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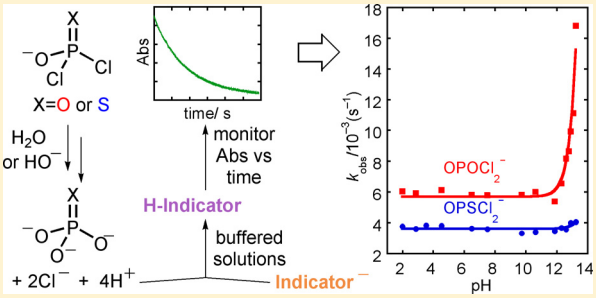
Hydrolysis Studies of Phosphodichloridate and Thiophosphodichloridate Ions

Richard J. Delley, AnnMarie C. O'Donoghue, and David R. W. Hodgson*

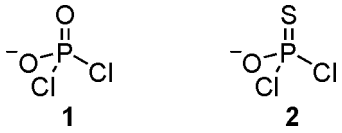
Department of Chemistry, Durham University, South Road, Durham DH1 3LE, United Kingdom

Supporting Information

ABSTRACT: We report the pH-k_{obs} profiles for the hydrolyses of phosphodichloridate and thiophosphodichloridate ions in aqueous solutions. Both species show broad pH−k_{obs} plateaus that extend to high pHs.



As part of an ongoing program to develop aqueous aminophosphorylation procedures,[1−3] we have investigated the reactivities of phosphodichloridate **1** and thiophosphodichloridate **2** ions as functions of pH as potentially more selective water-soluble alternatives to $POCl_3$ and $PSCl_3$.



1 **2**

Dichloridates **1** and **2** are the first hydrolysis products of the industrially important bulk chemicals $POCl_3$ and $PSCl_3$. Surprisingly little information is available on the reactivities of phosphodichloridate **1** and thiophosphodichloridate **2** ions in aqueous solutions. The solvolysis of **1** was assessed by Hudson and Moss in water, and a half-life of ∼3 min was observed.[4] Further studies were performed at pH 4 and 7 using an autotitrator, where similar half-lives were observed, however, other pHs were not considered. Hudson and Moss also reported on the reactivity of $POCl_3$ in 33% water in dioxane;[4] however, further studies in predominantly organic media have been published only recently.[5] The kinetic reactivity of thiophosphodichloridate ion **2** has been reported on the basis of ^{31}P NMR spectroscopy studies.[6] This data, however, was limited to one set of pH conditions and was presented only as a crude measure of half-life.

To assess the feasibility of using phosphodichloridate and thiodichloridate ions in aqueous solutions for synthetic procedures, we performed kinetic studies of the hydrolyses of these ions over a broad range of pH values. The syntheses of dichloridates **1** and **2** have been reported by Segall et al.[6] where bicarbonate ion was used as the oxygen nucleophile to displace chloride, and acetone was employed as the solvent. Subsequent decarboxylation of the carbonate adducts led to the dichloridic acid species that become deprotonated by additional bicarbonate ions to afford dichloridate salts **1** and **2**.[7] We chose to use acetonitrile in place of acetone in our procedures owing to its higher boiling point facilitating more accurate handling of volumetric solutions. We adopted the same reaction times as used by Segall et al., and we were able to prepare both dichloridate salts **1** and **2** in homogeneous forms without needing to perform further optimizations. We found that stock solutions of phosphodichloridate **1** were stable for a few days when stored at −18 °C, whereas solutions of thiophosphodichloridate **2** solutions were much more stable with no detectable decomposition after more than one month of storage at −18 °C. In both cases, similar stabilities were found by Segall et al. when acetone was used as the solvent.[6] Preliminary hydrolysis studies performed at pH ∼10 using ^{31}P NMR spectroscopy confirmed the clean conversions of dichloridate ions **1** and **2**, to inorganic phosphate and thiophosphate respectively with observed half-lives in the order of a few minutes, as seen by Segall et al. (Supporting Information, Figure S1).[6] As hydrolysis rates were expected to increase at higher pHs, an alternative technique for monitoring the hydrolysis processes was sought. Unfortunately, neither dichloridate possesses a convenient chromophore, thus, we adopted an indicator-based approach. The acid evolved from the displacement of chloride ions by water molecules was measured indirectly through absorbance changes arising from an added indicator species. The approach is based on that adopted by Khalifah,[8] where phenolate or other aromatic systems (see the Supporting Information) were employed (Scheme 1).

