Distillation afforded 9.9 g (90%) of acid chloride **3**: b.p. 42–43 °C (0.3 mm) [lit.[37] b.p. 88–91 °C (10 mm)]; IR (neat) ν 3040, 2960, 1810 cm^{-1}; ^1H NMR δ 0.81 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.5–2.8 (m, 5 H), 5.17 (br s, 1 H =CH); ^{13}C NMR δ 12.40 (q), 19.72 (q), 25.45 (q), 35.10 (t), 46.16 (d), 46.86 (s), 48.38 (t), 121.28 (d), 147.48 (s), 173.34 (s); MS, *m/z* (relative intensity): 127 (10%), 99 (25%), 88 (100%).

(1*S*,2*R*,5*R*,7*R*)-1,8,8-Trimethyltricyclo[3.2.1.$0^{2,7}$]octan-3-one (6). A 3-fold excess of diazomethane (48.2 mmol) in 160 mL of anhydrous ether at 0 °C was treated dropwise with a solution of 3 g (16.1 mmol) of acid chloride **3** in 50 mL of anhydrous ether and stirred magnetically for 5 h at 0 °C. The ether was removed on a rotary evaporator to give a residue that was dissolved in 100 mL of dry tetrahydrofuran. A catalytic amount (200 mg) of powdered copper metal was added and the mixture heated at reflux with magnetic stirring for 12.5 h. After filtration through Celite, the benzene was removed on a rotary evaporator to afford 2 g (76%) of crude cyclopropyl ketone **6**. Purity (95%) was determined by GC, and the sample could be further purified by preparative G.C. ^1H NMR δ 0.78 (m, 1 H), 0.97 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.3–2.5 (m, 6 H); ^{13}C NMR δ 14.04 (q), 19.54 (q), 23.99 (q), 30.19 (t), 30.83 (d), 38.38 (d), 40.01 (t), 40.19 (s), 40.42 (s), 40.83 (d), 208.39 (s). The crude material was used directly in the next step.

(+)-(1*S*,5*R*)-1,8,8-Trimethylbicyclo[3.2.1]octan-3-one (1).[9] A three-nick 500-mL round-bottomed flask, immersed in a dry ice–acetone bath (−78 °C) and equipped with a dry ice condenser (topped with a drying tube) and rubber septa, was filled with 300 mL of condensed liquid ammonia and a stirring bar. After 250 mg (36 mmole of lithium metal, which slowly dissolved (deep blue solution), was introduced, a solution of 850 mg (5.2 mmol) of cyclopropyl ketone **6** in 5 mL of dry ether was added via syringe. After being stirred with a magnetic stirrer for 30 min, 10 g of solid NH_4Cl was added (blue color faded). The dry ice–acetone bath was removed to let the ammonia evaporate over 6 h. The white residue was dissolved in 30 mL of ether and 10 mL of H_2O; the ether layer was isolated and washed with saturated aqueous NH_4Cl. The dried ($MgSO_4$) ether layer was concentrated to afford 600 mg (63%) of crude ketone **1**. The purity (90%) was determined by GC. Further purification (>99%) was achieved by preparative GC to afford pure ketone **1**: m.p. 173–175 °C, (lit.[9] m.p. 175 °C); $[\alpha]^{25}_D$ +39.5° (*c* 0.2, heptane) [lit.[9] $[\alpha]_D$ +25° (*c* 5)]1; UV ϵ_{270} = 19 (*n*-heptane), ϵ_{274} = 23 (methanol), ϵ_{276} = 15 (chloroform); CD R_{289} = +0.19, R_{316} = −0.01 (*n*-heptane), R_{295} = −0.44 (methanol), R_{300} = −0.32 (chloroform), values $\times 10^{-40}$ cgs at 24 °C; IR ($CHCl_3$) ν 2970, 1710 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table I.

Computational Details. Optimized molecular geometries of cyclohexanone, 4-*tert*-butylcyclohexanone, bicyclo[3.2.1]octan-3-one, and 1,8,8-trimethylbicyclo[3.2.1]octan-3-one (**1**) were calculated by using the molecular mechanics (MM2) method of 24. The first three ketones have a molecular symmetry plane that was reproduced by MM2. Ketone **1** would have a symmetry plane if the C_{11} CH_3 were replaced by H. Its optimized geometry was derived from a symmetrized structure that was allowed to relax. Calculated parameters for cyclohexanone and *tert*-butylcyclohexanone are given in Table II. Corresponding MM2 data for bicyclo[3.2.1]octan-3-one and **1** are given in Table V.

Acknowledgment. We thank the National Science Foundation for support of this work and the Stanford Magnetic Resonance Laboratory (NSF No. GP23633 and NIH No. RR00711) and its director, Dr. A. Rebiero, for assistance in obtaining the 360-MHz spectrum. We are particularly grateful to W. M. D. Wijekoon (this laboratory) for checking the Beer's Law behavior of **1** by running its CD spectra in *n*-heptane over a 77-fold concentration range: 0.077 M vs. 0.0010 M.

Registry No. 1, 33880-76-1; **2**, 28973-89-9; **3**, 82933-65-1; **6**, 33880-75-0; (+)-10-camphorsulfonic acid, 3144-16-9; bicyclo[3.2.1]octan-3-one, 14252-05-2; cyclohexanone, 108-94-1.

(37) Yurina, R. A.; Dembitskii, A. D.; Goryaev, M. I.: Bazalitskaya, V. S. *J. Gen. Chem. USSR Engl. Transl.* **1969**, *39*, 2492–2494.

(38) A referee has reminded us that ketones may form association complexes in hydrocarbon solvents. See: Allinger, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1958**, *2*, 64. In our work, we checked the Beer's Law behavior of ketone **1** by running CD spectra in *n*-heptane at 0.077 M and 0.0010 M concentrations. We found no difference in the shapes and $\Delta\epsilon$ for the curves. When the curves were subtracted (J-DPY data processor), only a flat line ($\Delta\epsilon$ = 0) remained. Consequently, we believe that we are not observing aggregation in the LCD spectra.

Sulfur–Sulfur Bond Cleavage Processes. Selective Desulfurization of Trisulfides[1]

David N. Harpp* and Roger A. Smith

Contribution from the Department of Chemistry, McGill University, Montreal, Quebec, Canada, H3A 2K6. *Received July 13, 1981*

Abstract: The selectivity of sulfur removal in the desulfurization of trisulfides by tertiary phosphorus compounds has been investigated in detail. A mechanistic rationalization is proposed to account for central/terminal sulfur extrusion variation as a function of substrate structure and solvent polarity.

The sulfur–sulfur bond is of considerable biological importance; it is present in the structures of a variety of natural products and contributes significantly to the tertiary structures of many proteins such as insulin and ribonuclease.[2] A major consequence of reactions involving the S–S linkage in such systems is the scission of this bond; the cleavage of disulfides by various species and disulfide interchange reactions therefore continue to be extensively studied.[3] Organic trisulfides (RSSSR′) are a closely related class of compounds having two adjacent sulfur–sulfur bonds. Such compounds play a role in biochemical systems, and a considerable number of trisulfides have been isolated from natural sources[4] including a variety of symmetrical and unsymmetrical trisulfides (e.g., **1a,b**) from plants in the onion family (genus *Allium*),[4b-e]

(1) Organic Sulfur Chemistry. Part 41. For Part 40, see: Harpp, D. N.; Smith R. A., Steliou, K. *J. Org. Chem.* **1981**, *46*, 2072.

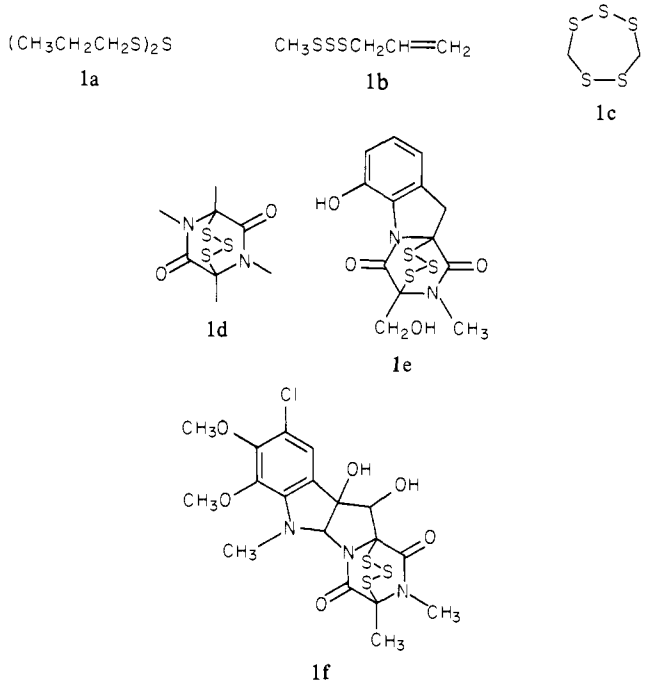
(2) For example, see: (a) Metzler, D. E. "Biochemistry. The Chemical Reactions of Living Cells"; Academic Press: New York, 1977. (b) Lehninger, A. L. "Biochemistry", 2nd ed.; Worth Publishers: New York, 1975.

(3) For some recent examples of this reaction class, see: (a) Nagano, T.; Arakane, K.; Hirobe, M. *Tetrahedron Lett.* **1980**, *21*, 5021. (b) Gilbert, H. F. *J. Am. Chem. Soc.* **1980**, *102*, 7059. (c) Szajewski, R. P.; Whitesides, G. M. *Ibid.* **1980**, *102*, 2011. (d) Cuomo, J.; Merrifield, J. H.; Keana, J. F. W. *J. Org. Chem.* **1980**, *45*, 4216. (e) Hupe D. J.; Wu, D. *Ibid.* **1980**, *45*, 3100. (f) Freter, R.; Pohl, E. R.; Wilson, J. M.; Hupe, D. J. *Ibid.* **1979**, *44*, 1771.

(4) (a) Sandy, J. D.; Davies, R. C.; Neuberger, A. *Biochem. J.* **1975**, *150*, 245. (b) Schreyen, L.; Dirinck, P.; Van Wassenhove, F.; Schamp, N. *J. Agric. Food Chem.* **1976**, *24*, 336 and 1147. (c) Galetto, W. G.; Bednarczyk, A. A. *J. Food Sci.* **1975**, *40*, 1165. (d) Komeoka, H.; Miyake, A. *Nippon Nogei Kagaku Kaishi* **1974**, *48*, 385; *Chem. Abstr.* **1974**, *81*, 152425c. (e) Dembele, S.; Dubois, P. *Ann. Technol. Agric.* **1973**, *22*, 121. (f) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 2465. (g) Morita, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1967**, *15*, 988. (h) Morita, K.; Kobayashi, S. *Tetrahedron Lett.* **1966**, 573. (i) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Cameron, A. F.; Freer, A. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 180. (j) Strunz, G. M.; Kabushima, M.; Stillwell, M. A. *Can. J. Chem.* **1974**, *53*, 295. (k) Minato, H.; Matsumoto, M.; Katayama, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1819. (l) Safe, S.; Taylor, A. *J. Chem. Soc. C* **1970**, 432. (m) Hodges, R.; Shannon, J. S. *Aust. J. Chem.* **1966**, *19*, 1059.

