Synthesis, Isolation, and Reactivity of a Deuterated Mustard Simulant: 2-(Phenylthio)ethyl-2,2-d_2 Chloride

Samuel P. McManus,* Rashid M. Karaman, Reza Sedaghat-Herati, Bruce A. Hovanes, Xin-Teng Ding, and J. Milton Harris*

Department of Chemistry, University of Alabama in Huntsville, Huntsville, Alabama 35899

Received January 28, 1993®

We have achieved the synthesis and isolation, without substantial label scrambling, of 2-(phenylthio)-ethyl-2,2-d_2 chloride (**2-Cl**), a compound useful in modeling reactions of mustard and other highly reactive β-thioethyl chlorides. **2-Cl** undergoes slow label scrambling upon dissolution in hot, dry acetonitrile or acetone. Rates of scrambling of the deuterium label in **2-Cl** have been measured by following proton NMR changes. Our present work clearly demonstrates that cyclic sulfonium ions are involved in these scrambling reactions. In anhydrous or aqueous acetone, thiourea traps the sulfonium ion intermediate to give stable, label-scrambled thiouronium salts. In anhydrous acetone, in competition with formation of the thiouronium salts, chloride return occurs giving **2-Cl** and its label-scrambled isomer, 2-(phenylthio)ethyl-1,1-d_2 chloride (**1-Cl**). However, no chloride return is observed in 60% aqueous acetone. Mechanistic implications of these results are presented.

Specifically labeled β-thioethyl halides, such as **1-Cl** or **2-Cl**, are highly useful model compounds for the insight that thay can provide to mechanistic studies of biochemical

$$\underset{\textbf{1-X (X = Cl, OBs, etc.)}}{PhSCH_2CD_2X} \qquad \underset{\textbf{2-X}}{PhSCD_2CH_2X}$$

alkylation pathways,[1] cyclization dynamics,[2] mustard hydrolysis,[3] and nucleophilic displacement reactions.[4,5] Despite their great scientific value, these compounds have repeatedly eluded isolation. Indeed, our own research group, in search of a specifically deuterated β-thioethyl chloride for use as a mustard simulant, previously attempted eight different procedures which yielded only label-scrambled chloride product. We have now developed methodology which allows synthesis, isolation, and study of a member of this important molecular class.

The key to the success of our present methodology is avoidance of ionizing conditions which may lead to formation of the relatively stable sulfonium ion intermediate. This means more than just employing nonacidic conditions. For example, the ready availability of deuterated β-thioethyl alcohols such as **1-OH** encouraged our attempts to prepare **1-Cl** by the various methods available for conversion of alcohols to halides.[6] When we found that even standard procedures using basic conditions, e.g., thionyl chloride in dry pyridine,[7] give product with complete scrambling (i.e., 50:50 **1-Cl**/**2-Cl**), we sought alcohol to chloride conversion procedures which employ nonpolar conditions. A method which seemed reasonable is one which employed Ph_3P in CCl_4, a nonpolar solvent.[8] However, our use of this method and similar ones proved futile as each method gave chloride product with complete scrambling of the deuterium label.

Our breakthrough occurred with the discovery that 2-(phenylthio)-1,1-d_2-*p*-bromobenzenesulfonate (brosylate) (**1-OBs**) undergoes bimolecular displacement by thiolate anions to give bis-sulfides (**1-SAr**), without label-scrambling, if the displacement is carried out in an aprotic solvent like dimethyl sulfoxide (DMSO).[4] This result cannot be obtained in protic solvents because the S_N2 process is slowed while formation of sulfonium ion is facilitated. Since the cyclic sulfonium ion intermediate, which forms in protic solvents, is symmetrical, label-scrambling results as the substitution product forms.

Following the success of the direct displacement reactions with thiolate ions in DMSO solution, we attempted the direct synthesis of **1-Cl** from **1-OBs** but obtained only label-scrambled product.[9] Thus, a route to **2-Cl** evolved as discussed below.

Results and Discussion

Synthesis and Isolation of 2-Cl. We set out to prepare **2-Cl** using the sequence shown in Scheme I.

