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Hydrolysis of Phosphoryl Trichloride ($POCl_3$): Characterization, in Situ Detection, and Safe Quenching of Energetic Metastable Intermediates

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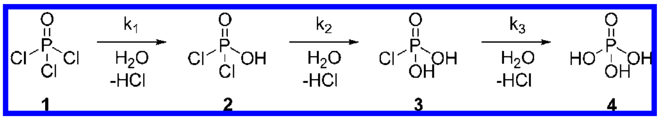
Abstract:

The accumulation of metastable intermediates resulting from the incomplete hydrolysis of phosphoryl trichloride-containing mixtures carries the risk of latent exothermic events. Significant accumulation of two P−Cl species containing reactive phosphorus−chlorine bonds was detected spectroscopically (^{31}P NMR) during inverse quench of $POCl_3$−MeCN mixtures under typical literature conditions. The dominant reactive intermediate was unequivocally assigned as phosphorodichloridic acid (X-ray, ^{31}P NMR). Quantitative ^{31}P NMR time-course experiments allowed for the determination of kinetic parameters of $POCl_3$ hydrolysis under synthetically relevant concentration and temperature conditions in batch settings. Development of an in situ Raman method allowed to further expand these studies to semibatch conditions under different pH regimes. Furthermore, we hereby describe an in situ Raman method suitable to ascertain completeness of the quench for large-scale preparations involving $POCl_3$. These analytical techniques can be supported by differential scanning calorimetry (DSC) and accelerated rate calorimetry (ARC) in order to confirm absence of reactive species.

Introduction

Phosphoryl trichloride[1] is a powerful dehydroxychlorinating agent commonly used to convert hydroxyheteroaromatics into the corresponding chloroheteroaromatics[2] or for in situ generation of the Vilsmeier−Haack reagent from DMF.[3] Most frequently at least one equivalent of phosphoryl trichloride is used in these transformations, thereby at the most employing only one P−Cl bond per $POCl_3$ molecule in a productive manner. Following the first substitution of chloride in $POCl_3$ the remaining two P−Cl bonds are kinetically less reactive and rendered sufficiently thermodynamically strong to be of lesser synthetic use. Nonetheless, all the remaining P−Cl bonds deserve care during hydrolytic processing in the workup as they contain significant additional energy. The thermodynamic values for the hydrolysis of $POCl_3$ have been reported in the literature and, depending on the amount of water that is present during the hydrolysis, either aqueous HCl or gaseous HCl is formed along with phosphoric acid.[4]

Scheme 1. **Hydrolysis of phosphoryl trichloride (1)**



$$POCl_3 + 13.5H_2O \rightarrow H_3PO_4 + 3HCl(aq) + 10.5H_2O + \Delta H$$
$$\Delta H = -286.19\ kJ/mol\ POCl_3 \tag{1}$$

$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl(g) + \Delta H$$
$$\Delta H = -89.54\ kJ/mol\ POCl_3 \tag{2}$$

The hydrolysis of $POCl_3$ predominantly follows the sequence shown in Scheme 1. A detailed mechanistic discussion of the hydrolysis of a range of phosphorus compounds including phosphoryl trichloride was published in a series of papers by Hudson et al.[5] Pseudofirst-order rate constants (k_1 and k_2) were determined in dilute aqueous dioxane solutions (10^{-5}−10^{-2} M) under mildly acidic to neutral conditions (pH 4−7) at 25 °C. The initial fast reaction ($k_1 \approx 66\ s^{-1}$, $t_{1/2} \approx 0.01$ s) led to the formation of phosphorodichloridic acid (**2**) followed by a slower process ($k_2 \approx 3 \times 10^{-3}\ s^{-1}$, $t_{1/2} \approx 250$ s) leading directly to phosphoric acid (**4**). Phosphorochloridic acid (**3**) was not observed suggesting that $k_3 \gg k_2$.[6] The rate of hydrolysis of **2** (k_2) was similar regardless of pH, showing that the main reaction pathway does not involve the undissociated acid. Moreover, a large rate increase by nucleophilic catalysis suggested that the hydrolysis of **2** proceeds through a bimolecular reaction between a water molecule and a phosphorodichloridate anion. Only recently[7] the intermediacy of the previously elusive **3** was unambiguously confirmed by Mitchell's ^{18}O-labeling experiments (Scheme 2). Phosphorus pentachloride was partially

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[†] Department of Chemical Process Research and Development.

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(1) Common synonyms: phosphorus oxychloride, $POCl_3$.

(2) (a) Albert, A.; Clark, J. *J. Chem. Soc.* **1964**, 1666. (b) Golovchinskaya, E. S. *Russ. Chem. Rev. (Engl. Transl.)* **1974**, *43*, 1089. (c) Robins, R. K.; Revankar, G. R.; O'Brien, D. E.; Springer, R. H.; Novinson, T.; Albert, A.; Senga, K.; Miller, J. P.; Streeter, D. G. *J. Heterocycl. Chem.* **1985**, *22*, 601. (d) Andersen, K.; Begtrup, M. *Acta Chem. Scand.* **1992**, *46*, 1130.

(3) (a) Dyer, U. C.; Henderson, D. A.; Mitchell, M. B.; Tiffin, P. D. *Org. Process Res. Dev.* **2002**, *6*, 311. (b) Miyake, A.; Suzuki, M.; Sumino, M.; Iizuka, Y.; Ogawa, T. *Org. Process Res. Dev.* **2002**, *6*, 922. (c) Bollyn, M. *Org. Process Res. Dev.* **2005**, *9*, 982.

(4) Kaspias, T.; Griffiths, R. F. *J. Hazard. Mater.* **2001**, *A81*, 223.

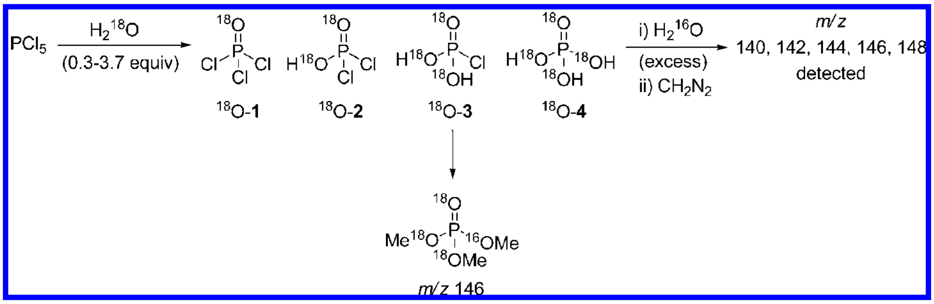
(5) Hudson, R. F.; Moss, G. *J. Chem. Soc.* **1962**, 3599.

(6) The rate in the phosphorochloridic acid series (k_1, $k_3 \gg k_2$) is in contrast to that found for the corresponding phosphorofluoridic acid series where $k_1 > k_2 > k_3$: Lange, W. *Ber.* **1929**, *62*, 786. *Ber. 62* 793; *Ber. 62*, 1084; Lange, W.; Livingstone, R. *J. Am. Chem. Soc.* **1950**, *72*, 1280.

(7) Mitchell, R. A. *J. Chem. Soc., Dalton Trans.* **1997**, 1069.

10.1021/op1001484

Scheme 2. **Demonstration of intermediacy of 3 in the hydrolysis of PCl_5 ($POCl_3$)**



hydrolyzed using $H_2{}^{18}O$ as a limiting reagent (0.28−3.72 equiv) and the hydrolysis was completed using a large excess of $H_2{}^{16}O$ followed by exhaustive methylation using diazomethane. The resulting mixture of trimethyl phosphate isotopomers (*m/z* = 140, 142, 144, 146, 148) was analyzed by GC/MS. A significant amount (≤30%) of *m/z* = 146 corresponding to $Me_3P^{18}O_3{}^{16}O$ was observed confirming the intermediacy of ^{18}O-**3** in the initial stage of hydrolysis.