0002-7863/82/1504-6045$01.25/0

the cyclic trisulfide lenthionine (**1c**),[4f-h] and fungal metabolites having the bicyclic epitrithiodioxopiperazine structure (**1d–f**).[4i-m]

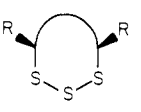


The desulfurization of trisulfides to disulfides may be accomplished by the use of inorganic species such as sulfite and cyanide salts.[5] However, the reaction is generally carried out by reaction with tertiary phosphorus compounds (eq 1). There are several

$$\underset{\mathbf{1}}{\mathrm{RSSSR}} + \underset{\mathbf{2}}{\mathrm{R'_3P}} \rightarrow \mathrm{RSSR} + \mathrm{R'_3P{=}S} \qquad (1)$$

reports of the desulfurization of trisulfides by triphenylphosphine (**2**, R′ = Ph).[6] In addition, research in our laboratory has demonstrated that tris(dialkylamino)phosphines (**2**, R′ = R_2N) are particularly efficient in this selective desulfurization of trisulfides to disulfides.[7]

It is of stereochemical and mechanistic importance to know which sulfur atom (central or terminal) is removed in these desulfurization reactions. Initial studies in this regard were performed by Safe and Taylor[6a,c] who showed by radiochemically labeling with ^{35}S that thiodehydrogliotoxin (**1e**) and sporidesmin E (**1f**) lost their central sulfur atom by reaction with triphenylphosphine. In recent years there has been considerable interest in the mechanism of desulfurization of the *di*sulfide analogues of such compounds,[8] a reaction that could be mechanistically similar to the removal of a terminal sulfur atom of the analogous trisulfide. Thus, removal or either central or terminal sulfur of an epitrithiodioxopiperazine appeared to be mechanistically possible. However, a generalization of the mechanism of desulfurization of trisulfides based only on these bicyclic examples is naive and might not apply to the more common class of trisulfides. Thus, we examined the desulfurization of ^{35}S-labeled dibenzyl trisulfide.[7c] We found that the amount of central sulfur removal was ca. 88% with triphenylphosphine and 72% with tri-*n*-butylphosphine, but only 4% with tris(diethylamino)phosphine. In these experiments the remaining label was found in the dibenzyl disulfide product (±3%). We[9a] and Ho[9b] have independently considered that this interesting dichotomy of behavior might be rationalized by the hard–soft acid–base (HSAB) theory developed by Pearson.[10] In this hypothesis, the central sulfur atom, being bonded to two soft sulfur atoms, would be a softer acceptor than a terminal sulfur atom that is bonded to a carbon atom. Consistent with this hypothesis Ph_3P and *n*-Bu_3P, considered softer bases than $(Et_2N)_3P$,[10] show a higher affinity for the soft central sulfur atom than does $(Et_2N)_3P$. Recently we demonstrated ca. 100% central-sulfur removal from ^{35}S-labeled di-4-tolyl trisulfide by treatment with either Ph_3P or $(Et_2N)_3P$.[7a] This result is understandable, as removal of a terminal sulfur atom of a diaryl trisulfide would require a displacement at the sp^2-hybridized α-carbon atom on the phenyl ring.[7a] We felt that reaction of a cis-α,α'-disubstituted cyclic trisulfide **3** with various phosphines



3

would provide valuable insight into the desulfurization mechanism,

Table I. Radiochemical Experiments

$$\mathrm{R{-}S{-}{}^{35}S{-}S{-}R + R'_3P \rightarrow R{-}S{-}{}^{35}S{-}R + R'_3P{=}{}^{35}S$$

expt	R	R′	solvent	T, °C	radioactivity/mol prod[a] RSSR	R′$_3$P=S
1	$PhCH_2$	C_6H_5	Et_2O	25.0	5.4	95.6
2	$PhCH_2$	C_6H_5	CH_3CN	25.0	4.7	92.9
3	$PhCH_2$	C_6H_5	CH_3CN	0.0	4.7	93.3
4	$PhCH_2$	C_6H_5	CH_3CN	50.0	5.2	96.1
5	$PhCH_2$	4-$CH_3C_6H_4$	Et_2O	rt[b]	3.6	95.4
6	$PhCH_2$	4-$CH_3OC_6H_4$	Et_2O	rt	7.0	90.8
7	$PhCH_2$	4-ClC_6H_4	CH_3CN	reflux[c]	2.6	99.0
8	$PhCH_2$	$(CH_3)_2N$	Et_2O	rt	92.5	6.8
9	$PhCH_2$	$(CH_3)_2N$	CH_3CN	rt	55.4	41.1
10	$PhCH_2$		Et_2O–CH_3CN (2:1)[d]	rt	91.2	6.8
11	$PhCH_2$		CH_3CN	rt	53.2	40.5
12	*n*-Pr	C_6H_5	CH_3CN	reflux	[e]	98.0
13	*n*-Pr	4-$CH_3C_6H_4$	CH_3CN	reflux		98.7
14	*n*-Pr	4-$CH_3OC_6H_4$	CH_3CN	reflux		97.7
15	*n*-Pr	4-ClC_6H_4	CH_3CN	reflux	no reaction[f]	
16	*n*-Pr	$(CH_3)_2N$	Et_2O	rt	74.0	29.2
17	*n*-Pr	$(CH_3)_2N$	CH_3CN	rt	40.8	62.6
18	*n*-Pr		CH_3CN	reflux		93.8

[a] Radioactivity/mol relative to RSSSR at 100, i.e., as a percentage of the radioactivity of RSSSR; measured by liquid scintillation method, compensated for quench. Each value given is the average of two experiments that generally differed by less than 1 unit (maximum difference was 3.8 units). For example, for RSSR and R′$_3$P=S: expt 1a had 4.9 and 96.1, 1b had 5.8 and 95.1; expt 2a had 5.1 and 93.0, 2b had 4.2 and 92.8. [b] Room temperature (rt) was ca. 21 °C. [c] Refluxing acetonitrile in a 100 °C bath, reaction temperature ca. 84 °C. [d] Tris(morpholino)phosphine is insoluble in diethyl ether. [e] Radioactivity not determined. [f] No reaction after 1 month at reflux (TLC).

(5) (a) Foss, O. In "Organic Sulfur Compounds"; Kharasch, N., Ed.; Pergammon Press: New York, 1961; Vol. 1, pp 75–96. (b) Milligan, B.; Saville, B.; Swan, J. M. *J. Chem. Soc.* **1963**, 3608.

(6) (a) Safe, S.; Taylor, A. *J. Chem. Soc. C* **1971**, 1189. (b) Rahman, R.; Safe, S.; Taylor, A. *Ibid.* **1969**, 1665. (c) Safe, S.; Taylor, A. *J. Chem. Soc. D* **1969**, 1466. (d) Brewer, D.; Rahman, R.; Safe, S.; Taylor, A. *Chem. Commun.* **1968**, 1571. (e) Fehér, F.; Kurz, D. *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **1968**, *23*, 1030. (f) Hayashi, S.; Furukawa, M.; Yamamoto, J.; Hamamura, K. *Chem. Pharm. Bull.* **1967**, *15*, 1310. (g) Moore, C. G.; Trego, B. R. *Tetrahedron* **1963**, *19*, 1251.

(7) (a) Harpp, D. N.; Ash, D. K.; Smith, R. A. *J. Org. Chem.* **1980**, *45*, 5155. (b) Harpp, D. N.; Adams, J.; Gleason, J. G.; Mullins, D.; Steliou, K. *Tetrahedron Lett.* **1978**, 3989. (c) Harpp, D. N.; Ash, D. K. *J. Chem. Soc. D* **1970**, 811.

(8) (a) Herscheid, J. M. D.; Tijhuis, M. W.; Noordik, J. H.; Ottenheijm, H. C. J. *J. Am. Chem. Soc.* **1979**, *101*, 1159. (b) Sato, T.; Hino, T. *Tetrahedron* **1976**, *32*, 507.

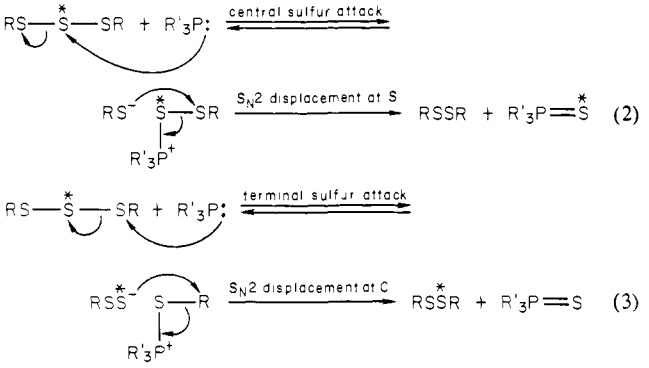
(9) (a) An account of our HSAB rationalization of central/terminal sulfur removal may be found in the thesis of our co-worker: Ash, D. K. Ph.D. Thesis, McGill University, 1973. (b) Ho, T.-L. "Hard and Soft Acids and Bases Principle in Organic Chemistry"; Academic Press: New York, 1977; p 113.

(10) Pearson, R. G., Ed., "Hard and Soft Acids and Bases", Dowden, Hutchinson and Ross: Stroudsburg, PA, 1973.

as removal of the central sulfur atom should yield the corresponding cis cyclic disulfide, whereas removal of a terminal sulfur atom should involve an inversion at one α-carbon and thus afford the trans cyclic disulfide.[11] However, all of our attempts to prepare such a monomeric α,α′-disubstituted cyclic trisulfide were unsuccessful.[12] We now report our studies of the factors that affect the relative selectivity of removing the central and terminal sulfur of trisulfides by tertiary phosphorus compounds and present a rationalization of this fascinating mechanistic problem.

Results and Discussion

In order to follow the presentation of our experimental observations and the mechanistic discussion that follows, it is instructive for one to examine reaction eq 2 and 3. We believe these



(2)

(3)

equations provide a general description of the desulfurization reactions we have studied, and indeed they form the backbone of our mechanistic interpretation of these processes. In order to gather more data on this desulfurization reaction, we required ^{35}S-labeled samples of dibenzyl (**1g**) and di-*n*-propyl (**1h**) trisulfides; these were prepared by a standard procedure (eq 4).[13]

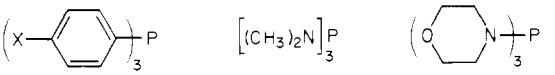
$$2RSH + {}^{35}SCl_2 \rightarrow RS\text{-}{}^{35}S\text{—}SR + 2HCl \quad (4)$$

1g, R = $PhCH_2$
1h, R = $CH_3CH_2CH_2$

The results for desulfurization of these two trisulfides for a variety of phosphines and reaction conditions are collected in Table I.[15]

Initial experiments with dibenzyl trisulfide (**1g**) and triphenylphosphine (Table I, experiments 1–4) confirmed our earlier findings[7c] that this reagent removed predominantly the central sulfur atom of **1g**. Additionally, it was found that neither reaction temperature (0–50 °C) nor solvent polarity (E_T values[17] of 34.6 for Et_2O and 46.0 for CH_3CN) had a significant effect on the selectivity of central/terminal sulfur removal.

