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Profiling the Formation of 2-Chloro-*N,N*-dimethylamino Trimethinium Chloride Salt, a Key Intermediate in the Manufacturing Process of Etoricoxib

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Abstract:

2-Chloro-*N,N*-dimethylamino trimethinium chloride salt (CDT-chloride) is a key intermediate in the synthesis of Etoricoxib, a selective COX-2 inhibitor developed by Merck & Co., Inc. The formation of CDT-chloride from a mixture of chloroacetic acid and $POCl_3$ in DMF was monitored by *in situ* IR and *in situ* NIR. The buildup of transient intermediates, starting material disappearance, and product/byproduct formation were effectively followed during the course of the reaction using both techniques. The observations confirmed the intermediacy of both chloroacetyl chloride and a Vilsmeier type reagent as well as document the evolution of carbon dioxide.

Introduction

Etoricoxib **1**, a nonsteroidal antiinflammatory drug, is a selective COX-2 inhibitor developed and marketed by Merck & Co., Inc (Scheme 1). The manufacturing synthesis of **1** involves the annulation of vinamidinium salt **2a** with ketone **3**.[1] Preparation of the vinamidinium salt comprises the slow addition of $POCl_3$ to a mixture of chloroacetic acid in *N*,*N*-dimethyl formamide at 75 °C for 3 h (Scheme 2). This optimized procedure provides 2-chloro-*N*,*N*-dimethylamino trimethinium chloride salt (CDT-chloride) **2b**, which is then directly quenched into an aqueous solution of $NaPF_6$ at <10 °C to afford **2a** as a light yellow salt >85% yield. This reaction protocol has been applied to the synthesis of a variety of vinamidinium salts.[2]

Vinamidinium salts have found wide application in organic synthesis as useful 3-carbon synthons. For example, vinamidinium salts have been applied successfully to the synthesis of trisubstituted pyridine derivatives,[3,4] 2,4-disubstituted pyrroles,[5] pyridine *N*-oxides,[6] and anilines.[7] Spectroscopic[8,9] and computational[10] studies on vinamidinium salts and their reactions have recently appeared in the literature. In this context, we sought to profile the formation of vinamidinium salt **2b** via *in situ* infrared (IR) and *in situ* near-infrared (NIR) in order to track and obtain a better understanding of chemical events during the course of the reaction.

In our studies described herein, *in situ* IR and *in situ* NIR were evaluated as potential real time monitoring techniques for the reaction described above. During the initial development of this chemistry, identification of an HPLC assay method to directly determine the degree of CDT-chloride **2b** formation during the course of the reaction proved to be very difficult.[11] Assay of the CDT-chloride is possible by ^{1}H NMR; however, this method is inconvenient for operations in pilot plant and manufacturing facilities. In addition, the reaction mixture is highly corrosive and thus requires a careful handling procedure and neutralization. An alternative method for determining the end of reaction was required. Thus, the immediate goal of the investigation was to be able to determine the end of reaction during real time and without sampling. Second, because of the obvious importance of the step, it became of interest to identify and subsequently follow the chemical events during the course of reaction. Specifically, these include tracking starting material disappearance and product formation, determining if and when intermediates are generated and consumed, and, finally, determining the end of reaction.

In situ IR and NIR spectroscopy are valuable tools widely employed in the pharmaceutical and chemical industries.[12] Their ability to gather process information during the course of the reaction with minimal physical disturbance is a major attraction to process development chemists and chemical engineers. The benefits offered by these techniques are significant: real-time multiple species tracking, fast analytical results for optimized control and reduction of cycle time, in-line sampling for better integrity and safer operation, and a reduction in analysis cost via automated analysis. In addition, these spectroscopic techniques offer a direct observation window into the chemical and physical trans-

(1) Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 8415−8420.

(2) Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Robbins, M. A.; Gerena, L.; Sidler, R.; Larsen, R. D.; Rossen, K.; Pye, P. J.; Ashok, M.; Sager, J.; Volante, S.; Tsuo, N.; Ball, R. G.; DiMichael, L.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571−4574.

(3) Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Tarrant, J. G.; Bruno, S. M.; Vargas, M.; Hosein, K. N.; Gupton, J. T. *Tetrahedron* **1995**, *51*, 1575−1584.

(4) Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339−2341.

(5) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W. *J. Org. Chem.* **1990**, *55*, 4735−4740.

(6) Davies, I. W.; Marcoux, J.-F.; Reider, P. J. *Org. Lett.* **2001**, *3*, 209−211.

(7) Davies, I. W.; Marcoux, J.-F.; Kuethe, J. T.; Lankshear, M. D.; Taylor, J. D. O.; Tsou, N.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1298−1308.

(8) Davies, I. W.; Tellers, D M.; Shultz, C. S.; Fleitz, F. J.; Cai, D.; Sun, Y. *Org. Lett.* **2002**, *4*, 2969−2972.

(9) Ostercamp, D. L.; Dinh, Y.; Graff, D.; Wiles, S. *J. Org, Chem.* **2003**, *68*, 3099−3105.

(10) Davies, I. W.; Marcoux, J.-F.; Kuethe, J. T.; Lankshear, M. D.; Taylor, J. D. O.; Tsou, N.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1298−1308

(11) After the studies described in this paper, a reverse phase ion-pairing HPLC method was developed for analysis of CDT using a YMC Basic column and acetonitrile/4 mM heptane sulfonic acid sodium salt as mobile phase. See ref 13.

(12) For an excellent discussion on Process Analytical Chemistry and Spectroscopy, see: Hassell, C. D.; Bowman, E. M. *Appl. Spectrosc.* **1998**, *52*, 18A−29A and references therein.

