dimer orientations has been reported for D_2O solutions at concentrations from 10 to 100 μM.[14-16] However, we conclude that our evidence in D_3COD supports a 1:1 stacked complex based on (1) the ^{13}C shifts in the quinoid portion of the phenoxazine ring, (2) the upfield shift in the ^1H NMR spectrum of the C(6) and C(4) methyl protons in actinomycin D, and (3) the upfield shift in the ^1H NMR spectrum for the C(10) or C(11) methylene protons of the indazole **1**. This evidence is not inconsistent with the postulated orientation shown in complex B (Figure 4).[17]

Experimental Section

General. The ^{13}C NMR spectra were recorded (at 37 °C) on a Varian XL-100(15) NMR spectrometer, equipped with a TT-100 PFT accessory, operating at 25.2 MHz with tetramethylsilane (Me_4Si) as an external reference. Field stabilization was accomplished via an internal deuterium lock with broad-band proton decoupling. The pulse width was 15.5 μs (90° flip angle). The spectral width was 6024 Hz, using 16K data points for the real and imaginary portions of the spectra, and a total of 6000 pulses were acquired for each spectra. The ^1H NMR spectra were recorded with the same spectrometer in the field-sweep mode, with Me_4Si again as the external reference at 37 °C (ambient probe temperature). An internal deuterium lock provided field stabilization. The preparation of **1** was reported previously.[18] All samples were weighed on a microbalance to the nearest 0.1 mg.

Sample Preparation. The ^{13}C and ^1H NMR spectra of actinomycin D were recorded at 25.2 MHz on a 12.7 mM D_3COD (99.5% *d*) solution. After addition of 10.8 mg (0.046 mmol) of the indazole **1**, the ^{13}C and ^1H NMR spectra were again examined. Separate spectra of **1** at the same concentration (15.3 mM) were recorded.

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Registry No.—**1**, 31184-51-7; actinomycin D, 50-76-0; 1–actinomycin D complex, 55006-96-6.

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Practical Synthesis of Deuterium-Labeled Methyl Sulfide, Methyl Disulfide, Methanethiol, and Methanesulfenyl Compounds

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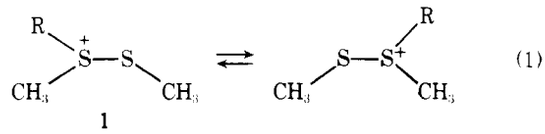
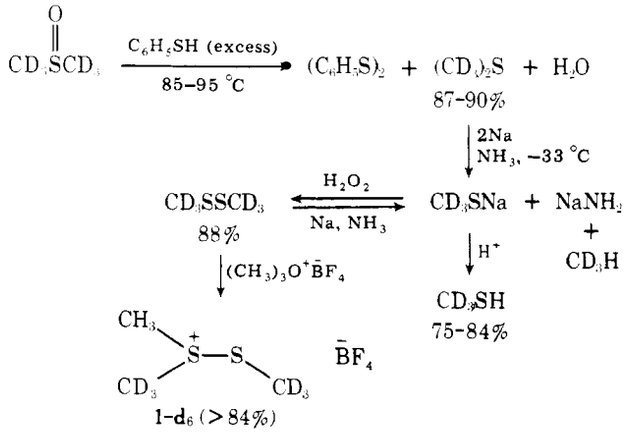
Previously we reported evidence that sulfenyl salts of the type shown in **1** can rearrange by migration of an alkyl group from positive sulfur to neutral sulfur (eq 1).[1,2] This rearrangement appears to be a reversible S_N1 dissociation when the R group can separate as a reasonably stable carbocation,[3] and a concerted 2,3-sigmatropic process when R is allylic.[4] The possibility of rearrangement occurring in the simplest analogue (R = CH_3) was considered unlikely but deserving of investigation. For this purpose we required a source of dimethyl-d_6 sulfide and disulfide. These labeled compounds are available commercially only by custom synthesis, and a recent price quotation for the synthesis of $(CD_3)_2S$ came in at $1500–2000 per 5 g. The high cost of this and related labeled methylthio compounds made it necessary to attempt the synthesis ourselves. The literature records the synthesis of methane-d_3-thiol by methylation of thiourea[5,6,7] and the synthesis of dimethyl-d_6 disulfide by the oxidation of methane-d_3-thiol. The yields are fair to good and the expense high because of the high cost of the methylating agents, CD_3I or $(CD_3)_2SO_4$.[8] We were forced to look for better procedures.