Experiments were then conducted with a series of phosphines (**2a–f**) that should represent a reasonable spectrum of hard-



2a, X = H
2b, X = CH_3
2c, X = CH_3O
2d, X = Cl

2e

2f

ness–softness (HSAB). Complete desulfurization of **1g** by reaction with triarylphosphines **2a–c** was achieved after 2–3 weeks at room temperature in Et_2O and after 18 h at reflux (82 °C) in CH_3CN with **2d**.[18] The effect of the para substituent of **2a–d** on central/terminal sulfur removal was demonstrated to be very small, as the central sulfur removal was ca. 91–99% for the four different para substituents (Table I, experiments 1, 5–7). For desulfurization of di-*n*-propyl trisulfide (**1h**), the substituent effect was insignificant, except for the reactivity (Table I, experiments 12–15). Assuming that electron withdrawal from the phosphorus atom of a phosphine decreases its polarizability, then the order of softness of these triarylphosphines is **2c > 2b > 2a > 2d**. Our results indicate a slight trend for increased removal of the central sulfur atom of **1g** with increased electron withdrawal by para substituents in Ar_3P. This trend would be *contrary* to the proposal[9] that increased central-sulfur-removal results from increased softness of the phosphine nucleophile. The trend, however, is not clear enough to rule out conclusively this rationalization of the problem.

Desulfurization of trisulfides **1g** and **1h** by aminophosphines **2e** and **2f** produced results that were much more striking. While reaction of **1g** with $(Me_2N)_3P$ in ether was essentially identical with that with $(Et_2N)_3P$,[7c] a unique solvent effect was observed in that central-sulfur removal was increased from 7% to 41% by changing the solvent from Et_2O to CH_3CN (Table I, experiments 8 and 9). Similar solvent effects were observed for the reaction of **1g** with tris(morpholino)phosphine (**2f**) (Table I, experiments 10 and 11) and the reaction of **1h** with **2e** (Table I, experiments 16 and 17). Interestingly, phosphine **2f** removed almost exclusively (94%) the central sulfur of **1h** in refluxing CH_3CN (Table I, experiment 18).

In summary, these radiochemical experiments show that desulfurization of dialkyl trisulfides by triarylphosphines results in 91–99% central sulfur removal, essentially independent of solvent (Et_2O or CH_3CN), reaction temperature (0–50 °C), type of trisulfide (dibenzyl or dipropyl), and para substituents on Ar_3P (CH_3O to Cl, electron-withdrawing substituents may slightly increase central sulfur removal). In sharp contrast to this, desulfurization of dialkyl trisulfides by aminophosphines results in preferential removal of a terminal sulfur atom in Et_2O, while in CH_3CN more than the statistical amount (33%) of central sulfur is removed.

In order to investigate this novel solvent effect on central/terminal sulfur removal by aminophosphines, we desired an alternative method of study. We considered that desulfurization of an optically active trisulfide having its chirality at the two α-carbons would be of interest. In this case, removal of the central sulfur atom does not affect the configuration at the α-carbons and thus gives the corresponding optically active disulfide (eq 2

(11) The desulfurization of a cis- or trans-α,α′-disubstituted cyclic disulfide with $(Et_2N)_3P$ affords the corresponding trans or cis cyclic monosulfide, respectively: (a) Harpp, D. N.; Gleason, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 2437. (b) Eliel, E. L.; Hutchins, R. O.; Mebane, R.; Willer, R. L. *J. Org. Chem.* **1976**, *41*, 1052.

(12) Harpp, D. N.; Smith, R. A.; Steliou, K. *J. Org. Chem.* **1981**, *46*, 2720.

(13) The high chemical yield of this preparation was accompanied by a low radiochemical yield, indicating that only 10–20% of the undiluted radioactive sample of SCl_2 was in the chemical form of SCl_2. Also, as $^{35}SCl_2$ is currently available only as a custom synthesis, we believe that the preparation of ^{35}S-labeled trisulfides from the corresponding ^{35}S-labeled *thiol* may be superior in terms of cost and radiochemical yield. $R^{35}SH$ may be prepared from RX by the use of $Mg/^{35}S_8$, $^{35}S{=}C(NH_2)_2$, $Na^{35}SSO_3Na$, or $K^{35}SCN$; all of these ^{35}S-labeled compounds are available from New England Nuclear, Boston, MS. For information regarding these thiol syntheses, see ref 14.

(14) (a) Ohno, A.; Oae, S. In "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum Press: New York, 1977; p 119. (b) March, J. "Advanced Organic Chemistry—Reactions, Mechanisms and Structures", 2nd ed.; McGraw-Hill: New York, 1977; pp 374–376, 377, 559.

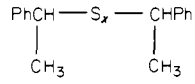
(15) The consistency of our results and the work of others[16] indicate that "scrambling" of the radiochemical label among central and terminal sulfur atoms does *not* occur.

(16) (a) Guryanova, E. N. *Q. Rep. Sulfur Chem.* **1970**, *5*, 113. (b) Wieland, T.; Schwahn, H. *Chem. Ber.* **1956**, *89*, 421; *Chem. Abstr.* **1956**, *50*, 14537h. (c) Ikeda, S.; Minoura, Y. *Nippon Kagaku Zasshi* **1954**, *75*, 260; *Chem. Abstr.* **1957**, *51*, 11278a.

(17) (a) Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98. (b) Abraham, M. H. *Prog. Phys. Org. Chem.* **1974**, *11*, 3. (c) Kosower, E. M. "An Introduction to Physical Organic Chemistry"; Wiley: New York, 1968; pp 301, 305.

(18) TLC analysis (SiO_2, hexane eluant) of an incomplete reaction revealed a component close to the disulfide–trisulfide spot that was identified as thiol, presumably formed by a reductive decomposition of phosphonium salt on the silica gel to give phosphine oxide and thiol. Chromatographic workup of these incomplete desulfurization reactions afforded disulfide contaminated with trisulfide and thiol, as well as phosphine, phosphine sulfide, and phosphine oxide; radioactivities of the recrystallized phosphine sulfide and disulfide products were inconsistent in these cases. Reproducible results for desulfurization by triarylphosphines were obtained only from reactions that had proceeded to completion, as evidenced by the absence of thiol by TLC (SiO_2, hexane).

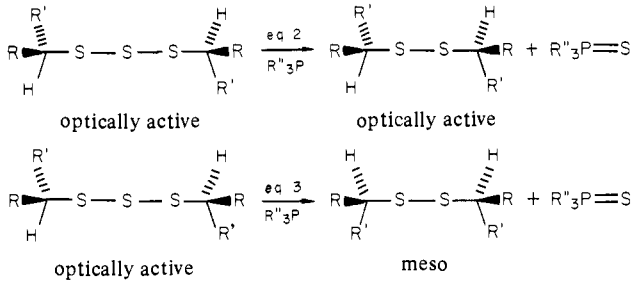
Table II. NMR Characteristics[a] of Meso and *d,l* Isomers of 1-Phenylethyl Mono-, Di-, and Trisulfide



compound	CH quartet[b] δ_{av}[c]	CH quartet[b] $\Delta\delta = \delta_{meso} - \delta_{d,l}$	CH_3 doublet[b] δ_{av}[c]	CH_3 doublet[b] $\Delta\delta = \delta_{meso} - \delta_{d,l}$	ref
RSR, $x = 1$	3.6	+0.30	1.4	+0.15	23
RSSR, $x = 2$	3.5	+0.09	1.5	<0.01	24; this work
RSSSR, $x = 3$	4.1	−0.05	1.7	<0.01	this work

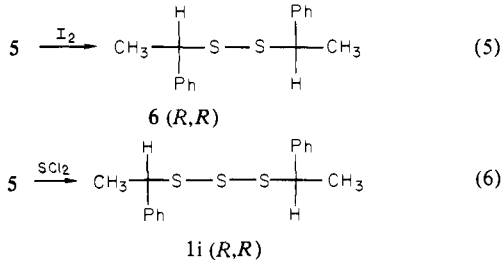
[a] In CCl_4 solution, TMS internal standard. [b] $J = 7$ Hz. [c] Average chemical shift of meso and *d,l* isomers.

mechanism). Extrusion of either terminal sulfur atom would be expected to proceed with inversion at one α-carbon,[19] thereby affording the optically inactive meso disulfide (eq 3 mechanism).



The desulfurization of such an optically active trisulfide should, therefore, give a mixture of optically active and meso disulfide diastereomers; the optical rotation of this disulfide product mixture relative to the optical rotation of the pure optically active disulfide provides a direct measurement of the relative central/terminal sulfur removal.

Preliminary desulfurization experiments with meso/*d,l* mixtures of bis(1-phenylethyl) trisulfide and bis(2-octyl) trisulfide[7a] indicated that optically active bis(1-phenylethyl) trisulfide would be the most practical substrate for study. The synthesis of (+)-(*R*)-1-phenylethanethiol (**5**) via the (+) isomer of the menthylxanthate esters (**4a,b**) was based on a recent procedure;[20-22] it was converted into the (+)-*R,R* disulfide **6** and (+)-*R,R* trisulfide **1i** (eq 5 and 6). The clean PhC*H* quartet in the ^1H NMR



spectrum of either **6** or **1i** indicated the absence of any meso (*R,S*) diastereomers (see Experimental Section); it is reasonable to assume that the *S,S* diastereomers were also absent (i.e., ca. 100% optical purities of **5**, **6**, and **1i**). It should be noted that a comparison of the ^1H NMR signals of bis(1-phenylethyl) mono-, di- and trisulfides (Table II) indicates that assignment of meso or *d,l* configuration to compounds of the type RS_xR ($x = 1, 2, 3...$) cannot be made solely on the basis of ^1H NMR data, as there is no apparent trend exhibited.

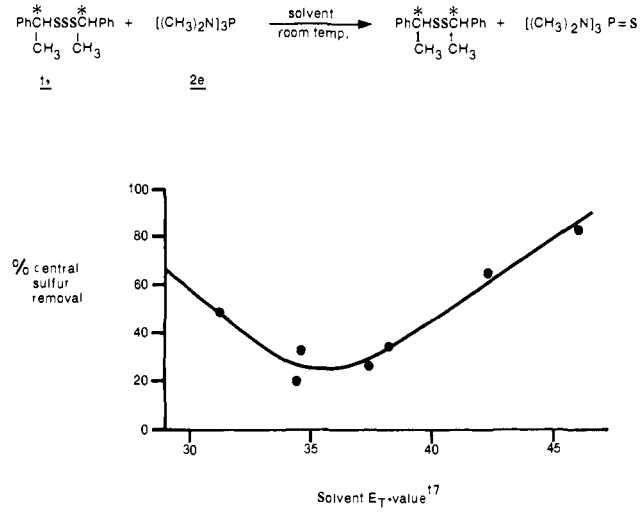
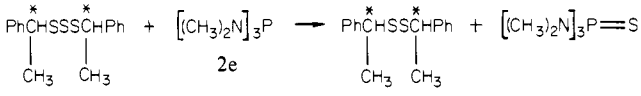


Figure 1. Solvent dependency of desulfurization of **1i**.