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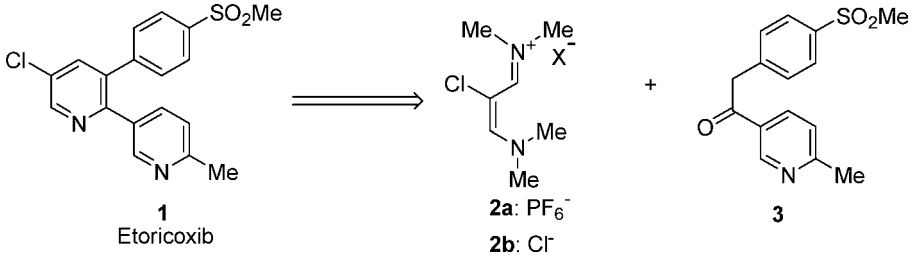
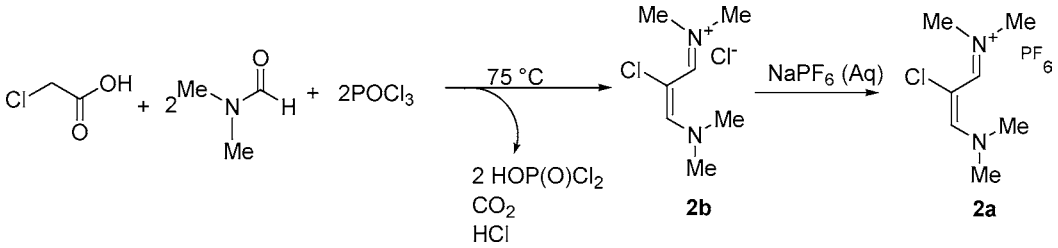
Scheme 1



Scheme 2



formations during chemical processing. This provides greater scientific understanding for development and optimization of efficient and safe chemical processes.

Due to lacking of a reliable reference method, *in situ* IR was used as a primary method in monitoring the process without calibration. This is possible thanks to the reasonably resolved spectral peaks associated with each component of interest. The peak heights or peak areas can be used directly, or with minimal math treatment, to track concentration changes during reaction. This quick profiling capability is one of the major attributes of *in situ* IR spectroscopy for its wide use in chemical and pharmaceutical process research where fast work pace and frequent changes in experiment conditions preclude complicated calibration. On the other hand, *in situ* NIR was evaluated primarily for the purpose of being used in a manufacturing environment. Mechanical stability and ease of installation make NIR suitable for the task, but its low spectral resolution requires calibration before use. In the circumstance of lacking a traditional reference method such as HPLC, *in situ* IR was used as the reference in calibration.

Experimental Section

Materials. The following chemicals were purchased from Aldrich Chemical Co. and used as received: anhydrous *N*,*N*-dimethyl formamide, chloroacetic acid, phosphorus oxychloride, (chloromethylene)dimethylammonium chloride (Vilsmeier Reagent), and chloroacetyl chloride.

Instrumentation. The infrared spectrometer used in the majority of the studies is a commercial FTIR unit (ReactIR 1000 from ASI Applied Systems, Mettler Toledo Company, Millersville, MD) equipped with an ATR (Attenuated Total Reflection) probe. The Sicomp ATR probe contains a chemical resistant silicon film as the ATR element. The NIR instrument consisted of a Foss NIR Systems 6500 spectrograph and a transmission probe (Foss NIR Systems, Inc., Silver Spring, MD) with its sampling gap set to 1 mm wide. The data collection rate was one spectrum for every 2 min for both FT-IR and NIR. To reduce spectral noise, 128 scans were averaged to produce one FT-IR spectrum, whereas, for an NIR spectrum, 32 scans were averaged.

Representative Procedure.[13] A DMF (321 mL, 4.14 mol) solution of chloroacetic acid (68.5 g, 0.725 mol) was heated to 75 °C followed by slow addition of $POCl_3$ (139.1 mL, 1.49 mol) over a 3 h period.

Reaction with Chloroacetyl Chloride in Place of Chloroacetic Acid. $POCl_3$ (69.6 mL, 0.725 mol) was added over 3 h to a DMF solution (321 mL, 4.14 mol) of chloroacetyl chloride (57.7 mL, 0.725 mol).

Results and Discussion

In situ IR was first examined as a possible spectroscopic method for monitoring the reaction in real time and to evaluate its ability to determine the end of the reaction. The reaction was performed according to the representative procedure described in the Experimental Section. The Sicomp ATR probe was placed directly into the reaction mixture. Figure 1 shows the time-resolved IR spectra of the reaction. Absorbences that can be attributed to a single known compound are identified and labeled in the figure. Figure 2 shows the time-resolved relative concentration profile of the known compounds plotted using the corresponding peaks.

As evident from Figures 1 and 2, the progress of the reaction can indeed be monitored in real time by *in situ* IR. Immediately upon addition of $POCl_3$ to the solution of chloroacetic acid in DMF, the absorbance at 1728.9 cm^{-1}, which is attributed to chloroacetic acid, diminishes and concomitantly, an absorbance at 1811.9 cm^{-1} increases. This absorbance at 1811.9 cm^{-1} is attributed to the carbonyl of chloroacetyl chloride. Complete conversion of chloroacetic acid to chloroacetyl chloride occurs approximately 50 min after the start of the addition of $POCl_3$. The concentration of chloroacetyl chloride starts to decrease after 50 min and is followed by the appearance of CO_2 (2338.6 cm^{-1}) and

(13) The general procedure has been published: Davies, I. W.; Marcoux, J.-F.; Taylor, *J. Org. Synth.* **2003**, *80*, 200. *Caution!* Phosphorous oxychloride is highly toxic and corrosive and reacts violently with water liberating HCl, phosphoric acid, and heat.

