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Proton Nuclear Magnetic Resonance Spectra of Sulfur Mustard and 2-Chlorotheyl ethyl Sulfide in Selected Solvents

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14. ABSTRACT
Our laboratory has a continuing interest in the analysis of sulfur mustard (HD) for the purpose of developing medical countermeasures. Nuclear magnetic resonance (NMR) spectroscopy is an important analytical technique for studying HD chemistry in simple solutions and in complex matrices. To support research in this area, we have developed a list of proton assignments for HD in a variety of suitable solvents. Because the half mustard 2-chloroethyl ethyl sulfide (CEES) is a non-surety analogue of HD we have added a list of proton assignments for CEES as well. In this study we used a 600 MHz NMR instrument to investigate 2-mM solutions of HD and CEES in deuterated solvents. These results can assist researchers in identifying HD and CEES in variety of solvents.

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sulfur mustard (HD), chloroethylethylsulfide (CEES), proton nuclear magnetic spectroscopy, 2 mM solutions, deuterated solvents

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Introduction

Sulfur mustard (HD) is a vesicating chemical warfare agent that has been investigated by our laboratory for the express purpose of developing medical countermeasures. Solutions of HD are prepared in a variety of solvents to aid researchers. In these investigations nuclear magnetic resonance (NMR) spectroscopy has been playing a larger roll in the analysis and study of HD.[1,2,3] In a recent work we measured the half-life of HD in D_2O.[4] This study required a demonstration of proton NMR spectral assignments for HD in D_2O because previous studies[5,6] indicated that solution of HD in aqueous media was followed instantaneously by hydrolysis. We verified the presence of HD by preparing 2-mM solutions of HD in D_2O containing 0.17 M NaCl. Five minutes after preparation of the solution, HD was extracted with deuterated hexane, and we demonstrated that the HD extracted had the same proton NMR spectra as a direct preparation of HD in deuterated hexane. The changes in the chemical shifts of HD in D_2O versus HD in deuterated hexane prompted us to undertake this study of HD and 2-chloroethyl ethyl sulfide (CEES) in a variety of available deuterated solvents.

We prepared 2-mM solutions of HD in nine solvents and 2-mM solutions of CEES in eight solvents. The proton spectra for each of these solutions demonstrate the changes that occur when HD and CEES respectively are placed in different solvents.

Materials and Methods

The sulfur mustard (2,2'-dichlorodiethyl sulfide, HD) employed in this study was obtained from the US Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD). The purity was 97.5% as determined by NMR spectroscopy. 2-chloroethyl ethyl sulfide (CEES, 98%), deuterated solvents (99+ %), and 3-(trimethylsilyl)-1-propanesulfonic acid-d_4 were obtained from Sigma-Aldrich and used as received.

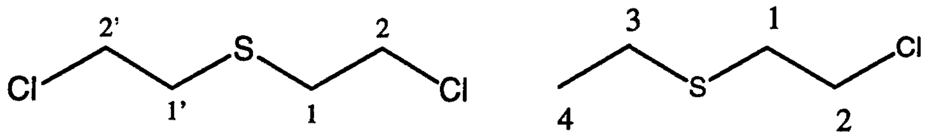
^{1}H NMR analysis

A previously prepared and frozen sample of 2 mM HD in D_2O was thawed to room temperature and thoroughly mixed by vortexing for three minutes. For the other solvents used in this work, 2-mM preparations were prepared volumetrically and stored at -70 °C. A 500 μL aliquot of the solution was transferred into 5-mm o.d. NMR tubes. All data were collected on a Varian Unity Inova 600 MHz NMR spectrometer using the standard ^{1}H pulse sequence. The WET pulse sequence for solvent suppression was utilized for the D_2O sample.[7] Probe temperature was calibrated to 22.0 ± 0.1 °C by standard means. Samples were referenced to residual proto-solvent peaks. The D_2O sample was referenced to 3-(trimethylsilyl)-1-propanesulfonic acid-d_4 at 0 ppm.

Results

Tables 1 and 2 list chemical shift and coupling constants for HD and CEES in the various solvents studied. Figure 1 shows the number scheme used for the protons in the tables.

Figure 1. Structures of HD and CEES and numbering scheme for the protons of HD and CEES.



