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Simple, Rapid, and Highly Sensitive Detection of Diphosgene and Triphosgene by Spectrophotometric Methods

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Abstract

Methods for the detection and estimation of diphosgene and triphosgene are described. These compounds are widely used phosgene precursors which produce an intensely colored purple pentamethine oxonol dye when reacted with 1,3-dimethylbarbituric acid (DBA) and pyridine (or a pyridine derivative). Two quantitative methods are described, based on either UV absorbance or fluorescence of the oxonol dye. Detection limits are $\sim 4 \mu\text{mol/L}$ by UV and $<0.4 \mu\text{mol/L}$ by fluorescence. The third method is a test strip for the simple and rapid detection and semi-quantitative estimation of diphosgene and triphosgene, using a filter paper embedded with dimethylbarbituric acid and poly(4-vinylpyridine). Addition of a test solution to the paper causes a color change from white to light blue at low concentrations and to pink at higher concentrations of triphosgene. The test strip is useful for quick on-site detection of triphosgene and diphosgene in reaction mixtures. The test strip is easy to perform and provides clear signal readouts indicative of the presence of phosgene precursors. The utility of this method was demonstrated by the qualitative determination of residual triphosgene during the production of poly(Bisphenol A carbonate).

Keywords

triphosgene; phosgene; spectrophotometry; spectrofluorimetry; test strip; poly(Bisphenol A carbonate)

Phosgene and its safer derivatives – diphosgene and triphosgene – are industrially important chemicals used in the manufacture of polyurethanes[1] and polycarbonates[2] and in the synthesis of various active pharmaceutical ingredients.[3] This market sector generates approximately 8 million tons of products and the global demand for phosgene is about 5 million tons per year.[4] Phosgene is very corrosive and has a high acute toxicity if inhaled. The danger of inhalation poisoning is particularly grave, since phosgene can be lethal before its odor is recognizable.[5]

Current methods for the detection of phosgene are predominantly electrochemical and spectrophotometric. [6,7] A cellulose tape impregnated with 4-nitrobenzylpyridine and benzyaniline has been developed for monitoring phosgene in air.[8] It has also been shown

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that 1,2-bis-nucleophiles like 2-aminophenol can be used to detect phosgene by mass spectrometry.[9]

Over the past few decades, safer alternatives to phosgene, e.g. diphosgene[10,11] and triphosgene,[12,13] have been developed. Diphosgene (trichloromethyl chloroformate), is a liquid and triphosgene (bis-(trichloromethyl) carbonate), a solid, at room temperature, making them much easier to handle than gaseous phosgene. In addition, they are more stable to decomposition. Recently colorimetric methods for the detection of diphosgene vapors were reported[14,15] and a FRET (Förster resonance energy transfer) method was developed for triphosgene.[16]

In spite of these advances, there is still a need for a quick and reliable test to detect phosgene precursors *in-situ*. In addition, since triphosgene is increasingly used as a reagent in chemical synthesis, it would be advantageous for the user to have a simple and quick method to detect triphosgene in reaction mixtures. In the current work, we demonstrate efficient detection systems for diphosgene and triphosgene, which have rapid response times and stable reaction products.

Kohn and coworkers developed a spectrophotometric method for the detection of organic cyanates[17] and carbodiimides[18] based on work by König [19] on colored oxonol dyes. They have shown that organic cyanates react with dimethylbarbituric acid in pyridine-water to produce an intensely colored purple oxonol dye. The mechanism of color formation is based on the nucleophilic reaction of pyridine with an activated electrophilic species. This reaction is also used for the detection and determination of HCN. [20] A similar reaction between phosgene precursors and pyridine, and the subsequent reaction of the resulting intermediate with dimethylbarbituric acid is employed here to detect nanomole quantities of diphosgene and triphosgene. In pyridine-H₂O, the oxonol dye can be detected by absorbance or fluorescence, the latter extending detection limits for triphosgene to <0.4 $\mu\text{mol/L}$ (or 0.4 nmoles of analyte in a 1 mL cuvette). Additionally a methodology for the preparation of a test strip is illustrated, which can be used for rapid visual detection and semi-quantitative estimation of triphosgene.