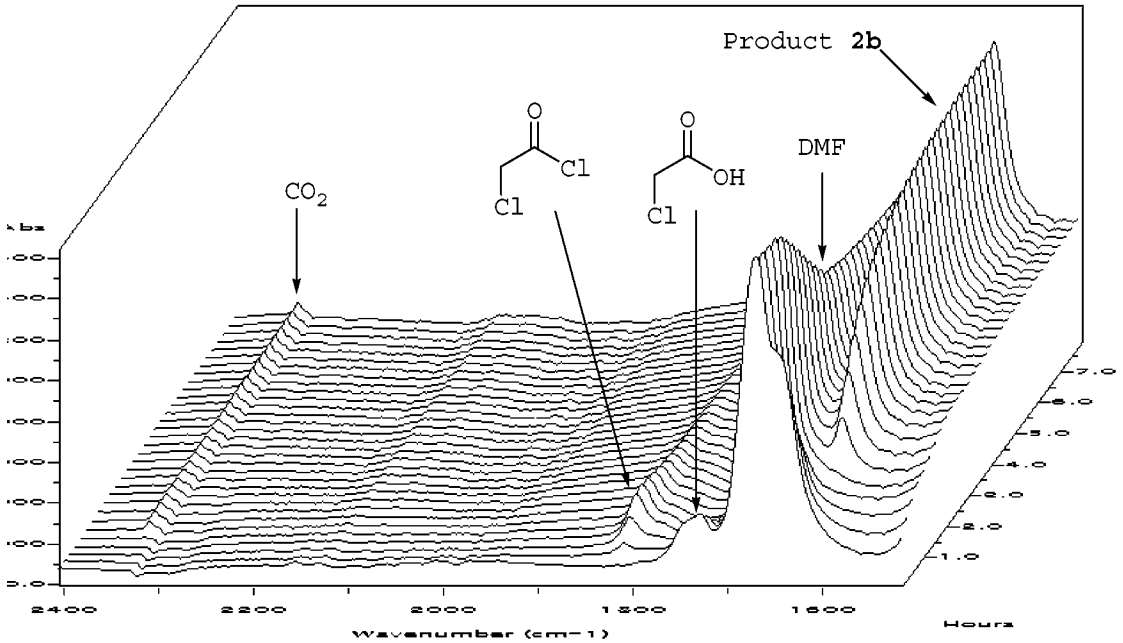


Figure 1. **Real time *in situ* IR profile of the formation of CDT-chloride.**

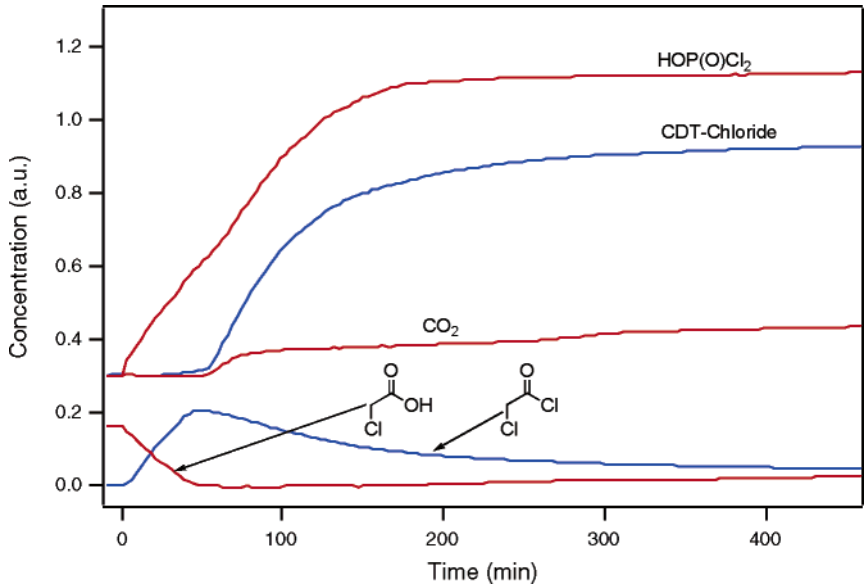


Figure 2. **Reaction profile over time as determined by *in situ* IR.**

product CDT-chloride (1609.2 cm^{-1}) at approximately 55 min after the start of the addition of $POCl_3$. Product formation is complete after approximately 400 min. The end of reaction is reached when the product peak stops to increase or the peak of the intermediate, chloroacetyl chloride, stops to decrease.

In situ NIR was next examined as an on-line method to evaluate its ability to determine the end of the reaction. Using the same procedure described for the *in situ* IR study, a reaction was performed in the presence of an NIR probe that was inserted into the reaction vessel. As a reference method, an *in situ* IR probe was also present in the reaction. In this experiment, the IR sampling method chosen was ASI's StreamLine flow cell, as this method would be more amenable to large scale processes. The NIR spectra are shown in Figure 3. Compared to the IR spectra, the NIR spectra do not have resolved peaks that correspond to individual reaction species. Multivariate calibration methods (chemometrics) are thus needed to extract the information about the individual species from the overlapping spectral peaks, using the concentration information of these species provided by a referee method. One of the widely used chemometric calibration algorithms is partial least squares (PLS). In PLS, latent variables are calculated from both spectral and concentration data as factors (principal components) of the calibration data set. A linear regression curve is established between the latent variables, contrary to traditional linear regression which uses the concentrations