Scheme I

$$\underset{\textbf{3}}{MeOC(=O)CH_2Cl} \rightarrow \underset{\textbf{4-OH}}{HOCD_2CH_2Cl} \rightarrow \underset{\textbf{4-OBs}}{BsOCD_2CH_2Cl} \rightarrow \underset{\textbf{2-Cl}}{PhSCD_2CH_2Cl}$$

2-Chloroethanol-1,1-d_2 (**4-OH**) is readily prepared by reduction of methyl 2-chloroacetate (**3**) with lithium aluminum deuteride in ether.[10] 2-Chloroethyl-1,1-d_2 brosylate (**4-OBs**) forms rapidly when a slight excess of freshly purified *p*-bromobenzenesulfonyl chloride is added to **4-OH** in dry pyridine. The brosylate is purified by

• Abstract published in *Advance ACS Abstracts,* October 1, 1993.

(1) Peterson, L.; Harris, T. M.; Guengerich, P. *J. Am. Chem. Soc.* **1988**, *110*, 3284. Following failure to obtain a deuterated β-thioethyl halide, these authors cleverly employed stereochemical deuterium labels that reveal an S_N2 process while rendering episulfonium ion formation invisible.

(2) Rosnati, V.; Saba, A.; Angius, A.; Casarini, D. *J. Org. Chem.* **1987**, *52*, 4094.

(3) McManus, S. P.; Neamati-Mazraeh, N.; Hovanes, B. A.; Paley, M. S.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3393.

(4) Sedaghat-Herati, M. R.; McManus, S. P.; Harris, J. M. *J. Org. Chem.* **1988**, *53*, 2539.

(5) Harris, J. M.; Sedaghat-Herati, M. R.; McManus, S. P. *J. Org. Chem.* **1988**, *53*, 3893.

(6) Harrison, I. T.; Harrison, S. *Compendium of Organic Synthetic Methods*; Wiley-Interscience: New York, 1971, 1974; Vols. I and II.

(7) Darzens, G. *Comput. Rend.* **1911**, *152*, 1601. We also employed liquid SO_2 without success: Paley, M. S.; McManus, S. P. Unpublished results.

(8) Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1146.

(9) McManus, S. P.; Sedaghat-Herati, M. R.; Karaman, R. M.; Neamati-Mazraeh, N. Cowell, S. M.; Harris, J. M. *J. Org. Chem.* **1989**, *54*, 1911.

(10) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1968; pp 581–586.

0022-3263/93/1958-6466$04.00/0

low-temperature recrystallization.[11] When a dry DMSO-d_6 solution of purified **4-OBs** is treated with equivalent amounts of thiophenol and butyllithium (in hexane),[4] ^{1}H NMR reveals the fast transformation of **4-OBs** to a mixture of **2-Cl** and **1-OBs**, the products resulting from competitive displacement of the brosylate and chloride groups, respectively, of **4-OBs**. The experimentally observed brosylate to chloride reactivity ratio is low (k_{OBs}/k_{Cl} = 6.5) as anticipated from studies of Bordwell and Hughes[12] who report a *p*-toluenesulfonate/chloride reactivity ratio of ca. 4 toward PhS^- in DMSO (from *n*-PrOTs/*n*-BuCl).

Specifically, for the major product, one sees ^{1}H NMR evidence of the disappearance of the methylene singlet at 3.66 ppm (–CH_2Cl in **4-OBs**) and the formation of a new singlet at 3.72 ppm (–CH_2Cl in **2-Cl**). The minor product from chloride displacement in **4-OBs** is observed by the appearance of a singlet at 3.12 ppm, which is due to the CH_2 group in **1-OBs**.[4] Determination of the relative areas of the two products by ^{1}H NMR peak integration gives a 6.5:1 ratio for **2-Cl** and **1-OBs**. $PhSCD_2CH_2SPh$, a possible product which could form from displacement of both the chloride and brosylate groups, may not have been detected because of overlap of the proton resonance of its CH_2 group (3.16 ppm) with that of the minor brosylate product, **1-OBs**.