EXPERIMENTAL SECTION

Materials

1,3-Dimethylbarbituric acid, 3-cyanopyridine, 4-(4-nitrobenzyl)-pyridine and poly(4-vinylpyridine) were obtained from Sigma Aldrich. 4-Cyanopyridine, 4, 4'-Bipyridine, 2, 2'-Bipyridine, cyanuric acid and dimethylaminopyridine and pyridine were obtained from Acros Chemicals.

Spot Test

Silica gels plates (0.5 $\times$ 5 cm) were dip coated with a solution of 1,3-Dimethylbarbituric acid (20 mg/mL) and poly(4-vinylpyridine) (15 mg/mL) in ethanol and air-dried overnight. Selectivity for various triphosgene type reagents was tested by spotting a solution (5 mg/mL) of each test compound on a silica gel plate previously moistened with a mist of water.

System 1

Absorbance Method—All absorption measurements were carried out on a Thermo-Fisher Evolution 100 UV-VIS spectrophotometer using 1cm quartz cuvettes at room temperature.

- i. Reaction of triphosgene with pyridine and 1,3-dimethylbarbituric acid: Triphosgene solutions of various concentrations (0.25 mg/mL – 2mg/mL) were prepared in CH₂Cl₂ and aliquots (5 – 50 μL) were added to solutions of 1,3-dimethylbarbituric

acid (30 mg, 0.19 mmol) in 1 mL of pyridine – H₂O (9:1, v/v). An intense blue colored solution with a red fluorescence developed instantly.

- ii. Reaction of triphosgene with pyridine derivatives and 1,3-dimethylbarbituric acid in methanol – H₂O: Triphosgene solutions of various concentrations (0.25 mg/mL – 2 mg/mL) were prepared in CH₂Cl₂ and aliquots (5 – 50 μ L) were added to solutions of 4,4'-bipyridine (30 mg, 0.19 mmol) and 1,3-dimethylbarbituric acid (30 mg, 0.19 mmol) in 1 mL of methanol- H₂O (9:1, v/v). A pink color developed within 10 seconds, which then changed to an emerald (greenish blue) color within 1 minute. The same protocol was used for the other pyridine derivatives. The absorption maximum was dependent upon the pyridine derivative.

System 2

Fluorescence Method—Fluorescence spectra were recorded on a Varian Eclipse spectrofluorimeter using a 1 cm quartz cuvette at room temperature. The emission spectrum was collected between 600 nm and 700 nm. All spectra were recorded at identical PMT voltage and slit widths.

Reaction of triphosgene with 1,3-Dimethylbarbituric acid in pyridine- H₂O: Triphosgene solutions of various concentrations (0.025 mg/mL – 0.2 mg/mL) were prepared in CH₂Cl₂ and aliquots (5 – 50 μ L) were added to solutions of 1,3-dimethylbarbituric acid (30 mg, 0.19 mmol) in 1 mL of pyridine – H₂O (9:1, v/v). An intense blue colored solution with a red fluorescence developed instantly.

System 3

Test strips

- i. For higher concentrations of triphosgene: 3-cyanopyridine (42 mg), poly(4-vinylpyridine) (14 mg) and 1,3-dimethylbarbituric acid (43 mg) were dissolved in ethanol (2 mL) and coated onto a filter paper (VWR 413) by dripping the solution as evenly as possible over the paper. The filter paper was dried. Prior to the test, the paper was moistened with a mist of water and drops of triphosgene solutions at two different concentrations (0.84 mM and 6.72 mM) were added onto the paper. Within 1–2 minutes, the filter paper became pink at the higher concentration of triphosgene and light blue at the lower concentration.
- ii. For lower concentrations of triphosgene: poly(4-vinylpyridine) (30 mg) and 1,3-dimethylbarbituric acid (40 mg) were dissolved in ethanol (2 mL) and coated onto a filter paper (VWR 413) by dripping the solution as evenly as possible over the paper. Drops of triphosgene solutions (0.84 mM and 6.72 mM) were added onto the paper and both the lower and higher concentrations of triphosgene gave a blue color to the test strip. The blue color was more intense for the higher concentration of triphosgene.

