### Synthesis of novel multi-cationic PEG-based ionic liquids

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Synthesis of novel multi-cationic PEG-based ionic liquids

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The syntheses of ten novel mono-, di- or tri-cationic poly(ethylene glycol)-based ionic liquids (ILPEGs), incorporating tetra-substituted ammonium cations, are described. The poly(ethylene glycol) chains could be bridged or not and bore the cation. In the di-cationic ILPEGs family, hydrophobic poly(methylene) or amphiphatic poly(oxyethylene) spacers, with various lengths, were designed to connect the polar heads, while in the tri-cationic ILPEGs, the spacer was constituted by substituted diamines. The thermophysical properties such as viscosity or thermal stability were also investigated.

Keywords: Poly(ethylene glycol), Ionic liquids, Microwaves, Solvent-free.

Ionic liquids (IL)1,2 and poly(ethylene glycol)s (PEG)3−5 have experienced a tremendous interest within the last decades with various applications. They are different from usual organic solvents, considering their intrinsic chemical and physical properties. They have good stability (thermal, chemical, redox, radiochemical), low or null vapour pressure, high thermal and ionic conductivity suitable for microwave assisted heating,6,7 possibility of recycling, ability to act as efficient solvents (also for gaseous reagents) and/or supports for reagent and catalyst immobilization. Among the diversity of functionalized ionic liquids, those incorporating poly(ethylene glycol) moieties (ILPEGs) into either cationic or anionic units, making the link between the two distinct but very similar fluids,4,8−12 sharing common properties as those ones illustrated so far, yield to a new appealing group of solvents finding applications across a range of disciplines including science, technology and engineering.8 Despite the plethora of possible applications for the ILPEG systems, only a limited number of examples were reported on their use as solvents for organic synthesis and catalysis.9 Different from PEGs or ionic liquids, PEG-based ionic liquids have been scarcely investigated and often neglected in recent literature.

[figure 1: Figure 1 Mono- and poly-cationic PEG-based ILs.]

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We have recently reported on the use of alkylammonium mono- and di-cationic \([\text{mPEG}_{350}\text{NMe}_2][\text{Br}]\) \(1\) and \([\text{mPEG}_{350}\text{NMe}_2\text{CH}_2\text{CH}_2][\text{Br}]\) \(3\) as useful solvents for the synthesis of dipeptides under microwave irradiation\(^{11}\) (Figure 1). We report herein the preparation of a novel family of poly(ethylene glycol)-based ionic liquids \(3-12\), having up to three ammonium groups in their structure (Figure 1). The physicochemical properties were also investigated in the perspective of using these new solvents as additives in organic synthesis and catalysis. Indeed, slight changes of the dimethylether-PEG chain \(1\) along with the chemical nature of the counter anion, made up with long functional mPEG derivatized cations, might have a significant effect on the thermophysical and viscosity properties of ILs and ionic liquids in general.\(^{8,9}\)

The poly(ethylene glycol) (PEG) chains bridged \(1\) or not \(2\) are on the cationic part of the molecule (Figure 1). In the case of the di-cationic ILs \(3-6\), the tetra-alkylammonium cations are interconnected by a hydrophobic poly(methylene) \(1\) or an amphiphilic poly(oxyethylene) unit \(2\), while a diethyl- or dipropyl-amine spacer was selected to access to ILs \(7-12\) (Figure 1). We previously reported\(^ {13}\) on the synthesis of mono-cationic ILs \(1\) and \(2\) via a two-step procedure. In the first step native MeO-PEG-\(OH\) \((n = 7-8\) ca.) was mono-brominated with \(\text{PBr}_3\) followed by direct alkylation of gaseous \(N,N\)-dimethyleamine with a two-fold excess of MeO-PEG-350-Br \(13\), for 72 h at room temperature (Scheme 1). However, formation of di-brominated \(Br_2\text{PEG}_2\text{Br}\) (a by-product difficult to eliminate) during the first step, and the need to carefully control the exact amount of gaseous amine introduced into the reaction vessel, to avoid formation of a mixture consisting in unreacted starting material and the desired \([\text{mPEG}_{350}\text{NMe}_2][\text{Br}]\) \(1\), led us to design a more straightforward and faster synthetic scheme overcoming these difficulties and based on a three-step procedure (Scheme 1).