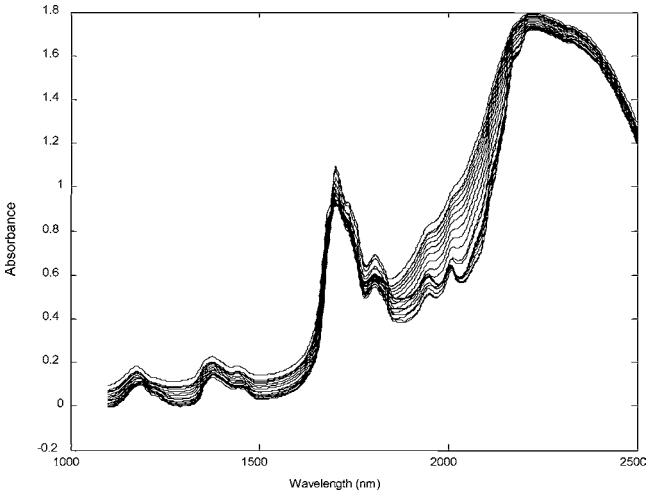


Figure 3. **Real time *in situ* NIR profile of the formation of CDT-chloride.**

Table 1. **PLS calibration parameters for species of interest**

analyte	spectral range (nm)	no. of factors	SEC (au)
CDT-chloride	1300−2340	4	0.0022
chloroacetic acide	1400−2300	3	0.0031
chloroacetyl chloride	1500−2340	3	0.0020
$POHCl_2$	1300−2340	4	0.0013

of a species and its spectral peaks.[14] Table 1 lists the parameters of PLS calibration for NIR using the IR absorbences as reference for each species of interest.

Figure 4 compares the prediction results of NIR (×) and the *in situ* IR (—) peak traces. It is evident from this figure that a strong correlation between NIR and IR was achieved. The prediction model developed from the PLS analysis using IR reference values allows the NIR spectrometer to track concentration profiles in real-time. Also note that the predicted profiles in Figure 4 are reported in absorbance units and not in concentration units, due to the use of *in situ* IR peak intensity (absorbance units) as the reference data. However, the lack of absolute concentration information only presents a minor inconvenience to determination of the reaction endpoint. Instead of relying on absolute concentrations, an endpoint detection method can monitor the temporal variations in the NIR profiles to decide if the endpoint has been reached. With process conditions held steady, the variations in the profiles of major reaction species should decrease to minimal at the end of reaction. To increase the sensitivity of the method and remove batch-to-batch differences in the profiles, derivative is applied to the profiles. The derivative profiles should reach near zero at the end of reaction. For this study, the derivative files of CDT-chloride (product) and chloroacetyl chloride (intermediate) are calculated and displayed in Figure 5. At the end of reaction both derivative profiles are close to zero, indicating no significant changes in the concentrations of these two species and the reaction has ended. Due to fluctuations in the profiles, very rarely do the derivatives reach zero. An acceptance zone can be established around the zero line based on statistical estimation using previous data. When the profiles consistently fall into this zone, the reaction is complete.

The reaction of interest was first performed and briefly studied by Arnold in the early 1960s.[15] From his studies, the following observations/facts are known: (1) CO_2 is evolved during the reaction; (2) reaction of $POCl_3$ with DMF affords an electrophilic Vilsmeier-type reagent;[16] (3) 2 equiv of $POCl_3$ relative to chloroacetic acid are required; (4)

