

Rates of Reaction of the Sulfoxides and Sulfones of Sulfur Mustard and 2-Chloroethyl Ethyl Sulfide with Hydroxide Ion in Water

R. Ian Tilley and D. Ralph Leslie

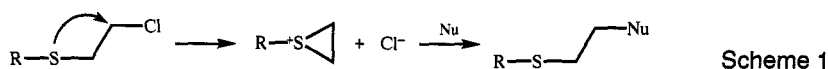
Aeronautical and Maritime Research Laboratory (AMRL)—DSTO,
P.O. Box 4331, Melbourne, Vic. 3001.

Abstract

The reactions of the sulfoxides and sulfones of sulfur mustard and an analogue, 2-chloroethyl ethyl sulfide, with hydroxide ion in aqueous solution at 25° have been studied. In contrast with the behaviour of the parent sulfides, for which exclusive substitution of chlorine is observed under comparable conditions, the oxidized compounds react through base-catalysed elimination of HCl to give the corresponding alkenes. Second-order rate constants for these reactions are reported and implications for the metabolism of sulfur mustard are discussed.

Introduction

Sulfur mustard [bis(2-chloroethyl) sulfide] is a potent vesicant, persistent in the environment and readily accessible through low technology processes. These characteristics have been exploited in its use as a chemical weapon, most recently in the Middle East.¹ The toxic effects of sulfur mustard *in vivo* arise from its alkylating ability which is related to the ease with which 2-chloroethyl sulfides form cyclic episulfonium ions through intramolecular substitution (Scheme 1).² Inhibition of internal substitution by oxidation of the sulfur to the sulfoxide or sulfone may be expected to result in compounds of lower toxicity. A recent review describes Oxone, a complex salt containing potassium peroxymonosulfate which oxidizes sulfides to sulfoxides and sulfones, as a superb decontaminant for sulfur mustard.³ While rapid reaction with Oxone is evident, the products are not without biological impact. Bis(2-chloroethyl) sulfoxide (1a) is not a vesicant but has been reported to exhibit acute toxicity comparable with that of sulfur mustard,⁴ and elimination of HCl from bis(2-chloroethyl) sulfone (2a) results in formation of the toxic vesicant divinyl sulfone.



Scheme 1

¹ United Nations Security Council, Report S-16433, 1984; Report S-17911, 1986; Report S-20134, 1988, New York.

² Somani, S. M., in 'Chemical Warfare Agents' (Ed. S. M. Somani) Ch. 2, pp 13-50 (Academic: San Diego 1992).

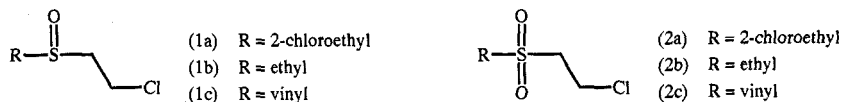
³ Yang, Y.-C., Baker, J. A., and Ward, J. R., *Chem. Rev.*, 1992, **92**, 1729.

⁴ Marshall, E. K., Jr, and Williams, J. W., *J. Pharmacol.*, 1920, **16**, 259.

In vitro investigations of the biochemical mode of action of sulfur mustard and related compounds are under way in this laboratory. Knowledge of the reactivity in aqueous media of the compounds used in the studies will facilitate design of experimental procedures and aid interpretation of data. The fundamental chemistry of oxidized 2-chloroethyl sulfides is also pertinent to the elucidation of the metabolism of sulfur mustard by mammals after intoxication.⁵

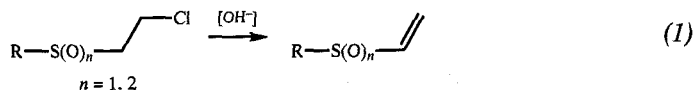
Reactions of the oxidized forms of 2-chloroethyl alkyl sulfides in aqueous solutions with a variety of nucleophiles have been investigated but few quantitative data are available.⁶⁻¹² Kinetic data have been reported only for reactions in ethanol/water and dioxan/water.^{11,12} Most recently, Cinquini and Colonna reported that 2-chloroethyl ethyl sulfoxide (1b) hydrolysed in ethanol/water (4:1 v/v) at 35° faster than the parent sulfide.¹¹ Furthermore, the reaction was reported to proceed through intramolecular substitution of chloride by the sulfoxide group oxygen. In contrast, other reports on the oxidized forms of 2-chloroethyl sulfides have shown that solvolysis rates are much less than those for the parent sulfides.^{6,7,12}

We have studied the reactions of the sulfoxides (1) and the corresponding sulfones (2) in aqueous media. Their rates of reaction with hydroxide in aqueous solution have been determined and reaction products identified.