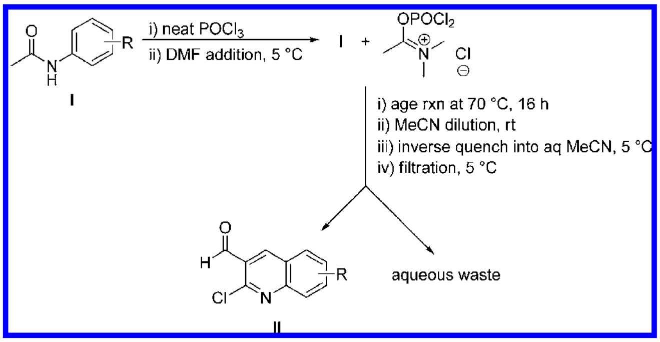
Examination of the recent literature related to the use of phosphoryl trichloride[8] showed that two general methods were primarily used to quench postreaction mixtures on large scale: (Method A) inverse quench into ice−water or (Method B) inverse quench into an aqueous base. Selection of the particular workup protocol (if discussed at all) was invariably dictated by product quality considerations (e.g., stability to aqueous base, ease of isolation). The composition of aqueous waste-streams resulting from workups was rarely discussed; leaving the impression that approaches Method A and Method B are equivalent in the sense of completeness of the hydrolysis of any residual byproduct containing P−Cl bonds. An additional complicating factor in the workup of some of these reactions is the use of a biphasic workup protocol due to the presence of a water-immiscible reaction solvent, leading to the potential for delayed quench due to mass transfer limited hydrolysis rate.

Rationale for Study

A significant quantity of a building block 2-chloroquinoline-3-carbaldehyde **II** was required for an ongoing program. The desired quinoline **II** could be synthesized from an acetanilide **I** using a classical Vilsmeier−Haack type process as described previously by Meth-Cohn (Scheme 3).[9] The reaction is noteworthy as three carbon−carbon bonds and one carbon-chlorine bond are formed in a single transformation.

An addition-controlled exothermic reaction of DMF with neat $POCl_3$ (6.0 equiv) at ≤5 °C afforded the Vilsmeier reagent. No reaction between **I** and $POCl_3$ was observed in the absence of DMF at this temperature. The formylation reaction between the Vilsmeier reagent and **I** was carried out at 70 °C. Any attempts to reduce the amount of $POCl_3$ in this reaction led to significantly decreased yields. The resulting viscous postreaction mixture containing a large excess of unreacted $POCl_3$ was diluted with acetonitrile (5.0 vol) and following Method A[10] was inversely quenched into 50:50 v/v acetonitrile/water (20 vol).[11] The rate of the addition was adjusted to control a significant exotherm and maintain the internal temperature below 5 °C. The desired **II** gradually crystallized out from the quench solution and was subsequently separated from the resulting highly acidic medium by filtration. The sequence described above was carried out reproducibly on multiple occasions on a bench scale (≤0.6 kg of $POCl_3$). Nevertheless, it was noted that an exothermic reaction occurred in the aqueous filtrates. The temperature profile of filtrates after product isolation is shown in Figure 1. Independent of the quench temperature (5 and 25 °C), a latent exotherm leading to a temperature increase of up to 50 °C was observed. Formation of a colorless crystalline material was also observed upon prolonged storage of these filtrates and analysis of these solids identified them as ammonium chloride. The observation of a latent and potentially uncontrollable exotherm in the filtrates prompted further investigation into the kinetic parameters of

Scheme 3. **Vilsmeier-Haack reaction, workup and isolation**



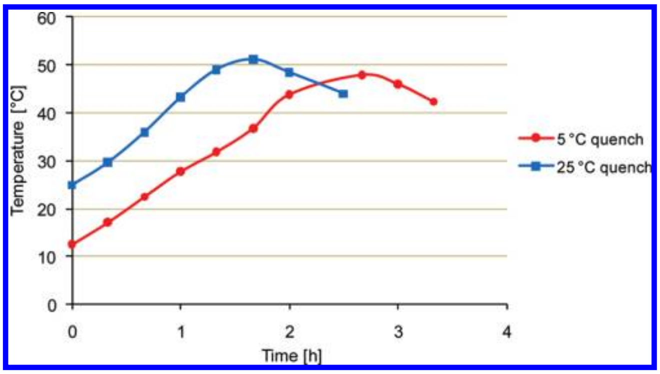


Figure 1. **Temperature profile of reaction filtrates (eq 1, 20 g of $POCl_3$). Monitoring began immediately following filtration.**

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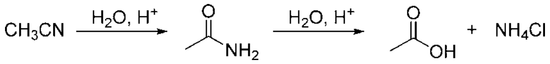
(8) Experimental procedures published in *Org. Process Res. Dev.*, *J. Org. Chem.*, *Tetrahedron* or *Tetrahedron Lett.* from 1998 to 2009. A total of 81 examples were found using from 10 g to 90 kg of $POCl_3$ per run.

(9) (a) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Tetrahedron Lett.* **1979**, *20*, 3111. (b) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539. (c) Ali, M. M.; Tasneem, K. C.; Rajanna, K. C.; Sai Prakash, P. K. *Synlett* **2001**, 251.

(10) Quench into an aqueous base (Method B) failed to provide product **II** with a sufficient purity.

Scheme 4. **Hydrolysis of acetonitrile**



the hydrolysis of $POCl_3$, ultimately resulting in the design of a safe quench.

Results and Discussion

Three potential sources were identified for the latent exotherm observed in the filtrates: (i) exothermic degradation of acetonitrile in the strongly acidic medium; (ii) delayed hydrolysis of phosphoryl trichloride (**1**) or its downstream byproduct (**2** and **3**); (iii) combination of the two events (first event triggered by second event).

Stability of Acetonitrile. The hydrolysis of acetonitrile in the presence of hydrogen chloride leads to the formation of acetic acid and ammonium chloride, with acetamide as an intermediate (Scheme 4).

The decomposition of acetonitrile in the presence of HCl was monitored by ^1H NMR spectroscopy.[12] Only trace amounts of decomposition (<1%) were observed over 24 h using 1 or 5 M HCl at room temperature or 60 °C. In the presence of concentrated HCl, however, acetonitrile readily decomposed at both room temperature and at 60 °C. Similarly decomposition was observed in a mixture that was obtained by adding $POCl_3$ to a mixture of acetonitrile and water followed by heating to 60 °C. In contrast, negligible decomposition was observed in this system at ambient temperature (Figure 2).

The conclusion that can be drawn from these data points is that the decomposition of acetonitrile was not the primary factor in the exothermicity of the filtrates. Decomposition of acetonitrile under strongly acidic conditions, however, can occur at elevated temperatures, and a suitable hazard evaluation is warranted when operating under these conditions.

Hydrolysis of Phosphoryl Trichloride ($POCl_3$). The composition of the aqueous filtrates was initially studied using ^{31}P NMR on a model system consisting of aqueous acetonitrile and $POCl_3$. It was reasoned that organic entities involved in the Vilsmeier−Haack reaction were unlikely to be of importance, since most of the mass balance resulting from acetanilide **I** was removed as 2-chloroquinoline-3-carbaldehyde **II** upon filtration of the aqueous solution prior to the exotherm. The postquench filtrates were modeled by diluting neat $POCl_3$ with acetonitrile (1.6 vol), followed by an inverse quench into 50:50 v/v acetonitrile/water (3.2 vol, 12 equiv of water per $POCl_3$) at less than 5 °C (see Scheme 5). The resulting solution was incubated at room temperature and analyzed periodically by ^{31}P NMR. The characteristic feature of these spectra was the presence of three ^{31}P resonances (singlets) at approximately -2, 0, and $+3$ ppm (Figure 3). Their intensities as a function of incubation period are shown in Chart 1.

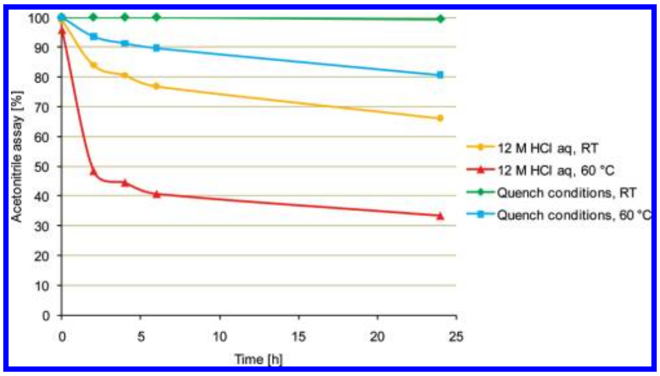


Figure 2. **Acetonitrile decomposition under acidic conditions.**

The peak at -2 ppm (initially >97% by area) was determined to gradually convert into the peak at 0 ppm (H_3PO_4). The intensity of the minor peak at $+3$ ppm remained relatively constant at approximately 2−5% of the intensity of the -2 ppm peak throughout the study. The peak at 0 ppm was assigned as H_3PO_4 by spiking experiments. The peak at -2 ppm was consistent with phosphorodichloridic acid, which was previously studied,[13] and recently indirectly demonstrated,[7] but never fully structurally characterized. The postulated 3,5,6-triphenyl-2,3,5,6-tetraza-bicyclo[2.1.1]-hex-1-ene (Nitron; $C_{20}H_{16}N_4$) complex of phosphorodichloridic acid ($\mathbf{2}\cdot C_{20}H_{16}N_4$), previously prepared by Grunze, was synthesized and recrystallized from hot acetonitrile (Scheme 6). The ^{31}P NMR spectra of both nonrecrystallized and recrystallized $\mathbf{2}\cdot C_{20}H_{16}N_4$ were identical with that of the material prepared by the quenching of $POCl_3$ in aq MeCN. All the spectra showed a single resonance at -2 ppm. The structure of phosphorodichloridic acid was elucidated by single crystal X-ray diffraction of the Nitron complex (Figure 4). To the best of our knowledge, this is the first X-ray crystal structure of a phosphorodichloridic acid complex.