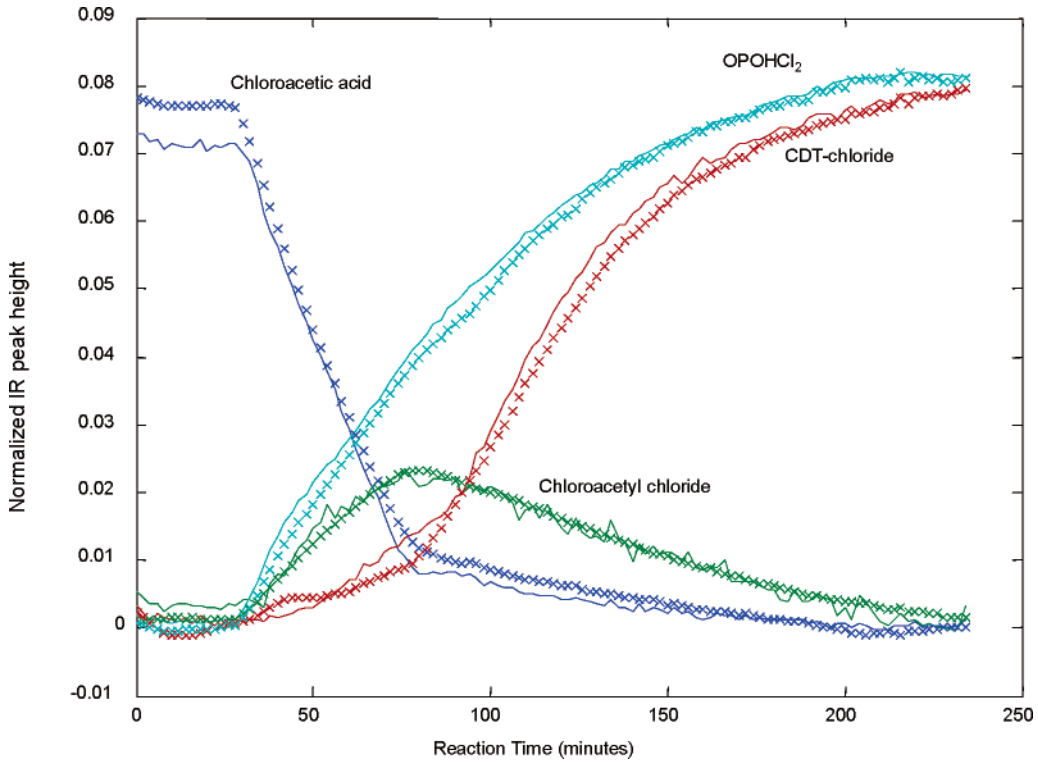


Figure 4. **Comparison of NIR predicted profiles (×) and IR profiles (—).**

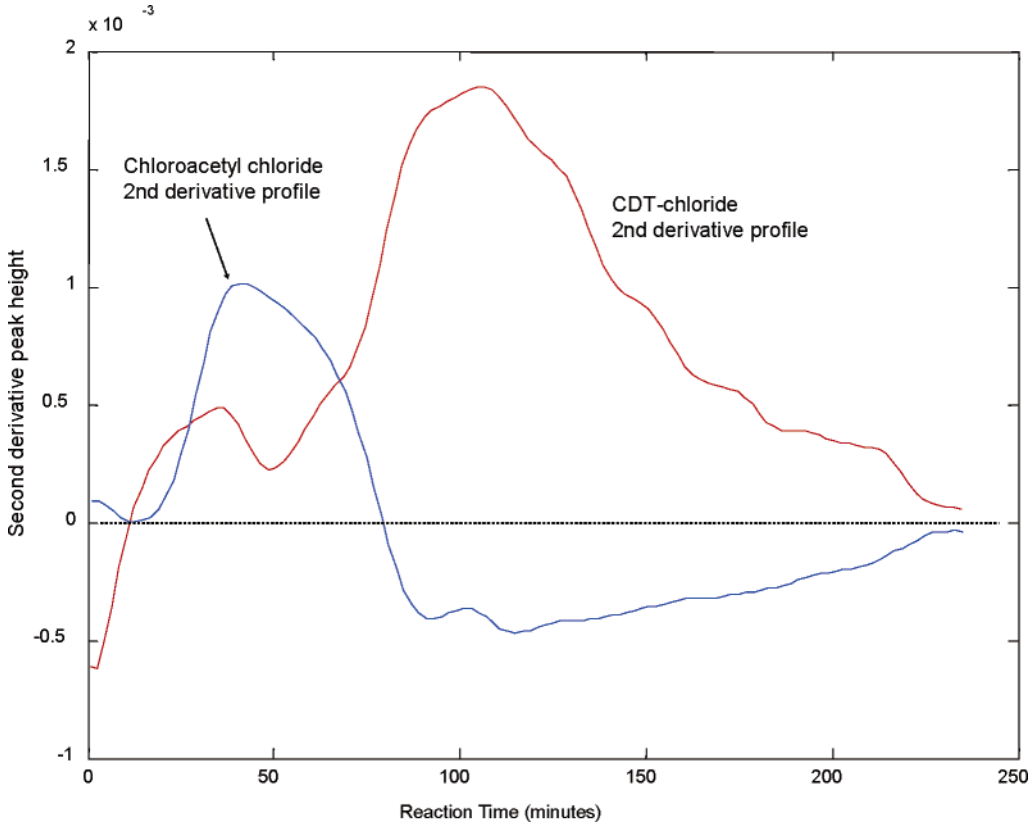


Figure 5. **Calculated derivative files of CDT-chloride and chloroacetyl chloride (intermediate).**

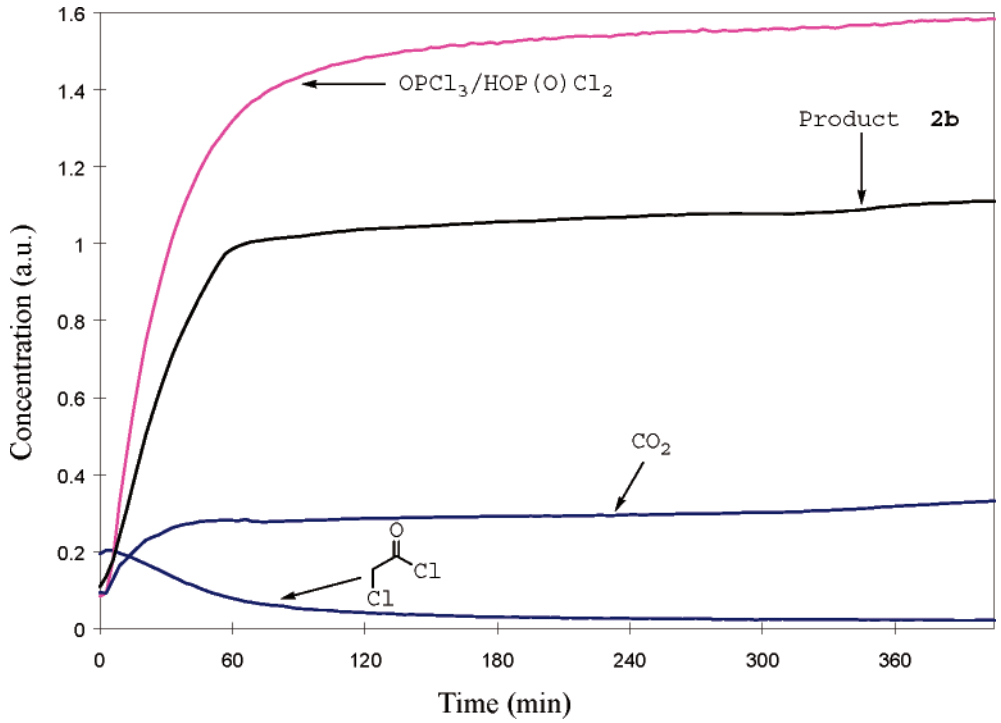


Figure 6. ***In situ*** **IR profile using chloroacethyl chloride as starting material.**

chloroacetyl chloride is an intermediate along the reaction pathway.[17] Since his studies, little effort has been put forth to support the listed observations/facts. Given the information-rich IR spectra, further studies directed toward identifying and understanding the chemical events of the reaction were carried out.

