Ionic liquids—media for unique phosphorus chemistry†

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Ionic liquids have been shown to offer hitherto unseen control as both a storage solvent for PCl₃ and POCl₃ and reaction media for fluorination and mixed anhydride formation under benign conditions.

Phosphorus trichloride (PCl₃) and phosphorus oxychloride (POCl₃) are major precursors for flame-retardant materials, pesticides, nerve gases and plasticizers,¹ as well as key reagents in numerous synthetic reactions such as chlorination reactions and Vilsmeier–Hack formulations of amines. Since the development of automated oligonucleotide synthesis, the use of PCl₃ has been extended to the manufacture of nucleoside phosphoramidites and related building blocks. Such automated processes rely on all synthetic precursors being of the highest purity.² This is often difficult to achieve as PCl₃, POCl₃ and many chlorinated derivatives are highly moisture sensitive and hydrolyse rapidly under conventional storage or standard reaction conditions. Furthermore, due to their high reactivity towards numerous reagents and solvents, there continue to be major limitations to their wider application. For example, although conventional solvents can be used for the preparation of dichlorokylphosphines, strictly anhydrous conditions and excess of PCl₃ must be employed in order to prevent reagent and product hydrolysis.³ Similarly, direct phosphorylation of nucleosides with POCl₃ must be limited to a few nucleosides and is performed in atypical solvents such as triethylphosphate.⁴

In order to overcome some of the limitations currently encountered in the preparation of nucleoside and carbohydrate containing phosphoramidites/phosphoramidates and introduce synthetic flexibility, the reactivity of PCl₃ and POCl₃ in ionic liquids (ILs) has been studied. To date, PCl₃ chemistry has only been reported in chloroaluminate ILs, which are inherently dry.⁵ The present work reports on the unexpectedly high hydrolytic stability observed for PCl₃ and POCl₃ in ILs and their reactivity towards nucleophilic anions to form novel phosphorus species.

The solubility and stability of PCl₃ and POCl₃ were analyzed by ³¹P- and ¹H-³¹P coupled-NMR over time in both air equilibrated “wet” and dry ILs stirred in air and argon, respectively. Table 1 summarizes the effect of dissolving 0.5 M PCl₃ and POCl₃ in a range of wet ILs. For comparison, the stability of PCl₃ and POCl₃ in THF stirred in air showed >25% hydrolysis after 15 min and no PCl₃ or POCl₃ remaining after 1 h.

In dry [C₄mim][OTf] and [C₄mim][OMs], PCl₃ reacted with the IL forming phosphate–sulfate and –sulfonate mixed anhydrides, both mono- and bis-chlorinated, via nucleophilic displacement of the halogen. Halogen exchange was also surprisingly rapid in dry [C₆mim][BF₄]. After 75 min, a ratio between PCl₃ (δ 220 ppm), PCl₃F (²³P-δ 218 ppm, J₉F-δ = 1332 Hz; ¹⁹F-δ - 78.5 ppm), PCIF₃ (²³P-δ 174 ppm, J₉F-δ = 1383 Hz; ¹⁹F-δ - 80.5 ppm) and PF₃ (²³P-δ 103 ppm, J₉F-δ = 1400 Hz; ¹⁹F-δ - 80.2 ppm) of 1 : 0.03 : 0.02 : 0.4 was found. This mixture gradually changed and, after 2 h, only PCl₃ and PF₃ were found with no hydrolysis products detected. This sample had a much reduced signal-to-noise ratio and eventually no phosphorus signal was measurable. PCl₃ in wet [C₄mim][BF₄] showed similar exchange products; however, after 2 h, significant hydrolysis occurred. In contrast, no hydrolysis was found for PCl₃ in wet [C₆mim][OMs] but oxidation from P(III) to P(V) did occur. This was unexpected as strong oxidants such as iodine are usually required, although some sulfate mixed anhydrides have been reported to be oxidised using air.⁶ In the [NTf₂]⁺-based ILs, PCl₃ was soluble at concentrations >20 M and in [C₄mim][NTf₂] was found to be hydrolytically stable (>95%) for weeks, even when stirred in air and without drying the IL. In wet [C₆mim][NTf₂], <10% hydrolysis of PCl₃ occurred after 3 h on stirring in air; however, after 72 h complete hydrolysis had occurred. The addition of 0.9 M [C₄mim]Br to [NTf₂]⁺-based ILs had little effect on the stability of PCl₃, and no bromide exchange could be detected by ¹³P-NMR. However, addition of 1.6 M CsF to PCl₃ in [C₄mim][NTf₂] resulted in the rapid formation of PF₃. Such exchange is not observed in conventional solvents such as chloroform or THF.

