38b, 126580-11-8; **38c**, 126580-12-9; **38d**, 126580-13-0; **40a**, 4027-57-0; **40b**, 6076-12-6; **40c**, 5932-30-9; **40d**, 6963-62-8; **41**, 126580-14-1; **42**, 4492-02-8; **43**, 126580-15-2; **45**, 81153-64-2; **46**, 126580-16-3; **48**, 126580-17-4; potassium phthalimide, 1074-82-4; ethyl 4-bromobutyrate, 2969-81-5; ethyl 4-phthalimidobutyrate, 10294-97-0; *N*-phenylmaleimide, 941-69-5; dimethyl acetylenedicarboxylate, 762-42-5; 4-oxo-1-pentanol, 1071-73-4; 2-methyl-1-penten-5-ol, 22508-64-1; 4-methyl-4-pentenal, 3973-43-1; ethyl lithiodiazoacetate, 55718-77-9; ethyl diazoacetate, 623-73-4; 4-oxopentanal, 626-96-0; acetone, 67-64-1; cyclopentanone, 120-92-3; acetophenone, 98-86-2; acrolein, 107-02-8; propionaldehyde, 123-38-6; phenylacetaldehyde, 122-78-1; ethyl 2-diazo-2-(1-hydroxycyclohexyl)acetate, 27262-60-8; cyclohexanone, 108-94-1; ethyl 2-diazo-3-hydroxy-4-phenylpentanoate, 126580-18-5; 2-phenylpropionaldehyde, 93-53-8; ethyl 2-diazo-4,4-diphenyl-3-hydroxybutyrate, 73295-49-5; diphenylacetaldehyde, 947-91-1.

Oxidation of 2-Chloroethyl Sulfides to Sulfoxides by Dimethyl Sulfoxide

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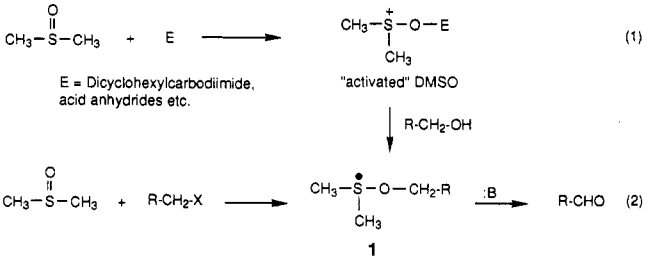
While most organic sulfides were not oxidized by dimethyl sulfoxide (DMSO), the alkyl 2-chloroethyl sulfides and bis(2-chloroethyl) sulfide slowly reacted with DMSO to produce the corresponding sulfoxides at 25–70 °C under nitrogen. The mechanism of the oxidation is proposed to involve nucleophilic substitution by DMSO followed by neighboring sulfur participation to form a transient sulfonium ion with a four-membered ring structure. The sulfonium ion intermediate rapidly reacts with the chloride ion to produce 2-chloroethyl sulfoxides. 2-Hydroxyethyl sulfoxides were also produced, probably due to the presence of a trace amount of water in the DMSO. This reaction demonstrates, for the first time, the unique reactivity of 2-chloroethyl sulfides in DMSO.

Introduction

The versatile chemical nature of dimethyl sulfoxide (DMSO) is well appreciated and has been the subject of many reviews.[1-8] Besides being one of the most prominent members of the family of polar, aprotic solvents,[1] DMSO also functions as a nucleophilic reagent at both the oxygen and sulfur terminals, and thus behaves as either a "hard" or a "soft" base. Because of this characteristic, DMSO has often been used as a mild oxidizing agent in organic synthesis.[2,5,6] The oxidizing capacity of DMSO was shown to be somewhat dependent on its ability to act as a nucleophile.[2] There was also a strong indication that most of the DMSO oxidations involved the same alkoxydimethylsulfonium salt intermediate, **1**.[2] This intermediate can be formed via the activating process illustrated in eq 1. For example, the oxidation of a primary alcohol to an aldehyde usually follows this mechanism.[5,6,8] On the other hand, the oxidation of a primary alkyl halide or tosylate to its corresponding aldehyde, known as the Kornblum reaction,[9-11] usually follows the mechanism descried by eq 2. However, in either case, a base is required in order to achieve the formation of the aldehyde or ketone.



