Indian Journal of Chemistry
Vol. 59B, September 2020, pp. 1400-1408

N,N-Dichlorobenzyl amine: An effective decontaminant for highly toxic chemical warfare agents sulfur mustard and VX

Pranav K Gutch*, Avik Mazumder & Arvind K Gupta

Defence R & D Establishment, Jhansi Road, Gwalior 474 002, India

E-mail: pkgutch@rediffmail.com

Received 19 November 2019; accepted (revised) 9 September 2020

The chemical decontamination of vesicant, bis(2-chloroethyl)sulfide (Sulfur Mustard, SM) and nerve agent *O*-ethyl *S*-2-(N,N-diisopropylaminoethyl) methylphosphonothiolate (VX) has been achieved by an operationally simple method by using a new positive chlorine bearing reagent N,N-dichlorobenzylamine. Deactivation of these highly toxic chemical warfare agents has been achieved in acetonitrile-water medium. Before attempting the reactions on these highly toxic real agents, the reagent has been successfully tested for its decontaminating efficiency on the non-toxic simulants (2-chloroethyl phenyl sulfide, a simulant of Sulfur Mustard and *O,S*-diethyl methylphosphonothioate, simulant of VX). Progress of the decontamination reactions have been monitored by gas chromatography coupled with a flame photometric detector working in sulfur detection mode (GC-FPD(S)), ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. The products obtained after decontamination of Sulfur Mustard (SM) and VX have been thereafter identified by GC-MS technique. This reagent has been found to be highly advantageous over earlier reported decontaminating reagents in terms of - ease of preparation, cost effectiveness, stability, good shelf life and instantaneous conversion of both SM and VX into nontoxic products at room temperature.

Keywords: Sulfur mustard, VX, N,N-dichlorobenzylamine, decontamination, NMR, GC-MS, chemical warfare agents

Chemicals are the basis of matter including all life forms. Humans have been using different types of chemicals knowingly or unknowingly for leading a better quality of life. Industrial revolution ushered un with the development of better understanding of chemical properties of a wide range of substances having rich and varied chemistry. Thereafter, large scale production and trade of various types of commercially important chemicals ensued. Although the research and production of these industrial products was mainly intended for enhancing the quality of human life; this also brought with them many undesirable consequences. These include unintentional overuse of non-renewable resources, pollution and most importantly intentional development, weaponization and use of highly toxic Chemical Warfare Agents (CWAs). The primary objective of these CWAs[1] was in the form of weapons of mass destruction. The possessors of the CWAs had a great tactical and psychological advantage[2-6].

Among all the CWAs *O*-ethyl *S*-2-(N,N-diisopropylaminoethyl) methylphosphonothiolate (VX) and its analoguesare the most toxic chemicals[7-9]. This class of chemicals rapidly inactivate the acetylcholinesterase (AChE)[10-12] enzyme by rapidly phosphorylating its active site. This leads to the accumulation of neurotransmitter acetylcholine. The resulting over-stimulation of cholinergic receptors leads to breakdown of neuromuscular function[13]. Due to its site of action being the neurons, VX has been classified as a nerve agent[14,15] (Schedule 1.A.3 of the Chemical Weapons Convention (CWC)[16]. Although massive use of this CWA has not been reported, its sporadic use on civilian targets is well documented[17,18]. Another dreaded chemical in this list is bis(2-chloroethyl)sulfide (Sulfur Mustard, SM). SM is a persistent and cytotoxic blistering agent (Schedule 1.A.4). It has been used with impunity against humans, on several occasions [19-22]. In line with the objective of the international treaty of CWC; the target of this paper is to demonstrate a safe and effective management of accidental and intentional release of these chemicals by effecting their complete and efficient chemical decontamination. There are three main modes of decontamination of chemical warfare agents (Figure 1). The prerequisite for a decontaminant is that it must instantly convert a CWA into nontoxic products. The highly efficient decontamination reactions demonstrated by these CWAs include some elementary reactions such as

nucleophilic displacement (hydrolysis[23-26]), elimination[27] and oxidation. Various methods for the decontamination have been reported in the literature, amongst them hydrolysis[28,29] and oxidative methods are the most preferred. However, both the CWA (Figure 2) are available in large quantity, therefore hydrolysis is not a method of choice for the bulk decontamination of these CWA. Alternative methods such as oxidation with supercritical water[30], photo-catalysis[31], household chemicals[32] have also been reported. But, none of these methods have been found to have practical utility.