Improvement in the first step consisted in the use of \(\text{Et}_3\text{N}\) as base during \(\text{PBr}_3\) mono-bromination of poly(ethylene glycol) mono-methylether MeO-PEG-350-\(OH\) and MeO-PEG-750-\(OH\).\(^ {14}\) The role of the base was to neutralize hydrobromic acid formed in the presence of traces of water and responsible for the formation of the Br-PEG-Br by-product. MeO-PEG-350-Br \(13\) and MeO-PEG-750-Br \(14\) were obtained in 97% and 67% yields respectively as pure compounds, after a simple chloroform extraction. Traces of unreacted MeO-PEG-\(OH\) or \(50\) [\(\text{CH}_2(\text{OCH}_2\text{CH}_2)_x\text{O}]\text{P(=O)}\text{OH}\) phosphoric diesters were eliminated in the aqueous layer. The second step consisted in the amination reaction of MeO-PEG-350-Br \(13\) and MeO-PEG-750-Br \(14\), leading to MeO-PEG-350-NMe\(_2\) \(15\) and MeO-PEG-750-NMe\(_2\) \(16\) respectively. In contrast to the two-step procedure\(^ {11}\) (needing an exact control of stoichiometry and not always easy from practical point of view), a large excess of gaseous \(N,N\)-dimethyleamine (with respect to MeO-PEG-\(Br\)) was condensed at -15°C in anhydrous ethanol, and heated in a sealed vessel under microwave irradiation (Scheme 1). The presence of poly(ethylene glycol) backbone was particularly adapted to microwave irradiation,\(^ {4,15-19}\) in which the heating characteristic of the solvent plays a crucial role,\(^ {2}\) speeding up

\[\text{SCHEME 1. Synthesis of mono-cationic ILs} 1 \text{ and } 2 \text{ and di-cationic } 3 \text{ and } 4 \text{ with hydrophobic spacers.}\]
The preparation of di2cationic IL was the amination reaction and leading to MeO-PEG-350-NMe₂ 15 and MeO-PEG-750-NMe₂ 16 in good yields after simple extraction (99% and 96% yields respectively) in only 30 minutes (Scheme 1). Mono-cationic [mPEG₃₅₀NMe₂][Br] 1 and 5 [mPEG₇₅₀NMe₂][Br] 2 IL₉₆ were finally obtained by reacting stoichiometric quantities of MeO-PEG₂-Br derivatives 13-14 with MeO-PEG₂-NMe₂ 15-16 respectively, under microwave irradiation (Scheme 1). At 80°C or 100°C, the nucleophilic substitution was not complete, even after prolonged heating (2 hours) or various irradiation cycles, with 120°C performing the best. The improved synthetic pathway illustrated in Scheme 1 using microwave irradiation was more convenient in terms of reaction time, but was also more flexible than the one previously reported. ³¹⁵ It allowed the synthesis of various dissymmetric IL₉₆ by reaction of multiple combinations of PEG-Br/PEG-amine derivatives having different PEG-chain lengths.