2,2'-chloroethyl sulfide (HD)

2-chloroethyl ethyl sulfide

Table 1. Chemical shift (ppm) and coupling constants (Hz) for HD in various solvents

Solvent	$H^{2,2'}$	$H^{1,1'}$
$CDCl_3$	3.65 (7.6)	2.92 (7.6)
CD_3CN	3.71 (7.6)	2.92 (7.6)
$CD_3C(O)CD_3$	3.75 (7.6)	2.98 (7.6)
CD_2Cl_2	3.66 (7.6)	2.92 (7.6)
$CD_3S(O)CD_3$	3.76 (7.6)	2.92 (7.6)
C_2D_5OD	3.66 (7.6)	2.92 (7.6)
C_3D_7OD	3.70 (7.6)	2.96 (7.6)
C_6D_{14}	3.60 (8.2)	2.92 (7.6)
D_2O (4)	3.74 (7.6)	3.00 (7.6)

Table 2. Chemical shift (ppm) and coupling constants (Hz) for CEES in various solvents.

Solvent	H^2	H^1	H^3	H^4
$CDCl_3$	3.64 (7.6)	2.87 (7.6)	2.61 (7.6)	1.28 (7.6)
CD_3CN	3.69 (7.6)	2.87 (7.6)	2.60 (7.6)	1.23 (7.6)
$CD_3C(O)CD_3$	3.70 (7.6)	2.87 (7.6)	2.62 (7.6)	1.23 (7.6)
CD_2Cl_2	3.64 (7.6)	2.86 (7.6)	2.59 (7.6)	1.26 (7.6)
$CD_3S(O)CD_3$	3.73 (7.6)	2.84 (7.6)	2.58 (7.6)	1.16 (7.6)
C_2D_5OD	3.62 (7.6)	2.83 (7.6)	2.59 (7.6)	1.24 (7.6)
C_3D_7OD	3.65 (7.6)	2.87 (7.6)	2.64 (7.6)	1.30 (7.6)
C_6D_{14}	3.59 (8.2)	2.87 (7.6)	2.63 (7.6)	a

a. Peak obscured by methyl groups in solvent.

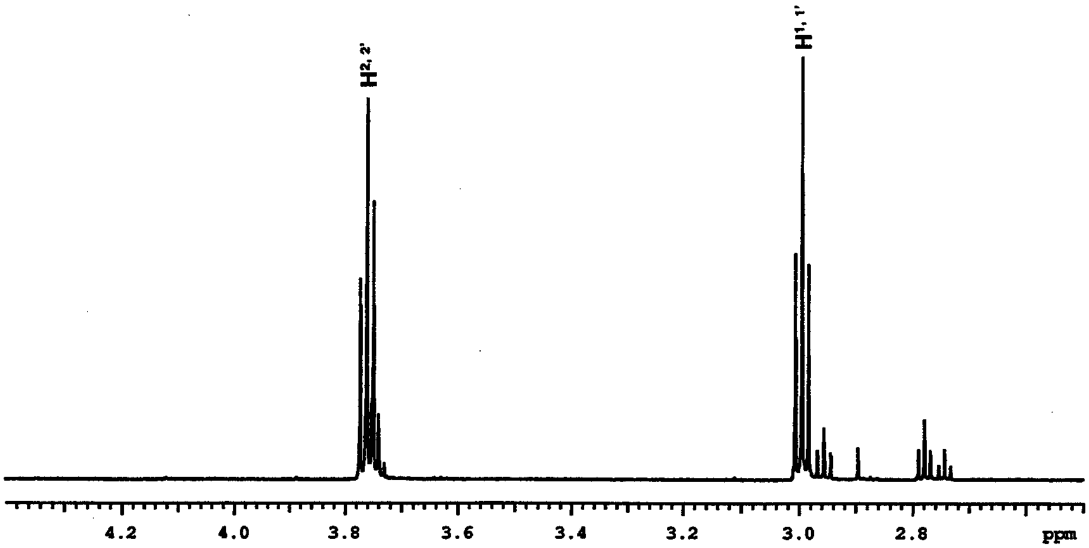
Discussion

The influence of solvent on chemical shift for HD is relatively small (Table 1). For methylene protons $H^{1,1'}$, beta to the chloride, the greatest downfield change occurs in D_2O at 3.00 ppm. This can be attributed, at least in part, to the large dielectric constant of D_2O. HD has limited solubility[8] in and reacts with D_2O to form deuterated thiodiglylcol (TDG).[4,8] In Figure 2, assignments for HD in D_2O are as follows: a region of overlapping methylene peaks for $-CH_2-Cl$ in HD and $-CH_2-OH$ in (TDG) at 3.7-3.8 ppm, methylene peaks for $-S-CH_2$ in HD at 3.00 ppm; peaks related to the reaction intermediate chlorohydrin at 2.96 and 2.78 ppm; 1,4 dithiane impurity at 2.90 ppm; and methylene peaks for $-S-CH_2$ in TDG at 2.74 ppm.