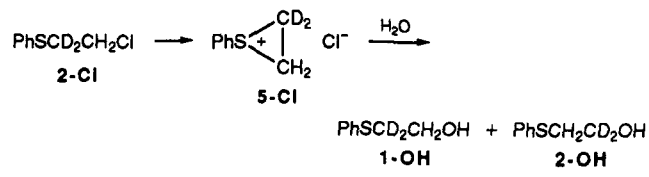
Two concerns caused us to modify the procedure. First, the competitive displacement, brosylate versus chloride, was not favorable to achieving maximum conversion to **2-Cl**. While we anticipated that **2-Cl** could be distilled from **1-OBs**, in practice this was unimportant because of the second problem: DMSO codistilled with **2-Cl**. Fortunately, a third concern, the fast scrambling of the label in DMSO, did not materialize (*vide infra*).

We attempted to solve the codistillation problem by use of acetonitrile as the solvent. Like DMSO, acetonitrile was found to be a good solvent for the conversion of **4-OBs** to label unscrambled **2-Cl**. We found that we could satisfactorily distill acetonitrile from **2-Cl** and the higher boiling byproduct (**1-OBs**) without substantial label-scrambling of **2-Cl** (*vide infra*) but the yield of pure chloride was low (17%).

To achieve even higher conversion of **4-OH** to **2-Cl**, while minimizing byproduct formation, we decided to use the very reactive trifluoroethanesulfonate (tresylate) leaving group[13] in place of the brosylate group. Thus, tresylate **4-OTres** was isolated in 79% yield by reacting **4-OH** with tresyl chloride in methylene chloride in the presence of triethylamine. Reaction of the sodium salt of thiophenol with **4-OTres** in acetonitrile occurred to give a high conversion to **2-Cl**. Despite careful handling, all synthetic procedures gave **2-Cl** contaminated with small amounts (<10%) of **1-Cl**, presumably due to the scrambling reaction occurring during workup and purification.

To test the assumption that the chloride readily scrambles, a sample of **2-Cl** was dissolved in pure, dry acetonitrile in a sealed NMR tube and then heated for determination (by NMR) of its scrambling rate. We were surprised to find that heating the sample to 110 °C was required to get a measurable half-life for the scrambling reaction. The methylene peak for **2-Cl** (3.68) became smaller with time as the peak for 1-Cl (3.28 ppm) grew and approached the area of the peak at 3.68 ppm. Fifteen spectral measurements recorded over 19 h allowed us to determine the first-order rate constants for disappearance of **2-Cl** and for the appearance of 1-Cl to be 5.22×10^{-5} and 6.33×10^{-5} s^{-1}, respectively. Thus, the half-life of **2-Cl** in pure acetonitrile is approximately 3 h at 110 °C! Since label-scrambling was observed under milder conditions during isolation of **2-Cl**, one must assume that traces of water and ionic impurities present during isolation dramatically influence ionization.

Scheme II



Hydrolysis of 2-Cl. Studies of **2-Cl** in 60% $(CD_3)_2CO$/40% D_2O were conducted to provide insight on the formation and reactivity of the cyclic sulfonium ion formed during hydrolysis reactions. From preliminary conductometric rate studies, 50 °C was suggested as a convenient temperature for additional rate measurements. Again using ^{1}H NMR, we observed the decrease in intensity of the methylene singlet (3.71 ppm) in **2-Cl** and the increase in intensity of the methylene resonance due to **1-Cl** (3.31 ppm). At the same time, new singlets of equal intensity formed and grew at 3.12 and 3.71 ppm. The latter peaks are due to the methylene resonances in $PhSCH_2CD_2OH$ (**1-OH**) and $PhSCD_2CH_2OH$ (**2-OH**), respectively.[4] Addition of 2,6-lutidine, which scavenges the acid formed, did not alter the results.

The ionization process is much slower in anhydrous acetone because of the solvent's poor ionizing properties. The rate constant determined at 110 °C in acetone is even slower than that measured in acetonitrile, as expected from the relative polarity of these solvents.[14] However, it is significant that, even under such mild ionizing conditions, there is clear NMR evidence that **2-Cl** ionizes to form the cyclic sulfonium ion. Although the slow rate introduces some experimental uncertainty, the measured rate (9.4×10^{-6} s^{-1} at 110 °C) is useful in comparative studies.