Results of the initial IR study, as shown in Figures 1 and 2, demonstrate that *in situ* monitoring not only can determine

(14) Martens, H.; Naes, T. *Multivariate Calibration*; John Wiley and Sons: August 1994; pp 116−125

(15) (a) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051−3057. (b) Arnold, Z. *Coll. Czech. Chem. Commun.* **1965**, *30*, 2125−2127.

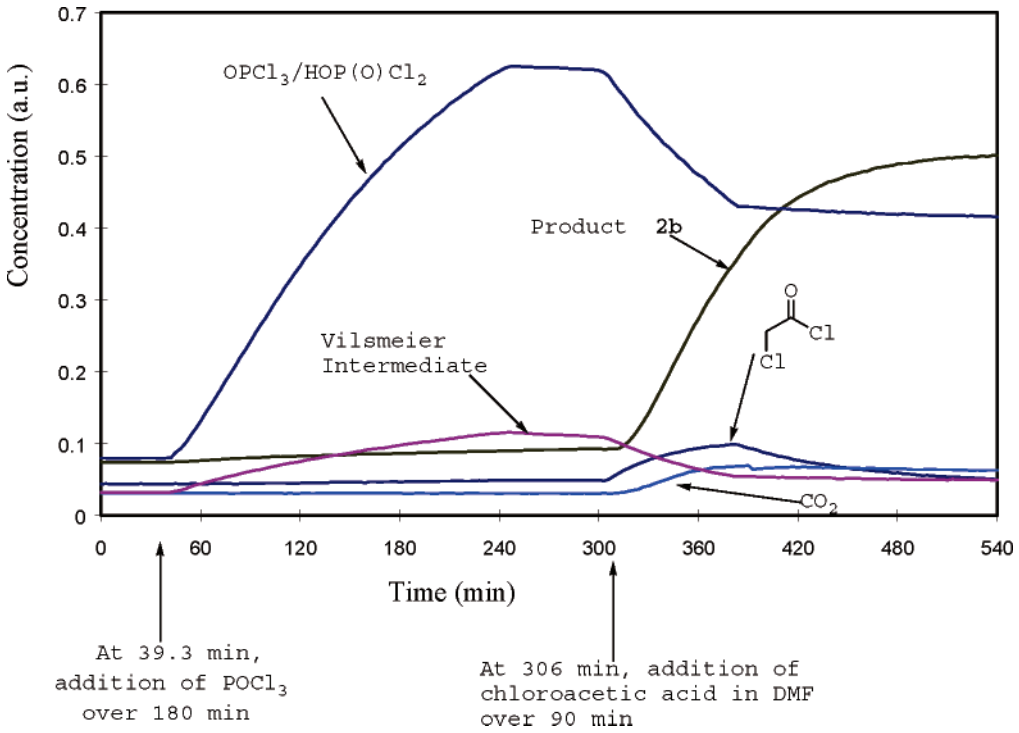
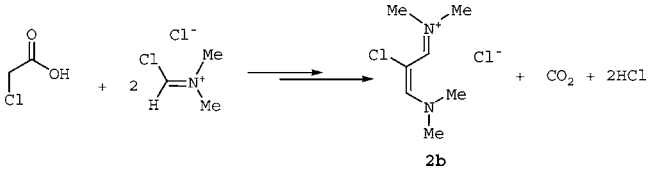


Figure 7. **Observation of the Vilsmeier intermediate via aging DMF and $POCl_3$.**

the end of reaction by monitoring intermediate disappearance or product formation but also can provide significant information on the chemical events occurring during the course of the reaction by detecting and identifying intermediates and byproducts. For example, Figures 1 and 2 clearly show that the first event is formation of chloroacetyl chloride and that product formation does not occur until after the chloroacetic acid is consumed. This observation along with the appearance of chloroacetyl chloride during the disappearance of chloroacetic acid suggests that chloroacetyl chloride is an intermediate along the reaction pathway.[18] In addition, the rather long induction period prior to product appearance and CO_2 byproduct appearance indicate that decarboxylation may be the last step prior to product formation. Note that the CO_2 profile does not match that of CDT-chloride because the system is open, allowing CO_2 to escape.

As previously suggested by Arnold and confirmed by *in situ* IR, the first step of the reaction is most likely the conversion of chloroacetic acid to chloroacetyl chloride.[19] Completion of this step is rapidly followed by simultaneous CDT-chloride and CO_2 formation. To demonstrate that chloroacetyl chloride is a plausible intermediate along the reaction pathway, commercially available chloroacetyl chloride and 1 equiv of $POCl_3$ were used in place of chloroacetic acid and 2 equiv of $POCl_3$. The results of the reaction as monitored by *in situ* IR are shown in Figure 6.

Scheme 3



2b

Chloroacetyl chloride and 1 equiv of $POCl_3$ can be used effectively in place of chloroacetic acid and 2 equiv of $POCl_3$.[20] As shown in Figure 6, product formation and CO_2 evolution occur immediately upon addition of $POCl_3$. This is in sharp contrast to the reaction performed with chloroacetic acid (Figure 3), in which an induction period is observed prior to product formation and CO_2 evolution. This result suggests that, in the reaction with chloroacetic acid, chloroacetyl chloride formation may be rate-limiting.