Table III. Desulfurization of (+)-(*R,R*)-Bis(1-phenylethyl) Trisulfide (1i) by Tris(dimethylamino)phosphine (2e)



reaction solvent[a]	solvent E_T value[17]	$[\alpha]^{20}_D$ of product (C_6H_6),[b] deg	% central sulfur removal[c]
MeCN	46.0	252	82
$Me_2C{=}O$	42.2	200	65
EtOAc	38.1	106	34
THF	37.4	80.0	26
Et_2O	34.6	102	33
C_6H_6	34.5	62.9	20
cy-C_6H_{12}	31.2	150	49

[a] Reaction performed at room temperature utilizing a 10-40% excess of 2e; reaction times, 2-20 days. [b] Each value given is the average of 3-6 experiments. For example, in acetonitrile: 247°, 254°, 256°; in acetone: 197°, 197°, 205°. [c] Calculated by $[\alpha]^{20}_D$ of product ÷ 309°.

Desulfurization of *R,R* trisulfide **1i** was carried out, and the optical rotation of the product was measured. The relative amounts of meso and *R,R* disulfide as determined by NMR analysis of the PhC*H* quartets of the disulfide diastereomers qualitatively confirmed the optical rotation measurements. This indicated that racemization was not occurring during the reaction. Similarly, the optical integrity of **1i** was maintained as evidenced by the clean PhC*H* quartet in the NMR analysis of incomplete reaction mixtures. The results obtained for desulfurization of **1i** by $(Me_2N)_3P$ (**2e**) in a variety of solvents are summarized in Table III and Figure 1. These results showed an Et_2O–CH_3CN solvent effect that was similar to that observed in the radiochemical experiments (Table I), thereby establishing the validity of this optical rotation method of study. Additionally, a general trend was noted, as an increase from ca. 35 to 56 in E_T solvent polarity[17] caused a gradual increase from ca. 25% to 82% central sulfur removal of **1i**. At low solvent polarity (cyclohexane), a deviation from this trend was observed, suggesting a change in reaction mechanism. That is, at low solvent polarity, desulfurization via a nonpolar transition state that involves only (or predominantly) central sulfur removal may become important. Such mechanisms involving, for example, thiosulfoxide intermediates or pentacovalent

(19) Desulfurization of a dialkyl disulfide by a phosphine is known to proceed with inversion at one α-carbon.[11a]
(20) Isola, M.; Ciuffarin, E.; Sagramora, L. *Synthesis* **1976**, 326.
(21) The configurations of esters **4a** and **4b** and of thiol **5** are based on the correlation of (−)-(*S*)-1-phenylethanethiol to (+)-(*S*)-mandelic acid.[22]
(22) Chiellini, E.; Marchetti, M.; Ceccarelli, G. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 73.
(23) Meyers, C. Y.; Malte, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 2123.
(24) Larsson, E. *Fresenius' Z. Anal. Chem.* **1973**, *266*, 205.

phosphine–trisulfide adducts have been described recently.[7a]

Desulfurization of **1i** by other phosphines unfortunately did not proceed to completion within a reasonable time period. However, ^{1}H NMR analysis of the incomplete reaction of **1i** with either Ph_3P or tris(morpholino)phosphine (**2f**) in CH_3CN indicated clean conversion of *R,R* trisulfide to *R,R* disulfide (no meso (*R,S*) disulfide). This implies ca. 100% central sulfur removal under these conditions, as would be expected on the basis of the radiochemical data (Table I).

In summary, desulfurization of trisulfide **1i** provided data that confirmed the radiochemical findings and additionally revealed a general trend in the solvent polarity effect on central/terminal sulfur removal. The steric hindrance provided by methyl substituents on the two α-carbons of **1i** relative to **1g** likely caused not only the decrease in the rate of desulfurization[7a] but also the increase in the percentage of central sulfur removal (from 7% to 33% in Et_2O; from 41% to 82% in CH_3CN).

It is instructive to examine the analogous reaction with disulfides in order to rationalize the different behavior of triaryl- and tris(dialkylamino)phosphines in the desulfurization of trisulfides. In this case, while aminohosphines efficiently desulfurize dialkyl disulfides to monosulfides,[11a] triphenylphosphine generally gives *no reaction*.[25] This might be considered to be due to the low nucleophilic reactivity of Ph_3P relative to $(R_2N)_3P$,[26] since it was concluded that desulfurization by aminophosphines proceeds via the rate-determining formation of a phosphonium salt.[7a,11a] However, we now report results that clearly indicate that Ph_3P is indeed capable of cleaving the sulfur–sulfur bond in a disulfide to form a phosphonium salt.[27] For example, a mixture of diphenyl and di-*p*-tolyl disulfides when treated with a catalytic amount of aminophosphine **2e** immediately afforded an equilibrium mixture of symmetrical and unsymmetrical disulfides presumably by exchange of the phosphonium salts; the same result was achieved by the use of a catalytic amount of triphenylphosphine (eq 7).

$$\mathrm{PhSSPh} + \mathrm{TolSSTol} \xrightleftharpoons{R_3P} 2\mathrm{TolSSPh} \qquad (7)$$

Although this result indicates Ph_3P displaces aryl mercaptide (ArS^-) from a disulfide, the rate of desulfurization of methyl phenyl disulfide ($PhSSCH_3$) by Ph_3P was found to be considerably less than the rate of Ph_3P-catalyzed disproportionation to symmetrical disulfides PhSSPh and CH_3SSCH_3; this appears to indicate that formation of the phosphonium salt intermediate is fast, relative to the collapse of the salt to form desulfurization products. This is in contrast to the rapid, quantitative desulfurization of $PhSSCH_3$ to $PhSCH_3$ by $(Et_2N)_3P$ *without* formation of any exchange products.[11a] The exchange reaction observed as indicated in eq 8 confirms that Ph_3P displaces the most stable mercaptide ion preferentially;[28] only disproportionation products resulting from displacement of ArS^- were observed. Clearly a free-radical mechanism would have afforded all possible unsymmetrical and symmetrical disulfides.

$$\mathrm{PhSSCH_3} + p\text{-}\mathrm{TolSSCH_2Ph} \xrightleftharpoons{Ph_3P} \mathrm{PhSSCH_2Ph} + p\text{-}\mathrm{TolSSCH_3} \qquad (8)$$

We also propose that triphenylphosphine is sufficiently nucleophilic to displace *aliphatic* mercaptide ions, as dibenzyl and di-*n*-butyl disulfides were exchanged by triphenylphosphine (eq 9). However, dibenzyl disulfide could not be desulfurized by Ph_3P

$$\mathrm{PhCH_2SSCH_2Ph} + \mathrm{BuSSBu} \xrightleftharpoons{Ph_3P} 2\mathrm{PhCH_2SSBu} \qquad (9)$$

even under more forcing conditions. In contrast, tris(dimethylamino)phosphine (**2e**) reacts with this disulfide mixture under similar conditions to afford both the exchange product ($PhCH_2SSBu$) and a desulfurized product ($PhCH_2SCH_2Ph$) at comparable rates.

From the experiments described above, we conclude that desulfurization of dialkyl disulfides by Ph_3P (**2a**) does not readily occur, *not* as a result of the relatively poor nucleophilicity of **2a** (since phosphonium salts are evidently readily formed[29]) but rather as a consequence of the inability of the mercaptide ion released to displace phosphine sulfide from the sp^3-hybridized carbon. In effect this means that the *second step* of the desulfurization by Ph_3P is rate determining (eq 10). In contrast, desulfurization

$$\mathrm{RSSR} + \mathrm{Ph_3P} \xrightleftharpoons{\text{fast}} \mathrm{Ph_3P^+\text{–}SR} + \mathrm{RS^-} \xrightarrow{\text{slow}} \mathrm{RSR} + \mathrm{Ph_3PS} \qquad (10)$$

of disulfides by tris(diethylamino)phosphine proceeds by a rate-determining *first step*.[11a] In order to determine if these conclusions could also be applied to the desulfurization of *tri*sulfides, we conducted further exchange experiments.

It was found that treatment of a mixture of dibenzyl and di-*p*-tolyl trisulfides with either phosphine **2a** or **2e** immediately gave the exchange product (*p*-$TolSSSCH_2Ph$) and desulfurization products. However, in the case of a less reactive mixture of trisulfides (**1j** + **1k**), it was found that reaction with Ph_3P gave complete exchange (i.e., formation of equilibium amounts of **1j**, **1k**, and **1l**; eq 11), *followed* by the formation of desulfurization products (eq 12). This permits us to conclude that desulfurization

$$\underset{\mathbf{1j}}{\mathrm{PhCH_2SSSCH_2Ph}} + \underset{\mathbf{1k}}{\mathrm{PrSSSPr}} \xrightleftharpoons{Ph_3P} 2\underset{\mathbf{1l}}{\mathrm{PrSSSCH_2Ph}} \qquad (11)$$

$$\mathbf{1j} + \mathbf{1k} + \mathbf{1l} \xrightarrow{Ph_3P} \mathrm{PhCH_2SSCH_2Ph} + \mathrm{PrSSPr} + \mathrm{PrSSCH_2Ph} \qquad (12)$$

of trisulfides by Ph_3P proceeds with the *second step* of the reaction (decomposition of the phosphonium salt) as rate limiting. Reaction of **1j** + **1k** with aminophosphine **2e** rapidly gave both exchange and desulfurization products within 5 min at room temperature.

It should be noted that desulfurization involving central sulfur removal should proceed via intermediate **7** (eq 2)[7a] However,

there are good reasons to conclude that formation of phosphonium salt **8** is much preferred (kinetically and thermodynamically) over formation of **7**.[7a] Thus, if central sulfur desulfurization of a trisulfide occurs with the *second step* of the reaction as rate determining, then a preequilibrium formation of *both* salts **7** and

(25) (a) Mukaiyama, T.; Takei, H. *Top. Phosphorus Chem.* **1976**, *8*, 587. (b) Moore, C. G.; Trego, B. R. *Tetrahedron* **1962**, *18*, 205. (c) Schönberg, A.; Barakat, M. Z. *J. Chem. Soc.* **1949**, 892. (d) Schönberg, A. *Chem. Ber.* **1935**, *68*, 163. (e) The successful desulfurization of several disulfides including dibenzyl disulfide by triphenylphosphine has been reported;[6f] however, we and several others[25a–d] have been unable to reproduce these results. (f) *Diaryl* disulfides are *not* desulfurized by either **2a**[25a] or **2e**,[11a] except at high temperature; see: Middleton, D. L.; Samsel, E. G.; Wiegand, G. H. *Phosphorus Sulfur* **1979**, *7*, 339. Harpp, D. N.; Kader, H. A.; Smith, R. A. *Sulfur Lett.*, in press. (g) Only acyl, aroyl, and bis(thiocarbamoyl) disulfides are readily desulfurized by triphenylphosphine.[25a]

(26) (a) Nucleophilic reactivity constants for reaction toward CH_3I [$n_{CH_3I} = \log (k_{Nu}/k_{CH_3OH})$] are 8.54 for $(Et_2N)_3P$ and 7.00 for Ph_3P (relative to 0.00 for CH_3OH): Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319. (b) Thorstenson, T.; Songstad, J. *Acta Chem. Scand., Ser. A* **1976**, *A30*, 781.