Results and Discussion

Elimination of HCl to form the corresponding alkene [equation (1)] is the only reaction observed for the β -chloroethyl sulfoxides (1) and sulfones (2) in basic aqueous solution:



Accumulation of substitution products during reactions of (1a,b) and (2a,b) in buffered D₂O (pD \approx 9-10) was not evident in ¹H n.m.r. spectra acquired during the course of the reactions. Previous studies have reported that in aqueous organic

⁵ Black, R. M., Brewster, K., Clarke, R. J., Hambrook, J. L., Harrison, J. M., and Howells, D. J., *Xenobiotica*, 1992, **22**, 405.

⁶ Helfrich, O. B., and Reid, E., *J. Am. Chem. Soc.*, 1920, **42**, 1208.

⁷ Stahmann, M. A., Golumbic, C., Stein, W. H., and Fruton, J. S., *J. Org. Chem.*, 1946, **11**, 719.

⁸ Cashmore, A. E., *J. Chem. Soc.*, 1923, 1738; Cashmore, A. E., and McCombie, H., *J. Chem. Soc.*, 1923, 2884.

⁹ Alexander, J. R., and McCombie H., *J. Chem. Soc.*, 1931, 1913.

¹⁰ Ford-Moore, A. H., *J. Chem. Soc.*, 1949, 2433.

¹¹ Cinquini, M., and Colonna, S., *Boll. Sci. Fac. Chim. Ind. Bologna*, 1969, **27**, 157.

¹² Böhme, H., and Sell, K., *Chem. Ber.*, 1948, **81**, 123.

solvents (ethanol/water, 4:1 v/v, and 20 M water in dioxan) sulfoxides (1a,b) hydrolyse to yield the corresponding β -hydroxy compounds.^{11,12} Furthermore, although divinyl sulfoxide and divinyl sulfone are reported to form 1,4-oxathian *S*-oxide and *S,S*-dioxide respectively in hot aqueous hydroxide solution,^{9,10} no further reaction of the alkene products was observed. No discernible reaction (elimination or substitution) was observed for substrates (1a,b) or (2a,b) in acidic solution (0.1 M HCl/D₂O, 260 h at 25°). Therefore, the contribution from acid- and water-catalysed reactions can be ignored in the analysis of our kinetic data.

The elimination of HCl from substrates (1) and (2) was found to follow second-order kinetics (first order with respect to both substrate and hydroxide). Previous work has shown that elimination reactions in this class of substrate proceed through the *E*1cB mechanism.^{13,14} The second-order rate constants (k_2) for the base-catalysed elimination of HCl from (1a-c) and (2a-c) in water at 25° are given in Table 1. Those for (1a) and (2a) are corrected for the presence of two equivalent reaction sites. Values of k_2 for (1b,c) were obtained by fitting experimental data directly to the integrated form of the second-order rate expression. Pseudo-first-order rate constants (k_ψ) were obtained at three or four pH values for hydroxide-catalysed elimination of HCl from (1a) and (2a-c). Plots of $\log k_\psi$ against pH for these substrates all exhibit gradients of 1.00 ± 0.01 , which confirm the first-order dependence of the eliminations on hydroxide concentration. Values of k_2 were obtained from the gradients of plots of k_ψ against hydroxide concentration ($pK_w = 14.00$ at 25°).

Table 1. Second-order rate constants for hydroxide-catalysed elimination of HCl from 2-chloroethyl sulfoxides (1) and sulfones (2) at 25°

Reported k_2 values are averages of 2-4 measurements. Uncertainties are standard deviations obtained from replicate experiments

| Substrate | k_2 (l. mol ⁻¹ s ⁻¹) | Substrate | k_2 (l. mol ⁻¹ s ⁻¹) |
|-----------|---|-----------|---|
| (1a) | 0.22 ± 0.02 | (2a) | 165 ± 3 |
| (1b) | 0.044 ± 0.002 | (2b) | 32.8 ± 0.3 |
| (1c) | 0.23 ± 0.03 | (2c) | 69.2 ± 0.3 |