In this manuscript, we report the use of a cheap, rich positive chlorine, stable and easy to prepare reagent N,N-dichlorobenzyl amine as an effective decontaminant against SM and VX. The reagent was first checked for its efficacy and ease of decontamination against the simulants of (SM) and (VX) before it was tested against these highly toxic CWAs.

Experimental Section

Materials and methods

Benzyl amine, 3-trimethylsilyl propionic acid-d_4 (TSP), $CDCl_3$, and acetonitrile-d_3 were purchased from Sigma Aldrich Chemical Company, Milwaukee, USA. Acetonitrile and glacial acetic acid of AR grade were purchased from S.D. Fine-Chem Ltd., India. Sodium hypochlorite was prepared by passing chlorine gas at flow of 1 gmin^{-1} in NaOH solution (15%, 100 mL) for 30 min. at 5°C. The CWA (SM andVX) were prepared in house with purity >99% by reported method[33]. Purity was checked by GC and GC-MS and NMR spectroscopy.

Fig. 1 — Methods of decontamination of CWAs.

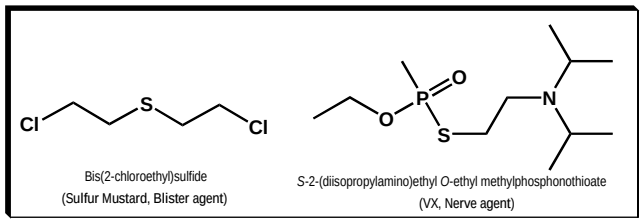

Fig. 2 — Chemical warfare agents taken up for the study.

Instruments used and conditions of analysis

The infrared (IR) spectra were recorded on BX-2 FT-IR spectrophotometer (Perkin-Elmer, USA) at a resolution of 4 cm^{-1}. The products of the decontamination were identified by7890 Agilent GC (Agilent Technologies, San Jose, CA, USA) coupled with 5975C mass selective EI detector (operating at 70 eV with ion source temperature at 200°C and emission current of 400μA). The experiments were performed in split less mode (constant pressure 7.64 psi) at a constant injector temperature of 250°C. The injector port was purged with an additional flow of helium at 50.0 mL/min (2.00 min). All experiments were carried out in gas saver mode (saver flow of 20.0 mL/min and saver time of 3.00 min). Separation was achieved on HP-5 capillary column (30.0 m × 250.00 μm × 0.25 μm) at a constant flow (1.0 mLmin^{-1}) of the carrier gas. The column was installed in the GC oven and the following temperature program was applied: initial temperature 50°C (equilibration time 0.50 min followed by 2.00 min hold) 20°Cmin^{-1} to 280°C (5.00 min hold) total run time 18.50 min. The GC-FPD(S) analysis was also performed. The gas chromatographic separation was achieved on HP-5 column (30 m × 320 μm × 0.25 μm film thickness) with a temperature program of 150°C for 2 min followed by a linear gradient to 250°C at 10°Cmin^{-1}, and hold at 250°C for 5 min (total run time 14 min.). The inlet temperature was maintained at 220°Cwith a split ratio of 10:1, septum purge flow of 3.0 mLmin^{-1} and total gas flow of 19.5 mLmin^{-1}. The detector was maintained at 200°C and the analytes were detected in a hydrogen-air flame maintained using a hydrogen gas flow 75 mLmin^{-1} and air flow of 100 mLmin^{-1} and additional makeup flow of 60 mLmin^{-1}. Due to the importance of NMR spectroscopy in the analysis of mixtures in general[34-36] and chemical warfare agents and their degradation products in particular[37-44] NMR spectra were recorded on 600 MHz Bruker AV III spectrometer equipped with a broadband observe smart probe head (BBFO). The spectrometer was controlled and data was acquired using Topspin 3.1 software of the instrument. Variable temperature unit of the spectrometer was used for carrying out the reactions at 25°C in 5 mm NMR tubes. All the

reactants and solvents were equilibrated for 10 min at the temperature at which the experiments were performed. Eight scans and four dummy scans were used for recording the solvent suppressed spectra using Bruker library pre-saturation pulse sequence *zgpr*. The data were Fourier transformed and processed with Gaussian baseline correction function with a filter width of 1 ppm to suppress the residual solvent peak.

Synthesis of N,N-dichloro benzylamine

A solution of benzylamine (10g,93mmol) in water (55 ml) containing concentrated hydrochloric acid (14 ml) was addedduring 30 min to an ice-cold suspension of 70% calcium hypochloride (38 g, 186 mmol) in water (150 mL). After the yellow green suspension was stirred for another 10 min, the layers were separated. The crude yellow oil (bottom layer) weighted 11.21g (68% yield) (Figure 3).