(27) (a) Control experiments conducted for all of the exchange experiments described in this article showed that no reaction occurred in the absence of a phosphine (see Experimental Section). (b) The reduction of disulfides to thiols by triphenylphosphine in aqueous media proceeds via sulfur–sulfur bond cleavage by Ph_3P: Overman, L. E.; O'Connor, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 771. (c) Disulfide exchange reactions and cleavage of the sulfur–sulfur bond of disulfides by various species are of biological importance and continue to be extensively studied. For recent examples of this reaction class, see ref 3.

(28) Relevant pK_a values (27 °C, 3:1 acetone–water) for the thiols are PhSH 8.6, *p*-TolSH 9.3, $PhCH_2SH$ 11.8 and *n*-BuSH 12.6: Dmuchovsky, B.; Zienty, F. B.; Vredenburgh, W. A. *J. Org. Chem.* **1966**, *31*, 865.

(29) Mixtures of dibenzyl disulfide with either phosphine **2a** or **2e** in a variety of solvents were analyzed by ^{31}P NMR; however, no measurable amounts of phosphonium salts could be detected. This does not preclude the existence of such species but merely indicates that if they do exist they are too short-lived to accumulate to a significant concentration. Similar experiments with trisulfides and **2a** or **2e** failed to detect phosphonium salts intermediates. We are grateful to Dr. D. J. H. Smith and K. Steliou for the measurement of the ^{31}P NMR spectra at the University, Leicester, England.

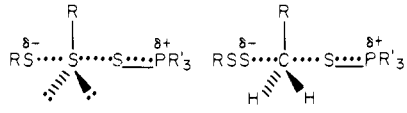
8 should exist. Indeed, we found that reaction of trisulfide **1j** with a 0.5 molar equiv of Ph_3P in benzene or acetonitrile provided *not* a 1:1 mixture of dibenzyl trisulfide and disulfide, but rather a mixture of di-, tri-, and ca. 7% *tetra*sulfide. This result is rationalized by an exchange between phosphonium salts **7** and **8** to afford disulfide and tetrasulfide (eq 13); the rapid desulfuri-

$$2RSSR + R'_3P \rightleftarrows \mathbf{7} + \mathbf{8} \rightleftarrows RSSSSR + RSSR + R'_3P \quad (13)$$

$$R = PhCH_2$$

zation of the tetrasulfide by Ph_3P presumably maintains the concentration of tetrasulfide at a low level. A more intriguing observation was that treatment of **1j** with a 0.5 molar equiv of $(Me_2N)_3P$ (**2e**) in acetonitrile gave a similar mixture of di-, tri-, and tetrasulfide, but in benzene a 1:1 disulfide–trisulfide mixture was formed containing *no* significant amount of tetrasulfide. We thus conclude that reaction of **1j** with **2e** *in benzene* proceeds by preferential formation of **8** followed by a *rapid* S_N2 displacement to give disulfide; in the more polar solvent acetonitrile, the transition state of the first step of the reaction is stabilized sufficiently to allow accumulation and exchange of both intermediates **7** and **8** before the (now rate-determining) second step occurs. This behavior of **1j** with **2e** in acetonitrile is similar to that of the reaction of **1j** with **2a** in either benzene or acetonitrile, as described above.

As a result of these numerous exchange experiments, we feel that a reasonable rationalization of the central/terminal sulfur removal is possible invoking eq 2 and 3. Considering the first steps of these mechanisms, we have concluded[7a] that formation of **8** is preferred over formation of **7**. However, the second steps of these processes also deserve scrutiny. Kice and Favstritsky[30] have shown that nucleophilic displacement at the sulfenyl sulfur in $MeS-{}^+SMe_2$ is at least 10^9–10^{10} times faster than the analogous displacement at the sp^3-hybridized carbon atom in $Me-{}^+SMe_2$; this is presumably due to the weaker bond energy of a sulfur–sulfur bond relative to a carbon–sulfur bond,[31] the polarizability of the sulfur atom, and participation of d orbitals in the transition state.[5a] This should also cause the free energy of the transition state **9**



9 10

of the second step of eq 2 to be lower than that of transition state **10** of the second step of eq 3. The enhanced nucleophilicity of RSS^- over RS^- due to the "α effect"[32] would appear to be one factor favoring the second step of eq 3 over that of eq 2; however, the magnitude of this effect is generally small or entirely absent for substitution at saturated carbon.[33] Thus, all considerations indicate that the second step of eq 2 (via **9**) should be a more favorable process than the second step of eq 3 (via **10**).

We may summarize our conclusions about eq 2 and 3, *for a situation where the first step is rate determining*, by the reaction coordinate given in Figure 2. This is only a qualitative comparison of the free energies of transition states a and b, e and f, and intermediates c and d, on the basis of the discussion given above. It serves to illustrate that when the first step of the desulfurization reaction is rate determining, the reaction pathway with the lowest activation energy (via b) is that which involves *terminal* sulfur removal (eq 3). Desulfurization of dialkyl trisulfides by aminophosphines in medium polarity solvents is thus rationalized by this reaction coordinate: the first step of the reaction is rate determining,[7a] the terminal sulfur (of **1g** or **1h**) is removed preferentially, and an inversion occurs at one α-carbon (demonstrated for trisulfide **1i**).

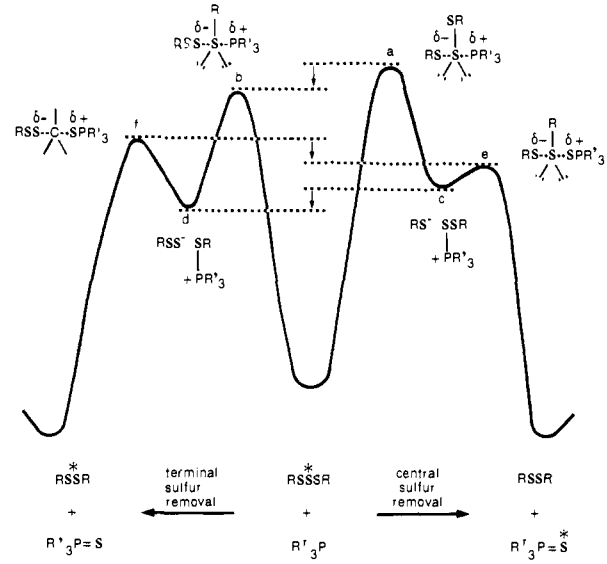


Figure 2. Desulfurization of trisulfides, first step rate limiting.

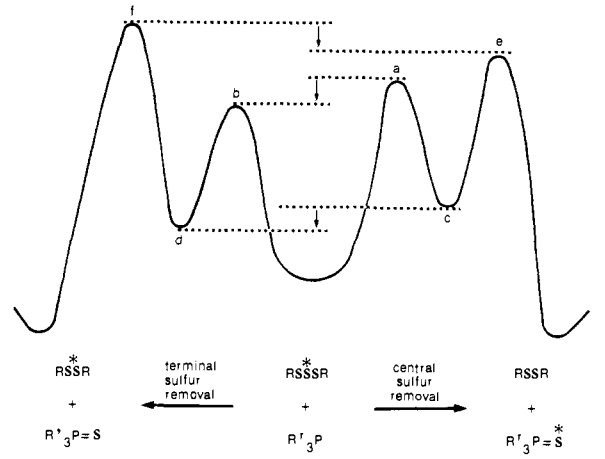


Figure 3. Desulfurization of trisulfides, second step rate limiting.

In the situation *where the second step is rate determining*, we believe the desulfurization mechanism is qualitatively summarized as in Figure 3. In this case, the relative free energies of a and b, c and d, and e and f are similar to those in Figure 2; however, since the second step is now rate limiting, the preferred reaction pathway (via e) is that which involves *central* sulfur removal (eq 2). This rationalizes the desulfurization of dialkyl trisulfides by triarylphosphines: the second step is rate limiting (demonstrated by the exchange experiments), the central sulfur (of **1g** or **1h**) is removed preferentially, and the reaction proceeds without inversion at either α carbon (demonstrated for **1i**). It is reasonable to consider that the transition state of the first step (formation of the phosphonium salt) is stabilized as the reaction solvent polarity increases. Sufficient stabilization of the first-step transition state in the case of desulfurization by aminophosphines may cause the second step of the reaction to become rate determining in high polarity solvents; this is consistent with the final exchange experiment described above and the increased amount of central-sulfur removal by aminophosphines with increased solvent polarity (as determined for trisulfides **1g**, **1h**, and **1i**).

Thus the reaction coordinates in Figures 2 and 3 represent a reasonable qualitative picture of the desulfurization of trisulfides by trivalent phosphorus compounds. All of the major effects observed in the radiochemical experiments, the reactions of optically active trisulfide **1i**, and the exchange reaction studies are in agreement with this hypothesis. Radiochemical experiment 18 is, however, not readily explained. The deviation in behavior

(30) Kice, J. L.; Favstritsky, N. A. *J. Am. Chem. Soc.* **1969**, *91*, 1751.
(31) Sulfur–sulfur bond enthalpies are considered to be ca. 5–10 kcal/mol less than carbon–sulfur bond enthalpies: (a) Pauling, L. "The Chemical Bond"; Cornell University Press: Ithaca, NY, 1967; p 60. (b) Johnson, D. A. "Sulfur in Organic and Inorganic Chemistry"; Senning, A., Ed.; Marcel Dekker: New York, 1972; Vol. 2, p 44.
(32) March, J. Reference 14b, p 325.
(33) Buncel, E.; Chuaqui, C.; Wilson, H. *J. Org. Chem.* **1980**, *45*, 3621 and references cited therein.

at low solvent polarity as shown in Figure 1 may be explained by the increased importance of a nonpolar desulfurization mechanism[7a] in low polarity media. This rationalization is based on tris(dialkylamino)phosphines reacting via a rate-determining first step and triarylphosphines reacting with the second step as rate determining. This is reasonable, as other related reactions having two consecutive steps have been concluded to have different rate-limiting steps.[34]

We conclude from this study that the interaction of phosphine with a trisulfide is a complex process, where the transition states of the two reaction steps in ionic desulfurization are of similar free energy, and that variations in phosphine type and reaction solvent may affect these transition states to alter the kinetically important step. For desulfurization without inversion at an α-carbon, triphenylphosphine is quite effective as it removes almost exclusively the central sulfur atom. However, for less reactive trisulfides, a tris(dialkylamino)phosphine would be required for a rapid desulfurization.[7a] In this case, desulfurization in benzene or ether provides a disulfide with predominant inversion at one α-carbon (via terminal sulfur removal), while in acetonitrile, a disulfide having predominantly retained stereochemistry at both α-carbons (via central sulfur removal) is obtained.