The hydrolysis of phosphoryl trichloride (Scheme 1) to phosphorodichloridic acid (k_1) is much faster than the following step (k_2) as determined by Hudson ($k_1 \approx 66\ s^{-1}$, $k_2 \approx 0.0031\ s^{-1}$)[13g] and confirmed recently by Mitchell.[7] Therefore, the initial formation of **2** can be regarded as essentially instantaneous. As will be evident from the data presented below, under highly acidic conditions the rate of hydrolysis of phosphorodichloridic acid (**2**) is significantly retarded relative to the dilute and mildly acidic systems studied by Hudson.[13g] The decay of phosphorodichloridic acid (**2**) (initially 1.22 M in 66:33 v/v acetonitrile/water) under controlled temperature conditions (25 °C) was quantified using ^{31}P NMR. A plot of $\ln([\mathbf{2}]_{t=0}/[\mathbf{2}]_t)$ versus time (Chart 2) showed good linearity ($R = 0.997$), confirming that the reaction is first order with respect to **2**. However, the k_{2obs} determined by measuring the slope is only $5.15 \times 10^{-5}\ s^{-1}$ ($t_{1/2} \approx 3.5$ h) as opposed to the corresponding value of $3.06 \times 10^{-3}\ s^{-1}$ ($t_{1/2} \approx 4$ min) reported by Hudson, giving the observed rate difference of 59 times.[14] The difference of the inherent

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(11) Fourteen equivalents of water per $POCl_3$.

(12) Integration of the protons on the methyl-group (acetonitrile [2.07 ppm], acetic acid [1.90 ppm], and acetamide [1.76 ppm]).

(13) (a) Meerwein, H.; Bodendorf, K. *Ber.* **1952**, *62*, 1952. (b) Van Wazer, J. R.; Fluck, E. *J. Am. Chem. Soc.* **1959**, *81*, 6360. (c) Goubeau, J.; Schulz, P. *Z. Anorg. Allg. Chem.* **1958**, *294*, 224. (d) Goubeau, J.; Schulz, P. *Z. Physik. Chem.* **1958**, *14*, 49. (e) Grunze, H. *Acta Chim. Acad. Sci. Hung.* **1959**, *18*, 303. (f) Grunze, H. *Z. Anorg. Allg. Chem.* **1961**, *313*, 316. (g) Hudson, R. F.; Moss, G. *J. Chem. Soc.* **1962**, 3599.

(14) Difference in the observed rates of hydrolysis: 59 times ($3.06 \times 10^{-3}\ s^{-1}/5.15 \times 10^{-5}\ s^{-1}$).

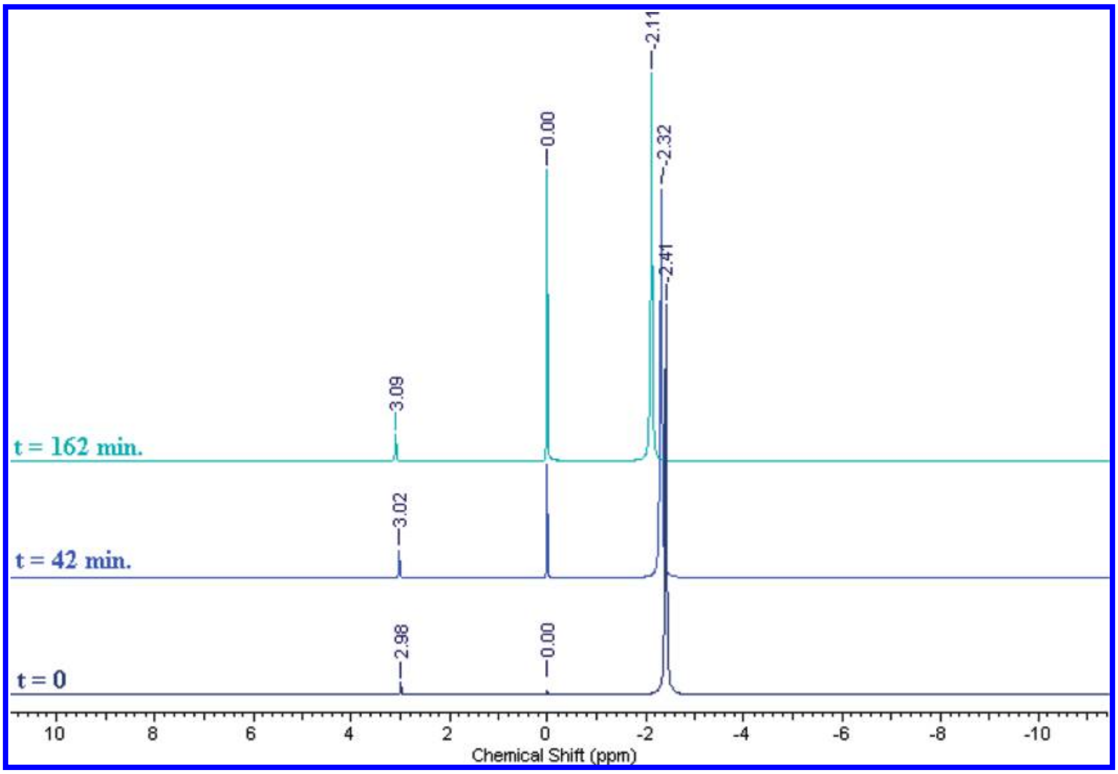
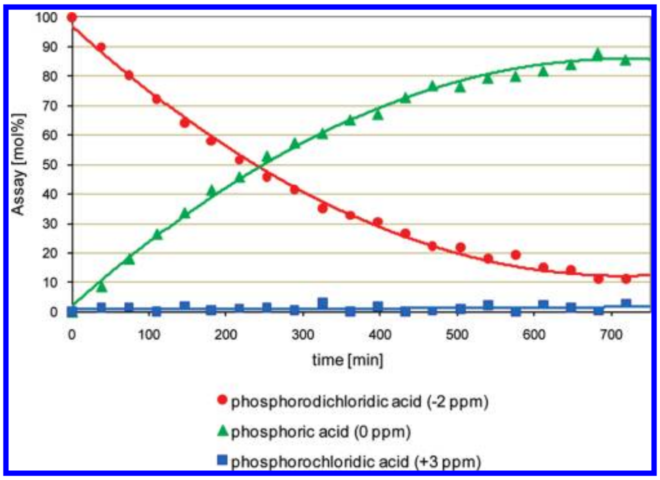


Figure 3. **Hydrolysis of $POCl_3$ in aq acetonitrile at room temperature. Overlay of ^{31}P NMR spectra at selected time points.**

Chart 1. **Hydrolysis of $POCl_3$; major species quantified by ^{31}P NMR**



reaction rate obtained by taking water concentration into account was 18 times.[15]

The reason for this disparity is likely two-fold. Sufficiently low pH keeps the phosphorodichloridate anion protonated (in the form of **2**), thus inhibiting the hydrolysis pathway via the phosphorodichloridic anion. This pathway is presumably replaced by a slower reaction via the undissociated phosphorodichloridic acid (**2**). Simultaneously, the nucleophilicity of the already sparse water molecules is greatly diminished under the strongly acidic conditions. Therefore, the kinetic parameters established by Hudson are no longer valid under the regime of high concentration and low pH since they are based on the assumption that the pH dependence is negligible. A likely candidate for the +3 ppm peak is phosphorochloridic acid (**3**) (Scheme 5). Its progenitor (**2**) was present in high concentration while the intensity of the peak at +3 ppm remained approximately constant relative to **2** (3−5 mol % of **2**). Furthermore, a highly acidic medium favors undissociated forms of acids **2** and **3** for which the relative rate constants k_2 and k_3 were shown to be comparable ($k_3/k_2 \approx 4$),[7] thereby supporting the accumulation of phosphorochloridic acid (**3**) under these conditions. The identity of the +3 ppm peak, however, has not been unequivocally confirmed. A rate of decay of phosphorodichloridic acid (**2**) to phosphoric acid measured at 5, 25, and 35 °C by ^{31}P NMR followed Arrhenius behavior with the approximate half-lives of 26 h, 4 h, and 1 h, respectively (Chart 3, Table 1).