Process for the neutralization of Sulphur Mustard in aqueous medium

N,N-dichlorobenzylamine (0.01 mol) was added to a stirred solution of SM (0.01 mol) in 3 mL CH_3CN:H_2O mixture (9:1). Aliquots were taken at different time intervals (upto 5 min) and extracted with dichloromethane (5 mL). The organic phase was analyzed for the residual SM and degradation products by GC-MS using HP-5 MS column. The reaction was also studied by variable temperature ^{1}H-NMR spectroscopy (Figure 1). To a 5 µL of SM dissolved in 400 µL of CH_3CN:H_2O mixture (9:1) 7.5 µL of N,N-dichlorobenzylamine was added and the contents were mixed on a vortex shaker momentarily before recording the NMR spectra. The samples were field frequency locked and referenced with respect to TSP dissolved in CD_3CN:H_2O mixture (9:1) taken in a stem coaxial insert. The reaction was found to proceed instantaneously at room temperature under these conditions. In order to confirm the absence of SMin the products, chemical shifts and $^3J_{H-H}$ of the vicinal protons of the SM were observed immediately after the reaction and again after storing it at room temperature for 24 h.

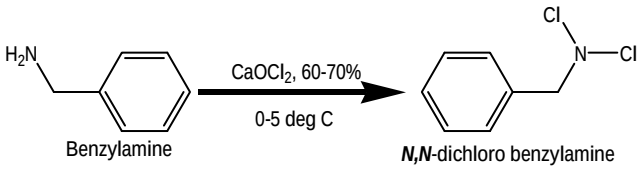

Fig. 3 — Synthesis of N,N-dichlorobenzylamine from commercially available chemicals.

Process for the neutralization of VX

N,N-Dichlorobenzylamine (3.0mmol) was added slowly to a stirred solution of VX (1.0 equiv.) in acetonitrile-water (9:1, 5 ml). The reaction was carried out at room temperature (35°C). The reaction mixture was split into two parts. One part was directly analyzed by selective ^{1}H and ^{31}P{^{1}H}-NMR spectroscopy. Another part of the reaction mixture was saturated with NaCl and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and injected into GC-FPD(S) (Figure 4) after enrichment. The chromatogram clearly showed the absence of VX and the formation of the degradation products (Figure 5, Figure 6 and Figure 7).

Stability study of the reagent

N,N-dichlorobenzylamine was prepared as per reported method and stored in a stoppered glass vial at room temperature. Active chlorine was determined periodically by iodometric titration using sodium thiosulphate and ^{1}H NMR. It was observed that the compound was highly stable up to 1 year and active chlorine content was found to decrease marginally [from 100 (44%) to 92% (43.12 %)] during this period.

Results and Discussion

Decontamination of SM was carried out using N,N-dichlorobenzylamine in aqueous medium (acetonitrile:water). Efficiency of the decontamination reaction was monitored using gas chromatograph coupled with flame photometric detector working in sulfur mode (GC-FPD(S)). In order to ensure that the reaction was complete before injecting the reaction mixture in the heated injector port of the GC-FPD(S), in-tube^{1}H NMR experiments were performed. NMR studies indicated instantaneous decontamination of SM in the reaction mixture. The absence of the vicinal methylene protons at 3.71 and 2.92 ppm of SM in the reaction mixture clearly indicated its complete destruction. The ^{1}H NMR spectrum showed several overlapped resonances in the region of 3.8-4.9 ppm, which were absent in either of the reactants. These signals were attributed to the degradation products of SM formed after the reaction with N,N-dichlorobenzylamine. While performing the reactions and NMR experiments, the temperature chain was maintained for the reactants and the reaction mixture. No discernable changes were observed when the sample was stored at room temperature and it was