Experimental Section[37]

^{35}S-Labeled Trisulfides (1g,h). Sulfur-^{35}S dichloride (2 mCi) was obtained as a custom preparation from New England Nuclear Co. A 1.0 mCi sample was diluted in 19.0 g of unlabeled SCl_2 that had been freshly purified;[38] this was used immediately in the preparation of the ^{35}S-labeled trisulfides **1g,h**[13] according to the procedure described earlier for the unlabeled trisulfides.[7a,38] Thus, from distilled phenylmethanethiol and $^{35}SCl_2$ was obtained **1g** [86%, mp 47–47.5 °C (hexanes) (lit.[6f] mp 49 °C)]. From distilled 1-propanethiol and $^{35}SCl_2$ was obtained **1h** [77%, bp 88–92 °C (2.6–2.8 mm) (lit.[39] bp 68–69 °C (0.9 mm)]; the main fraction of distillate, which consisted of 94% trisulfide **1h**, 1.5% di-*n*-propyl disulfide, and 4.5% unknown component by GC (6 ft of 10% Apiezon L, programmed 150–250 °C at 20°/min; or 6 ft of 10% Carbowax 20M, 100 °C), was used for all desulfurization experiments described in this article.

Phosphines 2a–f. The para-substituted triarylphosphines **2b–d** were obtained from the Maybridge Chemical Co. Ltd., Cornwall, U.K. Triarylphosphines **2a–d** were each recrystallized from absolute ethanol as nearly colorless crystals: **2a**, mp 79–80 °C (lit.[40] mp 79–80 °C); **2b**, mp 147–148.5 °C (lit.[40] mp 147–149 °C); **2c**, mp 129–131 °C (lit.[40] mp 133–134 °C); and **2d**, mp 97.5–98.5 °C (lit.[40] mp 102–103 °C). Commercially available tris(dimethylamino)phosphine (**2e**) was distilled before use and stored under dry nitrogen or argon. Tris(morpholino)-phosphine (**2f**) was prepared as described earlier.[7a]

Desulfurization of Trisulfides 1g,h. Each reaction was performed in duplicate by the following general procedure; specific details of trisulfide, phosphine, solvent, and reaction temperature are given in Table I. A solution of the trisulfide (2.0 mmol) in 10.0 mL of solvent was equilibrated to the prescribed reaction temperature. The phosphine (2.0 mmol) was then added, and the reaction was monitored by TLC. Reactions of triarylphosphines **2a–c** with **1g** required 2–3 weeks for complete reaction;[18] reaction of **2d** with **1g** required heating at reflux (bath 100 °C) in acetonitrile for 18 h; reactions of **2a–c** with **1h** were heated at reflux (bath 100 °C) in acetonitrile for 24 h; and no significant reaction of **2d** with **1h** was detected after heating at reflux in acetonitrile for 1 month. Reactions of **2e,f** with **1g** were stirred for 2 h at room temperature; the reaction of **2e** with **1h** was stirred overnight at room temperature, and reaction of **2f** with **1h** was heated at reflux in acetonitrile for 3 h.

After the reaction, each mixture was evaporated at room temperature under reduced pressure. The residue was then chromatographed over a column of 10 g of silica gel with 9:1 hexanes–chloroform as eluant to afford the disulfide product. Elution with chloroform afforded the phosphine sulfide. The exception was that the product mixture from **2d** with **1g** was chromatographed over 20 g of silica gel, eluting with 9:1 hexanes–CH_2Cl_2 followed by CH_2Cl_2. All crystalline products isolated were recrystallized from absolute ethanol. Thus, were obtained dibenzyl disulfide, mp 67–68 °C (lit.[6f] mp 71 °C); di-*n*-propyl disulfide (an oil), identical with an authentic sample by GC; $(C_6H_5)_3PS$, mp 159–160 °C (lit.[41] mp 158–160 °C); $(4\text{-}CH_3C_6H_4)_3PS$, mp 188–189 °C (lit.[42] mp 185–186 °C); $(4\text{-}CH_3OC_6H_4)_3PS$, mp 111–111.5 °C (lit.[42] mp 109–110 °C); $(4\text{-}ClC_6H_4)_3PS$, mp 151.5–152.5 °C (lit.[43] mp 152–153 °C); tris-(dimethylamino)phosphine sulfide (an oil), spectroscopically identical with an authentic sample;[7a] and tris(morpholino)phosphine sulfide, mp 145–146 °C (lit.[44] mp 145.5–146.5 °C). All products were homogeneous by TLC. The yields of products based on two crops of crystals were ca. 70% for dibenzyl disulfide and ca. 85% for phosphine sulfide; the oils PrSSPr and $(Me_2N)_3PS$ were obtained nearly quantitatively.

Measurement of Radioactivity. A sample of product (10–50 mg) was dissolved in 15.0 mL of a "cocktail" solution of PPO (2,5-diphenyloxazole) in toluene (both Scintillation Grade, 5.0 g/L). Radioactivity measurements were performed with a Beckman LS-150 Liquid Scintillation System for 0–1.71-MeV maximum energy.[45] The counts per minute (cpm) per millimole of product so determined was divided by the cpm per millimole of trisulfide starting material (measured immediately afterward) to give the percentage of radioactivity per mole of product as summarized in Table I.

(−)-Sodium *O*-Menthyl Dithiocarbonate. Sodium metal (16 g, 0.70 mol, cleaned as recommended by Fieser and Fieser[46]) was added to a solution of (−)-menthol (100 g, 0.64 mol) in 70 mL of dry toluene under a dry nitrogen atmosphere in a 1-L flask. This mixture was heated at reflux (bath 140 °C) with stirring under N_2 for 21 h. The mixture was then allowed to cool slowly without stirring so that large globules of solid sodium (excess) could form and be easily removed. A solution of carbon disulfide (50 g, 40 mL, 0.66 mol) in 250 mL of anhydrous diethyl ether was then gradually added to the above solution while stirring under N_2 in an ice–water bath. The yellow solution of (−)-sodium *O*-menthyl dithiocarbonate[47] obtained was filtered and then used directly in the next step.

(34) The desulfurization of disulfides by aminophosphines and the Arbuzov-type reaction of disulfides and trialkylphosphites are both believed to occur via the rate-limiting formation of phosphonium salt (first step).[25a] In contrast, the normal Arbuzov reaction of alkyl halides and trialkyl phosphites is generally believed to have a rate-limiting second step.[35] The reduction of disulfides to thiols by triphenylphosphine is implied to have the second step as rate determining at intermediate pH, since under these conditions the reversal of the first step becomes sufficiently important to complicate the kinetics of the reaction.[36]

(35) Harvey, R. G.; DeSombre, E. R. *Top.* Phosphorus *Chem.* **1964**, *1*, 57.

(36) Overman, L. E.; Matzinger, D.; O'Connor, E. M.; Overman, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 6081.

(37) Unless stated otherwise, chemical reagents were obtained from commercial sources and were used directly. Acetonitrile was purified by stirring with CaH, distillation from P_2O_5, and then refluxing over and slow distillation from CaH; commercial anhydrous diethyl ether was used directly; ethyl acetate was washed with 5% aqueous Na_2CO_3 and saturated $CaCl_2$, dried over K_2CO_3, and distilled from P_2O_5; tetrahydrofuran was distilled from the blue sodium ketyl of benzophenone; benzene and toluene were each distilled from sodium metal; these and all other solvents used were stored over 4-Å molecular sieves. Melting points were obtained on a Gallenkamp block apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectrophotometer, calibrated with the 1602-cm^{-1} band of a polystyrene film. Nuclear magnetic resonance spectra were measured with a Varian Associates T-60A spectrometer. Mass spectra were obtained on an LKB 9000 mass spectrometer at 70 eV using a direct insertion probe, while gas chromatographic–mass spectral analyses were performed by using a Hewlett-Packard 5984A system. Gas chromatographic analyses were obtained by using a Hewlett-Packard F & M Model 5751A research chromatograph equipped with a Perkin-Elmer Model 194B printing integrator; a 6 ft × 0.125 in. stainless steel column of 5% OV-101 on Chromosorb 750 (A/W-DMCS, 100/200 mesh), temperature programmed 50–300 °C at 20 °C/min, was used except where stated otherwise. Optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter. Chromatography was accomplished with E. Merck Silica Gel 60 F-254 sheets (Cat. 5775) for TLC and E. Merck Silica Gel 60 (Cat. 7734) for column work. Elemental Analyses were performed by Galbraith Laboratories, Knoxville, TN.

(38) Harpp, D. N.; Smith, R. A. *J. Org. Chem.* **1979**, *44*, 4140.

(39) Cairns, T. L.; Evans, G. L.; Larchar, A. W.; McKusick, B. C. *J. Am. Chem. Soc.* **1952**, *74*, 3982.

(40) Borowitz, G. B.; et al. *Phosphorus Relat. Group V Elem.* **1972**, *2*, 91.

(41) Olah, G. A.; Hehemann, D. *J. Org. Chem.* **1977**, *42*, 2190.

(42) Baliah, V.; Subbarayan, P. *J. Org. Chem.* **1960**, *25*, 1833.

(43) Schiemenz, G. P. *Chem. Ber.* **1966**, *99*, 504.

(44) Audrieth, L. F.; Toy, A. D. F. *J. Am. Chem. Soc.* **1942**, *64*, 1553.

(45) Sufficient disintegrations were measured such that the counting error was not more than 1.0% (2σ, 95% confidence level). The counts per minute (cpm) were corrected for background radiation and also for quench (counting efficiency). Compensation for quench either (a) by the use of a calibration curve of counting efficiency vs. "external standard ratio" for a set of ^{14}C standards (49×10^3 dpm), or (b) by the addition of <20 drops of chloroform (as an organic quench simulator) per sample to give equal "external standard ratios" was found to be equivalent within experimental error.

(46) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 1022.

(47) Tschugaeff, L. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3332.

(48) Holmberg, B. *Ark. Kemi, Mineral. Geol.* **1939**, *13A*, *No. 8*; *Chem. Abstr.* **1939**, *33*, 6278.

(49) Holmberg, B. *Ark. Kemi, Mineral. Geol.* **1937**, *12A*, *No. 14*; *Chem. Abstr.* **1937**, *31*, 4292.

