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 PCl$_3$ and POCl$_3$ and reaction media for fluorination and mixed anhydride formation under benign conditions.

Phosphorus trichloride (PCl$_3$) and phosphorus oxychloride (POCl$_3$) are major precursors for flame-retardant materials, pesticides, nerve gases and plasticizers,[1,2] as well as key reagents in numerous synthetic conversions such as chlorination reactions and Vilsmeier–Hack formylations of aromatics. Since the development of automated oligonucleotide synthesis, the use of PCl$_3$ has been extended to the manufacture of nucleosidic phosphor-amidites and related building blocks. Such automated processes rely on all synthetic precursors being of the highest purity.[3] This is often difficult to achieve as PCl$_3$, POCl$_3$ 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 dichloroalkoxyphosphines, strictly anhydrous conditions and excess of PCl$_3$ must be employed in order to prevent reagent and product hydrolysis.[4] Similarly, direct phosphorylation of nucleosides with POCl$_3$ is limited to a few nucleosides and is performed in atypical solvents such as triethylphosphate.[5]

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 PCl$_3$ and POCl$_3$ in ionic liquids (ILs) has been studied. To date, PCl$_3$ chemistry has only been reported in chloroaluminate ILs, which are inherently dry.[6] The present work reports on the unexpectedly high hydrolytic stability observed for PCl$_3$ and POCl$_3$ in ILs and their reactivity towards nucleophilic anions to form novel phosphorus species.

The solubility and stability of PCl$_3$ and POCl$_3$ were analyzed by ^{31}P- and ^{1}H–^{31}P 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 PCl$_3$ and POCl$_3$ in a range of wet ILs. For comparison, the stability of PCl$_3$ and POCl$_3$ in THF stirred in air showed >25 % hydrolysis after 15 min and no PCl$_3$ or POCl$_3$ remaining after 1 h.

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In dry [C$_2$mim][OTf] and [C$_2$mim][OMs], PCl$_3$ reacted with the IL forming phosphite–sulfate and –sulfonate mixed anhydrides, both mono- and bis-chlorinated, *via* nucleophilic displacement of the halogen. Halogen exchange was also surprisingly rapid in dry [C$_4$mim][BF$_4$]. After 75 min, a ratio between PCl$_3$ (δ 220 ppm), PCl$_2$F (^{31}P-δ 218 ppm, $J_{P–F}$ = 1332 Hz; ^{19}F-δ −78.5 ppm), PClF$_2$ (^{31}P-δ 174 ppm, $J_{P–F}$ = 1383 Hz; ^{19}F-δ −80.5 ppm) and PF$_3$ (^{31}P-δ 103 ppm, $J_{P–F}$ = 1400 Hz; ^{19}F-δ −80.2 ppm) of 1 : 0.03 : 0.02 : 0.4 was found. This mixture gradually changed and, after 2 h, only PCl$_3$ and PF$_3$ were found with no hydrolysis products detected. This sample had a much reduced signal-to-noise ratio and eventually no phosphorus signal was measurable. PCl$_3$ in wet [C$_4$mim][BF$_4$] showed similar exchange products; however, after 2 h, significant hydrolysis occurred. In contrast, no hydrolysis was found for PCl$_3$ in wet [C$_2$mim][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.[7] In the [NTf$_2$]$^-$-based ILs, PCl$_3$ was soluble at concentrations >20 M and in [C$_4$mpyrr][NTf$_2$] was found to be hydrolytically stable (>95%) for weeks, even when stirred in air and without drying the IL. In wet [C$_4$mim][NTf$_2$], <10% hydrolysis of PCl$_3$ occurred after 3 h on stirring in air; however, after 72 h complete hydrolysis had occurred. The addition of 0.9 M [C$_8$mim]Br to [NTf$_2$]$^-$-based ILs had little effect on the stability of PCl$_3$, and no bromide exchange could be detected by ^{31}P-NMR. However, addition of 1.6 M CsF to PCl$_3$ in [C$_4$mim][NTf$_2$] resulted in the rapid formation of PF$_3$. Such exchange is not observed in conventional solvents such as chloroform or THF.

Although the ILs halide purity is not important, PCl$_3$ stability is strongly affected by the presence of unreacted *N*-methylimidazole (NMI). Addition of NMI to a solution of PCl$_3$ in [C$_2$mim][OTf] resulted in the formation of a yellow precipitate, probably of [P(NMI)$_3$]Cl$_3$ (Scheme 1), which rapidly hydrolysed when exposed to air. Similar neutral adducts have been found on reacting POX$_3$ and SiCl$_4$ with aromatic bases.[8] Although the low solubility of [P(NMI)$_3$]Cl$_3$ prevented its identification by NMR, a triimidazolium phosphine derivative was identified. This was confirmed by reacting imidazole with PCl$_3$ in CDCl$_3$ and in [C$_4$mim][NTf$_2$]. It
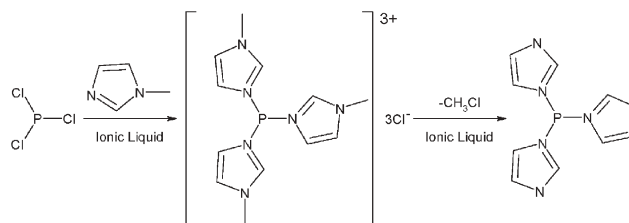
Scheme 1 Reaction between *N*-methylimidazole and PCl$_3$ in ILs.