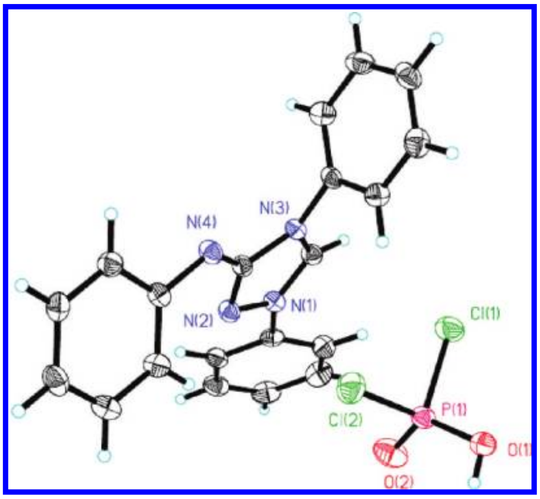


Figure 4. **X-ray structure of phosphorodichloridic Nitron complex ($2\cdot C_{20}H_{16}N_4$).**

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(15) $Rate_{obs} = k_{2obs} \times [HPO_2Cl_2] \approx k_2 \times [HPO_2Cl_2] \times [H_2O]$. Difference in the inherent rate of hydrolysis (k_2) obtained by taking concentration of water into account: 18 times (3.06×10^{-3} s^{-1} $\times$ 16.5 M)/(5.3×10^{-5} s^{-1} $\times$ 55.6 M).

Table 1. **Values of $k_{2\mathrm{obs}}$ and $t_{1/2}$ determined from the plot of $\ln([2]_{t=0}/[2]_t)$ against time (Chart 3)**

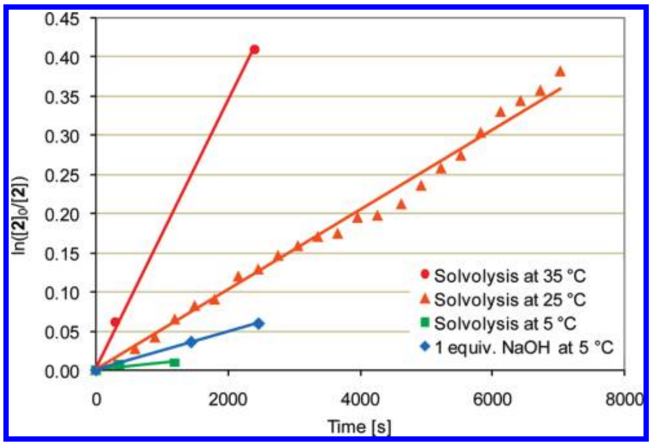
composition	temp (°C)	$k_{2\mathrm{obs}}$ [s^{-1}]	$t_{1/2}$	
water/MeCN (33:66 v/v)	5	7.1×10^{-6}	9.5×10^4 s	26 h
water/MeCN (33:66 v/v), 1 equiv of NaOH	5	2.4×10^{-5}	2.9×10^4 s	7.9 h
water/MeCN (33:66 v/v)	25	5.2×10^{-5}	1.3×10^4 s	3.7 h
water/MeCN (33:66 v/v)	35	1.7×10^{-4}	4.1×10^3 s	1.1 h

Additional ^{31}P NMR experiments were performed to understand the effect of base (aq NaOH) and water concentration on the kinetics of hydrolysis of phosphorodichloridic acid. Solutions of phosphorodichloridic acid used in these experiments were prepared by adding solutions of $POCl_3$ in acetonitrile to a 50:50 (v/v) acetonitrile−water mixture at ≤5 °C to ensure fast and quantitative conversion of $POCl_3$ to phosphorodichloridic acid. The resulting solutions ($[H_2O] = 16.5$ M) were diluted with water or aqueous NaOH to an approximately equal water concentration ($[H_2O] \approx 24$ M). The decay of phosphorodichloridic acid in the presence of varying amount of NaOH (0, 1, 2 equiv) was quantified by ^{31}P NMR at 25 °C. The plot of $\ln([\mathbf{2}]_{t=0}/[\mathbf{2}]_t)$ versus time (Chart 4) was used to determine $k_{2\mathrm{obs}}$ for each of the reaction composition. The inherent reaction rate constants (k_2) were derived directly from $k_{2\mathrm{obs}}$ and are compared in Chart 5.[16,17]

It is evident from Chart 5 that significant rate increase was observed only after addition 2 equiv of NaOH. The observed reaction rate increase ($k_{2\mathrm{obs}}$) in the presence of additional water with or without 1 equiv of NaOH was similar (proportional to $[H_2O]$) (Table 2). The peak at +3 ppm attributed to phosphorochloridic acid (**3**) was only observed in the absence of base.

All the plots show a slight downward trend—a deviation from first-order kinetics at high conversions. This is consistent with an inhibitory effect caused by HCl byproduct which lowers the fraction of ionized **2** (phosphorodichloridate). The nonionized phosphorodichloridic acid undergoes hydrolysis more slowly than phosphorodichloridate anion.[13g]

Chart 3. **Hydrolysis rate of 2 as a function of temperature**



Several conclusions can be drawn from the mechanistic studies that were performed on phosphorodichloridic acid. First, the hydrolysis of phosphorodichloridic acid (**2**) is first order in **2** and first order in H_2O, with Arrhenius behavior observed between 5 and 35 °C. Second, the hydrolysis of phosphorodichloridic acid (**2**) is the rate-limiting step of hydrolytic conversion of $POCl_3$ to H_3PO_4. However, the undesired accumulation of **2** can be minimized by either increasing the water concentration and/or by increasing pH of the solution. Third, the beneficial effect of increasing the pH with base has been demonstrated with 2 equiv of aq NaOH per **2**, whereas only a modest rate increase with 1 equiv of aq NaOH was observed relative to pure water.

Raman Spectroscopy: In Situ Monitoring of HPO_2Cl_2 (2). Due to the multistep nature of the hydrolysis of $POCl_3$ a specific, quantitative, and sensitive analytical method was desired to monitor the conversion of the intermediate species **2**. After a preliminary evaluation which considered the solvent

Chart 2. **Solvolysis of 2 at room temp; plot of $\ln([2]_{t=0}/[2]_t) = k_{2\mathrm{obs}} \times t$ provided $k_{2\mathrm{obs}} = 5.15 \times 10^{-5}\ s^{-1}$**

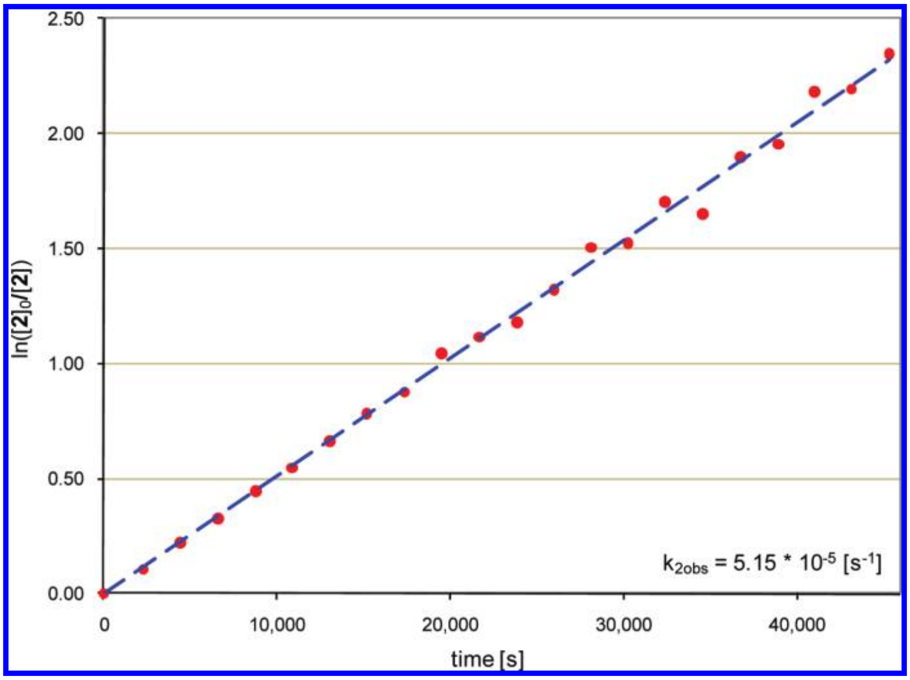
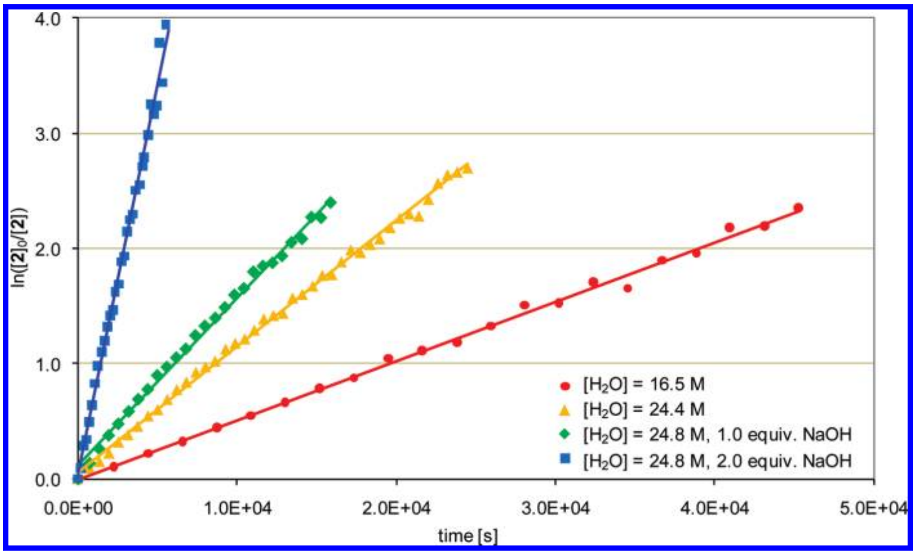