(−)-*O*-Menthyl *S*-1-Phenylethyl Dithiocarbonates (4a,b). The procedure was slightly different from that of Isola and co-workers.[20] (±)-1-Bromo-1-phenylethane (100 g, 0.54 mol) was added dropwise with stirring to the toluene–ether solution of (−)-sodium *O*-menthyl dithiocarbonate (0.64 mol) obtained above. After addition of ca. 50 g of the bromo compound, enough white precipitate (NaBr) had formed to render stirring impossible. Water was added to effect partial solution, and the addition of $PhCH(CH_3)Br$ was completed with stirring. After being heated at reflux for 4 h, the mixture was cooled, and the organic layer was separated, washed three times with water, dried ($MgSO_4$), and evaporated to afford 197 g of a yellow oily liquid. The addition of 300 mL of ethanol followed by cooling in the freezer gave 76.9 g (86%) of slightly yellow crystals of **4b**, mp 69–71 °C. Crystallization of the mother liquor from ethanol gave 86.5 g (95%) of white crystals of **4a**, mp 56–60 °C. Crystallization of the new mother liquor gave additional **4b** as a crude powder. The samples of **4b** were recrystallized from ethanol to constant melting point: 75.9 g (83%) of (*R*)-(+)[21]-xanthate ester **4b**, mp 71–72 °C, $[\alpha]^{20}_D$ +149° (*c* 2.52, C_6H_6) [lit.[20] mp 76–77 °C, $[\alpha]^{25}_D$ +148.8° (*c* 2.4, C_6H_6)]. The sample of **4a** was recrystallized from methanol to constant melting point: 77.1 g (85%) of the (*S*)-(−)[21]-xanthate ester **4a**, mp 63–64 °C, $[\alpha]^{20}_D$ −267° (*c* 2.46, C_6H_6); NMR nearly identical with that of **4b**; MS, *m/e* (rel intensity) 336 (0.5, M^+), 275 (1), 198 (4), 139 (25), 138 (50), 105 (74), 83 (100). Anal. Calcd for $C_{19}H_{28}OS_2$: C, 67.80; H, 8.39; S, 19.06. Found: C, 67.60; H, 8.34; S, 18.92.

(R)-(+)-1-Phenylethanethiol (5). Ethylenediamine (52 g, 0.87 mol) was added to a solution of pure (*R*)-(+)-xanthate ester **4b** (61.8 g, 0.184 mol) in 200 mL of benzene with stirring under N_2. The reaction appeared complete after 10 min (TLC); however, it was stirred overnight at room temperature. Volatiles were then removed under reduced pressure, and the residue obtained was mixed with an ice–water solution of H_2SO_4 (ca. pH 3) and extracted three times with diethyl ether. The combined ether phases were washed with 5% H_2SO_4, dried ($MgSO_4$), and evaporated to give a colorless oil. An attempt at distillation at this stage gave a clear liquid, bp 97–99 °C (19 mm) [lit.[20] bp 86–87 °C (17 mm) for (+)-$PhCH(CH_3)SH$], that consisted of a mixture of thiol and menthol (NMR). The distillate was thus chromatographed on a column of 250 g of silica gel with hexanes as eluant to afford 12.5 g (49%) of (*R*)-(+)-1-phenylethanethiol (**5**)[21] as a clear colorless liquid, $[\alpha]^{20}_D$ +91.8° (*c* 6.06, absolute EtOH) [lit.[20] $[\alpha]^{25}_D$ +91.7° (*c* 6.17, absolute EtOH)].

(*R*,*R*)-(+)-Bis(1-phenylethyl) Disulfide (6). A solution of iodine (761 mg, 3.0 mmol) in 10 mL of methanol was added dropwise to a solution of (*R*)-(+)-**5** (691 mg, 5.0 mmol) in 15 mL of methanol. After being stirred at room temperature for 3 h, TLC (pentane) indicated the absence of thiol. However, the solution was allowed to stand 2 days at room temperature, and then sufficient 10% aqueous $Na_2S_2O_3$ to decolorize the solution was added. The organic layer was separated, washed with saturated $NaHCO_3$ and twice with water, dried ($MgSO_4$), and evaporated to give 675 mg (98%) of (*R*,*R*)-(+)-bis(1-phenylethyl) disulfide (**6**) as a colorless oil, which did not crystallize in ethanol at −20 °C: $[\alpha]^{20}_D$ +277° (*c* 1.16, absolute EtOH) [lit.[48] $[\alpha]_D$ +271.9° (*c* 1, EtOH)]; also $[\alpha]^{20}_D$ +316°, $[\alpha]^{20}_{578}$ +332°, $[\alpha]^{20}_{546}$ +388°, $[\alpha]^{20}_{436}$ +772° (*c* 2.45, C_6H_6). There was no change in the optical rotation after 2 years of storage at room temperature. The NMR spectrum of **6** indicated a high optical purity (clean PhC*H* quartet at δ 3.5) and was identical with the NMR spectra of authentic crystalline (±)-bis(1-phenylethyl) disulfide.[48,49]

(*R*,*R*)-(+)-Bis(1-phenylethyl) Trisulfide (1i). In a manner similar to that described previously for the meso-*d*,*l* trisulfide (mixture of diastereomers),[7a] (*R*)-(+)-**5** and freshly purified SCl_2[38] were allowed to react to form (*R*,*R*)-(+)-bis(1-phenylethyl) trisulfide (**1i**). In this case, after workup, the oil was filtered through two times its weight of silica gel with hexanes and evaporated to give **1i** as a near-colorless oil (96% yield): $[\alpha]^{20}_D$ +218°, $[\alpha]^{20}_{578}$ +229°, $[\alpha]^{20}_{546}$ +266°, $[\alpha]^{20}_{436}$ +510° (*c* 1.98, C_6H_6). There was no change in the optical rotation after 0.5 year of storage at room temperature. The NMR spectrum of **1i** indicated a high optical purity (clean PhC*H* quartet at δ 4.1); comparison with the NMR spectra of the meso-*d*,*l* trisulfide,[7a] and of a mixture of **1i** and meso-*d*,*l* trisulfide, indicated the PhC*H* signal of the *d*,*l* diastereomer to be 0.05-ppm downfield from that of the meso diastereomer (Table II). In other respects (IR, TLC), **1i** was identical with the authentic meso-*d*,*l* trisulfide.[7a]

Desulfurization of Trisulfide 1i. Each experiment was performed in at least triplicate by the following general procedure. To trisulfide **1i** (40.0 mg, 0.131 mmol) in a 2-mL volumetric flask was added 2 mL of dry solvent. After complete dissolution, a 10–20% excess of distilled phosphine **2e** (26.2–28.5 μL, 0.144–0.157 mmol) was added and mixed thoroughly; the solution was allowed to stand under N_2 at room temperature for 1–3 weeks to ensure complete reaction. The solvent was then carefully evaporated by applying a gentle stream of nitrogen, followed by removal of last traces of solvent under high vacuum. Benzene was added to make a 2.0-mL solution, and the optical rotation was measured[50] (Table III). The solution was then concentrated and the NMR spectrum recorded to qualitatively confirm the result by comparison of the meso and *d* PhC*H* quartets of the disulfide.

Similar desulfurization of trisulfide **1i** by phosphine **2f** in acetonitrile-d_3 at 65 °C was only ca. 75% complete (NMR) after 10 days. Desulfurization of **1i** by phosphine **2a** in acetonitrile-d_3 at 65 °C was not complete after 3 weeks. NMR analyses of each of these incomplete reactions showed the disulfide product to have a clean PhC*H* quartet corresponding to that of the *R*,*R* disulfide **6** (i.e., no (*R*,*S*)-*meso*-disulfide formed).

Reaction of Diphenyl and Di-*p*-tolyl Disulfides with Phosphines 2a and 2e. Diphenyl disulfide (22 mg, 0.1 mmol) and di-*p*-tolyl disulfide (25 mg, 0.1 mmol) were dissolved in 1.5 mL of benzene. After 20 min at room temperature, GC analysis (OV-101) indicated no significant formation of phenyl *p*-tolyl disulfide. Addition of **2e** (ca. 5 mg, 0.03 mmol) gave equilibrium amounts (ca. 1:1:1) of diphenyl, phenyl *p*-tolyl, and di-*p*-tolyl disulfides within 1 min, as originally observed by Gleason.[51] Identical results were obtained when the experiment was repeated, utilizing **2a** (ca. 1 mg) in place of **2e**; addition of more **2a** (26 mg, 0.1 mmol) had no effect (other than producing a peak for **2a** in the GC trace).

Methyl Phenyl Disulfide. An ca. 8-year-old sample (Aldrich, not presently available) of this disulfide was found to be a mixture of MeSSMe, MeSSPh, and PhSSPh by GC. Distillation afforded methyl phenyl disulfide, by 83–84 °C (1.0 mm), n^{25}_D 1.6181 (lit.[52] $n^{26.5}_D$ 1.6125), pure by GC and NMR analyses.

Reaction of Methyl Phenyl Disulfide with 2a. To a solution of pure MeSSPh (55 mg, 0.35 mmol) in 3 mL of dry benzene was added **2a** (110 mg, 0.70 mmol). The resulting solution was heated at 75 °C under N_2 and monitored by GC: there was no apparent reaction after 16 h, but after 2.7 days there was ca. 20% disproportionation to MeSSMe and PhSSPh. When the above reaction was repeated, utilizing 3 mL of dry acetonitrile in place of benzene, there was ca. 35% disproportionation products (MeSSMe + PhSSPh) after 45 min, and after 14 h there was 14% MeSPh and 44% disproportionation products; after 2.6 days there was no significant amount of MeSSPh remaining. Each GC peak was identified by the use of authentic samples.

In the absence of **2a**, MeSSPh showed no change (GC) after 14 h at 75 °C in acetonitrile.

Reaction of a Mixture of Two Alkyl Aryl Disulfides with 2a. To a solution of pure methyl phenyl disulfide (78 mg, 0.5 mmol) and benzyl *p*-tolyl disulfide[53] (123 mg, 0.5 mmol) in 2.5 mL of dry benzene was added **2a** (131 mg, 0.5 mmol). The solution was then heated at reflux (bath 100 °C) and monitored by GC: after 5 min a small amount of $PhCH_2SSPh$ had formed, and after 5 h there was a clean mixture of ca. equimolar amounts of MeSSPh, *p*-TolSSMe, $PhCH_2SSPh$, and *p*-$TolSSCH_2Ph$. GC coinjection of this equilibrium solution with authentic samples of benzyl methyl disulfide[38] and dibenzyl disulfide confirmed their absence in the equilibrium mixture. GC/MS analysis confirmed the identity of each peak; for methyl *p*-tolyl disulfide, MS, *m/e* (rel intensity) 170 (100, M^+), 155 (13, $M^+ - CH_3$), 123 (28, $M^+ - CH_3S$), 91 (50, $M^+ - CH_3SS$); and for benzyl phenyl disulfide, MS, *m/e* (rel intensity) 232 (37, M^+), 141 (3, $M^+ - PhCH_2$), 123 (10, $M^+ - PhS$), 109 (10, $M^+ - PhCH_2S$), 91 (100, $C_7H_7^+$). It should be noted that all possible monosulfides and symmetrical disulfides, benzyl methyl disulfide, and phenyl *p*-tolyl disulfide were clearly *not* present in the equilibrium mixture of compounds. When the above reaction was repeated, utilizing 2.5 mL of dry acetonitrile in place of benzene, the same equilibrium mixture was obtained in 30 min at room temperature. In the absence of **2a**, there was no trace of reaction (GC) after 12 h at room temperature in acetonitrile.