Table 1 Time variation of species on dissolving 0.5 M PCl_3 and $POCl_3$ in a range of wet ILs stirred in air at 20 °C

Ionic liquid[a]	[H_2O] (wt%)	PCl₃				POCl₃			
		Time/min	Chemical shift/ppm	Intensity (%)	Species	Time/min	Chemical shift/ppm	Intensity (%)	Species
[C_4mim][NTf_2]	0.15	75	220	100	PCl_3	75	6	82	$POCl_3$
		1440	8	100	HPOClOH		3	18	$PO(OH)_2Cl$
[C_4mpyrr][NTf_2]	0.31	4320	220	100	PCl_3	240	6	78	$POCl_3$
							1	22	$PO(OH)_3$
[C_4mim][BF_4]	8.44	75[b]	220	84	PCl_3	135[b]	4	1	$PO(OH)Cl_2$
			103	6	PF_3		−8	9	$PO(OH)_2F$
			8	7	HPOClOH		−19	10	$PO(OH)F_2$
[C_2mim][OTf]	0.35	135[b]	220	41	PCl_3	135	6	55	$POCl_3$
			183	1	$PCl_2(OTf)$		1	45	$PO(OH)_3$
			23	17	$HPO(OTf)_2$				
			10	24	HPOCl(OTf)				
			−2	11	$HPOCl_2$				
[C_2mim][OMs]	1.06	75	167	8	$PCl_2(OMs)$	15	−9	95	$POCl_2(OMs)$
			133	12	$PCl(OMs)_2$		−15	5	$POCl(OMs)_2$
			−9	38	$POCl_2(OMs)$				
			−15	17	$POCl(OMs)_2$				
			−24	25	$PO(OMs)_3$				
[C_5mim][FAP]	0.03		Immiscible			1440	6	84	$POCl_3$
							4	8	$PO(OH)Cl_2$
							3	2	$PO(OH)_2Cl$
							1	6	$PO(OH)_3$

[a] $[C_n\text{mim}]^+$ = 1-alkyl-3-methylimidazolium, $[C_4\text{mpyrr}]^+$ = 1-butyl-1-methylpyrrolidinium, $[NTf_2]^-$ = bis{(trifluoromethyl)sulfonyl}amide, $[OTf]^-$ = triflate, $[OMs]^-$ = mesylate, $[FAP]^-$ = trifluorotris(perfluoroethyl)phosphate. [b] Balance is unassigned hydrolysis products.

must be noted that in NMI-contaminated [C_2mim][OTf], this phosphine can only form *via* demethylation of the methyl imidazole *in situ* in the presence of PCl_3.

$POCl_3$ was found to be stable in dry $[OTf]^-$ and $[NTf_2]^-$-based ILs; however, in dry [C_2mim][OMs] mixed anhydrides, again both mono- and bis-chlorinated, were formed. As found with PCl_3, $POCl_3$ also underwent rapid halogen exchange in [C_4mim][BF_4] with a ratio between $POCl_3$ (δ 6 ppm), $PO(OH)_2F$ (^{31}P-δ −8 ppm, J_{P-F} = 928 Hz; ^{19}F-δ −60 ppm) and $PO(OH)F_2$ (^{31}P-δ −19 ppm, J_{P-F} = 968 Hz; ^{19}F-δ −69 ppm) of 1 : 0.3 : 0.3. Unlike for PCl_3, no POF_3 was detected and the composition, as well as the signal-to-noise ratio, remained unchanged over 2 h. With the exception of [C_5mim][FAP], stirring $POCl_3$ in wet ILs in air resulted in rapid hydrolysis, even those based on $[NTf_2]^-$. In wet [C_5mim][FAP], $POCl_3$ showed <20% hydrolysis after 24 h in air.

There are two possible sources of the fluoride which exchanges for chloride in PCl_3 and $POCl_3$ in [C_4mim][BF_4]: an impurity from hydrolysis of the anion[9] or that from the equilibrium:[10]

$$[BF_4]^- \rightleftharpoons BF_3 + F^-$$

Due to the high concentration of PCl_3/$POCl_3$ compared with the amount of fluoride generated from IL hydrolysis[11] and the fact that quantitative exchange occurs, the equilibrium reaction must be the source. Such rapid exchange is not achievable in conventional solvents at room temperature.[12] Similar exchange reactions have been observed using $Na[BF_4]$ and $Na[PF_6]$ dissolved in glyme, but only at 200 °C.[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 PCl_3 is due to evaporation of PF_3, which has a boiling point of −101 °C. This low boiling point reduces its concentration in solution whereon further PCl_3 is reacted to re-establish the equilibrium until all the PCl_3 has been exhausted.

The ability of the ILs to stabilize PCl_3 and $POCl_3$, 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 [H_2O] <2 M.[13] At higher water concentrations, Lynden-Bell and Hanke predicted a bimodal distribution using molecular dynamics simulations with aggregated water also being present.[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.[15] For hydrophilic ILs, although PCl_3 and $POCl_3$ 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.[16] Although significant hydrolysis occurs in most ILs on stirring in air, no hydrolysis is found in wet [C_4mim][NTf_2] for PCl_3 and in wet [C_5mim][FAP] for $POCl_3$ 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 PCl_3 and $POCl_3$.

Whilst only a small library of ILs was screened, it is clear that ILs are a highly suitable storage solvents for PCl_3 and $POCl_3$. In addition, ILs also provide a medium for the synthesis, under benign conditions, of compounds which have not been reported to

date, or which require a long reaction time, energetically demanding processes or strong oxidants.

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