**Scheme 2** Synthesis of IL₉₆ with poly(oxymethylene) spacer

With the purpose to widen the diversity of this class of solvents, the synthesis of other new polycationic IL₉₆ 7-12 was also investigated (Figure 1). Therefore, pentamethyldiethylenetriamine (PMDT) or 2,6,10-trimethyl-2,6,10-triazaundecane (TMTAU) were alkylded in the presence of an excess of the intermediate MeO-PEG-350-Br 13, in neat conditions (Scheme 3). The synthetic strategy illustrated in Scheme 3 was versatile. At room temperature, only the di-alkylated di-cationic IL₉₆ [(mPEG₃₅₀)(PMDT)][Br] 7 and [(mPEG₃₅₀)(TMTAU)][Br] 8 were obtained, as confirmed by ¹H NMR and MALDI-TOF analyses. By extending the reaction time to 6 days and increasing the temperature to 60°C, the more challenging trialkylation was possible leading quantitatively to the tri-cationic [(mPEG₃₅₀)(PMDT)][Br] 10 or [(mPEG₃₅₀)(TMTAU)][Br] 12 counterparts, after removing the excess of alkylating agent MeO-PEG-350-Br 13 with hexane (Scheme 3).
Similarly, tri-alkylated IL\textsubscript{PEG\textsubscript{8}} ([mPEG\textsubscript{1250}]Me(PMDT))[Y] \textsuperscript{9} and ([mPEG\textsubscript{1250}]MeTMTAU)[Y] \textsuperscript{11} were obtained when methyl iodide was used as alkylating agent (Scheme 3). The \textsuperscript{1}H NMR spectra of di-alkylated IL\textsubscript{PEG\textsubscript{8}} \textsuperscript{7} and \textsuperscript{8} showed the presence of a singlet at 2.32 ppm, attributed to the methyl protons of the internal nitrogen atom. This signal disappeared after nitrogen quaternarization, giving a new singlet at 3.32 ppm assigned to the three and six hydrogens belonging to the methyl groups of the internal ammonium salt of IL\textsubscript{PEG\textsubscript{8}} \textsuperscript{9}, \textsuperscript{11} and of \textsuperscript{10}, \textsuperscript{12} respectively. It is worth to notice that when ethanol, acetonitrile or dioxane were used in the first step, the analysis performed on the crude revealed the presence of a mixture of di-alkylated ([mPEG\textsubscript{1250}]PMDT)[Br] \textsuperscript{7} and ([mPEG\textsubscript{1250}]TMTAU)[Br] \textsuperscript{8} and tri-alkylated ([mPEG\textsubscript{1250}]PMDT)[Br] \textsuperscript{10} 15 ([mPEG\textsubscript{1250}]TMTAU)[Br] \textsuperscript{12} IL\textsubscript{PEG\textsubscript{8}} that could not be separated.

Then, attention was focused on the investigation of their physical properties such as thermal stability and viscosity, in view of their possible application as neoteric solvents in organic synthesis or as liquid supports for catalysis. Decomposition temperatures \(T_d\) measured for different IL\textsubscript{PEG\textsubscript{8}} (Table 1 and Figure 2), were close to 300°C, in agreement with the reported value for cationic ionic liquids composed with an ammonium positive group and a halide counter ion.\textsuperscript{13,20}

| IL\textsubscript{PEG} | \(T_d\) (°C) | \(\eta_{60°C}\) (Pas) | \(E_a\) (Activation energy) (kJ.mol\textsuperscript{-1}) |
|---------------------|-------------|----------------|---------------------------------
| ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] | 3 | 2.04 | 0.806 |
| ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] | 4 | 2.75 | 0.818 |
| ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(PEG\textsubscript{600})[Br] | 6 | 0.25 | 0.392 |
| ([mPEG\textsubscript{1250}](PMDT))[Br] | 7 | 18.1 | 0.813 |
| ([mPEG\textsubscript{1250}]MeTMTAU)[Y] | 11 | 15.8 | 0.896 |
| ([mPEG\textsubscript{1250}](TMTAU))[Br] | 12 | 14.2 | 0.724 |

The thermal stability of IL\textsubscript{PEG\textsubscript{8}} was demonstrated to notably depend on the chemical nature of the counter anion and to a smaller extent on the chemical nature of the cation head and its side chain.\textsuperscript{22} Moreover it was expected that long PEG chains were flexible enough to wrap the cationic head. As a result, the induced steric hindrance by PEG chains did not facilitate the nucleophilic attack of the anion involved in the Hoffmann-type thermal decomposition of the ammonium bearing IL\textsubscript{PEG\textsubscript{8}}. According to, ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(PEG\textsubscript{600})[Br] \textsuperscript{6} having the longest PEG chain, displayed an increased stability (up to 310°C). In addition, the increase of thermal stability of di-cationic IL\textsubscript{PEG\textsubscript{8}} was observed to slightly increase with the spacer length (Figure 2).