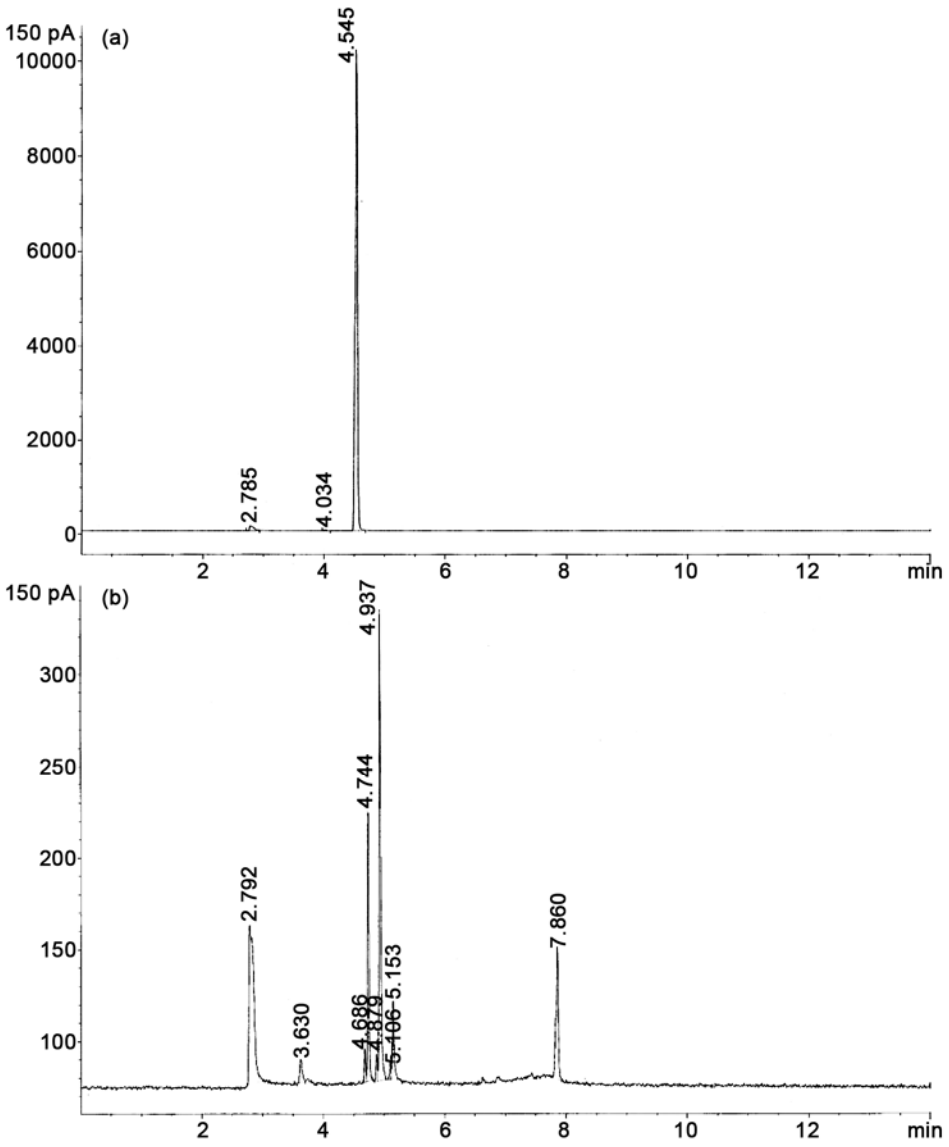

Fig. 4 — SM ((a) top chromatogram) was decontaminated ((b) bottom chromatogram) as mentioned in the text and monitored by GC-FPD (S).

repeatedly analyzed over a period of 24 hrs. This was conclusively showed that the reaction did not proceed further after the instantaneous formation of products upon storage.

Thereafter, the products were identified by chromatograph coupled with mass spectrometer coupled to electron ionization detector (GC-MS-EI). The experiments were performed by directly injecting the reaction mixture after dilution with dichloromethane and separation of the organic phase. In another set of experiment the dichloromethane layer was derivatized with Bis-trimethylsily ltrifluoroacetamide (BSTFA). This was mainly performed in order to detect if any polar and over oxidized products were formed. In both the experiments chloroethyl vinyl sulfone and divinylsulfone were found to be the major products.

On the basis of these experiments and existing literature, a probable mechanism of the reaction has been proposed (Figure 8). Like other N-chloramines, in which chlorine is directly attached to nitrogen, N,N-dichlorobenzylamine generates positively charged chlorine (Cl^+) as the active oxidizing species. The reaction is initiated by nucleophilic attack of the lone pair of electrons of SM on the chlorine atom of the reagent. This is followed by nucleophilic