Although the ILs halide purity is not important, PCl₃ stability is strongly affected by the presence of unreacted N-methylimidazole (NMI). Addition of NMI to a solution of PCl₃ in [C₄mim][OTf] resulted in the formation of a yellow precipitate, probably of [P(NMI)₃]Cl₃ (Scheme 1), which rapidly hydrolysed when exposed to air. Similar neutral adducts have been found on reacting POCl₃ and SiCl₄ with aromatic bases.⁷ Although the low solubility of [P(NMI)₃]Cl₃ prevented its identification by NMR, a trimidazolium phosphate derivative was identified. This was confirmed by reacting imidazole with PCl₃ in CDCl₃ and in [C₆mim][NTf₂]. It

Scheme 1 Reaction between N-methylimidazole and PCl₃ in ILs.
must be noted that in NMI-contaminated [C₄mim][OTf], this phosphine can only form via demethylation of the methyl imidazole in situ in the presence of PCl₃. POCl₃ was found to be stable in dry [OTf]⁻ and [NTf₂]⁻-based ILs; however, in dry [C₄mim][OMs] mixed anhydrides, again both mono- and bis-chlorinated, were formed. As found with PCl₃, POCl₃ also underwent rapid halogen exchange in [C₄mim][BF₄] with a ratio between POCl₃ and PCl₃ also underwent rapid halogen exchange in [C₄mim][BF₄] be the source. Such rapid exchange is not achievable in ILs; however, in dry [C₂mim][OMs] mixed anhydrides, again both mono- and bis-chlorinated, were formed. As found with PCl₃, POCl₃ was found to be stable in dry [OTf]⁻ and [NTf₂]⁻-based ILs, but only at 200 °C. 2.13 At higher water concentrations, Lynden-Bell and Hanke predicted a bimodal distribution using molecular dynamics simulations with aggregated water also being present. 2.14 The strong hydrogen bonding interaction with the anion breaks up the water–water interactions and the nucleophilicity of the water is decreased, reducing its hydrolysis activity. This may be compared with mixtures of water in alcohols, for example, where the mixtures phase-separate on a microscopic scale to form hydrophobic regions and hydrophilic regions. 2.15 For hydrophilic ILs, although PCl₃ and POCl₃ are stable initially, the higher water content results in higher rates of hydrolysis. In all the ILs, as hydrolysis proceeds, the dissolved chloride increases the hydrophilicity, which increases the rate. Similar stabilization of reagents with respect to hydrolysis has also been observed in catalytic applications of ILs. 2.16 Although significant hydrolysis occurs in most ILs on stirring in air, no hydrolysis is found in wet [C₄mim][BF₄] for PCl₃ and in wet [C₄mim][FAP] for POCl₃ over 24 h in air. There are two possible sources of the fluoride which exchanges for chloride in PCl₃ and POCl₃ in [C₄mim][BF₄]: an impurity from hydrolysis of the anion 2 or that from the equilibrium: 2.19

\[ \text{[BF₄]}^- \rightleftharpoons \text{BF}_3 + \text{F}^- \]