Di-cationic IL\textsubscript{PEG\textsubscript{8}} ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{3} and ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{4} (or ([mPEG\textsubscript{1250}](TMTAU))[Br] \textsuperscript{12}) exhibited a \(T_d\) of 280°C and 291°C respectively, as the spacer length increased from 2 to 6 ethylene units (Figure 1). The viscosity (\(\eta\)) of IL\textsubscript{PEG\textsubscript{8}} used as media in different applications, is an important parameter involved in the rate of mass transport, which may be a limiting factor for chemical or electrochemical applications (Table 1, Figure 3). The viscosity of IL\textsubscript{PEG\textsubscript{8}}, based on a number of ethylene oxide units greater than three, largely depended on van der Waals interactions, hydrogen bonding, on the nature of the counter anion and the rotational freedom within the cationic moieties.\textsuperscript{22} Moreover, the viscosity temperature dependence of IL\textsubscript{PEG\textsubscript{8}} was also important as reactions in these new media are often carried out at temperatures higher than room temperature (Figure 3). Accordingly, the reported viscosities in Table 1 were measured at 60°C, temperature at which we performed dipeptide synthesis under microwave irradiation using monocationic ([mPEG\textsubscript{1250}NMe\textsubscript{2}][Br] \textsuperscript{1} or di-cationic ([mPEG\textsubscript{1250}NMe\textsubscript{2}](CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{3} and ([mPEG\textsubscript{1250}NMe\textsubscript{2}](CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{4} as hydrophilic solvents.\textsuperscript{13}

The increase of the spacer length (\(x\)) from 1 to 3, was responsible for enhanced van der Waals interactions between alkyl groups, leading to a higher viscosity, \(\eta_{60°C} = 2.04\) Pas and 2.75 Pas for ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{3} and ([mPEG\textsubscript{1250}NMe\textsubscript{2}](CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{4}, respectively.

![Figure 2](image2.png)

**Figure 2** Differential thermogravimetric profile of IL\textsubscript{PEG\textsubscript{8}}

The increase of the spacer length (\(x\)) from 1 to 3, was responsible for enhanced van der Waals interactions between alkyl groups, leading to a higher viscosity, \(\eta_{60°C} = 2.04\) Pas and 2.75 Pas for ([mPEG\textsubscript{1250}]NMe\textsubscript{2})(CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{3} and ([mPEG\textsubscript{1250}NMe\textsubscript{2}](CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{4}, respectively.

![Figure 3](image3.png)

**Figure 3** Viscosity dependence on temperature.

It was also observed a large viscosity decrease by substituting the alkyl spacer by a poly(oxyethylene) group, \(\eta_{60°C} = 2.75\) Pas for ([mPEG\textsubscript{1250}NMe\textsubscript{2}](CH\textsubscript{2}CH\textsubscript{2})[Br] \textsuperscript{4} and...
expected that interactions of the ammonium group-PEG moieties decreases dissociation of anionic counter ions with cationic dimeric headgroups, leading to a viscosity decrease. Moreover, the PEG$_{500}$ used as a spacer in [(mPEG$_{350}$NMe$_2$)$_2$](PEG$_{600}$)][Br] 6 was larger and much more flexible than the corresponding hexyl counterpart of IL$_{PEG}$ [(mPEG$_{150}$NMe$_2$)$_2$(CH$_2$CH$_3$)][Br] 4, and thereby the cation moiety displayed a faster relaxation time associated with a reduced viscosity.\(^{15}\) As reported in Table 1, increasing the number of cationic groups in the ionic liquid molecules made the tri-cationic IL$_{PEG}$\(^8\) [(mPEG$_{350}$)Me(TMTAU)][Y] 11 and [(mPEG$_{350}$)(TMTAU)][Br] 12 more viscous than di-cationic IL$_{PEG}$\(^8\) [(mPEG$_{350}$NMe$_2$)$_2$(CH$_2$CH$_3$)][Br] 3, [(mPEG$_{150}$NMe$_2$)(CH$_2$CH$_3$)][Br] 4 or [(mPEG$_{350}$NMe$_2$)$_2$(PEG$_{600}$)][Br] 6, as reported in Table 1. The high viscosity of tri-cationic IL$_{PEG}$\(^8\)