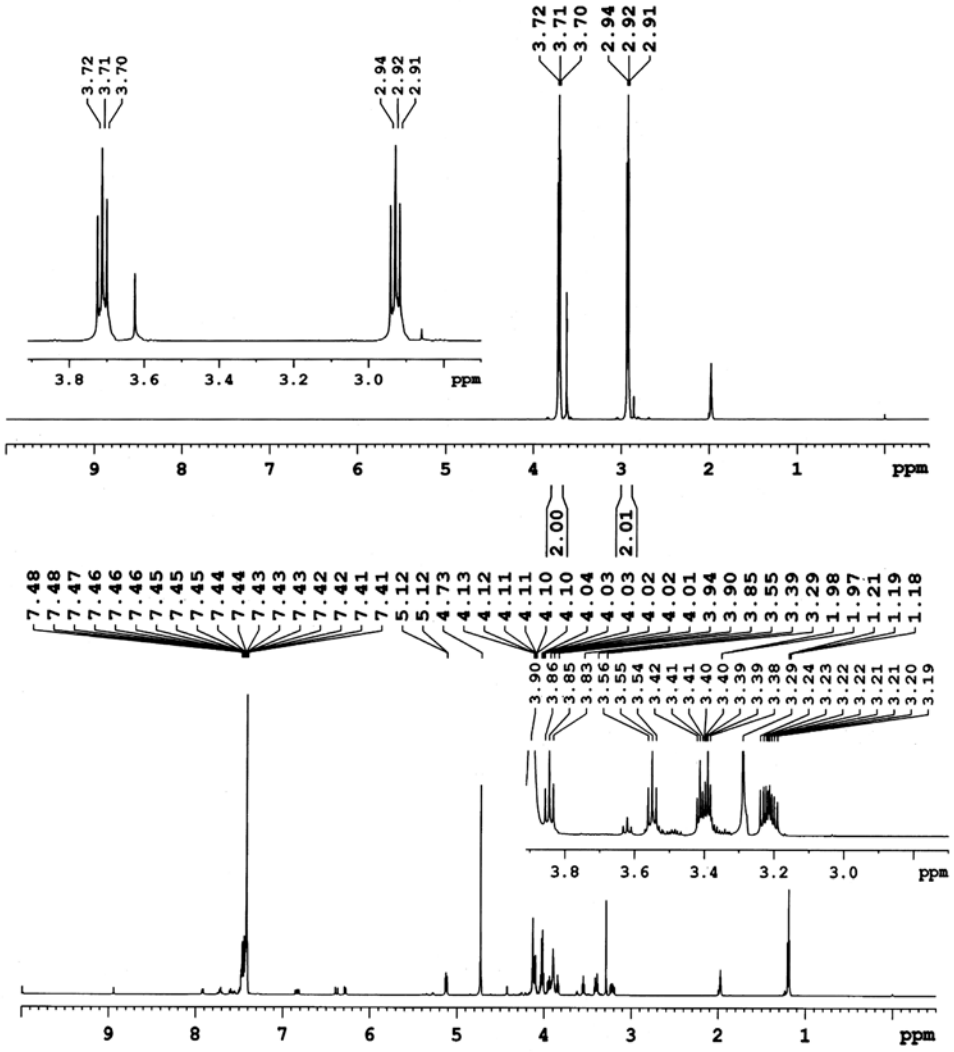

Fig. 5 — Decontamination of SM (top ^{1}H-NMR spectrum) using N,N-dichlorobenzyl amine for the complete decontamination of SM (bottom ^{1}H-NMR spectrum).

displacement of chlorine from the sulfur atom of the sulfonium ion by water present in the mixture. The benzylamine present in the mixture scavenges this HCl, thus driving the reaction in the forward direction. The sulfoxide undergoes further oxidation and sulfone is formed. Since the α-hydrogens of the sulfone have been rendered acidic due to the stabilization of the incipient carbanion, elimination aided by benzylamine takes place with the formation of chloroethylvinylsulfone and divinylsulfone respectively as the products of decontamination.

In order to achieve a uniform condition for the decontamination of the CWAs SM and VX, the reaction with VX was also studied in acetonitrile:water (80:20) medium. In-tube reactions were carried out and the products were observed by using NMR spectroscopy. The reaction was found to proceed smoothly and instantaneously with the concomitant disappearance of VX. The phosphorus-31 NMR experiments clearly indicated that *O*-ethyl methylphosphonate was the phosphorus containing product. Whereas, the GC-MS-EI experiments conducted on the reaction mixture that was first evaporated to dryness and then derivatized with BSTFA; clearly indicated the presence of 2-(diisopropylamino)-ethanesulfonate (DIES). On the basis of structure of the products and product composition and existing literature[46-50], mechanism of the decontamination of VX was proposed (Figure 9).

