Reaction of Bis(2-chloroethyl) Sulfide with *N,N′*-Dichlorobis(2,4,6-trichlorophenyl)urea

D. K. Dubey,* R. C. Malhotra,
R. Vaidyanathaswamy, and R. Vijayaraghavan

Defence R. & D. Establishment, Jhansi Road, Gwalior 474002 M.P., India

Received May 12, 1999

Introduction

Bis(2-chloroethyl) sulfide (HD) is a potent chemical warfare agent with serious toxic effects.[1] There is no specific antidote available against HD, and antidotes that were screened in laboratory animals gave only limited protection against its systemic toxicity.[2,3] The chemical decontamination of HD immediately after contact is still the best method of protection. The prerequisite for such a decontaminating chemical is that it must instantly convert HD into nontoxic products. In comparison to hydrolysis and other oxidation reactions,[4] the reaction of HD with an organic chloramine such as dichloramine-T is rapid enough to decontaminate it instantly, even at subzero temperatures.[5] On the basis of these results, decontamination formulations containing dichloramine-T and another chloramine, *N,N′*-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2), were prepared with different matrixes, such as petroleum jelly, fuller's earth, and gum acacia, which varied in their polarity and protic environment. Experiments have shown that while dichloramine-T based formulations were found to be unstable and the available chlorine decreased with time, CC-2-based formulations exhibited higher stability. These were therefore evaluated for their decontamination efficiency against dermally applied HD in mice. It is interesting to note that formulations exhibited excellent protection and the results of these animal experiments are reported elsewhere.[6]

With regard to the chemical decontamination of a potent toxic compound like HD, it is necessary to know the nature of the products arising from such decontamination reaction for obvious reasons. We report here the complete reaction profile of HD with CC-2 in varying proportions and in medium of different polarity. Keeping in view the requirement for large quantities of CC-2 for decontamination formulations, an improved commercially viable synthetic procedure for *N,N′*-dichlorobis(2,4,6-trichlorophenyl)urea is also reported.

Results and Discussion

HD was reacted with CC-2 in both hydrophobic and hydrophilic environments, as the formulations made and screened[6] were also of varying polarity. Two reactants were also treated in different mole ratios, since in a given decontamination scenario they are likely to react in arbitrary proportions. Results show that the nature of the products formed in these reactions depended on the reaction medium and the mole ratios of the reactants.

In protic medium (CH_3CN:H_2O, 50:50), the product profile of bis(2-chloroethyl) sulfide and *N,N′*-dichlorobis(2,4,6-trichlorophenyl)urea depended on their respective mole ratios (Scheme 1). When the HD:CC-2 ratio was 1:0.5, the major degraded product was bis(2-chloroethyl) sulfoxide (**3**) (Scheme 1a). At equimolar concentration (Scheme 1b), instead of the expected bis(2-chloroethyl) sulfone, the main product obtained was 2-chloroethyl 1,2-dichloroethyl sulfoxide (**5**) with a small quantity of **3**. At a 1:1.5 mole ratio of HD:CC-2 (Scheme 1c), bis(1,2-dichloroethyl) sulfoxide (**6**) was the major degraded product rather than bis(2-chloroethyl) sulfone (**7**). In all the reactions CC-2 was quantitatively converted into bis-(2,4,6-trichlorophenyl)urea (**4**). The remaining about 10−20% products were higher chlorinated sulfoxides and sulfones (based on GC−MS data) which could not be characterized as they formed an intractable mixture. Separate reactions of bis(2-chloroethyl) sulfoxide with CC-2 also yielded the same compounds, i.e., **5**−**7**, similar to Scheme 1b,c. All of these products are nontoxic compared to the bis(2-chloroethyl) sulfide, as is evident from our earlier reported animal experiments,[6] where no mortality and vesication were observed in mice even after applying $6LD_{50}$ of HD topically and decontaminating it with CC-2 based formulations. Moreover, in the majority of recommended decontamination reactions of HD the compounds **3** and **7** are the main products.[4] The additional compounds formed in this reaction are α-chlorinated sulfoxides (in protic medium), and sulfide (in aprotic medium); and reduction in the toxicity and vesication action of HD on introduction of chlorine at the α-position is well-documented.[7]

