vic-Disulfoxides and *OS*-Sulfenyl Sulfinates

FILLMORE FREEMAN

Department of Chemistry, University of California, Irvine, California 92717

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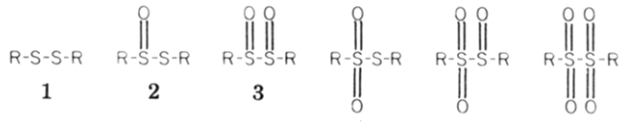
I. Introduction

Sulfur atoms participating in disulfide bonds (**1**) have electron pairs available for covalent bonding with oxygen. The oxygenated structures that still retain the

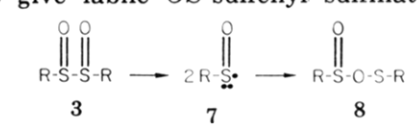


S–S bond are sulfinothioic acid *S*-esters (thiosulfinates; **2**), *vic*-disulfoxides (**3**),[1–35] sulfonothioic acid *S*-esters (thiosulfonates; **4**), sulfinyl sulfones (**5**), and *vic*-disulfones (**6**). Although examples of compounds **2**, **4**, **5**, and **6** are known and have been isolated, transient *vic*-disulfoxides (**3**) have been only recently observed in low-temperature ^{1}H NMR and ^{13}C NMR studies.[3–6]

Fillmore Freeman received his B.S. (1957) from Central State University, Wilberforce, OH, and his Ph.D. (1962) from Michigan State University. After 2 years (1962–1964) at the California Research Corporation, he was an NIH Postdoctoral Fellow (1964–1965) at Yale University. He joined the faculty at the University of California, Irvine, in 1973 after 8 years at California State University, Long Beach. He has been a Visiting Professor at the Université de Paris VII, at the University of Illinois—Chicago Circle, at the Max-Planck-Institut für Biophysikalische Chemie, Göttingen, and at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette. He was a Fulbright–Hays Senior Research Scholar and a Fellow of the Alexander von Humboldt Foundation. In addition to oxidation mechanisms, Dr. Freeman's research interests include organosulfur chemistry, heterocyclic chemistry, carbohydrate chemistry, organometallic chemistry, and addition reactions of unsaturated compounds.

The question of whether 1,2-disulfide dioxides possess the *vic*-disulfoxide (**3**) or the thiosulfonate (**4**) structure has generated considerable controversy. Theoretical calculations,[1,2] a comparison of the infrared and Raman spectra of a number of related oxygen–sulfur compounds,[36] and X-ray diffraction studies[37] have shown that the thiosulfonate structure **4** is considerably more stable than the isomeric *vic*-disulfoxide structure **3**.

Although the chemistry of diastereomeric *vic*-disulfoxides (**3**) is relatively unknown,[4–6] it is reasonable to postulate that homolytic cleavage of the S–S bond in **3** will yield sulfinyl radicals (**7**)[1,2] which can recombine to give labile *OS*-sulfenyl sulfinates (**8**).[38–40]



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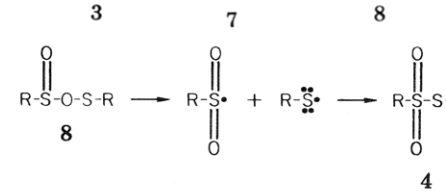

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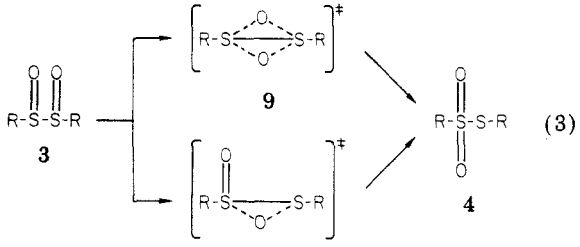
TABLE I. A Comparison of Calculated and Observed Bond Angles (deg) and Bond Lengths (Å) of Hydrogen Persulfide (H-S-S-H, 13) and Its Corresponding Oxide Derivatives[a]

sulfur compd	no.	$\angle O_1S_1H_1(C_1)$	$\angle OSS$	$\angle S_2S_1H_1(C_1)$	r_{SO}	$r_{S_1S_2}$
H-S-S-H	13			99.0		2.057
	14	109.1	113.5	87.9	1.473 (1.457)	2.104
	15 (*meso*)	110.4	104.8	89.4	1.484	2.144
	16 (*R, S*)		103.3, 106.4	90.3, 88.4	1.486, 1.483	2.144
	17a		110.5	110.5	1.447	2.084
	18	110.2	106.5	97.8	1.426	2.072

[a] Reference 1.

Subsequently, unstable **8** collapses to sulfenyl and sulfonyl radicals, which can recombine at the sulfur atoms to yield thiosulfonate **4**.[1,2,4-6,12,16,35,38-42]

Although the radical reactions shown in eq 1 and 2 are reasonable, *vic*-disulfoxides (**3**) and *OS*-sulfenyl sulfinates (**8**) may rearrange to thiosulfonates (**4**) via concerted mechanisms (eq 3, 4, 5).[4-9,12-16,43,44]



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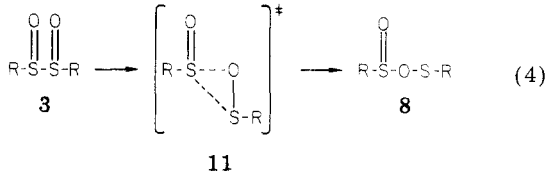

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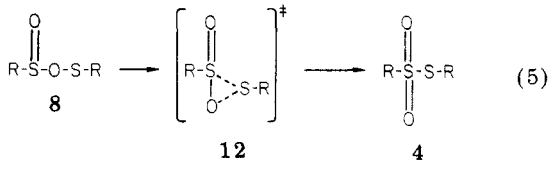

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The more than hundred-year-old question of whether *vic*-disulfoxides (**3**) and *OS*-sulfenyl sulfinates (**8**) are transient intermediates in certain reactions has generated considerable controversy.[1,4-6,11,12-16,18,32,41,45,46] It is the purpose of this review to correlate and analyze in terms of structure and mechanisms some of the vast amount of information that has been published in this area of organosulfur chemistry.