Unlike the parent sulfides, the oxidized compounds (1a-c) and (2a-c) do not undergo intramolecular substitution as shown in Scheme 1. This is not unexpected as oxidation of sulfur is known to reduce its nucleophilicity.¹⁵ A possible alternative intramolecular substitution pathway for the sulfoxides (1), with the oxygen acting as a nucleophile, is also unobserved.^{11,15} Hydrolysis of the cyclic intermediate in this pathway would yield β -hydroxyethyl sulfoxides.¹⁶ Anchimeric assistance has been estimated to enhance the rate of hydrolysis of the chloro groups in β -chloroethyl sulfides more than a millionfold.¹⁷ Without this

¹³ Stirling, C. J. M., *Int. J. Sulfur Chem., Part C*, 1971, **6**, 41.

¹⁴ Marshall, D. R., Thomas, P. J., and Stirling, C. J. M., *J. Chem. Soc., Chem. Commun.*, 1975, 940.

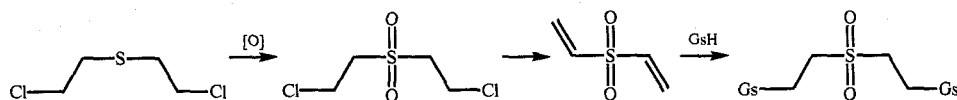
¹⁵ Durst, T., in 'Comprehensive Organic Chemistry' (Ed. D. Neville Jones) Vol. 2, Parts 11.6 and 11.7 (Pergamon: Oxford 1979).

¹⁶ Hsu, F.-L., Szafraniec, L. L., Beaudry, W. T., and Yang, Y.-C., *J. Org. Chem.*, 1990, **55**, 4153.

¹⁷ Sedaghat-Herati, M. R., McManus, S. P., and Harris, J. M., *J. Org. Chem.*, 1988, **53**, 2539.

facile substitution process, the usual competing elimination reaction is relatively more important for (1) and (2). In addition, the propensity for elimination of HCl from the substrates is enhanced by the electron-withdrawing sulfoxide and sulfone groups which increase the acidity of the hydrogen atoms on the carbon β to the leaving group.¹⁸ The higher elimination rates of the sulfones compared with those of the sulfoxides is consistent with both the greater electron-withdrawing power of the sulfone compared with that of the sulfoxide group,¹⁹ and the greater resonance stabilization of the transition state provided by the sulfone.

Our results are pertinent to the elucidation of the pathways for metabolism of 2-chloroethyl sulfides in mammals. Black and coworkers have identified a number of metabolites of sulfur mustard (in which the sulfur atom is oxidized) that are formed by conjugation with glutathione and further metabolism.⁵ The preference for elimination of HCl from (1) and (2) over substitution observed in aqueous solution provides support for their proposal that most of the oxidation on sulfur occurs after hydrolysis or conjugation with glutathione. However, the rates determined in this work suggest an alternative route for the formation of metabolites containing the sulfone moiety and exhibiting conjugation with glutathione (Scheme 2). Under physiological conditions (pH \approx 7.4, 35°) elimination of HCl from (2a) [and (2c)] to yield vinyl sulfones will be relatively fast. General base-catalysed addition of thiols to the vinyl sulfone products is known to be fast.¹⁰ While the absence of (2a,c) among the identified metabolites of sulfur mustard militates against this pathway,⁵ it does not exclude the possibility that it contributes to the metabolism of sulfur mustard.



Scheme 2

GsH = glutathione

Experimental

¹H n.m.r. spectra were recorded at 300 MHz for product analyses and substrate stability in acidic solutions. Chemical shifts were referenced against sodium 3-trimethylsilyl(2,2,3,3-D₄)propionate (D₂O solutions). Melting points were determined on a hot-stage microscope and are uncorrected.

Materials

Sulfur mustard (purity >97%) was obtained by bulb-to-bulb distillation of laboratory stocks at 86°/5 mm. 2-Chloroethyl ethyl sulfide was obtained from Aldrich (purity 98%) and used as received.* All other chemicals were analytical grade materials obtained from commercial sources.