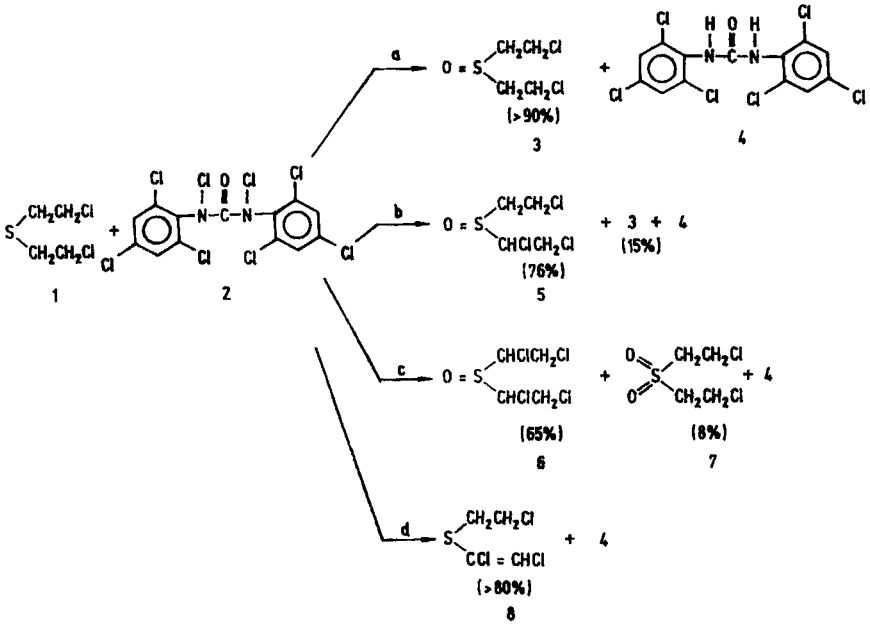
Proposed Mechanism

Mechanistically it is established that in aqueous medium the first step in chlorination of sulfides is electrophilic attack of chlorine on sulfur, generating sulfonium cation[8] (**C**) (Scheme 2). Subsequently nucleophilic displacement of chlorine by water with elimination of HCl produces sulfoxide (**E**). The nitranium ion (**D**) formed on CC-2 molecule after expelling positive chlorine most likely picks up the proton either from the aqueous environment or from liberated HCl. If the concentration of CC-2 is half than that of HD, the reaction stops here only. This means that almost all the sulfide gets con-