As stated previously, reaction of $POCl_3$ with DMF affords a Vilsmeier-type reagent. However, that Vilsmeier-type reagent was not detected by *in situ* IR under the described conditions. Consequently, a reaction was performed, in the presence of an *in situ* IR probe, in which $POCl_3$ was added over a 3 h period to DMF (in the absence of chloroacetic acid) at 75 °C. This was then followed by slow addition of a DMF solution of chloroacetic acid over a 1.5 h period. Under these conditions, buildup of the Vilsmeier intermediate should be observed prior to the addition of the chloroacetic acid solution. The results of the reaction as monitored by *in situ* IR are shown in Figure 7.

Slow buildup of the Vilsmeier intermediate (804 cm^{-1}) was observed during the addition of $POCl_3$ to DMF (Figure

(16) (a) Vilsmeier, A.; Haack, A. *Chem. Ber*. **1927**, *60*, 119. (b) Paquette, L. A.; Johnson, B. A.; Hinga, F. M. *OSC* **1973**, *5*, 215.

(17) Arnold demonstrated that reaction of chloroacetyl chloride (in place of chloroacetic acid) with $POCl_3$ in DMF affords the desired product.

(18) The identity of the chemical species associated with the absorbances in Figure 1 were confirmed by IR of authentic samples.

(19) Reaction of organic acids with $POCl_3$ is known to afford the acid chloride derivative. See: Ansell, M. F. In *The Chemistry of Acyl Halides*; Patai, S., Ed. Interscience Pusblisher: New York, 1972; pp 35−69.

(20) Use of chloroacetyl chloride in place of $POCl_3$ affords CDT-PF6 (after anion exchange) in 78−80% yield as compared to 74−75% yield using chloroacetic acid. However, both reactions are essentially quantitative as determined by ^1H NMR. Thus 20−25% of the product is lost during anion exchange

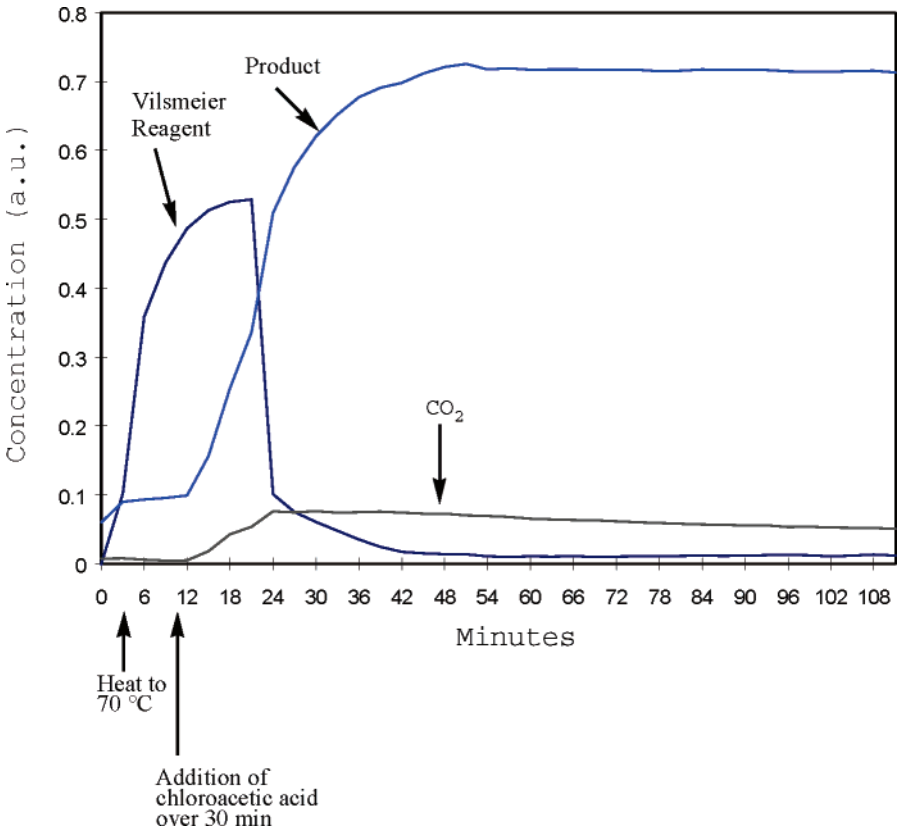


Figure 8. **Reaction profile using commercial Vilsmeier reagent with chloroacetic acid.**