RESULTS AND DISCUSSION

Phosgene precursors react with 1,3-dimethylbarbituric acid (DBA) in pyridine- H₂O (9:1, v/v) to produce an intense blue colored solution (λ_{max} 598 nm) with a red fluorescence. As shown earlier by Kohn *et al.*[17] for organic cyanates and carbodiimides, the species at 598 nm is the pentamethine oxonol dye that is formed by the reaction with DBA in pyridine-H₂O. From the proposed mechanism, phosgene precursors should react with DBA similarly to the cyanates and carbodiimides to produce the same oxonol dye. Support for this comes from the similarity of the absorption spectra of the oxonol dye (prepared by Kohn *et al.*) in pyridine-H₂O (9:1) and that of the reaction between triphosgene and DBA in pyridine-H₂O (9:1) (Figure 1).

First, the selectivity of the assay was established by comparing the reaction of the phosgene precursors on silica gel plates that were dip coated with a solution of 1,3-dimethylbarbituric acid and poly(4-vinylpyridine). Each test solution (5 mg/mL) was spot tested on the silica gel plates using a capillary tube. The solution of triphosgene gave a purple spot that turned to a blue spot in < 1 min. Diphosgene also gave a purple / pink spot instantly. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N,N'-dicyclohexylcarbodiimide (DCC) also gave a purple spot, although the color formation with carbodiimide was much slower (2–3h). Acetyl chloride, di-*t*-butyl dicarbonate (Boc₂O) and benzylchloroformate gave a faint yellow color, and all other compounds failed to produce any color (Table 1). This established the potential of the current assay for the rapid and selective detection of diphosgene and triphosgene. We then developed three different analytical methods.

System 1

Absorbance measurements—Two quantitative assays for triphosgene were developed. The first method was based on the reaction between triphosgene and pyridine and the subsequent reaction with 1,3-dimethylbarbituric acid in pyridine-H₂O, which yields an oxonol dye with λ_{max} at 598 nm. Quantitative determination of triphosgene concentration was established by monitoring the absorbance of the oxonol dye at this wavelength. As seen in Figure 2, the detection limit was about 2 $\mu\text{mol/L}$, and the dynamic range extends to 80 $\mu\text{mol/L}$.

In order to extend the dynamic range, we evaluated other pyridine derivatives. In agreement with the proposed mechanism, the λ_{max} of the absorbing species depends upon the pyridine derivative. Noteworthy is the fact that derivatives that contain electron-withdrawing groups give a positive test, (4-cyanopyridine λ_{max} 648 nm; 4-(4-Nitrobenzyl)pyridine λ_{max} 624 nm; 3-Cyanopyridine λ_{max} 563 nm; 4,4'-Bipyridine λ_{max} 618 nm), while those that contain electron-donating groups like dimethylaminopyridine do not produce colored products.

For development of an analytical method we selected 4,4'-bipyridine due to its relatively quick response time (< 1 minute), high absorbance and stability of the colored product (12–18 h). Immediately after the addition of triphosgene to a solution of 4,4'-bipyridine and DBA in MeOH-H₂O (9:1, v/v), a pink solution forms that turns to an emerald (greenish blue) colored solution within 1 minute. As expected from the proposed mechanism, the absorbance maximum of the oxonol dye is red shifted to 618 nm due to a more delocalized structure resulting from 4,4'-bipyridine. The quantitative determination of triphosgene was established by monitoring the absorbance of the oxonol dye at this wavelength. The range of detection of triphosgene is between 4 and 230 $\mu\text{mol/L}$ of triphosgene (Figure 3). Similar results were obtained when the experiment was done in ethanol-H₂O, isopropanol-H₂O or sec-butanol-H₂O.