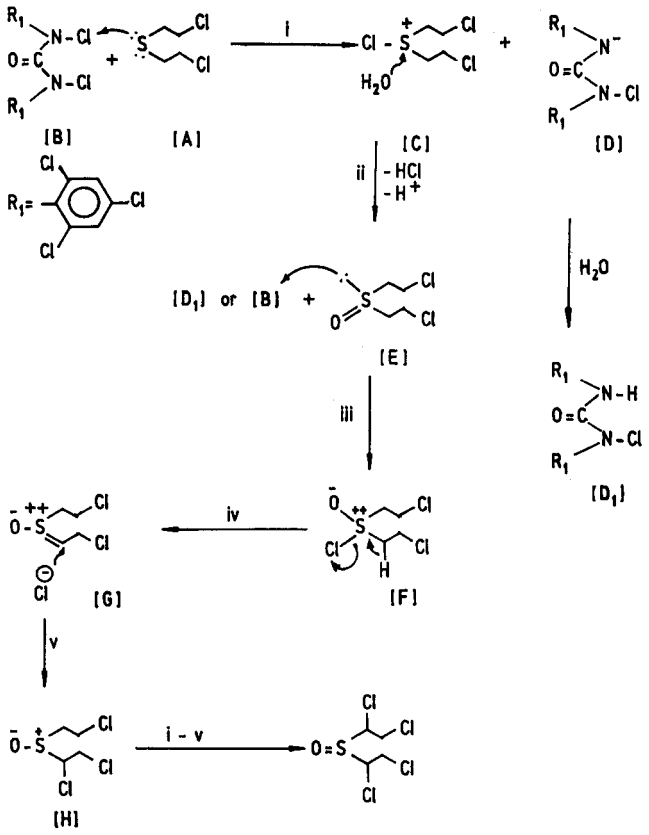
(1) (a) Papirmeister, B.; Feister, A. J.; Robinson, S. I.; Ford, R. D. *Medical Defence Against Mustard Gas*; CRC Press Inc.: Boca Raton, FL, 1991. (b) Dacre, J. C.; Goldman, M. *Pharmacol Rev.* **1996**, *48*, 290.
(2) (a) Callaway, S.; Pearce, K. A. *Br. J. Pharmacol.* **1958**, *13*, 395. (b) Vojvodic, V.; Milosavljevic, B; Bojanic, N. *Fundam. Appl. Toxicol.* **1985**, *5*, 160. (c) Vijayaraghavan, R.; Sugendran, K.; Pant, S. C.; Husain, K.; Malhotra, R. C. *Toxicology* **1991**, *69*, 35.
(3) Somani, S. M.; Babu, S. R. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1989**, *27*, 419.
(4) (a) Yang, Y. C.; Baker, J. A.; Ward, J. R. *Chem. Rev.* **1992**, *92*, 1729. (b) Yang, Y. C. *Chem. Ind.* **1995**, 1 May, 334.
(5) Dubey, D. K.; Nath, R.; Malhotra, R. C.; Tripathi, D. N. *Tetrahedron Lett.* **1993**, *34*, 7645.
(6) (a) Vijayaraghavan, R.; Reddy, P. M. K.; Dubey, D. K.; Kumar, P.; Singh, R. Second C. B. Medical Treatment Symposium, 7−12 July, 1996, NC laboratory Speiz, Switzerland. (b) Reddy, P. M. K.; Dubey, D. K.; Kumar, P.; Vijayaraghavan, R. *Ind. J. Pharmacol.* **1996**, *28*, 227.
(7) Sartori, M. F. *The War Gases*; Van Nostrand: New York, 1939; Part 1, pp 228−232.
(8) Senning, A. *Sulfur in Organic and Inorganic Chemistry*; Marcel Dekker: New York, 1982; Vol. 4, pp 201−218.

10.1021/jo990783a CCC: $18.00
Published on Web 09/30/1999

Scheme 1



Scheme 2



verted into sulfoxide, as 1 mol of CC-2 contains two positive chlorine. At higher concentrations of CC-2, further α-chlorination of sulfoxide takes place; the probable mechanism[9] involves formation of chlorosulfoxonium ion (**F**) by electrophilic attack of chlorine from CC-2. A subsequent elimination addition sequence of chlorine from **F** and **G** respectively generates α-chlorinated sulfoxide.

At still higher concentrations of CC-2, the repetition of this sequence with **H** leads to α,α′-dichloro sulfoxide. The remaining small quantity of nonchlorinated sulfoxide **3** (Scheme 1b) further oxidizes to the corresponding sulfone. It is interesting that gem-dichlorination does not occur from **H** inspite of the fact that the CHCl proton of the 2-chloroethyl 1,2-dichloroethyl sulfoxide is certainly more acidic than those on the other α-carbon. The exact reason for this is not known, but it can probably be attributed to the fact that sulfoxides have strong conformational preferences,[9] and it is possible to selectively remove one of the diastereotopic protons from conformationally biased oxochlorosulfoxonium ion similar to the α,α′-dichlorination of sulfoxides observed by Klein.[9b]

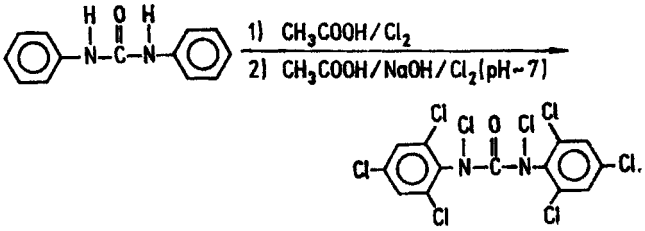
In aprotic medium and at equimolar concentration, the reaction of HD and CC-2 yields 2-chloroethyl 1,2-dichlorivinyl sulfide along with complete conversion of CC-2 to bis(2,4,6-trichlorophenyl)urea (Scheme 1d). The reaction is assumed to proceed in similar fashion as that of HD and dichloramine-T.[5] If the mole ratio of HD:CC-2 is 1:0.5, some amount of HD remains unreacted. This indicates that for complete decontamination of HD in aprotic environment at least an equimolar amount of CC-2 is necessary, while in aqueous medium even 0.5 mol of CC-2 is sufficient for complete conversion of sulfur-mustard to its sulfoxide.