Reaction of a Mixture of Two Dialkyl Disulfides with 2a. To a solution of dibenzyl disulfide (246 mg, 1.0 mmol) and di-*n*-butyl disulfide (178 mg, 1.0 mmol) in 5 mL of dry acetonitrile was added **2a** (262 mg, 1.0 mmol). After 4 h at reflux (bath 100 °C), complete exchange to a clean mixture (ca. 1:2:1) of $BuSSBu$, $BuSSCH_2Ph$, and $PhCH_2SSCH_2Ph$ was observed (GC). Injection of an authentic sample of $BuSSCH_2Ph$[38] and GC/MS analysis confirmed the identity of the new peak: for benzyl *n*-butyl disulfide, MS, *m/e* (rel intensity) 212 (20, M^+), 91 (100, $C_7H_7^+$).

(50) Each optical rotation value ($[\alpha]^{20}_D$) was divided by 309° to obtain the percentage central sulfur removal (Table III) since a 1:1 mixture of disulfide **6** and $(Me_2N)_3PS$ had $[\alpha]^{20}_D$ +309° (*c* 2.01, C_6H_6) (addition of up to 0.5 mol equiv of phosphine **2e** to this sample had a negligible effect on this optical rotation).

(51) Gleason, J. G., Ph.D. Thesis, McGill University, 1970.

(52) Oki, M.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1223.

(53) Harpp, D. N.; Friedlander, B. T.; Larsen, C.; Steliou, K.; Stockton, A. *J. Org. Chem.* **1978**, *43*, 3481.

(54) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem., Part A* **1971**, *1A*, 211.

It should be noted that *no* desulfurization products (monosulfides) were observed. When the above reaction was performed at room temperature in acetonitrile for 20 h or at room temperature in benzene for 4 days, no reaction was observed.

In the absence of **2a**, there was no trace of reaction (GC) after 16 h at reflux in acetonitrile.

Attempted Desulfurization of Dibenzyl Disulfide by 2a. A solution of dibenzyl disulfide (246 mg, 1.0 mmol) and **2a** (288 mg, 1.1 mmol) in 5 mL of dry acetonitrile or benzene was heated at reflux (bath 100 °C); after 14 h there was no reaction observed (GC).

Reaction of a Mixture of Two Dialkyl Disulfides with 2e. This reaction was performed as described above for the analogous reaction with **2a**, utilizing **2e** (163 mg, 1.0 mmol) in place of **2a**. In this case, $BuSSCH_2Ph$ (exchange product) and $PhCH_2SSCH_2Ph$ + $(Me_2N)_3PS$ (desulfurization products) were formed at similar rates (GC) for reaction at room temperature in acetonitrile, 50 °C in benzene, and room temperature in benzene.

Reaction of a Mixture of Dibenzyl and Di-*p*-tolyl Trisulfides with 2a or 2e. To a solution of dibenzyl trisulfide[38] (278 mg, 1.0 mmol) and di-*p*-tolyl trisulfide[38] (278 mg, 1.0 mmol) in 6 mL of benzene was added **2a** (262 mg, 1.0 mmol). Analysis by NMR (C_6H_6) after 5 min at room temperature indicated the presence of *p*-$TolSSSCH_2Ph$ ($PhCH_2$, δ 3.75), *p*-$TolSSCH_2Ph$ ($PhCH_2$, δ 3.65), $(PhCH_2S)_2S$ ($PhCH_2$, δ 3.72), $(PhCH_2S)_2$ ($PhCH_2$, δ 3.38); presumably $(p\text{-TolS})_2S$ and $(p\text{-TolS})_2$ were also present ($4\text{-}CH_3\text{-}C_6H_4$, coincidental at δ 2.0). Except for the benzyl *p*-tolyl trisulfide peak for which no authentic sample was available, the identities of all peaks were confirmed by the addition of authentic samples. (Analysis by GC or GC/MS was not possible due to decomposition of the trisulfides in the GC). Reaction as above utilizing **2e** in place of **2a** gave similar results.

Reaction of a Mixture of Dibenzyl and Dipropyl Trisulfides (1j,k) with 2a or 2e. To a solution of dibenzyl trisulfide (**1j**) (28 mg, 0.1 mmol) and di-*n*-propyl trisulfide (**1k**)[38] (18 mg, 0.1 mmol) in 0.5 mL of benzene was added **2a** (26 mg, 0.1 mmol). The reaction at room temperature was monitored by both GC and NMR; after 3 h, a small amount of $PrSSSCH_2Ph$ (**1l**) had formed, after ca. 15 h, complete exchange had occurred ($PrSSSCH_2Ph$:$(PhCH_2S)_2S$ = 2:1 by NMR) without formation of any disulfides, and after 5 days the desulfurization reaction was essentially complete, resulting in a mixture of the three possible trisulfides and three possible disulfides and Ph_3PS. The identities of these components were confirmed by GC/MS and comparison (GC, NMR) with authentic samples: for benzyl *n*-propyl trisulfide (**1l**),[7a,54] NMR (C_6H_6) δ 3.80 (s, $PhCH_2$); chemical ionization (isobutane) MS, *m/e* (rel intensity) 231 (92, $M^+ + 1$), 199 (100, $M^+ + 1\text{-}S$); and for benzyl *n*-propyl disulfide,[7a] NMR (C_6H_6) δ 3.50 (s, $PhCH_2$); MS, *m/e* (rel intensity) 198 (7, M^+), 91 (100, $C_7H_7^+$); chemical ionization (isobutane) MS, *m/e* 199 (100, $M^+ + 1$). When the above reaction was repeated, utilizing 0.5 mL of acetonitrile-d_3 in place of benzene, complete exchange to $PrSSSCH_2Ph$ without formation of any disulfides occurred within 7 min at room temperature (NMR); complete desulfurization to a mixture similar to that obtained above was achieved within 23 h at room temperature. When the above two experiments were repeated, utilizing **2e** (16 mg, 0.1 mmol) in place of **2a**, NMR and GC analyses showed a mixture of exchange reaction and desulfurization products to be present after 5 min at room temperature.

In the absence of **2a** or **2e**, there was no trace of reaction or exchange after 14 days at room temperature in either acetonitrile-d_3 or benzene.

Reaction of Dibenzyl Trisulfide (1j) with 0.5 Molar Equiv of 2a or 2e. A solution of **1j** (28 mg, 0.1 mmol) and **2a** (13 mg, 0.05 mmol) in 0.5 mL of benzene showed no reaction (NMR) after 20 h at room temperature, but within 24 h at ca. 65 °C, a mixture of dibenzyl trisulfide and disulfide (ca. 1:1) plus tetrasulfide (ca. 7%) had formed. For $(PhCH_2SS)_2$, NMR (C_6H_6) δ 3.8 (s, $PhCH_2$); the identity of this peak was confirmed by the addition of authentic dibenzyl tetrasulfide.[55] When the above reaction was repeated, utilizing 0.5 mL of acetonitrile-d_3 in place of benzene, essentially identical results were obtained within 5 h at room temperature. When the above two experiments were repeated, utilizing **2e** (9.1 μL, 0.05 mmol) in place of **2a**, reaction in CD_3CN gave similar results (ca. 8% tetrasulfide) within 30 min at room temperature, but in benzene there was no significant formation of tetrasulfide; the products formed within 30 min at room temperature were 1:1 dibenzyl trisulfide and disulfide.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work. We are most grateful for helpful discussions on radiochemistry and radiochemical techniques with Professor J. J. Hogan.

Registry No. 1g, 27694-48-0; **1h**, 82891-19-8; **1i**, 82916-72-1; **1j**, 6493-73-8; **1k**, 6028-61-1; **1l**, 75030-40-9; **2a**, 603-35-0; **2b**, 1038-95-5; **2c**, 855-38-9; **2d**, 1159-54-2; **2e**, 1608-26-0; **2f**, 5815-61-2; **4a**, 82891-20-1; **4b**, 82902-14-5; **5**, 33877-16-6; **6**, 82916-73-2; $^{35}SCl_2$, 31602-27-4; ethylenediamine, 107-15-3; phenylmethanethiol, 100-53-8; 1-propanethiol, 107-03-9; (−)-sodium *O*-methyl dithiocarbonate, 37601-89-1; (−)-menthol, 2216-51-5; (±)-1-bromo-1-phenylethane, 38661-81-3; di-*p*-tolyl disulfide, 103-19-5; methyl phenyl disulfide, 14173-25-2; benzyl *p*-tolyl disulfide, 16601-19-7; methyl *p*-tolyl disulfide, 57266-34-9; benzyl phenyl disulfide, 16601-17-5; dibenzyl disulfide, 150-60-7; di-*n*-butyl disulfide, 629-45-8; benzyl *n*-butyl disulfide, 16601-16-4.

(55) Harpp, D. N.; Steliou, K.; Chan. T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222.

O-Sulfated β-Lactam Hydroxamic Acids (Monosulfactams). Novel Monocyclic β-Lactam Antibiotics of Synthetic Origin[1]

E. M. Gordon,* M. A. Ondetti, Jelka Pluscec, C. M. Cimarusti, D. P. Bonner, and R. B. Sykes

Contribution from The Squibb Institute for Medical Research, Princeton, New Jersey 08540.
Received January 27, 1982

Abstract: Monocyclic β-lactams bearing an $O\text{–}SO_3^-$ substituent at N-1 have been shown to be isolable chemical entities and represent a novel class of totally synthetic monocyclic β-lactam antibiotics. Several syntheses and the biological activity of such O-sulfated β-lactam hydroxamic acids are described.

Several years ago we set out to test the hypothesis that antimicrobial activity in β-lactam antibiotics was not rigidly dependent upon the bicyclic framework possessed by most β-lactam antibiotics. Rather, we postulated that a bicyclic ring fused azetidinone structure may be only one method of achieving suitable β-lactam activation[2] and that if sufficient ring reactivity could be induced by an alternative mechanism, within the constraints imposed by other well-documented structural requirements,[3] antimicrobial activity might be achievable. Thus, simple monocyclic β-lactams, when suitably equipped with electron-withdrawing substituents, could prove to possess significant antimicrobial ac-

(1) Dedicated to the memory of Professor David Perlman.

(2) Bioactivation of bicyclic azetidinone antibiotics may occur by "flattening", as suggested by: Rando, R. *Acc. Chem. Res.* **1975**, *8*, 281.

(3) A properly positioned anionic charge and (in most cases) a 3β-amido substituent are crucial. The importance of azetidinone nitrogen in enzyme binding has also been studied. Gordon, E. M.; Pluscec, J.; Ondetti, M. A. *Tetrahedron Lett.* **1981**, 1871.

0002-7863/82/1504-6053$01.25/0