HD is much more stable in the remaining solvents in Table 1 than in D_2O. Figure 3 demonstrates this stability of HD in hexane. This stability gives the researcher a range of solvent choices to study HD. For methylene protons $H^{2,2'}$, alpha to the chloride, in HD there is a slightly larger influence of solvent on chemical shift.

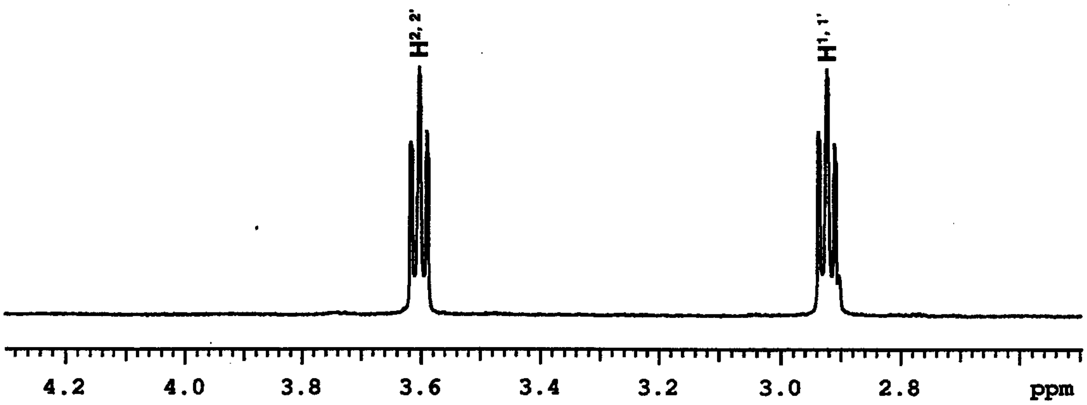
The chemical shifts for CEES in Table 2 show little solvent influence. H^1 and H^2 chemical shifts for the one-armed mustard CEES are located near $H^{1,1'}$ and $H^{2,2'}$ values for HD, and this is expected based on the similar molecular environment for these methylene protons in CEES and HD (Figure 1). The remaining methylene protons H^3 and methyl protons H^4 are at 2.6 ppm and 1.2-1.3 ppm respectively. Representative proton NMR spectra are shown for CEES in deuterated chloroform, Figures 4, and deuterated acetonitrile, Figure 5. The additional peaks in these figures are due to water and non-deuterated solvent impurities. These data provide a reference source for the proton NMR chemical shifts of CEES and HD in the solvents studied.

Figure 2. HD in D_2O, containing 0.17 M NaCl, approximately 15 min. after preparation



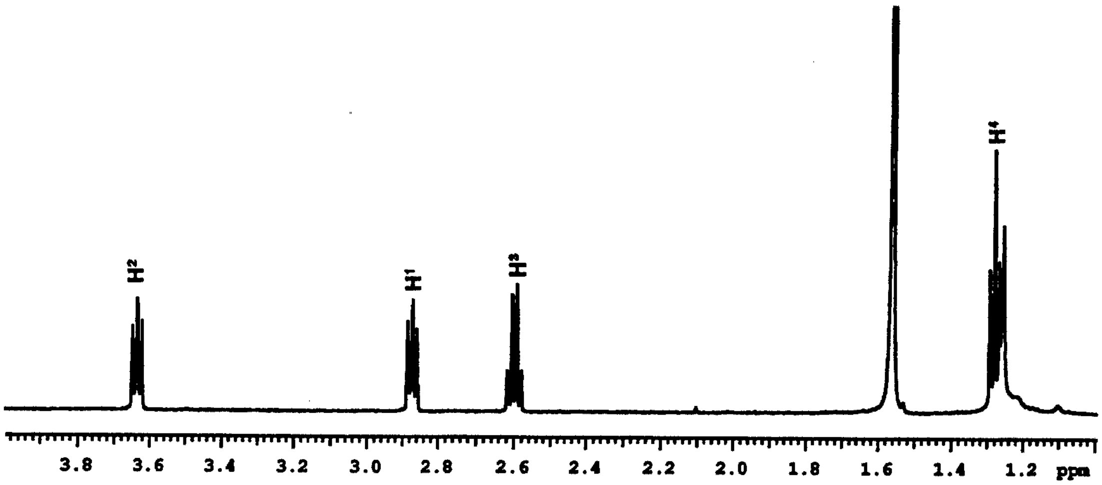
Proton NMR of HD and solvolysis products of HD in D_2O, containing 0.17 M NaCl, approximately 15 min after thawing and vortexing a 2 mM preparation.

