125 cm^{-1}, and S—H stretching at approximately 985 cm^{-1}. B—F and P—F stretches are visible at 1225 cm^{-1} and 850 cm^{-1} respectively for the liquids containing BF_4^- and PF_6^- counterions respectively.

Mass Spectrometry

High resolution mass-spectrometry measurements are presented in Table 3. Often phosphonium ionic liquids exhibit both the naked cation and the undissociated ion pair, for example, the characteristic fragmentation pattern of $NopylPBu_3OMs$ is: $[NopylPBu_3]$ at m/e=351 and $[NopylPBu_3]\cdot[OMs]$ at m/e=447. The figures quoted in Table 1 correspond to the observed masses for the cation-anion pair, with each example showing the correct mass for the corresponding IL.

Thermogravimetric Analysis

To establish the suitability of the ILs for use at elevated temperatures, their thermal stability was studied by thermogravimetric analysis (TGA). In common with other ILs, PILs do not boil at high temperatures but do show upper limits to thermal stability. TGA data for each of the new ILs are presented in in Figures 3 and 4. Each graph shows the percentage mass loss as a function of temperature with the test material being heated at a rate of 5 °C min^{-1}, to a maximum temperature of 450 °C. The collated data indicate that the majority of the new ILs are stable to

approximately 300 °C for the PBu_3 series, and to approximately 200 - 250 °C for the $POct_3$ derivatives. For both sets of compounds, initial weight loss around 110 °C was the result of volatile material such as residual toluene evaporating and thus does not represent true decomposition. Within the two series, stability dependence on the nature of the anion followed similar overall trends with PF_6^- and BF_4^- being the most stable (50% mass loss at approx. 400 °C for the PBu_3 series and up to 420 °C for $NopylPOct_3BF_4$); the bromide and iodide salts were the least stable (50% mass loss around 360 °C for the PBu_3 and 340 °C for the $POct_3$ series), with the sulfonate salts displaying varying stabilities.

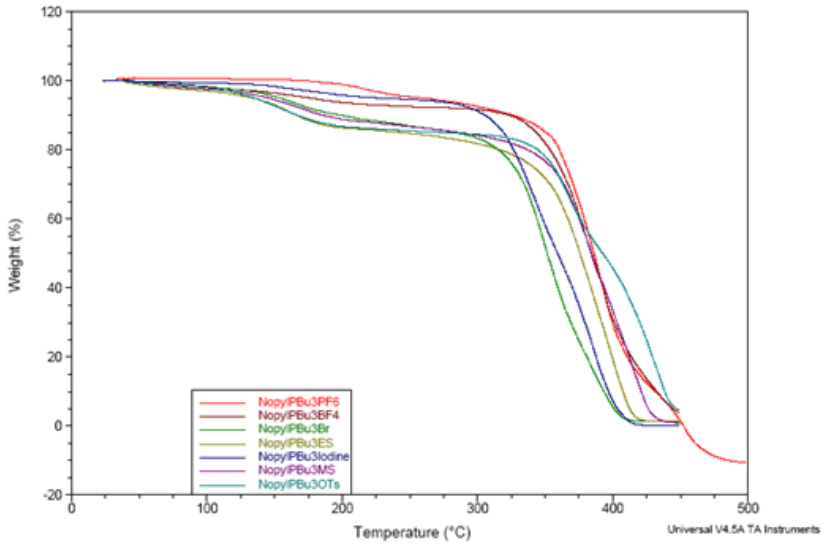


Figure 3. TGA data for the tributylphosphonium series of ILs. The graph shows (%) mass change with increasing temperature (5 °C min^{-1}) for $NopylPBu_3PF_6$, $NopylPBu_3BF_4$, $NopylPBu_3Br$, $NopylPBu_3OEs$, $NopylPBu_3I$, $NopylPBu_3OMs$ and $NopylPBu_3OTs$.