Chart 4. **Effect of base and water concentration on k_{2obs}**



Scheme 5. **Hydrolysis of $POCl_3$ in aq MeCN at room temperature**

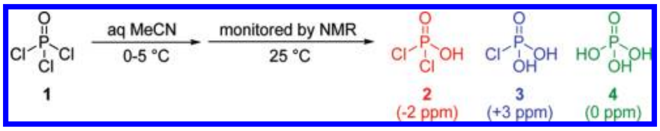


Chart 5. **Effect of base and water concentration on k_2**

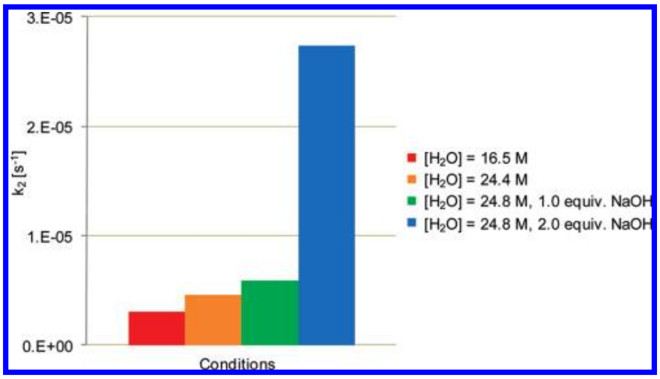


Table 2. **Values of k_{2obs} and k_2 determined from the plots shown in Charts 4 and 5**

conditions	k_{2obs} [s^{-1}]	k_2 [s^{-1}]
$[H_2O] = 16.5$ M, MeCN, 25 °C	5.2×10^{-5}	3.1×10^{-6}
$[H_2O] = 24.4$ M, MeCN, 25 °C	1.1×10^{-4}	4.6×10^{-6}
$[H_2O] = 24.8$ M, 1.0 equiv NaOH, MeCN, 25 °C	1.5×10^{-4}	5.9×10^{-6}
$[H_2O] = 24.8$ M, 2.0 equiv NaOH, MeCN, 25 °C	6.8×10^{-4}	2.7×10^{-5}

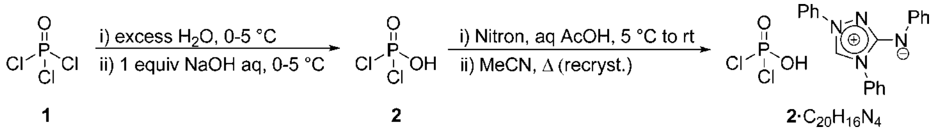
compatibility (aqueous acetonitrile) and method specificity, Raman spectroscopy was determined to be a more suitable method than FTIR. Subsequently, all the Raman peaks were assigned to the known $POCl_3$ hydrolysis intermediates/products and confirmed with the actual reaction mixture. The first step evaluated the specificity and peak assignments. Several key Raman shifts had been identified: (i) 204 cm^{-1} corresponding to the PCl_2 deformation, (ii) 546 cm^{-1} corresponding to the P−Cl stretch, and (iii) 889 cm^{-1} corresponding to the P−O stretch (Figure 5).[18,19]

Consequently, simultaneous appearance and increase in intensity of 204 and 546 cm^{-1} Raman shifts correlated with a formation and accumulation of phosphorodichloridic acid (**2**) during the first step of $POCl_3$ hydrolysis (Figure 6). A simultaneous and gradual disappearance of these bands with concomitant gradual appearance of 889 cm^{-1} Raman shift was indicative of the rate-limiting hydrolysis of **2** resulting in formation of phosphoric acid (**4**). Increasing rate of conversion of **2** to **4** consistent with the Arrhenius model was observed by increase in temperature from 5 to 15 to 25 °C. Autoinhibition previously noted by ^{31}P NMR was evident at high conversions (Figure 7). The limit of detection of phosphorodichloridic acid (**2**) by the in situ Raman was determined by spiking an aqueous acetonitrile medium with known amounts of $POCl_3$ leading to immediate formation of HPO_2Cl_2 (**2**). A clear response at 204 cm^{-1} was observed at concentrations of **2** as low as 0.015 M (Figure 8). More than 99% conversion of HPO_2Cl_2 (**2**) to H_3PO_4 (**4**) could be ascertained under most of the realistic applications, including the previously studied quench conditions.

In summary, the in situ Raman method was developed as a complementary method for monitoring the $POCl_3$ hydrolysis reaction. It allows for monitoring of formation and disappearance of phosphorodichloridic acid (**2**) in aqueous acetonitrile mixtures at concentrations as low as 0.015 M. While no attempts have been made to use the current Raman method for quantitation, it was capable of semiquantitative monitoring of processes involving $POCl_3$. In particular, its usefulness for a real-time monitoring of accumulation of reactive intermediates containing P−Cl bonds during aqueous quenches of $POCl_3$-containing mixtures has been demonstrated. Additionally, ^{31}P NMR spectroscopy allows for a straightforward quantitation of the reactive species and determining the kinetic parameters in batch settings.

Hazard Evaluation of $POCl_3$ Hydrolysis Using Calorimetry. In order to understand the latent exotherm in the reaction filtrates, the quench experiments were conducted on a simplified model system. The reaction was performed in the reaction calorimeter (RC-1) by adding a solution of $POCl_3$ in acetonitrile into a mixture of acetonitrile and water over 2 h, maintaining an internal temperature between 0 and 5 °C. The amount of water (43 equiv) was sufficient to completely dissolve the

Scheme 6. **Preparation of a crystalline phosphorodichloridic Nitron complex ($2\cdot C_{20}H_{16}N_4$)**



generated HCl. A sample of the reaction mixture was investigated by accelerated rate calorimetry (ARC) showing three exothermic events at ~25 °C, 80 and 180 °C (Figure 9). These exothermic events could also be detected using DSC as analytical technique. The temperatures of the observed exothermic events coincide with the observations from the ARC (Figure 10). Estimation of the reaction mixture composition by ^{31}P NMR showed 25% phosphoric acid and 75% phosphorodichloridic acid upon the completion of the $POCl_3$ addition. The reaction mixture was warmed to 20 °C, and aged for 18 h at which point analysis followed by ^{31}P NMR showed 98% phosphoric acid and 2% phosphorodichloridic acid. Analysis of a sample of the reaction mixture by ARC showed that the low-temperature exotherm was no longer present (Figure 11), and instead the first exotherm was observed around 90 °C. This exotherm is most likely related to decomposition of acetonitrile under the strongly acidic conditions, as it was absent from the sample that was investigated after complete neutralization of the reaction mixture with NaOH.