The indicator method produced good first-order kinetic plots in all cases. A range of buffers was used in order to assess both hydroxide ion reactivity (k_{OH}), reactivity toward water (k_0), and

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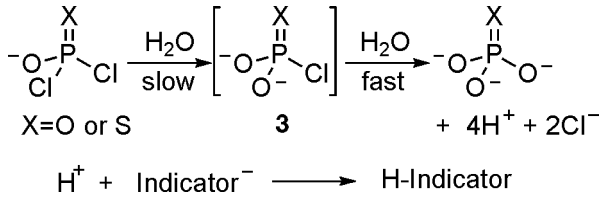
Scheme 1. Indicator Method Employed for Monitoring Phosphodichloridate and Thiophosphodichloridate Hydrolyses



the potential for general base catalysis of these hydrolysis processes. (Buffers of varying strengths were employed at each pH value. In all cases, no increase in observed rate constant was observed with increasing buffer concentration, confirming that general base catalysis was not present.) Kinetic data are plotted as a function of the buffer pH (Figure 1). We are satisfied that

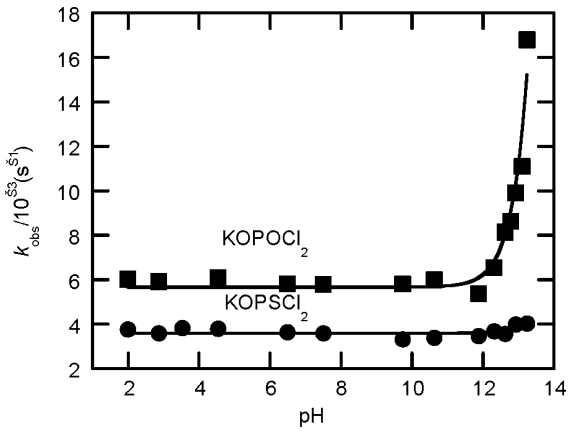


Figure 1. k_{obs}–pH profiles for the hydrolyses of phosphodichloridate **1** (■) and thiophosphodichloridate **2** (●) ions.

the loss of the first chloride ion, of the two present in both substrates, to give monochloridate intermediate **3** is rate limiting. (Based on Kirby and Jencks' Brønsted leaving group correlation for phosphate monoester dianions,[10] log k_{hyd} = 2.64 − 12.3pK_a, and employing a pK_a value of −6.1 for HCl[11] to account for the chloride leaving group, we predict k_{hyd} = 5.5 × 10^8 s^{-1} for the monochloridate dianion species PO_3Cl^{2-}. While this is an extremely large extrapolation, it serves to illustrate that this step is highly unlikely to be rate-determining in aqueous solutions.)

In the case of phosphodichloridate ion **1**, a plateau in reactivity was observed up to pH ∼12 with k_0 = (5.7 ± 0.2) × 10^{-3} s^{-1}. At higher pH values, the observed rates of hydrolysis increased with hydroxide ion concentration, giving a second-order rate constant k_{OH} = (5.6 ± 0.2) × 10^{-2} mol dm^{-3} s^{-1} where the kinetic data were fitted to eq 1 across the pH range.

$$k_{obs} = k_0 + k_{OH}[OH^-] \quad (1)$$

The thiophosphodichloridate ion **2**, on the other hand, showed essentially constant reactivity across the pH range from ∼2 to ∼13, with k_0 = (3.6 ± 0.06) × 10^{-3} s^{-1}, with only a limited suggestion of upward curvature at the highest pH extreme. This demonstrates that thiophosphodichloridate ions **2** do not show significant reactivity toward hydroxide ions over and above reactivity with water, at least for situations where [OH^-] < ∼0.2 mol dm^{-3}. The observed "thio-effect" on the k_0 values for the attack of water as the nucleophile on species **1** and **2** is a 1.6-fold reduction on substituting oxygen with sulfur. For the k_{OH} term, however, an upper limit on the value of k_{OH} for thiophosphodichloridate ion **2** may be estimated on the basis of the assumption that the upward trend in the pH–log k_{obs} profile for **2** must occur at pH's *at least* 1.5 units higher than for **1**. On this basis, the thio effect for the attack of hydroxide ions, i.e., k_{OH} (O)/ k_{OH} (S) must amount to at least $10^{1.5}$ (∼31). Thio effects of 4–11 have been observed for phosphodiesters where concerted S_N2(P) mechanisms are expected, whereas values of 0.1–0.3 have been observed for monoesters where more dissociative mechanisms dominate. Thus a simplistic interpretation of the 1.6-fold effect on k_0 values is that the mechanism for nucleophilic attack by water retains S_N2(P)-like character, as proposed by Hudson and Moss.[4] However, owing to the good leaving group properties of chloride, its departure may lead nucleophile attack to a greater extent than for oxy-leaving groups seen in phosphoesters, with the transition state moving toward being more dissociative in nature. Larger thio effects (10–160) have been noted for phosphate triester systems where, owing to the lack of charge near the central phosphorus atom, associative mechanisms are encountered.[9] With this in mind, the large thio effect on k_{OH} that we observe for dichloridates **1** and **2** could be attributed to the differing extents to which oxygen and sulfur can stabilize negative charge in the transition state. Thus, the increased nucleophilicity of hydroxide ions over water could result in a move toward a more associative mechanism in the case of phosphodichloridate **1**, with the greater anionic change at the transition state being accommodated by the more electronegative oxygen substituent (and chlorine atoms). With thiophosphodichloridate **2**, on the other hand, the less electronegative sulfur substituent, is less able to accommodate this build up of negative charge and a lower k_{OH} is observed.