The major degradation products were identified by NMR such as benzylamine, ethyl methylphosphonic acid (EMPA), 2-(diisopropylamino)-ethanesulfonate

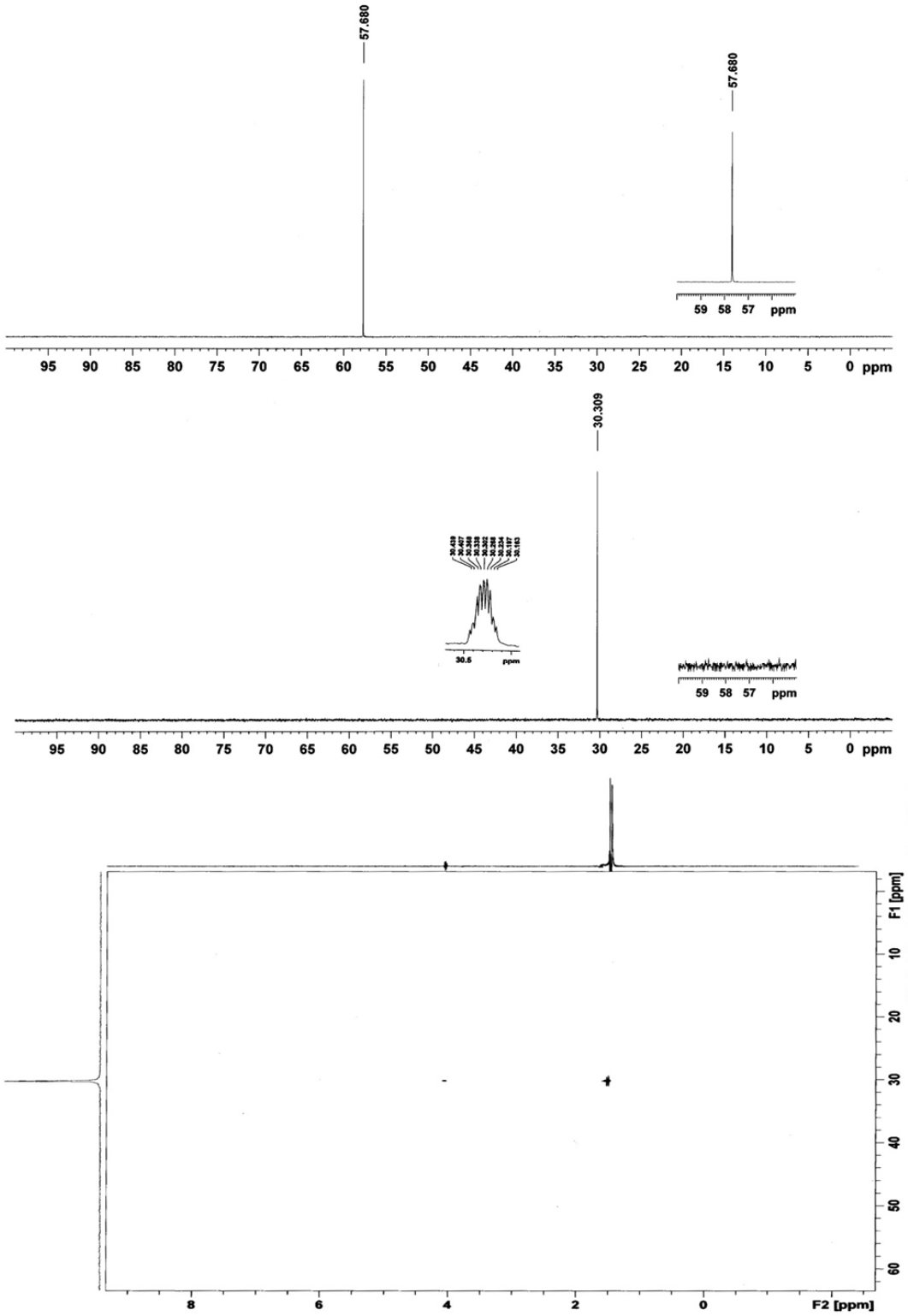

Fig. 6 — Decontamination of nerve agent VX ($^{31}P^{45}$-NMR, top spectrum) with N,N-dichlorobenzyl amine leads to complete decontamination of VX is shown by $^{31}P\{^{1}H\}$-NMR (middle spectrum) and the formation of *O*-ethyl methylphosphonic acid as the sole phosphorus containing reaction product is shown by the ^{31}P-$^{1}H\}$ FAST-HMQC NMR experiment (bottom spectrum).