* *Warning.* Sulfur mustard is a general cell poison which can cause serious lung damage if inhaled, or significant tissue damage if liquid contacts the skin. It must be manipulated with extreme care in high-efficiency fume hoods whose exhausts are provided with efficient filter material, e.g., activated charcoal, to prevent the escape of toxic vapours. 2-Chloroethyl ethyl sulfide, though not as toxic as sulfur mustard, must also be manipulated in this way.

¹⁸ Sykes, P., 'A Guidebook to Mechanism in Organic Chemistry' (Longmans: London 1962).

¹⁹ Swain, C. G., Unger, S. H., Rosenquist, N. R., and Swain, M. S., *J. Am. Chem. Soc.*, 1983, **105**, 492.

Bis(2-chloroethyl) sulfoxide (1a). Hydrogen peroxide (5 cm³, 34% w/v solution in H₂O) was added to a solution of sulfur mustard (0.95 g, 6.0 mmol) in 45 cm³ of propan-2-ol. After stirring at room temperature for 27 h the reaction mixture was extracted with CH₂Cl₂ (3×20 cm³). The organic layer was washed with water, then dried over Na₂SO₄, and the solvent removed at reduced pressure to yield a white solid (>50%), m.p. 108–110°, (lit.⁶ 109.5°).

2-Chloroethyl ethyl sulfoxide (1b). Oxidation of 2-chloroethyl ethyl sulfide by the method described for the synthesis of (1a) gave (1b) as a brown solid (68%). A near-colourless waxy solid, m.p. <10°, was obtained after bulb-to-bulb distillation, oven 75°/0.1 mm (lit.²⁰ 137–139°/26 mm).

Bis(2-chloroethyl) sulfone (2a). Oxidation of sulfur mustard to its sulfone was achieved by a method similar to that described by Schultz *et al.*²¹ Na₂WO₄·2H₂O (0.01 g), dissolved in the minimum volume of water, and sulfur mustard (1.0 g, 6.3 mmol) were added to 50 cm³ of methanol. Hydrogen peroxide (3.5 cm³, 34% w/v solution in H₂O) was added dropwise to the stirred solution, the mixture heated to 50–60° and additional peroxide solution (2.0 cm³) added. After heating for 2 h the solution was cooled then extracted with CH₂Cl₂ (2×25 cm³). The organic layer was washed with water, then dried over Na₂SO₄, and the solvent removed at reduced pressure to yield a white solid (>50%), m.p. 53–54° (lit.⁶ 56°).

2-Chloroethyl ethyl sulfone (2b). Oxidation of 2-chloroethyl ethyl sulfide by the method described for the synthesis of (2a) gave (2b) as yellow solid (63%). Bulb-to-bulb distillation (oven 95°/0.2 mm) gave a colourless liquid which solidified on cooling, m.p. 17–19° (lit.²² 20°).

Ethyl vinyl sulfoxide and ethyl vinyl sulfone were prepared according to literature procedures.^{23,24}

Kinetics

2-Chloroethyl ethyl sulfide derivatives. Reaction of (1b) (4.0×10⁻³ M) with hydroxide ion (0.01 M) in water at 25° was followed by titrating the liberated chloride in aliquots of the reaction mixture with standard silver nitrate at various time intervals. The second-order rate constant, (*k*₂) was obtained by fitting pairs of data for the concentration (*x*) of liberated chloride at time *t* to equation (2), in which *a* and *b* are the initial concentrations of base and substrate respectively.

$$k_2 = \{1/[t(a-b)]\} \ln\{b(a-x)/[a(b-x)]\} \quad (2)$$

Reactions of (2b) (6.9×10⁻⁴ M) at constant pH values of 9.3, 9.6, 9.9 and 10.2 in water at 25° were followed using the pH-stat technique by titrating with 0.010 M NaOH. The apparatus and method have been described previously.²⁵

Pseudo-first-order rate constants (*k*_ψ) were calculated by fitting the volume of base consumed (*V*_{*t*}) against time (*t*) to equation (3) with standard non-linear least-squares procedures:

$$V_t = V_0 + V_m[1 - \exp(-k_\psi t)] \quad (3)$$

In equation (3), *V*₀ is the volume of base at *t* = 0, and *V*_{*m*} is the volume of base consumed by the completed reaction. *V*₀, *V*_{*m*} and *k*_ψ were all calculated by the fitting procedure.

Sulfur mustard derivatives. The pH-stat technique was used to follow the two consecutive elimination reactions of (2a) (3.6×10⁻⁴ M) at 25° and pH values of 8.9, 9.2 and 9.5.