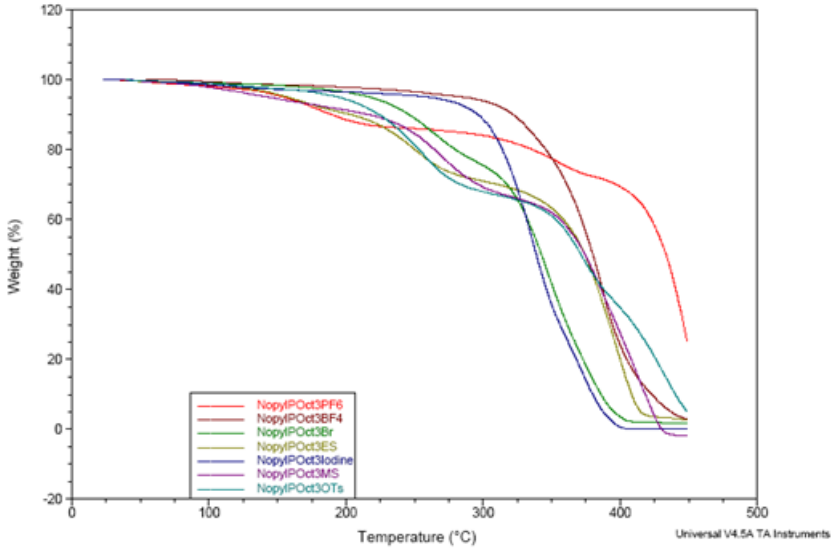


Figure 4. TGA data for the trioctylphosphonium series of ILs. The graph shows (%) mass change with increasing temperature (5 °C min^{-1}) for $NopylPOct_3PF_6$, $NopylPOct_3BF_4$, $NopylPOct_3Br$, $NopylPOct_3OEs$, $NopylPOct_3I$, $NopylPOct_3OMs$, $NopylPOct_3OTs$.

Differential Scanning Calorimetry

The nopyltributyl and nopyltrioctyl PILs showed no freezing point or melting point. Large heat flow changes were observed for the BF_4 nopyl PILs; the smallest changes were noticed for the PF_6 nopyl PILs.

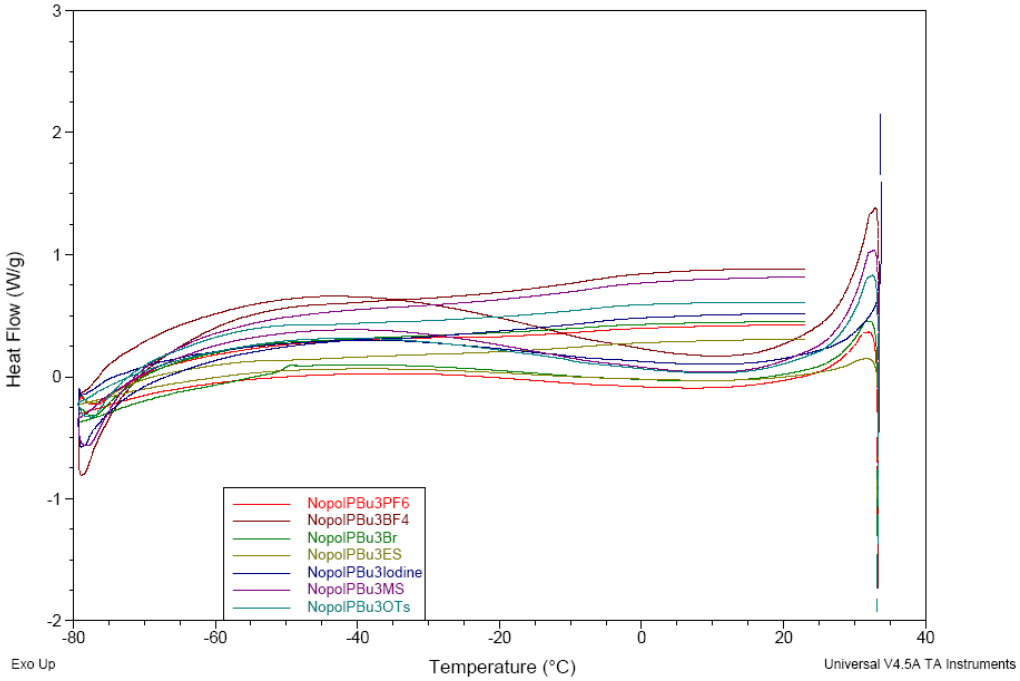


Figure 5: DSC profiles (wg^{-1} vs T (^oC)) of tributyl nopyl PILs ($NopylPBu_3PF_6$, $NopylPBu_3BF_4$, $NopylPBu_3Br$, $NopylPBu_3OEs$, $NopylPBu_3I$, $NopylPBu_3OMs$, $NopylPBu_3OTs$).