Bis(2-chloroethyl) sulfide (mustard, **2a**), is a toxic chemical agent due to its high reactivity toward proteins and DNAs to induce systematic biochemical and morphological changes in mammalian tissues.[12,13] Its tendency to form a reactive, three-membered ring sulfonium ion in polar media also accounts for its susceptibility to a variety of nucleophiles, including water.[14] Interestingly, its sulfoxide and especially its hydrolysis product, thiodiglycol, are relatively harmless,[12] and these compounds are often goals in the chemical detoxification of mustard. It is the purpose of this study to examine the possible oxidation of mustard and other 2-chloroethyl sulfides by the nucleophilic oxidizing agent, DMSO, in an inert atmosphere and in the absence of any other reagents such as base at relatively mild temperatures.

Results and Discussion

Reaction Products. ^{13}C NMR spectroscopy (see the Experimental Section) was used to monitor the oxidation of 2-chloroethyl sulfides in DMSO. The ^{13}C NMR chemical shifts of several compounds containing alkyl sulfides and their sulfoxides have been reported in the literature.[15,16] It was observed that the chemical shifts of the

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Table I. Observed ^{13}C NMR Chemical Shifts (ppm) of Sulfides and Sulfoxides Studied in DMSO

compound	CH_3S	CH_3CH_2S	CH_3CH_2S	SCH_2CH_2X	SCH_2CH_2X
2a, $ClCH_2CH_2SCH_2CH_2Cl$	–	–	–	32.5	42.9
6a, $ClCH_2CH_2SOCH_2CH_2Cl$	–	–	–	52.5	37.2
2b, $CH_3SCH_2CH_2Cl$	13.8	–	–	34.4	42.4
6b, $CH_3SOCH_2CH_2Cl$	37.1	–	–	54.7	37.2
7b, $CH_3SOCH_2CH_2OH$	37.6	–	–	53.2	55.9
2c, $CH_3CH_2SCH_2CH_2Cl$	–	13.9	24.4	37.2	42.8
6c, $CH_3CH_2SOCH_2CH_2Cl$	–	5.6	43.8	52.1	37.2
7c, $CH_3CH_2SOCH_2CH_2OH$	–	5.6	43.8	53.2	53.0
2d, $ClCH_2CH_2SCH_2CH_2OH$	–	–	–	32.8	41.0 (X = Cl)
				33.1	60.2 (X = OH)
6d, $ClCH_2CH_2SOCH_2CH_2OH$	–	–	–	52.9	37.3 (X = Cl)
				53.0	53.6 (X = OH)
7d, $HOCH_2CH_2SOCH_2CH_2OH$	–	–	–	53.2	54.1
2e, $C_6H_5SCH_2CH_2Cl$	–	–	–	33.9	41.9
9, $CH_3SCH_2CH_2OH$	14.1	–	–	35.0	59.4

Table II. The Reaction of 2-Chloroethyl Sulfides with DMSO

	initial concn, M	reactn cond: temp, °C	reactn cond: time	product composition,[a] %				
				2a	**2d**	**6a**	**6d**	**7d**
2a	1.0	25	30 days	17	4	9	33	38
				2b		**6b**		**7b**
	1.0	25	30 days	66		28		6
2b	0.5	70	14 h	14		42		44
	0.2	70	14 h	9		53		38
				2c		**6c**		**7c**
	1.7	25	30 days	46		48		6
2c	0.9	70	14 h	62		29		9
	0.4	70	14 h	11		23		66

[a] The percentages (±5%) were determined from the integration of specific peaks in the ^{13}C NMR spectrum of the reaction mixture (cf. Table I).

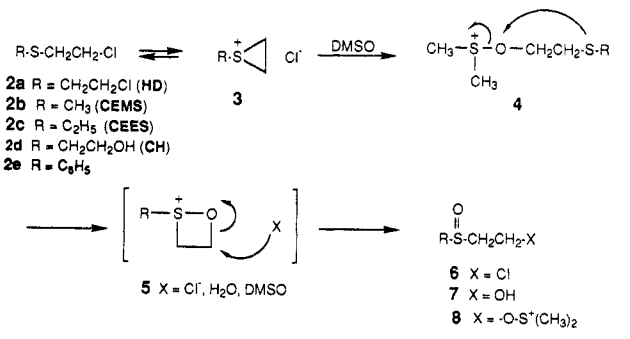
carbons adjacent to the sulfoxide group were deshielded by 13–23 ppm compared to the corresponding sulfides. This characteristic was utilized to analyze the oxidation products in this study.