Due to the high concentration of PCl₃/POCl₃ compared with the amount of fluoride generated from IL hydrolysis 2.11 and the fact that quantitative exchange occurs, the equilibrium reaction must be the source. Such rapid exchange is not possible in conventional solvents at room temperature. 2.12 Similar exchange reactions have been observed using Na[BF₄] and Na[Pf₆] dissolved in glyme, but only at 200 °C. 2.10 The exchange observed in the ILs is significantly more facile than those reported in aprotic high dielectric solvents employed thus far. The decrease in intensity found for PCl₃ is due to evaporation of PF₃, which has a boiling point of −101 °C. This low boiling point reduces its concentration in solution whereon further PCl₃ is reacted to re-establish the equilibrium until all the PCl₃ has been exhausted. The ability of the ILs to stabilize PCl₃ and POCl₃, even in the presence of significant concentrations of water, may be understood by considering the distribution of water in ILs. Cammarata et al. found that water in ILs may be considered as molecularly dispersed at [H₂O] < 2 M. 2.13 At higher water concentrations, Lynden-Bell and Hanke predicted a bimodal distribution using molecular dynamics simulations with aggregated water also being present. 2.14 The strong hydrogen bonding interaction with the anion breaks up the water–water interactions and the nucleophilicity of the water is decreased, reducing its hydrolysis activity. This may be compared with mixtures of water in alcohols, for example, where the mixtures phase-separate on a microscopic scale to form hydrophobic regions and hydrophilic regions. 2.15 For hydrophilic ILs, although PCl₃ and POCl₃ are stable initially, the higher water content results in higher rates of hydrolysis. In all the ILs, as hydrolysis proceeds, the dissolved chloride increases the hydrophilicity, which increases the rate. Similar stabilization of reagents with respect to hydrolysis has also been observed in catalytic applications of ILs. 2.16 Although significant hydrolysis occurs in most ILs on stirring in air, no hydrolysis is found in wet [C₄mim][NTf₂] for PCl₃ and in wet [C₄mim][FAP] for POCl₃ over weeks open to air without stirring. The deactivation of the water is clearly illustrated by examining the mole : mole ratio of solvent to water. Even in dry ILs which contain ~0.1 wt% water content, the molar ratio is 1 water molecule for every 50 IL cation–anion pairs. This is in contrast with dry THF (0.005 wt% water content), for example, where the molar ratio is 1 water molecule for 5000 THF molecules. By organic solvent standards, ILs would be considered as highly unsuitable media for reagents such as PCl₃ and POCl₃.}

### Table 1: Time variation of species on dissolving 0.5 M PCl₃ and POCl₃ in a range of wet ILs stirred in air at 20 °C

<table>
<thead>
<tr>
<th>Ionic liquid*</th>
<th>[H₂O] (wt%)</th>
<th>Time/min</th>
<th>Chemical shift/ppm</th>
<th>Intensity (%)</th>
<th>Species</th>
<th>Time/min</th>
<th>Chemical shift/ppm</th>
<th>Intensity (%)</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C₄mim][NTf₂]</td>
<td>0.15</td>
<td>75</td>
<td>220</td>
<td>100</td>
<td>PCl₃</td>
<td>75</td>
<td>6</td>
<td>82</td>
<td>POCl₃</td>
</tr>
<tr>
<td>[C₄mim][NTf₂]</td>
<td>0.31</td>
<td>1440</td>
<td>8</td>
<td>100</td>
<td>HPOClOH</td>
<td>3</td>
<td>18</td>
<td></td>
<td>PO(OH)Cl</td>
</tr>
<tr>
<td>[C₄mim][BF₄]</td>
<td>8.44</td>
<td>135b</td>
<td>220</td>
<td>84</td>
<td>PCl₃</td>
<td>135b</td>
<td>4</td>
<td>1</td>
<td>PO(OH)Cl</td>
</tr>
<tr>
<td>[C₄mim][OTf]</td>
<td>0.35</td>
<td>135b</td>
<td>220</td>
<td>84</td>
<td>PCl₃</td>
<td>135b</td>
<td>4</td>
<td>1</td>
<td>PO(OH)Cl</td>
</tr>
<tr>
<td>[C₄mim][OMs]</td>
<td>1.06</td>
<td>15</td>
<td>167</td>
<td>8</td>
<td>PCl₃(OMs)</td>
<td>−9</td>
<td>5</td>
<td>95</td>
<td>POCl₃</td>
</tr>
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<td>[C₄mim][OMs]</td>
<td>1.06</td>
<td>15</td>
<td>133</td>
<td>12</td>
<td>PCl₃(OMs)</td>
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<td>[C₄mim][OMs]</td>
<td>1.06</td>
<td>15</td>
<td>−24</td>
<td>25</td>
<td>POCl₃(OMs)</td>
<td>−24</td>
<td>5</td>
<td>95</td>
<td>POCl₃</td>
</tr>
<tr>
<td>[C₄mim][FAP]</td>
<td>0.03</td>
<td>Immiscible</td>
<td>1440</td>
<td>6</td>
<td>PCl₃</td>
<td>1440</td>
<td>6</td>
<td>84</td>
<td>POCl₃</td>
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date, or which require a long reaction time, energetically demanding processes or strong oxidants.

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Notes and references