Taken together, these data demonstrate that both phosphodichloridate **1** and thiophosphodichloridate **2** ions are potentially useful phosphorylating agents across a broad range of pHs in aqueous solutions. The half-lives of **1** and **2**, which are ∼2 min and ∼3.2 min, respectively, within the pH-independent regions, allow for thorough mixing of solutions of the ions with aqueous solutions without needing special precautions. By contrast, $POCl_3$ with half-life ∼10 ms[4] is much more susceptible to mixing phenomena, and $PSCl_3$ shows very poor solubility in water, even with significant proportions (∼33%) of THF as the cosolvent.[1] In particular, in respect of the use of amine nucleophiles, we expect to see good selectivity toward aminolysis over hydrolysis processes in aqueous reaction mixtures given the intrinsic nucleophilicity of *N*-nucleophiles. The ability to use higher pHs without deleterious reactions between the dichloridate ions and hydroxide ion should allow even the most basic alkyl amines (i.e., pK_{aH} ∼10) to be used in their neutral nucleophilic forms. Finally, solid forms of the potassium salts of both dichloridates **1** and **2** are known to show increased stabilities over the acetonitrile solutions that we have employed in this kinetic study and the acetone solutions employed by others.[6] With this in mind, coupled with the half-lives of dichloridates **1** and **2** in water we expect that the solid salts could prove to be effective synthetic reagents that could be used "off the shelf" even after prolonged storage.

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EXPERIMENTAL SECTION

Stock solutions of potassium salts of oxyphosphodichloridate and thiophosphodichloridate ions were prepared on the basis of the approach of Segall et al.;[6] however, acetone was replaced by acetonitrile as the solvent.

Potassium Phosphodichloridate (1). A solution of phosphorus oxychloride (1.275 g, 8.33×10^{-3} mol) in anhydrous acetonitrile (25 mL) was added to a flask containing oven-dried potassium hydrogen carbonate (1.675 g, 0.0167 mol). The mixture was stirred vigorously under argon for 10 min, and the KCl precipitate that formed was removed by filtration to give potassium phosphodichloridate **1** as a 0.33 M solution in dry MeCN (^{31}P NMR: −8.0 ppm, 100%). Stock solutions were prepared regularly and stored in sealable screw top vials that were placed in polythene bags containing anhydrous calcium chloride. Under these conditions, stock solutions showed ∼5% hydrolysis of the dichloridate **1** to inorganic phosphate over the course of a week.

Potassium Thiophosphodichloridate (2). A solution of thiophosphoryl chloride (1.410 g, 8.33×10^{-3} mol) in anhydrous acetonitrile (25 mL) was added to a flask containing oven-dried potassium hydrogen carbonate (1.675 g, 0.0167 mol). The mixture was stirred vigorously under argon for 12 h, and the KCl precipitate that formed was removed by filtration to give potassium thiophosphodichloridate **2** as a 0.33 M solution in dry MeCN (^{31}P NMR: 39.8 ppm, 100%). Stock solutions were stored in sealable screw top vials that were placed in polythene bags containing anhydrous calcium chloride. Under these conditions, the material showed no apparent decomposition over one month.

UV−vis Spectrophotometry-Based Kinetic Measurements. The hydrolyses of phosphodichloridate **1** or thiophosphodichloridate **2** were monitored in buffered aqueous solutions ranging from pH 1.99 to 13.23. Non-nucleophilic indicators were used in combination with non-nucleophilic (nonindicating) buffers to follow the progress of hydrolysis at several different pH values and buffer strengths. Indicators were matched to buffers of near-identical pK_a (max ±0.15 pK_a unit difference) to ensure that both indicator and buffer were ionized to approximately the same extent throughout the reaction. Reaction solutions (3 mL) were transferred to a cuvette via a volumetric glass pipet. Each sample was allowed to equilibrate at 25 ± 0.1 °C in the Peltier thermostatted cell holder for 15 min prior to the addition of either potassium phosphodichloridate **1** or potassium thiophosphodichloridate **2** as a solution in anhydrous MeCN (see the Supporting Information for individual experimental details) via Hamilton syringe. The change in absorbance of the indicator was followed until a constant A_{inf} value was observed, and these absorbance−time data were fitted to an exponential decay function using least-squares fitting software to obtain rate constants. Typically for hydrolysis, a decrease in aborbance of ∼0.1 was observed for each reaction. Representative absorbance plots are provided in the Supporting Information. The pH of each reaction solution was measured prior to, and following, each hydrolysis experiment. Decreases in pH of ∼0.2 were measured for the hydrolyses of $KOPOCl_2$ **1** and $KOPSCl_2$ **2** in solutions of potassium hydroxide (pH 11.88−13.23) which led to an absorbance change of ∼0.1. For these reactions, the observed pseudo-first-order rate constants, k_{obs}, were determined from kinetic data for the first 25% of the reaction, corresponding to a pH decrease of ∼0.05.

ASSOCIATED CONTENT

Supporting Information

Initial ^{31}P NMR spectroscopy experiments, detailed kinetic methods, and k_{obs} values for hydrolysis under each set of buffer conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: d.r.w.hodgson@durham.ac.uk.

Notes

The authors declare no competing financial interest.

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