The above results are significant because they provide definitive evidence for previous suppositions regarding the behavior of mustards that were based on studies of labeled brosylates, tosylates, and dinitrophenolates.[2-5] These NMR studies and rate experiments are compelling support for formation of the cyclic sulfonium ion, **5**, as the intermediate which leads to label scrambling of chloride **2-Cl**. Water or chloride ion attack the cyclic sulfonium cation indiscriminately at the CH_2 and CD_2 positions.

As mentioned above, in the presence of water **2-Cl** ionizes to form the chloride ion and sulfonium ion **5**, which reacts competitively with water (to give scrambled alcohol **1-OH** and **2-OH**, Scheme II) and chloride ion (to give scrambled chloride, **1-Cl** and **2-Cl**). This result differs qualitatively from that obtained with brosylate **1-OBs**. In aqueous acetone, **1-OBs** gives scrambled alcohol products without scrambling itself,[4] which is consistent with brosylate ion being a weaker nucleophile than chloride ion.[15] There may also be differences in the types of ion pairs that result

(11) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1968; pp 1179–1181.
(12) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224.
(13) Crossland, R. K.; Wells, W. E.; Shiner, V. J. *J. Am. Chem. Soc.* **1971**, *93*, 4217.
(14) Reichardt, C. *Solvent Effects in Organic Solvents*, 2nd ed.; Verlagsgesellschaft mbH: Weinheim, 1988.
(15) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 308.

from 1-**OBs** and **2-Cl** in aqueous acetone. This point is considered further in the next section.

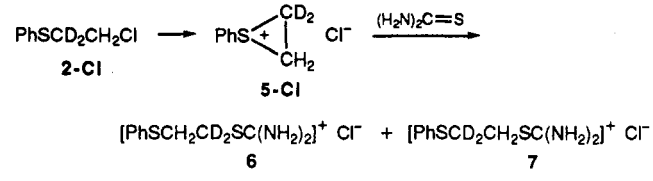
With the ^1H NMR rate measurements now available, we can compare our previously reported conductometric rate constants for hydrolysis. Before doing this it is necessary to see if the deuterium label significantly affects the rates. Using conductometric procedures, rates and β-deuterium isotope effects were determined at 60.0 °C in 60% aqueous acetone (v/v) by simultaneously determining first-order rate constants for duplicates of **2-Cl** and the undeuterated parent chloride. Two separate duplicate determinations gave $k_H/k_D = 0.997 \pm 0.003$ and 0.996 ± 0.001, showing that deuterium substitution has little effect on rate.

The conductometric rate constant (pseudo-first order) determined for hydrolysis of **2-Cl** at 50 °C in 60% aqueous acetone, in the presence of 2,6-lutidine, is $9.42 \pm 0.14 \times 10^{-5}$ s^{-1}. Because the ^1H NMR signals for the $-CH_2Cl$ in **2-Cl** and the $-CH_2O-$ in **2-OH** overlap at 3.71 ppm, it is difficult to determine rate constants for appearance or disappearance of all the species present in 60% aqueous acetone. However, the rate constant for appearance of 1-**Cl** in the presence of 2,6-lutidine can be determined to be 2.35×10^{-5} s^{-1} while the rate of formation of 1-**OH** (and presumably **2-OH**) is 8.8×10^{-5} s^{-1}. Therefore, under these conditions hydrolysis is more than three times faster than scrambling.

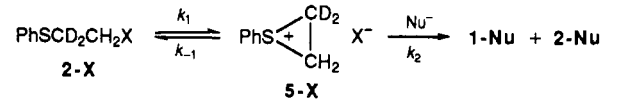
Effects of Added Thiourea on Rates and Products. Ion Pair Nature of the Intermediates from Ionization of 2-Cl. Our extensive report on the use of thiourea as a probe for S_N2 behavior of alkyl substrates included an evaluation of the effect of thiourea concentration on the rate of hydrolysis of 2-(methylthio)ethyl chloride in 70% aqueous acetone.[16] The results of that study are pertinent since it is clear from the present study that the first step in the reaction of **2-Cl** in aqueous acetone is direct ionization of **2-Cl** to a cyclic sulfonium ion (**5**). The earlier study showed that addition of thiourea failed to produce a rate increase for 2-(methylthio)ethyl chloride in 70% aqueous acetone.[16] We have confirmed this result for reaction of **2-Cl** in 60% aqueous acetone (v/v). As reported earlier a slight rate retardation is observed upon adding thiourea to 2-(phenylthio)ethyl chloride; for a 0.1 M solution, the conductometric first-order rate constant at 50 °C is $9.35 \pm 0.2 \times 10^{-5}$ s^{-1} without thiourea and $8.6 \pm 0.7 \times 10^{-5}$ s^{-1} with 0.2 M thiourea.