²⁰ Thompson, R. B., Chenicek, J. A., and Symon, T., *Ind. Eng. Chem.*, 1958, **50**, 797.

²¹ Schultz, H. S., Freyermuth, H. B., and Buc, S. R., *J. Am. Chem. Soc.*, 1963, **28**, 1140.

²² Goldsworthy, L. J., Harding, G. F., Norris, W. L., Plant, S. G. P., and Selton, B., *J. Chem. Soc.*, 1948, 2177.

²³ Prilezhaeva, E. N., Tsybmal, L. V., Domnina, O. N., Shkurina, T. N., and Shostakovskii, M. F., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1960, 724 (*Chem. Abstr.*, 1960, **54**, 22323b).

²⁴ Kränzlein, G., Schuhmacher, W., and Heyna, J., Ger. Pat., 877,607 (1953) (*Chem. Abstr.*, 1958, **52**, 9206e).

²⁵ Tilley, R. I., *Aust. J. Chem.*, 1993, **46**, 293.

Pseudo-first-order rate constants for the consecutive reactions were calculated by fitting the volume of base consumed (V_t) against time (t) to equation (4) with standard non-linear least-squares procedures:

$$V_t = V_0 + V_m \{ [2 - (2r - 1)/(r - 1)] \exp(-k_{\psi_1} t) + [1/(r - 1)] \exp(-k_{\psi_1} r t) \} \quad (4)$$

In equation (4), V_0 , V_m and t have the same meaning as in equation (3), r is the ratio k_{ψ_2}/k_{ψ_1} where k_{ψ_1} and k_{ψ_2} are the pseudo-first-order rate constants for elimination from (2a) and (2c) respectively. V_0 , V_m , k_{ψ_1} and r were all calculated by the fitting procedure.

Values of k_{ψ_1} and k_{ψ_2} for elimination of HCl from (1a) and (1c) could not be obtained in the same manner as for (2a) and (2c) as their reactions were too slow. The pH-stat technique was used to collect data for the calculation of k_{ψ_1} for (1a) (4.1×10^{-4} M) at pH values of 10.2, 10.3, 10.5 and 10.6. For each set of data, 20–30 values of an 'apparent' k_{ψ_1} were calculated by fitting the initial part of the pH-stat curve to equation (3) for time intervals in the range corresponding to consumption of *c.* 20–50% of the theoretical amount of base for completion of the first elimination (estimated from the production of HCl). These values increase with time due to an increasing contribution by elimination from (1c) formed in the reaction. The true value of k_{ψ_1} was calculated by extrapolation of the 'apparent' k_{ψ_1} values to $t = 0$.

Elimination of HCl from (1c) was followed by monitoring the pH of partially hydrolysed solutions of (1a) (4.0×10^{-4} M) in 0.01 M NaOH maintained at 25°. Only data collected after sufficient time to ensure >96% of the first elimination was completed (*c.* 20 min) were used to calculate k_{ψ_2} according to equation (2), with x representing the concentration of HCl produced by elimination from (1c) after the time chosen to commence collection of data. The initial concentration (b) of substrate was calculated as twice the initial concentration of (1a) less the concentration of HCl produced in the period allowed for the first elimination to approach near completion, and a was obtained from the pH of the solution.

Product Analyses

Solutions of substrates (0.004 M) were prepared in D₂O buffer [(1a,b) and (2b), pD \approx 9; (2a), pD \approx 10]. ¹H n.m.r. spectra were acquired at intermediate stages of reaction and also after the reactions were complete. A solution of (2b) (5.6×10^{-3} M) was prepared in 0.01 M NaOD (D₂O). The ¹H n.m.r. spectrum was acquired after completion of reaction. Products were identified by comparison of the ¹H n.m.r. spectra with those of authentic ethyl vinyl sulfoxide, ethyl vinyl sulfone, divinyl sulfoxide and divinyl sulfone in the same media. Another set of solutions of (1a,b) and (2a,b) (4.0×10^{-4} M) were prepared in 0.1 M HCl in D₂O, and maintained at 25° for 260–300 h. ¹H n.m.r. spectra were acquired prior to, and after, heating. The signal-to-noise ratio of all spectra was sufficient to allow detection of products present at 2% of the initial substrate concentration.