The ^{13}C NMR data of mustard[17] and its sulfoxide[18] have been reported previously. The observed ^{13}C NMR parameters for the sulfides used in this study are summarized in Table I together with the observed chemical shifts of the DMSO reaction products. As can be seen, the chemical shifts of the α-carbons in the products were shifted downfield 15–23 ppm relative to the chemical shifts of these carbons in the starting materials, indicating the formation of the sulfoxides in agreement with the reported data.[15,16] All of the reaction products were subsequently confirmed by GC/MS.

As shown in Table II, a 1.0 M solution of 2-chloroethyl methyl sulfide (**2b**) in DMSO was converted to 28% 2-chloroethyl methyl sulfoxide (**6b**), 6% 2-hydroxyethyl methyl sulfoxide (**7b**), and dimethyl sulfide after 30 days at room temperature. The formation of **6b** and **7b** was greatly enhanced at 70 °C. Interestingly, the amount of the hydrolysis product, **7b**, increased with decreasing concentration of **2b** as shown in Table II. Similar behavior was observed for solutions of 2-chloroethyl ethyl sulfide (**2c**) and mustard (**2a**) in DMSO (cf. Table II). In all cases, the oxidation was highly selective and no sulfone nor elimination products were detected by NMR or GC/MS analyses.

Proposed Mechanism. Based on the ^{13}C NMR data in Table I, it was concluded that oxidation of the 2-chloroethyl sulfides occurred. Furthermore, dimethyl sulfide, at 16.5 ppm,[15] was observed in all reaction systems from the reduction of the DMSO. The mechanism of the DMSO oxidation in these reactions is proposed in Scheme I. It involves the formation of a three-membered ring sulfonium ion intermediate, **3**, in the first step,[14] followed by the nucleophilic addition of DMSO to form **4**. Alternatively, it is also possible that **4** forms directly from an S_N2 nucleophilic substitution of chloride by DMSO without the formation of **3**. Particularly, Harris et al.[19] reported that the displacement of a series of 2-chloroethyl sulfides by a number of strong nucleophiles in DMSO proceeds via an S_N2 mechanism. Subsequently, the neighboring sulfur-assisted displacement of dimethyl sulfide occurs in **4** to form a sulfonium ion, **5**, as the rate-determining step for the oxidation. Due to ring strain, this four-membered cyclic sulfonium ion rapidly reacts with any nucleophiles present in the DMSO, such as chloride ion or water, to yield 2-chloroethyl and 2-hydroxyethyl sulfoxide, **6** and **7**, respectively. It is also likely that sulfonium ion **5** reacts

Scheme I



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with DMSO to form a sulfoxide dimethylsulfonium ion, **8**, which then reacts with chloride or water to produce **6** or **7** and regenerates DMSO. However, **8** was not detected in the reaction mixture, if it were formed, possibly indicating the rapid reaction of **8** with chloride ion and water.

The presence of the intermediate **4** was detected in the ^{13}C NMR spectra of both **2b** and **2c** in DMSO. A methyl resonance at 25.3 ppm consistent for a CH_3S^+ moiety[15] was observed in each solution before oxidation was complete. However, no resonances consistent with the intermediate **5** were detected.

To ascertain the participation of the neighboring sulfur atom in **2** and **4** in the reaction mechanism, a solution of 0.1 M 2-chloroethyl phenyl sulfide (**2e**) in DMSO was examined, since the nucleophilicity of the sulfur in **2e** is poor relative to that in **2b** and **2c**.[18] Indeed, no sulfoxide was observed when the solution was kept either at room temperature for 60 days or heated at 70 °C for 40 h. This indicates that oxidation is dependent on the nucleophilicity of the sulfur in the substrates. Furthermore, under identical conditions, diethyl sulfide (13.6 and 23.5 ppm) was found to be inert to DMSO oxidation. This is not surprising, since both diethyl sulfide and DMSO behave as nucleophiles. Nevertheless, it was reported that dialkyl sulfides, such as *n*-propyl, *n*-butyl, and tetramethylene sulfide, could be oxidized to the corresponding sulfoxides at 160–175 °C in DMSO.[20]

Although the mechanism in Scheme I has never been proposed, it has been reported that chloromethyl methyl sulfide was oxidized by DMSO to produce formaldehyde, dimethyl sulfide, and other products generated from methanesulfenyl chloride similar to eq 2.[21] In contrast, we found that the 2-chloroethyl sulfides react with DMSO to form sulfoxides.