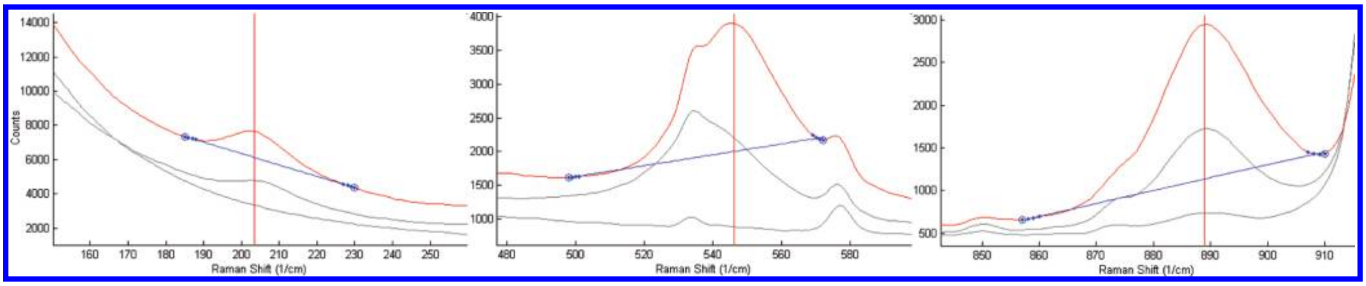


Figure 5. **Raman bands: PCl_2 deformation (204 cm^{-1}), P−Cl stretch (546 cm^{-1}), P−O stretch (889 cm^{-1}).**

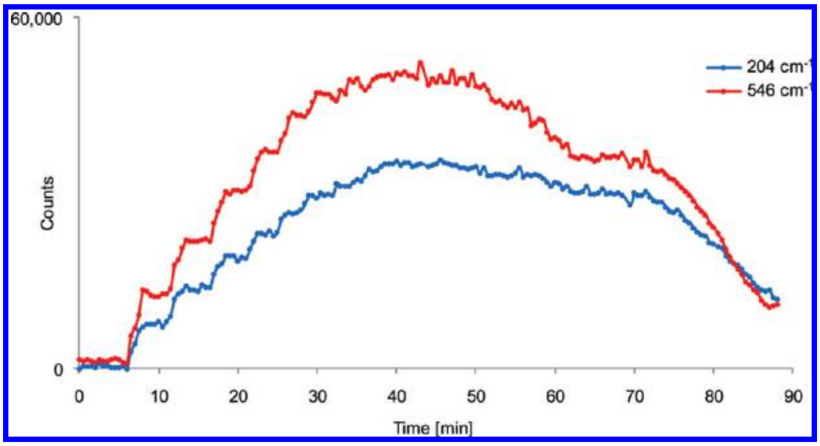


Figure 6. **Phosphorodichloridic acid (2) monitored by Raman at 204 and 546 cm^{-1}.**

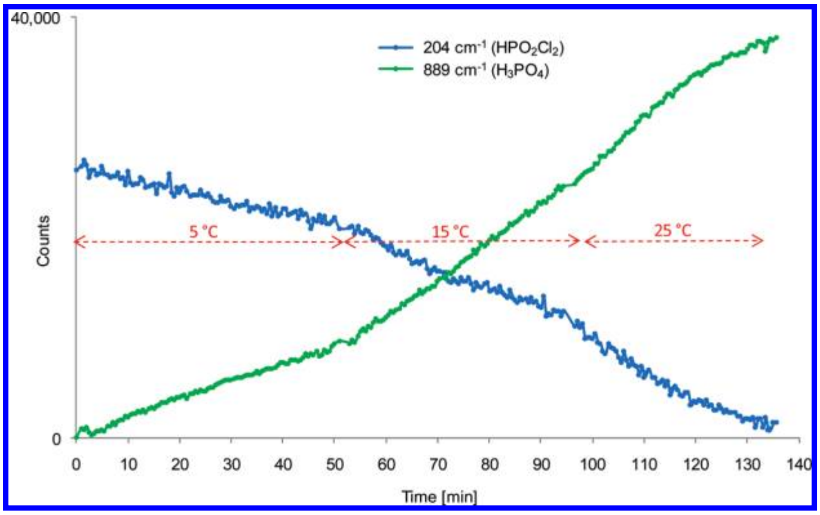


Figure 7. **Effect of temperature on hydrolysis of HPO_2Cl_2 monitored by Raman.**

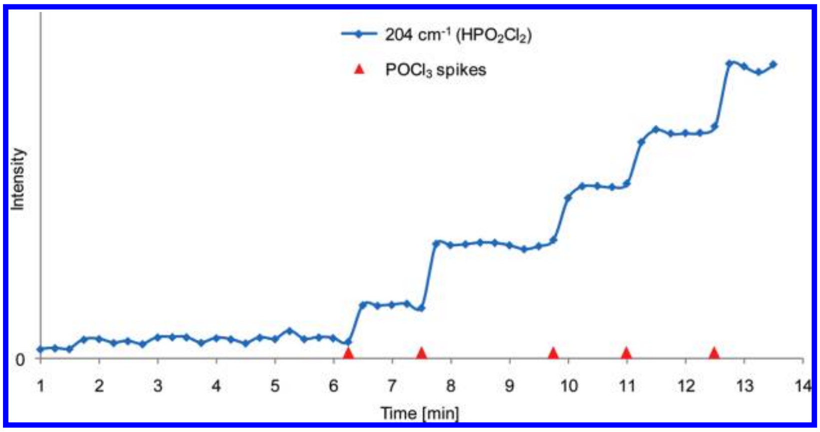


Figure 8. **Limit of detection of phosphorodichloridic acid by in situ Raman ($\leq$0.015 M at 204 cm^{-1}).**

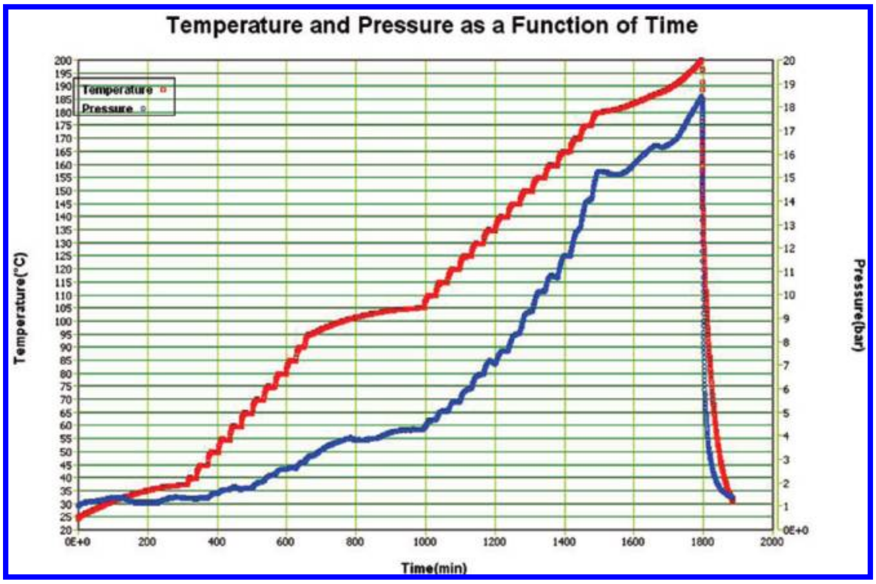


Figure 9. **ARC after $POCl_3$ addition to mixture of acetonitrile/water at 0−5 °C.**

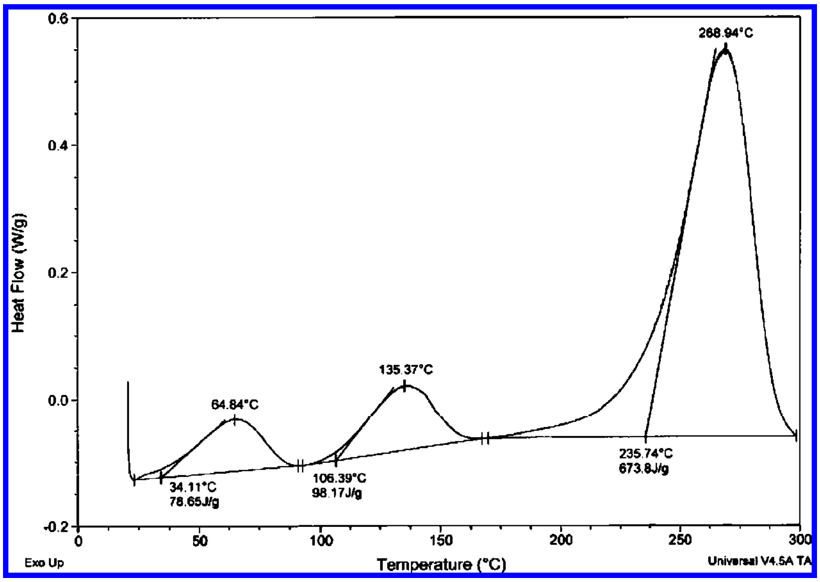


Figure 10. **DSC after $POCl_3$ addition to mixture of acetonitrile/water at 0−5 °C.**

The hazard studies on the model system highlight the potential for significant latent exothermic events in the hydrolysis of $POCl_3$, especially if the quench is conducted at low temperatures and in the absence of base. These findings led to the requirement to design a safe quench for the heterocycle synthesis described above.