Figure 3. HD in deuterated hexane



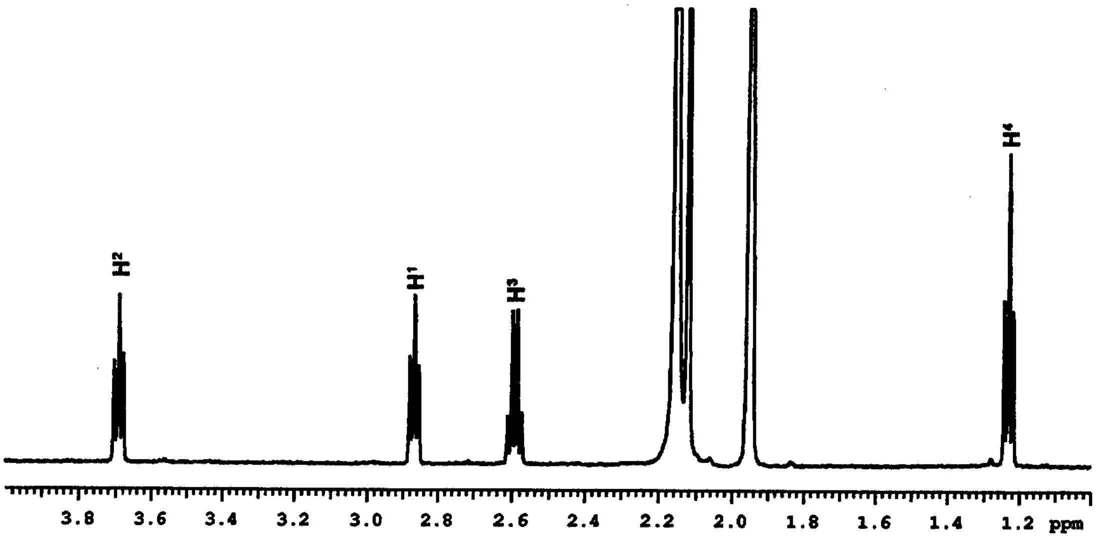
HD in deuterated hexane after extraction from HD in D_2O containing 0.17 M NaCl.

Figure 4. CEES in deuterated chloroform



CEES in deuterated chloroform at 2 mM; peaks in addition to those listed in Table 2 are due to water and non-deuterated solvent impurities.

Figure 5. CEES in deuterated acetonitrile



CEES in deuterated acetonitrile at 2mM; peaks in addition to those listed in Table 2 are due to water and non-deuterated solvent impurities.

References

1. Arroyo C.M., Schafer R.J., and Carmichael A.J. (2000) Reactivity of chloroethyl sulfides in the presence of a chlorinated prophylactic: A kinetic study by EPR/spin trapping and NMR techniques. Journal of Applied Toxicology 20, 7- 12.
2. Shih M.L., Korte W.D., Smith J.R., and Szafraniec L.L. (1999) Reactions of Sulfides with S-330, a Potential Decontaminant of Sulfur Mustard in Formulations. Journal of Applied Toxicology 19, S83- S88.
3. Shih M.L., Korte W.D., Smith J.R., and Szafraniec L.L. (1999) Analysis and Stability of the Candidate Sulfur Mustard Decontaminant S-330. Journal of Applied Toxicology 19, S89- S95.
4. Logan T.P. and Sartori D.A. (2001) Nuclear Magnetic Resonance Analysis of the Solution and Solvolysis of Sulfur Mustard in D_2O submitted to Toxicology Methods.
5. Yang Y.-C., Szafraniec L.L., Beaudry W.T., Ward J.R. (1988) Kinetics and Mechanism of the Hydrolysis of 2-Chloroethyl Sulfides. J. Org. Chem. 53, 3293-3297.
6. Yang Y.-C., L.I. Szafraniec L.L., Beaudry W.T., Ward J.R. (1987) Direct NMR Measurements of Sulfonium Chlorides Produced from the Hydrolysis of 2-Chloroethyl sulfides. J. Org. Chem. 52,1637-1638.
7. Smallcombe S.H., Patt S.L., Keifer P.A. (1995) WET Solvent Suppression and Its Applications to LC NMR and High-Resolution NMR Spectroscopy. J. Magn. Res. A117, 295-303.
8. Papirmeister B., Feister A.J., Robinson S.I., and Ford R.D. (1991) Medical Defense Against Mustard Gas: Toxic Mechanisms and Pharmacological Implications, Toxicodynamics of Sulfur Mustard, 92, CRC Press, Boca Raton, FL.