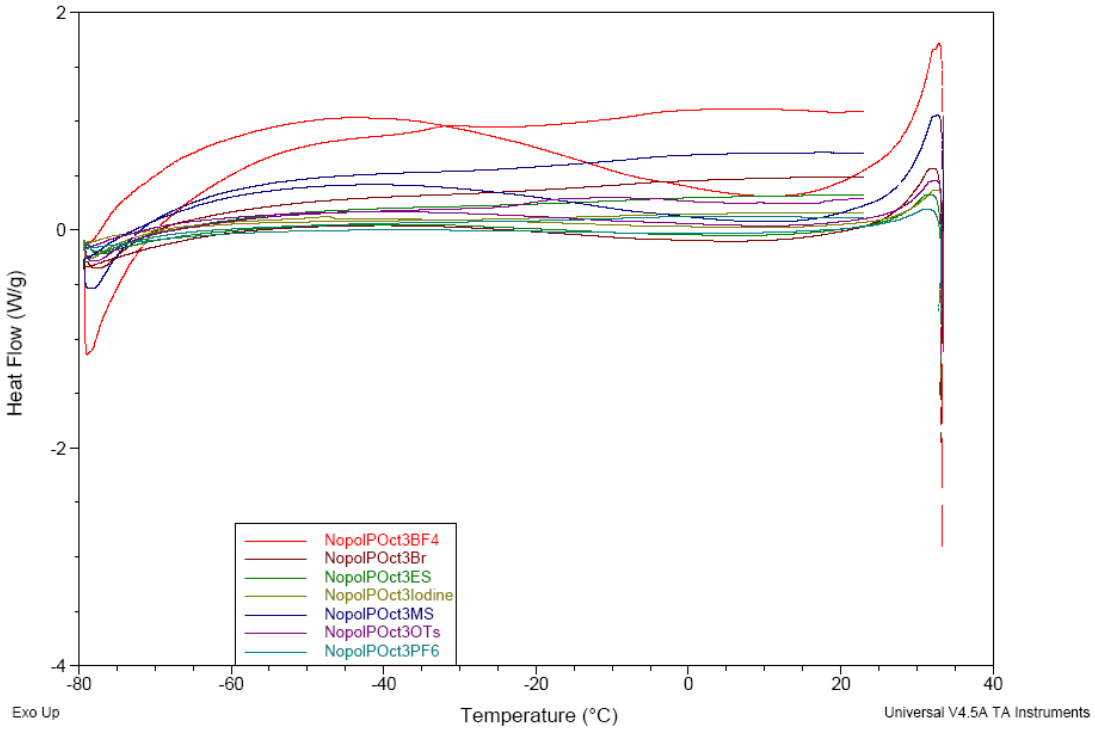


Figure 6: DSC profiles (wg^{-1} vs T (^oC) of PILs trioctyl Nopyl PILs ($NopylPOct_3PF_6$, $NopylPOct_3BF_4$, $NopylPOct_3Br$, $NopylPOct_3OEs$, $NopylPOct_3I$, $NopylPOct_3OMs$, $NopylPOct_3OTs$).

Conclusions

The synthesis and physical characteristics of 16 novel nopol-derived, chiral phosphonium ionic liquids has been reported. These ionic liquids were isolated in good yields, in high purity with each showing good thermal stability and desirable physical properties. Overall, the Bu_3P series is more stable than the $POct_3$ by approx. 30 °C; both series appear suitable for applications up to 300 °C, with the PF_6^- salts offering scope to extend the working temperature towards 400 °C. The application of these ionic liquids in catalysis and chiral induction, as well as their biological effects on multidrug-resistant bacterial cell lines is currently being investigated within our laboratories and will be reported in due course.

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