Hydrolysis Products. Because of a small amount of water present in the DMSO, the formation of the 2-hydroxyethyl sulfoxides, **7**, from DMSO oxidation might be derived via three possible routes: (1) the direct oxidation of the 2-hydroxyethyl sulfides, a possible hydrolysis product from the 2-chloroethyl sulfides; (2) the hydrolysis of the 2-chloroethyl sulfoxide, **6**; and (3) the nucleophilic addition of water to the sulfonium ion **5** (cf. Scheme I). To examine these possible pathways, the oxidation of 2-hydroxyethyl methyl sulfide (**9**) by DMSO was investigated. No oxidation product was detected either at room temperature for 16 days or at 70 °C for 40 h. This result was not unexpected since **9** does not have a leaving group for nucleophilic substitution either by DMSO or by a neighboring sulfur-assisted S_N1 mechanism. As described previously, alcohols are inert in DMSO and require an "activated" DMSO as shown in eq 1. In addition, the formation of the 2-hydroxyethyl sulfides from the hydrolysis of 2-chloroethyl sulfides is highly unlikely as the dimeric sulfonium ion products predominate.[17] Furthermore, it has been reported that bis(2-chloroethyl) sulfoxide (mustard sulfoxide, **6a**) is stable in water and that hydrolysis in neutral solution is extremely slow.[22] This observation rules out the possible formation of **7** from **6**. Thus, the formation of **7** from the oxidation of **2** in the DMSO solution most likely results from the attack of water on the intermediate **5**. This is supported by the observed increase in the amount of the hydrolysis products with decreasing concentration of substrate (cf. Table II).

Conclusion

The 2-chloroethyl sulfides are known to be less reactive than alkyl sulfides toward a neutral, nonnucleophilic oxidant[18] since the presence of the electron-withdrawing chlorine reduces the nucleophilicity of the sulfur making it less reactive. On the other hand, because of the nucleophilic character of DMSO and the electrophilic property of the 2-chloroethyl sulfides, they become more reactive than dialkyl sulfides to DMSO oxidation.

The oxidation of 2-chloroethyl sulfides to sulfoxides by DMSO is very selective, occurs under relatively mild conditions, and is near completion after 14 h at 70 °C. Further oxidation of the sulfoxide product to sulfone by DMSO is not possible since the sulfoxide sulfur is too weak to act as an internal nucleophile to displace the chloride in the first step.[22] Even if it were possible, the neighboring sulfur participation of the intermediate **4** in the second step is also highly unlikely. Therefore, to the best of our knowledge, this represents the first example of the unique oxidative reactivity of 2-chloroethyl sulfides in DMSO and the active participation of intramolecular sulfur in the Kornblum reaction.

Experimental Section

The synthesis of mustard has been described previously;[22] it was prepared in-house and was greater than 95% pure by NMR and GC analyses. *CAUTION*: Mustard is a toxic vesicant and should only be used by trained professionals in properly equipped facilities. The other sulfide substrates were obtained commercially either from Fairfield Chemical Co. or from Aldrich Chemical Co. All of the compounds were greater than 95% pure by ^1H and ^{13}C NMR and were used as received. The DMSO (Fisher Scientific Co.) was dried over 4A molecular sieve before use.

The samples were placed into 5-mm o.d. Pyrex NMR tubes, and the ^{13}C NMR spectra were recorded using a Varian XL-200 FTNMR system operating at 50 MHz. Spectra were recorded at probe temperature (20–22 °C) in double precision using a pulse width of 3.1–5.1 μs (36–60°), an acquisition time of 1.6 s, a pulse delay of 1-2.5 s, and full-proton WALTZ decoupling. Accumulation times varied depending on the signal-to-noise ratio required or desired. Spectra were internally referenced to the DMSO resonance at δ 39.5 ppm, and quantitative information was obtained from the digital integration of peak areas from similar type resonances (i.e., SCH_2 vs SCH_2 or CH_3 vs CH_3) with ±5% error.

Acknowledgment. We thank Dennis K. Rohrbaugh, Chemical Research, Development, and Engineering Center, for GC/MS identification of the reaction products.

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