The availability of deuterium-labeled chloride **2-Cl** allowed us to seek evidence on the details of the displacement mechanism by thiourea with 2-(phenylthio)ethyl chloride in aqueous acetone. Thus, we prepared a solution of **2-Cl** and 1 equiv of thiourea in 60% $(CD_3)_2CO$/40% D_2O in a sealed NMR tube. The initial ^1H NMR spectrum shows a large singlet for the methylene singlet of **2-Cl** at 3.70 ppm and a small peak due to residual 1-**Cl** at 3.31 ppm. With time the **2-Cl**/1-**Cl** ratio does not change, but these peaks both slowly decrease in intensity. As these peaks decrease, two singlets of equal intensity, attributable to the products of thiourea attack on the cyclic sulfonium ion (Scheme III), arise at 3.22 ppm and 3.32 ppm. The singlet at 3.22 ppm is assigned to the methylene group in **6**, and the singlet at 3.32 ppm is assigned to the methylene group in **7**. No alcohol products are evident. Also, the fact that the **2-Cl**/1-**Cl** ratio does not change indicates

Scheme III



Scheme IV



that chloride ion attack on the intermediate sulfonium ion *is not occurring* under these conditions even though, as discussed above, *both* water and chloride ion can be observed to attack the sulfonium ion in the absence of thiourea. We interpret this result after revealing the results of one additional experiment.

We repeated the thiourea trapping experiment in pure, dry acetone-d_6 at 110 °C. The solution in a sealed NMR tube, containing 0.077 M **2-Cl** and 0.153 M thiourea, gave a proton NMR spectrum containing a methylene peak at 3.69 ppm, owing to **2-Cl**, which slowly disappeared as three new peaks grew: 3.30 ppm due to the methylene groups in 1-**Cl**, 3.26 ppm due to the methylene group in **7**, and 3.20 ppm due to the methylene group in **6**. Ultimately, the signal due to 1-**Cl** receded as **6** and **7** were the stable products. Thus, chloride attack on sulfonium ion **5** occurs in pure acetone although it is absent in 60% aqueous acetone. Since we[9] and others[17] have shown that mustard or substrates similar to **2-Cl** are sensitive to common ion rate depression, it is likely that both free ions and solvent-separated ion pairs are present in some aqueous solvents.[18] However, because of low solvent polarity, dissociation of the initially formed **5-Cl** ion pair is not favored in pure acetone. Therefore, the reactivity of the **5-Cl** ion pair can be understood by considering the generalized reaction in Scheme IV. The three reactions available to **5-X** are solvent dependent because of the polar effects on the dissociation of **5-X**. Water specifically solvates small ions like chloride stabilizing them and making them less reactive. This leads to ion separation. Large, resonance-stabilized ions like brosylate are less affected by solvation. Therefore, with **2-Cl** as the reactant, upon changing from dry acetone to aqueous acetone, k_2 is favored over k_{-1}. Also, changing the anion from OBs^- to Cl^- favors k_{-1} relative to k_2, while adding thiourea, a nonionic nucleophile, favors k_2.

In summary, an efficient method for preparing a specifically labeled β-thioethyl chloride derivative has been presented. We have used this derivative to measure rates of label scrambling in **2-Cl** in various solvents. **2-Cl** is found to be more stable to scrambling than previously thought. Therefore, if one takes care to handle such derivatives in relatively nonpolar solvents, the compounds can be manipulated and used to study reaction mechanisms. Our studies in pure and aqueous acetone are consistent with the scrambling of **2-Cl** through formation of a cyclic sulfonium ion.

(16) McManus, S. P.; Neamati-Mazraeh, N.; Karaman, R. M.; Harris, J. M. *J. Org. Chem.* **1986**, *51*, 4876.