A large quantity of *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea is required for the preparation of decontamination formulations, and early reported synthetic procedures were inadequate to meet the requirement, as they were either time-consuming, low yielding,[10a] or required phosgene[10b] as one of the starting materials, which is toxic to handle. A convenient, one-pot, high-yielding commercially viable method was developed for the synthesis of CC-2. This was done by chlorination of diphenylurea in two steps; it was first chlorinated in acetic acid and then in acetic acid + NaOH (pH 7.0) by passage of chlorine gas. Successive aromatic and N-chlorination

(9) (a) Klein, J. *Chem. Lett.* **1979** *4*, 359. (b) Klein, J.; Stollar, H. *J. Am. Chem. Soc.* **1973**, *95*, 7437.

(10) (a) Chattaway, F. D.; Orton, K. J. P. *Berichte* **1901**, *34*, 1073. (b) Pfansteil, R.; Pralatowski, F. M.; Scruton, H. A. US Patent 2,936,322, 1960.

Scheme 3



yielded the desired product (Scheme 3). Use of Lewis acid catalysts such as $AlCl_3$ and BF_3 offered no additional advantage.

Conclusion

This paper describes the reaction profile of bis(2-chloroethyl) sulfide and *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea, with the aim of using it as a potential decontaminating agent. CC-2-based preparations can be used as effective decontamination formulations against HD, even at lower temperature, where other methods become inoperable, as the reaction of CC-2 and HD is instant at subzero temperature in both aprotic and protic (aqueous) medium. Also, the convenient, one-pot, high-yielding synthesis of CC-2 is reported, which can be commercially exploited. Moreover, the synthetic utility of CC-2 as a chlorinating agent parallel to *N*-chlorosuccinimide can be further explored owing to its greater stability and high positive chlorine content.

Experimental Section

The synthesis of bis (2-chloroethyl) sulfide has been described previously.[11] It was prepared inhouse and was greater than 98% pure by NMR and GC analysis. **CAUTION: HD is a carcinogen, vesicant, and cytotoxic agent. This compound should be handled in a fume cupboard by an experinced person, with proper personal protective measures.** Diphenyl urea was obtained from Aldrich Chemical Co. and was used as such without further purification. Chlorine gas was purified by passing through a calcium chloride tower.

General Reaction Procedure of HD (1) and CC-2 (2). (i) In Aqueous Medium. To a stirred and cooled (−10 °C) solution of HD (0.06 mol) in CH_3CN was added a suspension of CC-2 (0.03−0.095 mol in different reactions) in CH_3CN:H_2O (50:50). The reaction was monitored by GC. Immediately after addition of **2** an aliquot from the reaction mixture showed no HD. After 10−15 min the precipitate of **4** was filtered off and the solvent was removed via rotary evaporation from the filtrate. The remaining crude product was purified by column chromatography over silica gel with benzene:acetone (95:5% v/v) as eluent. Compounds **3**, **5**, and **6** could be well separated using the above conditions.

2-Chloroethyl 1,2-dichloroethyl sulfoxide (5): flakes from *n*-hexane, mp 68 °C. ^{1}H NMR (90 MHz) ($CDCl_3$): δ 4.75 (dd 1H), 4.0 (m 4H), δ, 3.25 (m, 2H). IR (KBr): 2962, 1044, 704 cm^{-1}. MS (EI): *m*/*z* 209 $(M + H)^+$, 211 $(209 + 2)^+$, 213 $(209 + 4)^+$, 192, $(209 - 17)^+$, 194 $(192 + 2)^+$, 196 $(192 + 4)^+$, 145 $(209 - 64)^+$, 147 $(145 + 2)^+$, 112 $(209 - 97)^+$, 114 $(112 + 2)^+$. Anal. Calcd for $C_4H_7OCl_3S$: C, 22.91; H, 3.34; Cl, 50.83; S, 15.27. Found: C, 22.61; H, 3.52; Cl, 50.51; S, 15.11.