System 2

Fluorescence measurements of the reaction of triphosgene with 1,3-Dimethylbarbituric acid in pyridine- H₂O—The high sensitivity of fluorescence based detection methods have resulted in their use for the detection of a wide variety of chemicals. [21] The reaction of triphosgene with 1,3-dimethylbarbituric acid in pyridine-H₂O produces an oxonol dye, which has a very high extinction coefficient and is also highly fluorescent. Hence the possibility of detecting and estimating the amount of triphosgene from the fluorescence of the pentamethine oxonol dye was examined. The fluorescence was recorded between 600 nm and 700 nm and the λ_{max} of the emission peak is at 624 nm. As seen in Figure 4, even a concentration of 0.4 $\mu\text{mol/L}$ of triphosgene can be reliably measured and the resulting plot of fluorescence intensity and concentrations has a high correlation. Potentially, an even lower amount of triphosgene can be detected by increasing the amount of DBA in the reaction

mixture and/or increasing the sensitivity of the instrument. A recent study [16] has shown that triphosgene can be detected by FRET at concentrations at relatively high concentrations of 5×10^{-5} M. The detection limit of this current spectrofluorimetric method is significantly lower.

System 3

Fabrication of test strips for the detection and estimation of triphosgene—A test strip, similar to pH paper, a glucose test[22] or a pregnancy test[23] is widely used and highly desirable for simple and rapid monitoring. In order to facilitate the adoption of our methodology by end users – for example chemists using triphosgene as a reagent, it would be advantageous to develop a test where the user adds a drop of the reaction mixture to the test strip and determines the presence of a phosgene precursor by the color of the strip. To develop such a test strip, we employed the pyridine derivative – poly(4-vinylpyridine).

A filter paper (VWR 413) was coated with a solution of poly(4-vinylpyridine) (15 mg) and DBA (20 mg) in 1 mL ethanol, which was then dried. Addition of a triphosgene test solution (in CH_2Cl_2) to the strip (pre-moistened with a mist of water) produces a blue color within 1 minute. This method was able to clearly indicate the presence of triphosgene since the color change is very discernible from white to light blue (Figure 5).

Although this is a powerful ‘yes’ or ‘no’ method for the presence of triphosgene, it is not very useful for the semi-quantitative estimation of triphosgene. To generate a more quantitative method, a system that produces a different color for two different concentrations of triphosgene was designed:

Test strips were prepared using a combination of polyvinylpyridine (14 mg) and 3-cyanopyridine (42 mg) along with DBA (43 mg) in 2 mL ethanol. A triphosgene solution at a concentration of 6.7 mM resulted in a pink color on the paper, while a triphosgene concentration of 0.84 mM produced a blue color. Without the 3-cyanopyridine, both the higher and lower concentrations of triphosgene give a blue color although the intensity of the color is less for the lower concentration. These results provide the basis to develop semi-quantitative methods for the determination of the amount of triphosgene. Due to the non-homogeneous nature of our coating process, there is variability in the color generated on various parts of the paper. However this is a simple and promising method for the semi-quantitative detection and estimation of triphosgene. In contrast, the published cellulose tape method for the estimation of phosgene shows only a single color at all concentrations.

This test strip also works for phosgene vapors. The decomposition of a 5% solution of diphosgene in toluene was initiated with triethylamine and a test strip positioned above this solution turns red immediately. However, the test strip decolorizes within a few minutes due to the presence of HCl vapors.

Utilization of the Assay to Indicate the End-Point of Polycarbonate Synthesis

Polycarbonates such as poly(bisphenol A carbonate) and tyrosine derived polycarbonates, are commercially valuable materials that are efficiently synthesized using triphosgene [24] [25]. Due to its toxicity, it is crucial that all excess triphosgene be quenched prior to work up and precipitation of the polymer. The utility of the current assay was demonstrated by using it to test for the presence of triphosgene during the polymerization reactions of poly(bisphenol A carbonate) and tyrosine polycarbonates and to confirm that all the triphosgene was quenched prior to precipitation of the polymer. During the course of the reaction, aliquots of the reaction mixture were taken and added to solutions of 1,3-dimethylbarbituric acid (30 mg) in pyridine- H_2O , and the presence of triphosgene was indicated by the formation of a blue solution. After

the reaction was quenched, the same test produced a colorless solution indicating that the triphosgene has been consumed (within the limits of detection of this test).