At the present time, the least expensive deuterium-labeled methylthio compound is dimethyl-d_6 sulfoxide,[8] and reduction of the sulfoxide to dimethyl-d_6 sulfide in modest yield has been reported.[9] We have found that reduction of $(CD_3)_2SO$ gives high yields of $(CD_3)_2S$ by the method of Yiannios and Karabinos[10] which involves heating the sulfoxide with excess benzenethiol. In turn, reductive cleavage of the labeled sulfide with sodium metal in liquid ammonia gives sodium methiolate-d_3 which can be converted to methane-d_3-thiol as desired by acidification. In the cleavage step, CD_3Na formed is subsequently lost as CD_3H. Sodium methiolate-d_3 with a molar equivalent of 30% hydrogen peroxide proved to be a convenient route to dimethyl-d_6 disulfide,[11] and methylation of the d_6 disulfide gave the labeled methanesulfenyl salt **1**-d_6. The disulfide can easily be reconverted to sodium methiolate-d_3 and hence to methane-d_3-thiol on treatment with sodium in liquid ammonia.



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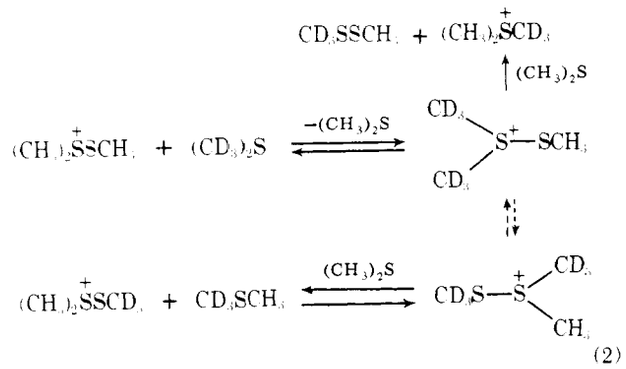
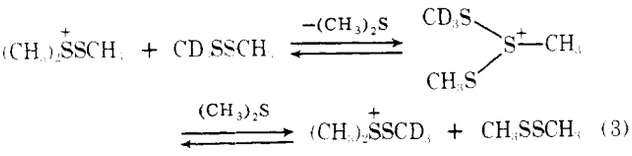
Because these reactions utilize relatively inexpensive materials, are simple to perform, and give good to excellent yields, they deserve attention as practical routes to the labeled products in question.

To solve the question of a degenérate rearrangement in dimethyl(methylthio)sulfonium fluoroborate (1, R = CH_3) the unlabeled salt was mixed with a slight excess of dimethyl-d_6 sulfide in nitromethane at 25 °C. It is known from NMR studies that a rapid exchange reaction occurs between 1 and dimethyl sulfide[12] while a slower irreversible displacement leads to trimethylsulfonium fluoroborate and methyl disulfide (eq 2). If methyl migration in 1 occurs within the time



(2)

span of these reactions, then methyl exchange in dimethyl sulfide will be observed. Mass spectral analysis of recovered dimethyl sulfide from the reaction showed molecular ions corresponding to *m/e* 62 (CH_3SCH_3) and *m/e* 68 (CD_3SCD_3) only. The absence of *m/e* 65 means that CD_3SCH_3 is *not* formed, and therefore that 1 does *not* rearrange. On the other hand, MS analysis of recovered methyl disulfide showed molecular ions at 94:97:100 corresponding to CH_3SSCH_3, CD_3SSCH_3, and CD_3SSCD_3 in the ratio of 36:29:7. This result is attributable to methylthio exchange between disulfide and 1 as has been observed previously (eq 3).[12]



(3)

Preparation of the labeled salt 1-d_6 by methylation of dimethyl-d_6 disulfide confirmed the absence of methyl transfer. Thus solutions of 1-d_6 in nitromethane showed no NMR resonance at 2.90 ppm corresponding to the sulfenyl methyl over a period of 3–4 days at 25 °C or 2–3 h at 60 °C. Only a single resonance at 3.27 ppm was observed corresponding to the unlabeled sulfonium methyl. We conclude therefore that alkyl rearrangement in thiosulfonium salts of type 1 is confined to alkyl groups that can form stabilized cations, and that cleavage of CH_3–S^+ bonds in 1 is a straightforward S_N2 displacement at carbon.