(17) Bartlett, P. D.; Swain, C. G. *J. Am. Chem. Soc.* **1949**, *71*, 1406.

(18) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1974; Chapter 3.

Experimental Section

Solvents and reagents of the highest quality were purchased from Aldrich or Fisher. Acetone, acetonitrile, and dimethyl sulfoxide were dried[19] to remove traces of water, distilled under dry nitrogen, and stored over 3-Å molecular sieves until used. Proton NMR spectra were obtained on an IBM-Bruker AFT-200 (200 MHz) spectrophotometer and are referenced to internal tetramethylsilane. GCMS experiments were performed using a Hewlett-Packard Model 5890A/5970 instrument fitted with a OV-101 capillary column (25 m). Conductometric kinetics were measured as previously described.[9]

2-Chloroethanol-*1,1-d*$_2$ (4-OH). To a stirred solution of lithium aluminum deuteride (LAD) (5.0 g, 0.119 mol) in 170 mL of anhydrous ether was added a solution of methyl chloroacetate (23.0 g, 0.188 mol) in 20 mL of ether. The ester solution was added at such a rate that the ether refluxed gently. The reaction mixture was refluxed for 3 h with stirring. The excess LAD was decomposed by the dropwise addition of 5 mL of water, with cooling and stirring, and the mixture was allowed to stir overnight. To this solution was added successively and dropwise 5 mL of 15% NaOH and 15 mL of water. After filtering, the residue was washed with two 50-mL portions of ether, dried ($MgSO_4$), and distilled through a fractionating column to give 7.6 g of **4-OH** (49.0%): bp 127–129 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 1H, OH) and 3.63 ppm (s, 2H, $-CH_2Cl$).

2-Chloroethyl-*1,1-d*$_2$ Tresylate (4-OTres). To a solution of 2-chloroethanol-*1,1-d*$_2$ (2.15 g, 0.026 mol) and trifluoroethanesulfonyl (tresyl) chloride (5.0 g, 0.027 mol) in methylene chloride (32 mL), cooled to −10 °C, was added dropwise a solution of triethylamine (2.88 g, 0.028 mol) in 5 mL of CH_2Cl_2 over 0.25 h. After being stirred for 1 h, the mixture was washed successively with ice cold wtaer (25 mL), 5% HCl (30 mL), 5% $NaHCO_3$ (30 mL), and water (25 mL × 3), dried ($MgSO_4$), and distilled to give 4.70 g of product (78.8%): bp 76–77 °C/0.6 mmHg; ^{1}H NMR (DMSO-d_6) δ 5.01 (q, 2 H, CF_3CH_2) and 3.90 ppm (s, 2 H, $-CH_2Cl$).

2-(Phenylthio)ethyl-*2,2-d*$_2$ Chloride (2-Cl). To a 25% solution of sodium methoxide in methanol (4.71 g, containing 21.8 mmol of CH_3ONa) was added thiophenol (2.40 g, 21.8 mmol). The methanol was evaporated by use of a strong current of dry N_2 until the reaction mixture became a very viscous paste. Dry acetonitrile (10 mL) was added to dissolve the semisolid into a clear solution. A solution of 2-chloroethyl-*1,1-d*$_2$ tresylate (3.52 g, 14.4 mmol) in dry acetonitrile (5 mL) was added over 20 min, and stirring was continued for 12 h. The mixture was cooled to 0 °C and then filtered and washed with 30 mL of acetonitrile. The acetonitrile was distilled, and then the residue was distilled to give 2.0 g (79.4%) of **2-Cl**: bp 82–83 °C/1 mmHg; ^{1}H NMR (CD_3CN) δ 7.41–7.19 (m, 5H, ArH), 3.65 (s, 2H, $-CH_2Cl$), and 3.25 ppm (s, $-SCH_2-$ in **1-Cl**, <10% by integration); *m/e* 174, 176 (M^+), 139 (5^+). The GC retention time was identical to that of a sample of the protiated product.

Acknowledgement is made to the U.S. Army Research Office and to the U.S. Army Edgewood Research, Development and Engineering Center for support and encouragement for this research (Contract Nos. DAAL03-89-K-0076 and DAAL03-92-G-0393).

(19) See ref 14, pp 407–416.