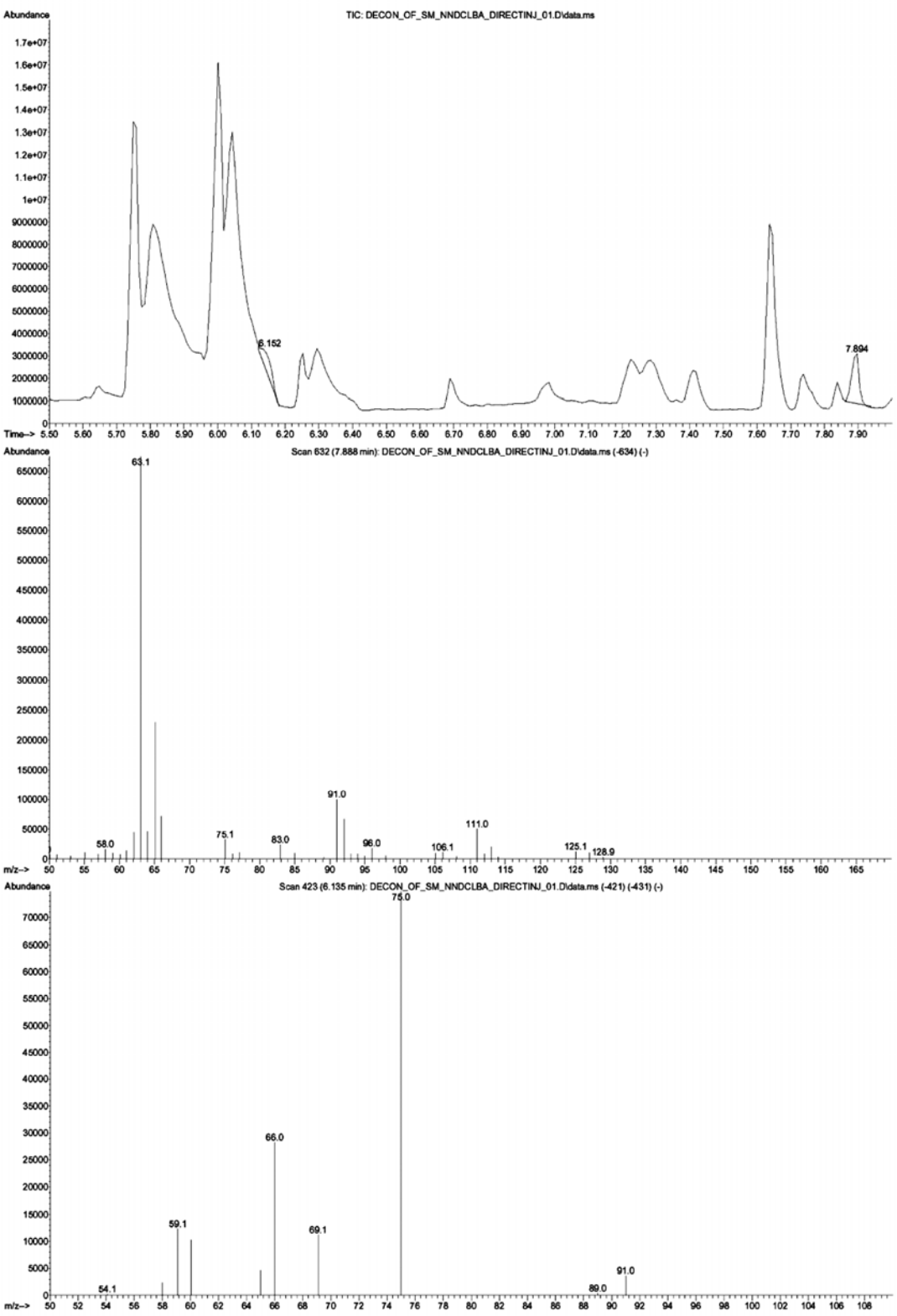

Fig. 7 — Decontamination of SM usingN,N-dichlorobenzyl amine as the decontaminating reagent, leads to complete decontamination of SM. This is shown in TIC ofGC-MS (Top)an EI-mass spectra of chloroethyl vinyl sulfone (middle) and divinylsulfone (bottom) obtained by direct injection of the decontamination formulation into GC-MS.

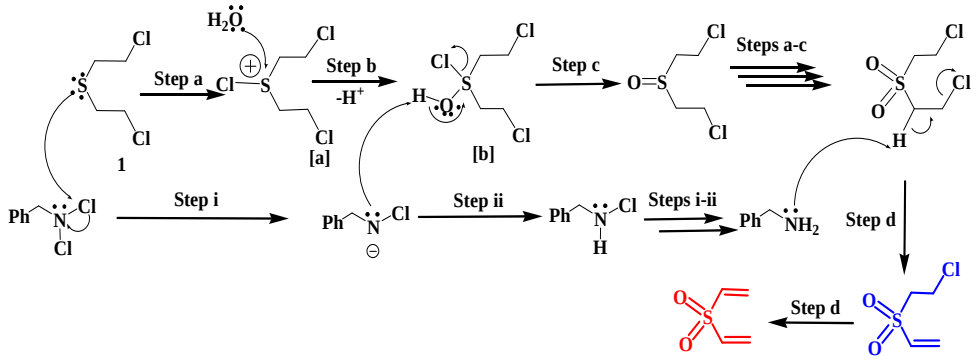

Fig. 8 — The proposed mechanism of decontamination of SM by using NCBA in acetonitrile/water (80:20) medium.