Comparison between the Current Assay and an Established Method

A published method for the determination of phosgene is to use a mixture of 4-(4-nitrobenzylpyridine) and N-phenylbenzylamine, which produces a yellowish-orange color to indicate the presence of phosgene. Although the above protocol is most commonly used for the detection of phosgene or diphosgene in air samples, we compared our assay with this published procedure under the same experimental conditions. In the experiment, aliquots of triphosgene in CH_2Cl_2 were added to either a solution of 1,3-dimethylbarbituric acid in pyridine-water (test method) or to a solution of 4-(4-nitrobenzylpyridine) and N-phenylbenzylamine (control method) in methanol. In the test method, the change in color was obvious and readily discernable – from a clear solution to a blue / red solution while in control method the change in color before (light yellow) and after (yellowish-orange) addition of triphosgene was subtle and more difficult to detect. Hence the assay developed here presents a clearer indication of the presence of phosgene precursors.

CONCLUSION

Due to the increased use of phosgene precursors (notably diphosgene and triphosgene) in industrial and academic laboratories, and their potential toxicity, methods for in-situ detection and estimation of these reagents are very useful. The reaction system consisting of pyridine and dimethylbarbituric acid system described here is an efficient method for in-situ detection and estimation of diphosgene and triphosgene. The long wavelength absorbance (or fluorescence) of the resulting oxonol dye decreases the possibility of interference from other chemicals in the reaction mixture. In addition, this reaction system is highly sensitive, allowing the detection of phosgene precursors in nanomole quantities of analyte. Three different protocols were developed which makes it feasible for the end user to adopt a method based on the user's needs and available instrumentation.

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Figure 1.
Comparison of absorption spectra of the dye prepared by the method in reference 16 and that of the reaction product of triphosgene and DBA in pyridine-H₂O.

Figure 2.
Dynamic range of detection of triphosgene utilizing the 1,3-dimethylbarbituric acid / pyridine- H_2O method showing breakdown of linearity at 80 μM .

Figure 3.

Dynami range of detection of triphosgene utilizing the 1,3-dimethylbarbituric acid / 4,4'-bipyridine in MeOH-H₂O method showing enhanced linearity over system shown in Figure 1.

Figure 4. Fluorescence spectra of pentamethine oxonol dye formed from the reaction of triphosgene, 1,3-dimethylbarbituric acid (DBA) in pyridine-H₂O (9:1). Shown are spectra taken upon addition of aliquots of a triphosgene solution to a solution of DBA in pyridine-H₂O.

DBA / PVP		DBA / PVP / 3CN-Py	
TP conc:		TP conc:	
0.84 mM 1	6.7 mM 2	0.84 mM 3	6.7 mM 4

Figure 5.

Test strips contain PVP and DBA (**1,2**) or PVP, 3-CN Py and DBA (**3,4**) embedded within a filter paper. The tests show a difference in color with and without 3-CN Py.

PVP: poly(4-vinylpyridine); 3CN-Py: 3-cyanopyridine; DBA: dimethylbarbituric acid; TP: triphosgene

Scheme 1.

Mechanism of formation of pentamethine oxonol dye.

Table 1

Selectivity of the Assay

Test Compound	Test Result
Triphosgene (TP)	Purple spot turning to blue spot in ~ 20 sec
Diphosgene	Pink spot
DCC	Pink spot; slower response time (2–3 h)
EDC	Pink spot; slower response time (2–3 h)
Acetyl chloride	Faint yellow spot
Benzyl chloroformate	Faint yellow spot
FMOC-Cl	Faint yellow spot
Di-t-butyl dicarbonate (Boc ₂ O)	Yellow spot
Oxalyl chloride	Colorless
Carbonyldiimidazole (CDI)	Colorless
Disuccinimidyl carbonate (DSC)	Colorless
Trifluoroacetic anhydride	Colorless
PyBOP	Colorless
Choline chloroformate HCl	Colorless