Experimental Section

Dimethyl-d_6 Sulfide. A mixture of benzenethiol (76.2 g, 0.69 mol) and dimethyl-d_6 sulfoxide (28.8 g, 0.34 mol, 99.5 atom % D) was heated while stirring within the temperature range 78–95 °C as the product, dimethyl-d_6 sulfide, distilled from the mixture. When the temperature of the distillate reached 55 °C, heating was discontinued. Redistillation gave 21.1 g (91%) of pure sulfide-d_6 (99.5 atom % D, bp 36.5 °C).

Dimethyl-d_6 Disulfide. Ammonia (~200 mL) was condensed into a 500-mL three-neck flask fitted with a mechanical stirrer, dry-ice condenser, and gas-inlet tube. Methyl-d_6 sulfide (23 g, 0.34 mol) was added followed by addition of sodium metal (15.5 g, 0.675 g-atom) in small pieces until the blue color persisted for up to 2 h. The ammonia was allowed to evaporate overnight and the white residue, which was a mixture of $NaSCD_3$ and $NaNH_2$, was dissolved in 100 mL of ethanol and 100 mL of water. To this stirred solution was added 20 mL of 30% hydrogen peroxide (17.5 mmol) while the temperature of the mixture was maintained at 65–8 °C. The mixture was cooled and the organic and aqueous phases separated. The aqueous layer was extracted twice with 25-mL portions of pentane. The organic layer was diluted with 200 mL of water and extracted with two 75-mL portions of pentane. The combined pentane extracts were washed with water, dried ($MgSO_4$), and distilled. The fraction of bp 96–8 °C was dimethyl-d_6 disulfide (14.6 g, 88%, >99 atom % D).

Methane-d_3-thiol and Sodium Methiolate. Method A. The white residue obtained after evaporation of ammonia from the reaction of $(CD_3)_2S$ (6.8 g, 0.1 mol) and sodium (5.4 g, 0.23 mol) described earlier was dissolved in 50 mL of 1,2-ethanediol. The pressure was reduced to 10–20 mm (house vacuum) for 1 h and the volatiles were trapped in liquid nitrogen. The flask was then equipped with a distillation head and a dropping funnel. Concentrated H_2SO_4 (~12 g) was added to the mixture as methane-d_3-thiol was liberated and condensed into a receiver cooled in a dry-ice–isopropyl alcohol bath. The clear liquid condensate was then treated with anhydrous $MgSO_4$ and redistilled. The yield of methane-d_6-thiol was 3.8–4.3 g (75–84%). Mass spectral analysis showed no isotopic dilution. **Method B.** Dimethyl-d_6 disulfide (10 g, 0.1 mol) was converted to sodium methiolate-d_3 by adding freshly cut sodium metal (4.7 g, 0.2 mol) in 200 mL of liquid ammonia as described for the reductive cleavage of $(CD_3)_2S$. After evaporation of the ammonia, the white solid residue was treated with 1,2-ethanediol following the procedure described in method A. Methane-d_3-thiol was obtained in 80% yield.

Preparation of 1-d_6. To a cold solution of trimethyloxonium fluoroborate (4.5 g, 30 mmol) in 10 mL of acetonitrile (dried over $CaCl_2$ and freshly distilled before use) was slowly added dimethyl-d_6 disulfide (3.1 g, 31 mmol, 99 atom % D). The mixture was stirred in an ice–water bath for 1 h after which the salt 1-d_6 was precipitated by the addition of anhydrous ether (50 mL). The crystalline white precipitate was collected by filtration and recrystallized from acetonitrile and ether which gave 5.1 g (84%) of salt 1-d_6, mp 84–6 °C (lit.[13] mp 81.5–84 °C). NMR analysis of the salt indicates the purity of 1-d_6 as 98% (NMR (CD_3NO_2) δ 3.27 with a minor singlet at 2.96 corresponding to $(CH_3)_2S^+CD_3BF_6^-$ which is formed as a byproduct).

Acknowledgment. This investigation was supported by Grant No. CA 19944, awarded by the National Cancer Institute, DHEW.

Registry No.—1-d_6, 67612-76-4; dimethyl-d_6 sulfide, 926-09-0; dimethyl-d_6 disulfide, 7282-94-2; methane-d_3-thiol, 7175-74-8; sodium methiolate-d_3, 67612-77-5; dimethyl-d_6 sulfoxide, 2206-27-1; trimethyloxonium fluoroborate, 420-37-1.

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Rates of Cycloaddition of Tetracyanoethylene to α,β-Unsaturated Sulfides and Ethers

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Thermal 2 + 2 cycloaddition of tetracyanoethylene (TCNE) to enol ethers has been extensively investigated by Huisgen