Bis(1,2-dichloroethyl) sulfoxide (6): needles from *n*-hexane, mp 126 °C. ^{1}H NMR (90 MHz) ($CDCl_3$): δ 5.12 (t, 2H), 4.1 (m, 4H). IR (KBr) 2962, 1066, 735 cm^{-1}. MS (EI): *m*/*z* 243 $(M + H)^+$, 245 $(243 + 2)^+$, 247 $(243 + 4)^+$, 249 $(243 + 6)^+$, 252 $(243 + 8)^+$, 146 $(243 - 97)^+$, 148 $(146 + 2)^+$, 150 $(146 + 4)^+$, 111 $(146 - 35)^+$, 113 $(111 + 2)^+$, 97, 99 $(97 + 2)^+$, 101 $(97 + 4)^+$, 61 $(97 - 35)^+$, 63 $(61 + 2)^+$. Anal. Calcd for $C_4H_6OCl_4S$: C, 19.67; H, 2.45; Cl, 58.19; S, 13.11. Found: C, 19.89; H, 2.62; Cl, 58.28; S, 13.00.

Compounds **3** and **7** were also characterized from their spectral data.[12]

(ii) In Aprotic Medium. The reaction of **1** with **2** was instant in apolar carbon tetrachloride medium also. The procedure is similar to that already reported for HD and dichloramine-T.[5] Analytical data for compound **8** were also reported earlier.[5]

Synthesis of *N*,*N*′-Dichlorobis(2,4,6-trichlorophenyl)-urea (2). Bis(diphenyl)urea (∼25 g, 0.117 mol) was dissolved in ∼200 mL of acetic acid at 70 °C by stirring. It was chlorinated by passing chlorine for 4 h with stirring; absorption of chlorine ceased with complete precipitation of bis(2,4,6-trichlorophenyl)urea. This indicated the completion of aromatic chlorination. The mixture was cooled to ∼10 °C in an ice bath, and sodium hydroxide was added in portions to bring the pH of the mixture to almost 7. Chlorine was further passed till all the organic matter was redissolved. The mixture was poured into water to precipitate CC-2, which was washed with water, filtered, and recrystallized from toluene or hexane:dichloromethane. After drying the yield was 51 g (88%) of prismatic crystals, mp 178−180 °C. The positive chlorine content of **1** was checked by standard iodometric titration.[13] It was found to be 14.51% (theoretical value 14.54%). ^{1}H NMR (90 MHz) ($CDCl_3$): δ 7.2 (s). IR (KBr): 3066, 1717, 1284, 822 cm^{-1}. MS (EI): *m*/*z* 484 $(M)^+$, 486 $(M + 2)^+$, 488 $(M + 4)^+$, 490 $(M + 6)^+$, 492 $(M + 8)^+$, 449 $(M - 35)^+$, 451 $(449 + 2)^+$, 453 $(449 + 4)^+$, 455 $(449 + 6)^+$, 457 $(449 + 8)^+$, 414 $(M - 70)^+$, 416 $(414 + 2)^+$, 418 $(414 + 4)^+$, 420 $(414 + 6)^+$.

JO990783A

(11) Reid, E. E., ed. *Chemistry of Bivalent Sulfur*; Chemical Publishing Co. New York, 1960, Chapter 5.

(12) (a) Hsu, F. L.; Szafraniec, L. L.; Beaudry, W. T.; Yang, Y. C. *J. Org. Chem*. **1990**, *55*, 4153. (b) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Davis, F. A. *J. Org. Chem*. **1990**, *55*, 3664.

(13) Kirk, R. E.; Othmer, D. F. *Encyclopedia of Chemical Technology* 4th ed.; John Wiley & Sons: New York, 1992; Vol. 4, p 274.