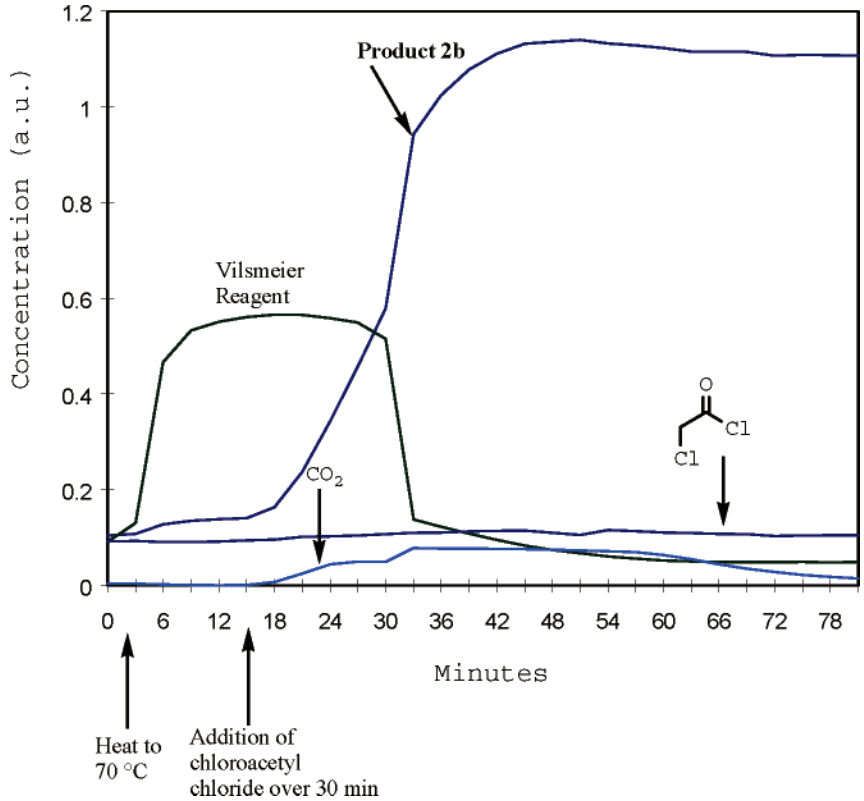
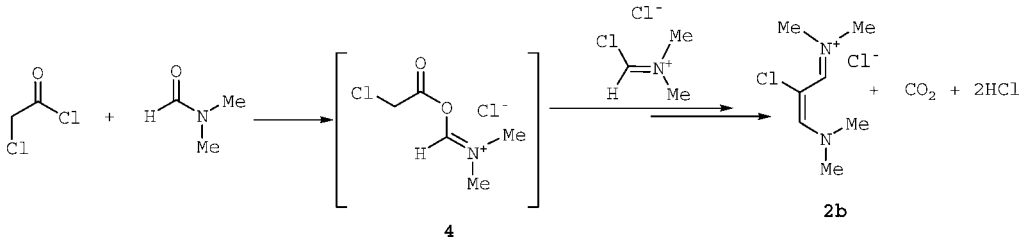


Figure 9. **Reaction profile using commercial Vilsmeier reagent with chloroacetyl chloride.**

7). Immediately upon addition of the chloroacetic acid solution (DMF) to the reaction mixture, consumption of the Vilsmeier intermediate and formation and subsequent disappearance of chloroacetyl chloride were observed. The fact that chloroacetic acid was not observed by IR suggests that, upon dissolution, it immediately reacts to form chloroacetyl

Scheme 4



chloride. Approximately 6 min after the start of the addition of the chloroacetic acid solution, product formation and CO_2 evolution occur.

To confirm that a Vilsmeier-type intermediate is along the reaction pathway, the use of commercially available Vilsmeier reagent was examined. A 2 equiv amount of the Vilsmeier reagent relative to chloroacetic acid was used, as two alkylations are required for product formation, Scheme 3. Thus a solution of the Vilsmeier reagent (4.04 g, 0.030 mol) was placed in a flask containing 15 mL of DMF. The solution was heated to 70 °C. After 8 min at 70 °C, a solution of chloroacetic acid (1.42 g, 0.15 mol) in 7 mL of DMF was added over a 30 min period. Immediately upon addition, product formation and CO_2 evolution was observed (Figure 8). Chloroacetic acid was not observed in the reaction, suggesting that it reacts immediately with the Vilsmeier reagent upon dissolution and is completely consumed in the reaction. This result is similar to the result observed from the reaction in which the Vilsmeier reagent was generated *in situ* from $POCl_3$ and DMF. Chloroacetyl chloride was also not observed during the reaction. These results suggest that chloroacetyl chloride may not be a necessary intermediate in the reaction. In addition, it is unclear whether the decarboxylation occurs after the first alkylation or the second.

Finally, the commercially available Vilsmeier reagent was examined in a reaction with chloroacetyl chloride in equal molar amounts (Figure 9). Thus, the Vilsmeier reagent (4.04 g, 0.030 mol) was placed in a flask along with 20 mL of DMF. The reagent is sparingly soluble in DMF at room temperature. The solution was heated to 70 °C. At this temperature, the majority of the reagent is in solution. After 13 min at 70 °C, chloroacetyl chloride (2.39 mL, 0.030 mol) was added over a 30 min period. Immediately upon addition of chloroacetyl chloride, product formation, Vilsmeier reagent consumption, and CO_2 evolution were observed.

Previously we have shown that the product can be formed from either chloroacetic acid and 2 equiv of $POCl_3$ in DMF or chloroacetyl chloride and 1 equiv of $POCl_3$. In both cases CO_2 evolution is observed. For the case in which chloroacetyl chloride is used, it is assumed that one of the two oxygens in CO_2 must come from DMF, since DMF is the only compound in the reaction mixture that contains an available oxygen. In addition, the stoichiometry of the reaction suggests that 2 equiv of the Vilsmeier intermediate are incorporated into the product (Scheme 4). Both assumptions can be rationalized if intermediate **4**, a Vilsmeier reagent equivalent, is invoked.

Conclusion

Both *in situ* IR and *in situ* NIR were found to be effective at determining the end of reaction in the formation of CDT-chloride. In addition, *in situ* IR was found to be an effective tool for determining and tracking the chemical events of the reaction. Using *in situ* IR, a better understanding of the chemical process was obtained. The buildup of transient intermediates, starting material disappearance, and product and byproduct formation were effectively followed during the course of the reaction using both techniques. The observations confirmed the intermediacy of both chloroacetyl chloride and a Vilsmeier type reagent as well as document the evolution of carbon dioxide.

Note Added after ASAP Publication: In the version published on the Internet January 15, 2005, a production error caused the asterisk for one of the authors to be deleted. The final version published January 18, 2005, and the print version are correct.

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