Development of the Improved Quench Protocol. An improved quench protocol was devised on the basis of

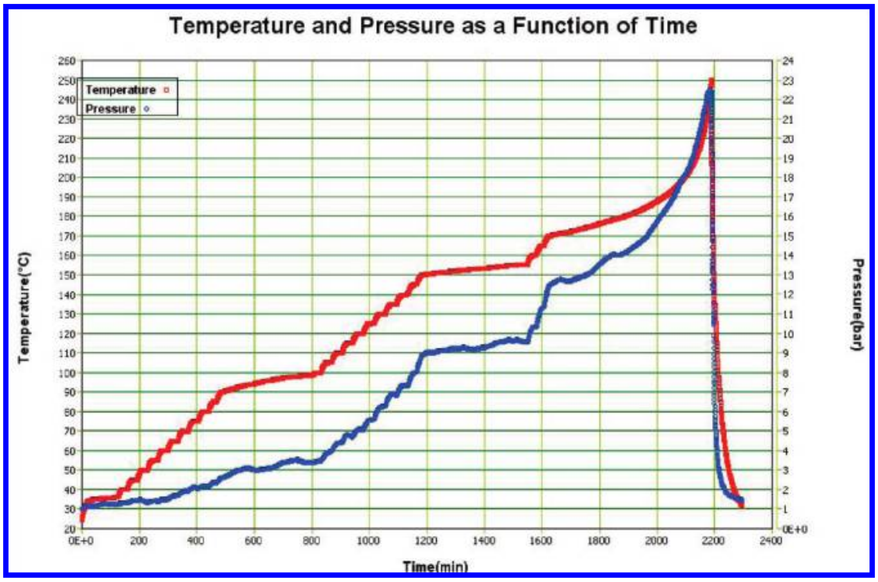


Figure 11. **ARC after stir-out for 18 h at 20 °C.**

mechanistic studies. It was decided to continue to use acetonitrile as a cosolvent for the quench since it has significant miscibility with the aqueous system, thereby making it inherently safer in the quench as compared to water immiscible solvents. The generated data also supported that acetonitrile showed suitable stability under the quench conditions if a partial neutralization with NaOH was performed.

Different approaches in employing a partial neutralization during the quench were investigated. Complete neutralization of the supernatant was attempted first. Two methods were examined: (A) a reverse quench into a precalculated amount of NaOH so that the final pH would be 7 and (B) a simultaneous addition of aq NaOH during the normal reverse quench which would keep the pH 6−7.[20] While both of these methods eliminated the latent exotherm and fully quenched all P−Cl bonds,[21] the quality and yield of the isolated product was unacceptable. The increased amounts of salts and water introduced into the crystallization caused the acetonitrile and water to phase split, lowering the isolated yields and resulting in the product oiling out of solution. The majority of the mass recovered was actually determined to be sodium phosphate salts.

After the difficulties of achieving a neutral pH in the supernatant before filtration, a study was conducted to examine the feasibility of using aq NaOH to accelerate the hydrolysis of reactive P−Cl bonds while only partially neutralizing the reaction mixture before filtration, thereby avoiding the problems caused by salt formation and phase separation. Between 1 and 3 equiv of 5 N NaOH (based on the initial amount of $POCl_3$) were added simultaneously during the quench, keeping the pH < 7 and the temperature below 25 °C. Phase separation of the supernatant was observed when ≥2 equiv NaOH were employed. The pH of the filtrate was determined in all cases, and with the exception of the addition of 3 equiv of NaOH (pH = 1.6) the resulting filtrates where strongly acidic (pH < 1). The latent exothermic events previously observed in the filtrates were eliminated by aging the quenched mixture at 20 ± 5 °C until >97% of active P−Cl bonds had been quenched as monitored by ^{31}P NMR. It was concluded that the optimal conditions involved using 1.5 equiv of NaOH, since this was the largest amount of base that could be added without an impact on product quality. The new conditions were successfully demonstrated on 50-g scale (98.3% LCAP, 58.1% yield). Analysis by ^{31}P NMR immediately before filtration showed the active species was >97% quenched.

A safety evaluation was performed in the RC-1. The quench was performed over 2 h, and the reaction mixture was allowed to age for over an additional hour before filtration. The quenching of the P−Cl bonds was monitored by ^{31}P NMR and was shown to be ≥98% complete before filtration. An ARC of the final filtrates taken immediately after the quench was complete (Figure 12) and 2 h later after filtration (Figure 13) showed no exothermic events, which led to the conclusion that all the P−Cl bonds were sufficiently hydrolyzed and that the product filtrates from this process are sufficiently neutralized to avoid the exothermic decomposition of acetonitrile.

Conclusions

The individual intermediates in the hydrolysis of phosphoryl trichloride ($POCl_3$) were characterized: phosphorodichloridic acid (**2**, HPO_2Cl_2) by a combination of ^{31}P NMR and X-ray crystallography, and phosphorochloridic acid (**3**, H_2PO_3Cl) by ^{31}P NMR. Two complementary analytical methods were developed to monitor the completeness of the hydrolysis of phosphoryl trichloride: ^{31}P NMR and in situ Raman spectros-

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(16) A correct rate law should use activities instead of concentrations. For simplicity it was assumed that activities of components are equal to their concentrations.

(17) The hydrolysis of phosphorodichloridic acid is first order in **2** according to the approximate rate equation: $\text{Rate}_{\text{obs}} = k_{2\text{obs}} \times [\mathbf{2}]$. However, it is also first order in water: $\text{Rate}_{\text{obs}} = k_2 \times [\mathbf{2}] \times [H_2O]$. Therefore, the inherent rate constant (k_2) can be calculated from: $k_2 = k_{\text{obs}}/[H_2O]$, assuming $[H_2O] \approx$ const.

(18) Infrared and Raman spectra, conformational stability, and normal coordinate analysis of ethyldichlorophosphine−borane: Odom, J. D.; Hizer, T. J.; Stanley, A. E.; Tonker, T. L.; Durig, J. R. *Spectrochim. Acta* **1988**, *44A*, 631.

(19) Rudolph, W. W.; Irmer, G. *Appl. Spectrosc.* **2007**, *61*, 1312.

(20) Thiel, O. R.; Achmatowicz, M.; Bernard, C.; Wheeler, P.; Savarin, C.; Correll, T. L.; Kasparian, A.; Allgeier, A.; Bartberger, M. D.; Tan, H.; Larsen, R. D. *Org. Process Res. Dev.* **2009**, *13*, 230.

(21) The progress of the P−Cl bond quenching was quantitatively monitored by ^{31}P NMR.