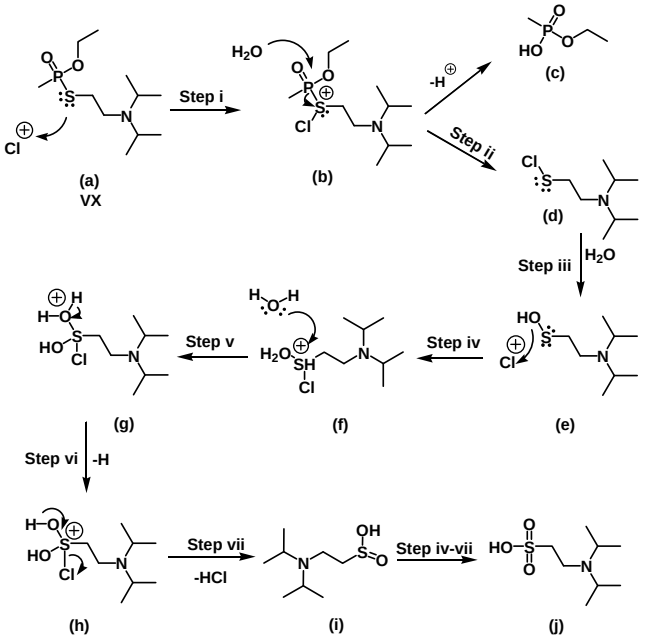

Fig. 9 — Plausible mechanism of decontamination of VX by using N,N-dichlorobenzylamine.

(DIES). On the basis of reported literature[51,52]; plausible mechanism of decontamination of VXis proposed (Figure 8). Once the sulfoniumion intermediate **b** is formed (similar to that in the reaction with SM), cleavage of the P–S bond of VX takes place by nucleophilic attack of water on phosphorus atom. This leads to the formation of protonated ethyl methylphosphonate (EMPA) **c** and 2-(N,N-diisopropylamino)ethanesulfenyl chloride **d**. Thereafter, ethyl methylphosphonate (EMPA), **c** is formed by removal of proton from this intermediate. Thereafter step (iii) occurs by hydrolysis S–Cl bond and subsequent removal of HClto form an intermediate **d**. This intermediate undergoes further hydrolysis to form the protonated salt **e**. In the step (iv) positive chlorine is again attacked by the lone pair of electrons present on sulfur atom to form a species **f**. Lone pair of electrons on oxygen atom of water molecule attacks on this sulfur and leads to the formation of unstable dicationic species **g**. The presence of positive charge and vacant *d*-orbitals on the sulfur atom of **f** facilitates these two reactions. The species **g** then gets converted into intermediate **h**. Elimination of HCl from intermediate **h** in the step (vii) produces sulfonic acid derivative (i). Furthermore repetition of steps iv–vii leads to the formation of sulfonic acid product 2-(N,N-diisopropylamino)ethanesulfonate **j**. Since the oxidation reactions are relatively faster than hydrolysis reactions and they yield products of lower toxicity than that of the parent compound *N*-chloramines and CWAs, these reactions are very useful for decontamination.

Conclusion

In conclusion, we have presented a simple and economical method for chemical destruction of SM and VX in aqueous medium at room temperature using N,N-dichlorobenzylamine. This reagent has several advantages over earlier reported ones[26] in terms of use of inexpensive starting material, cost effective method of preparation, ease of synthesis, high stability of the reagent and instantaneous decontamination of SM and VX at room temperature. Based on the chemistry that we have explored herein we also foresee that this reagent will also be effective in the decontamination of thickened forms of these agents alongside other OPS pesticides like chlorpyriphos.

Acknowledgements

The authors thank DRDO, New Delhi for funding the research work. The authors also thank Dr. D. K. Dubey, Director, DRDE, Gwalior for his keen interest in this work and Dr. Meehir Palit for

performing the GC-MS analysis. This article bears the DRDE accession no. DRDE/SC/019/2018.

Author contribution

PKG conceptualized the study, synthesized the reagent, optimized the reaction conditions by performing GC-FPD(S)/GC-MS analyses and drafted the manuscript. AM planned and executed sample preparation, analysis of the decontamination reaction mixture by different NMR based experiments and edited the manuscript. AKG provided the CWAs used for this study and technical inputs during different stages of the work.

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