including a short alkyl spacer (ethyl or propyl group) resulted in an increase of inter-ionic Coulombic interactions, enhancement of van der Waals interactions associated with reduced rotational freedom of the cation, larger and less flexible than di-cationic moieties. Surprisingly, the di-cationic [(mPEG$_{350}$)PMDT][Br] 7, made up with a diethylmethylamine spacer, exhibited the highest viscosity of the studied IL$_{PEG}$\(^8\), due to the enhancement of the cohesion of the ionic liquid. Indeed, the presence of a ternary amine in di-cationic [(mPEG$_{350}$)PMDT][Br] 7 led to the apparition of a permanent dipole between the cationic ammonium groups and the high electronic density of the amine function. As a result, this additional dipolar interaction strongly increased the ionic liquid cohesion consistent with the high value of the viscosity. As shown in Figure 3, the IL$_{PEG}$\(^8\) viscosity decreased as $T^\circ$ increased according to an Arrhenius type law $\eta=\eta_0 e^{\Delta F/RT}$, while the activation energy ($\Delta F$) (Table 1), decreased for [(mPEG$_{350}$NMe$_2$)$_2$(PEG$_{600}$)][Br] 6 and [(mPEG$_{350}$)(TMTAU)][Br] 12 that contained the highest number of poly(oxyethylene) groups as side chains or spacer. This behavior was in agreement with the non-linear conformation of the PEG chains as previously reported.\(^{20}\)

Conclusions

The preparation of various novel mono- and poly-cationic PEG-based ionic liquids under microwave irradiation was reported. According to our previous results\(^{11}\) their application as alternative reaction solvents was demonstrated. However, in contrast to their ‘parent’ compounds ionic liquids and PEGs, IL$_{PEG}$\(^8\) have been less investigated and more research needs to be performed to shed light on their full potential and versatility as neoteric solvents to perform organic synthesis or for improved catalytic processes. The PEG chain(s) could act as metal stabilizing ligands,\(^{22}\) avoiding aggregation. Although classical ionic liquids are able to stabilize nanoparticles, the presence of a PEG chain enhances this property through steric stabilization. Consequently, the presence of the polyoxyanated backbone could be able to modulate the reactivity of the system, especially for metal-catalyzed processes,\(^{13}\) differently than the classical ionic liquids, where the modulation of the properties depends on the nature of cation and/or the anion. Moreover, due to the presence of highly adsorbing PEG chains, microwave irradiation was particularly suitable, decreasing dramatically the reaction times with respect to conventional heating,\(^4\) also allowing syntheses in neat conditions. It should not be neglected that the presence of a biocompatible\(^{24}\) PEG moiety open new perspectives towards future studies on the ecotoxicity and biodegradability of this unexplored class of neoteric solvents.

The physical properties of these ionic liquids were also investigated in terms of the nature of the spacer (hydrophobic or amphipathic) connecting the quaternary ammonium,\(^9\) as well as on the PEG chain length. Other studies will be performed in the future to facilitate the process of a reaction by a simple product recovery. This would be possible after investigation of their thermomorphic properties (leading to a temperature-dependent biphasic system in the presence of a suitable organic solvent), or exploiting their solubility in water (due to the presence of PEG chains), allowing an easy extraction of the product. Current studies are in progress to show their possible applications.

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Notes and references