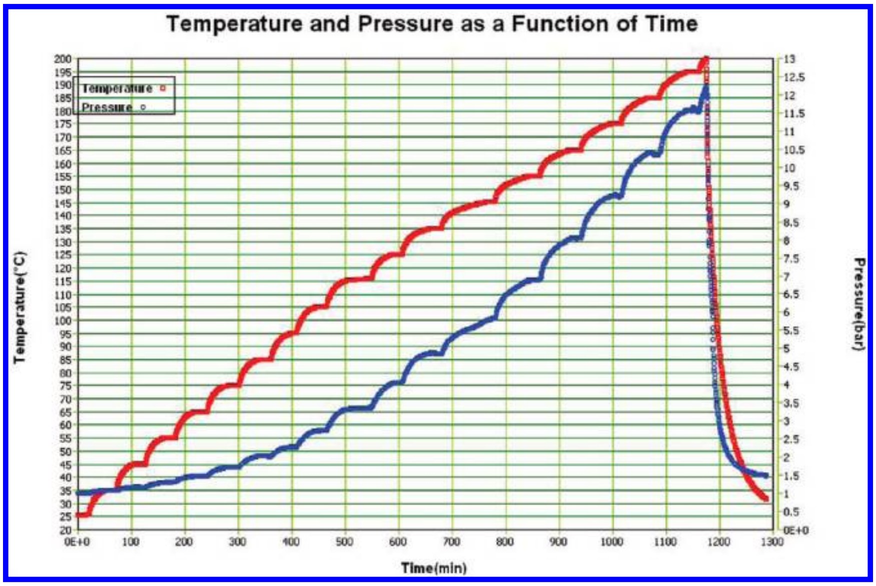


Figure 12. **ARC of reaction solution immediately after the quench.**

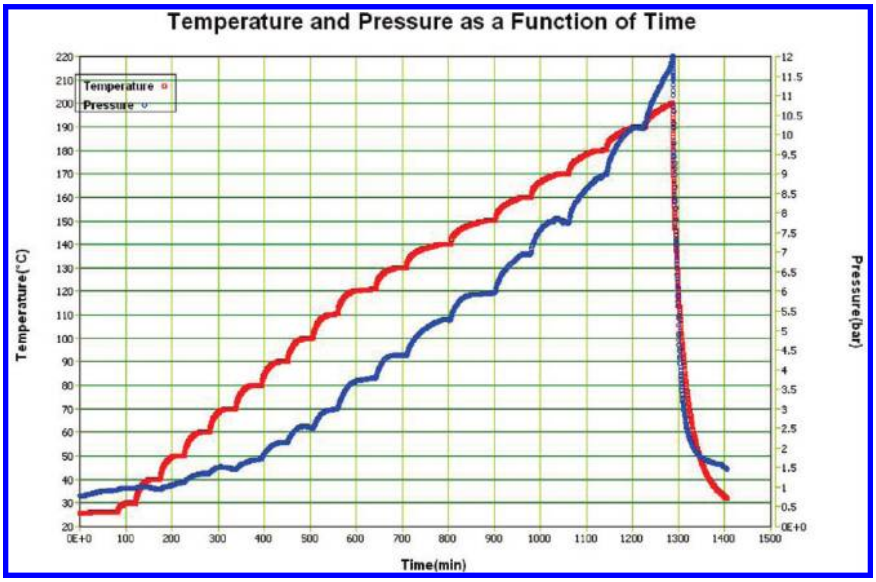


Figure 13. **ARC of the final filtrate.**

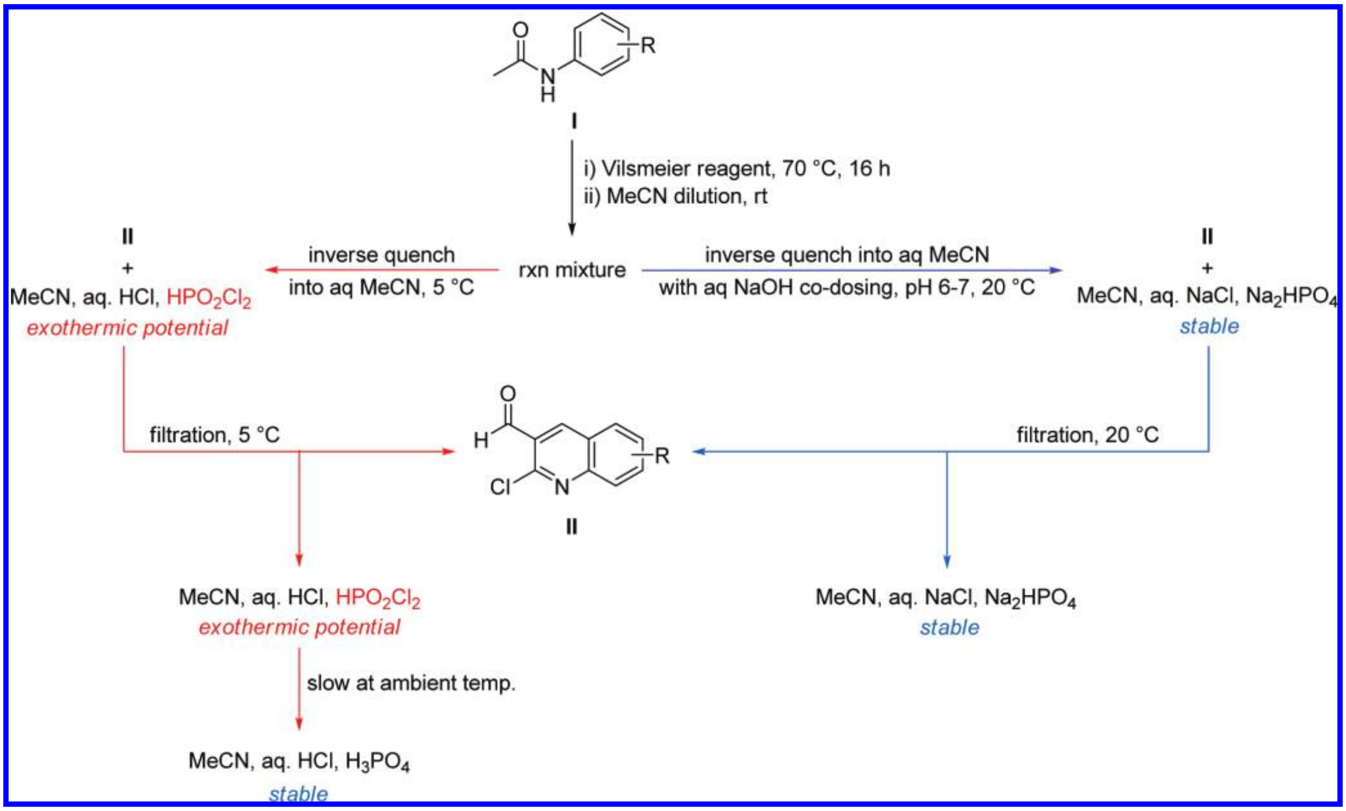
copy. ^{31}P NMR provides a reliable tool to quantify the different phosphorous species. Raman spectroscopy can be used as an in situ tool, but the method needs to be individually developed in order to ensure no interference with the solvent or substrate. The successful employment of this technique may also be complicated by the presence of solids in the reaction mixture, leading to an unpredictable increase of the Raman scattering due to solids in the interrogation volume of the probe.

The mechanistic studies shown have allowed the design of a safe quench for the specific reaction (Scheme 7). In general, an inverse quench at 20 °C in presence of base was shown to be preferred. When applying the recommended quench conditions to specific reactions, additional parameters such as solvent and product formation need to be taken into account. In the example highlighted within this manuscript, 1.5 equiv of NaOH was co-dosed with the reaction solution during the quench in order to avoid accumulation of intermediates containing P−Cl bonds, which was confirmed via ^{31}P NMR spectroscopy and ARC. It needs to be emphasized that, while these quench conditions can serve as a starting point for other reactions, a full hazard evaluation of the reaction, quench, and filtrates using calorimetry is strongly recommended for all reactions involving $POCl_3$. Overall our studies emphasize the importance of confirming the completeness of a quench prior to a scale-up to ensure safe operations.

Experimental Section

Synthesis of 2-Chloroquinoline-3-carbaldehyde II Using an Improved Quench Protocol. A dry 2.0-L reactor was equipped with an addition funnel and overhead stirring and was flushed with N_2. Acetanilide **I** (330 mmol) was charged to the reactor, and the reactor temperature was set to 0 ± 5 °C. Phosphoryl trichloride (183 mL, 1.96 mol) was charged to the reactor, stirring was initiated, and the mixture was stirred until homogeneous. The addition funnel was charged with *N*,*N*-dimethylformamide (63.5 mL, 820 mmol), which was slowly added to the reactor, keeping an internal temperature of 0 ± 5 °C. The solution was heated to 70 ± 5 °C and held at that

Scheme 7. **Comparison of the initial workup and isolation conditions (red arrows) with the improved protocol (blue arrows)**



temperature for >16 h. The reaction solution was then cooled to 20 ± 5 °C and assayed for progress. Acetonitrile (5 vol) was added slowly to the 2.0-L reactor and stirred until homogeneous. A 5.0-L reactor was equipped with an addition funnel, pH probe and overhead stirring and was placed under N_2. The 5.0-L reactor was charged with acetonitrile (10 vol) and water (10 vol) and set to an internal temperature of 20 ± 5 °C. The addition funnel for the 5.0-L reactor was charged with 5 N NaOH (2.94 mol). The contents of the 2.0-L reactor were charged into the 5.0-L reactor simultaneously with the 5 N NaOH, keeping the internal temperature at 20 ± 5 °C and the pH < 7. The mixture was held at 20 ± 5 °C for 1 h with stirring after the addition was complete. The filtrates were assayed for product loss, the contents of the 5.0-L reactor were filtered, and the solids were collected on an M-grade frit. The filtrates were charged back into the 5.0-L reactor and analyzed by ^{31}P NMR prior to disposal for complete $POCl_3$ hydrolysis. The solids were washed with a 50:50 v/v acetonitrile/water mixture (5 vol) and water (5 vol). The isolated compound **II** was dried to a constant mass under vacuum/N_2 at 20 °C.

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Supporting Information Available

Description of experimental methods including Raman, NMR, calorimetry (ARC and DSC), and X-ray crystallography. Crystallographic data for 3,5,6-triphenyl-2,3,5,6-tetraza-bicyclo[2.1.1]-hex-1-ene phosphorodichloridic acid complex (**2**·$C_{20}H_{16}N_4$). This material is available free of charge via the Internet at http://pubs.acs.org.

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