II. Theoretical Calculations

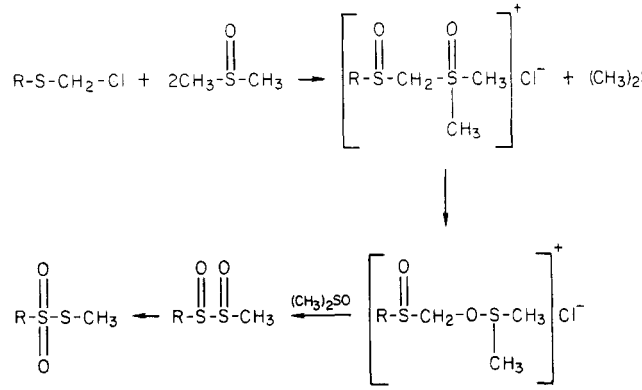
The structures of hydrogen persulfide (HSSH, **13**) and its monoxide (HS(O)SH, **14**), dioxides (*meso*-HS(O)S(O)H, **15**; (*R,S*)-HS(O)S(O)H, **16**; HSO_2SH, **17**) and tetraoxide (HSO_2SO_2H, **18**) derivatives were examined by ab initio molecular-orbital calculations at the HF/3-21G* and 6-31G* levels (Table I, II).[1,2] The energetics of the rearrangement of *vic*-disulfoxides (**15** and **16**) to thiosulfonate (**17**) via *OS*-sulfenyl sulfinate (HS(O)OSH, **19**), sulfinyl radical, sulfenyl radical,

TABLE II. Total Energies of Some Sulfur Derivatives[a]

		total energy, au	
sulfur compd	no.	3-21G*	6-31G*
H-S-S-H	13	-792.4832	
	14	-866.8485	
	15	-941.2084	-945.7345
	16	-941.2084	-945.7344
	19	-941.2806	-945.7796
	17b	-941.3111	-945.8189
	18	-1090.0692	
		-545.0897	
		-470.6430	
H-S·		-396.2180	

[a] Reference 1.

SCHEME I

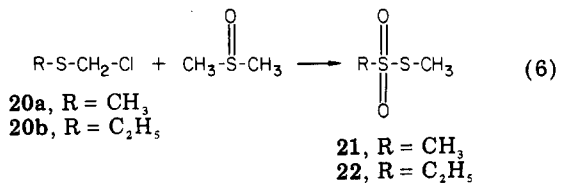


and/or sulfonyl radical were calculated. The ab initio molecular-orbital calculations on the simplest model support the mechanism proposed for the rearrangement of *vic*-disulfoxides (**3**, **15**, **16**) via sulfinyl radicals (**7**) to thiosulfonates (**4**, **17**).[1]

III. Reactions Postulated To Involve vic-Disulfoxides and OS-Sulfenyl Sulfinates

A. Alkyl α-Haloalkyl Sulfides and Dimethyl Sulfoxide

Treating methyl chloromethyl sulfide (**20a**) with excess dimethyl sulfoxide led to the formation of *S*-methyl methanesulfonothioate (*S*-methyl methanethiosulfonate, **21**.[47] Paraformaldehyde and possibly trimethylsulfonium chloride were also isolated.



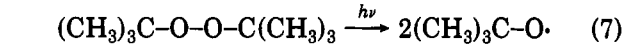
(6)

An almost quantitative yield of *S*-methyl ethanesulfonothioate (**22**) or its isomer, instead of *S*-ethyl ethanesulfonothioate ($CH_3CH_2SO_2SCH_2CH_3$), was obtained from the reaction of ethyl chloromethyl sulfide (**20b**) with dimethyl sulfoxide. The formation of **22** supports the proposed mechanism (Scheme I) and proves that the methylthio group (CH_3S) in **21** and **22** arose from dimethyl sulfoxide. It is also of interest to note the proposed unsymmetrical *vic*-disulfoxide in Scheme I led *exclusively* to one thiosulfonate (**22**).[43,47]

B. Sulfenic Acids

1. Photolysis of Sulfenic Acids

Ultraviolet irradiation of a hydrocarbon solution of di-*tert*-butyl peroxide (DTBP) and 2-methyl-2-propanesulfenic acid (**23**) produced an ESR spectrum which was consistent with the 2-methyl-2-propanesulfinyl radical (**24**).[38,40] At −100 °C, 2-methyl-2-



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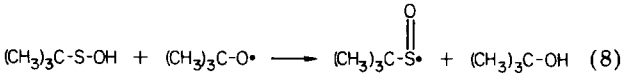
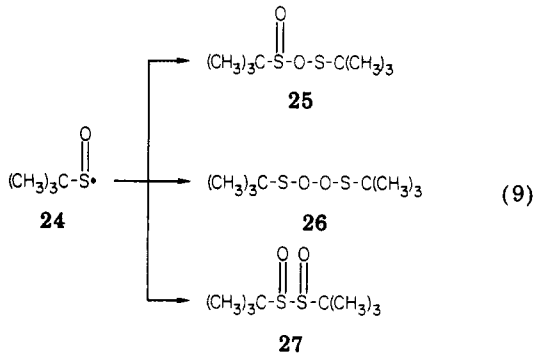


(8)

propanesulfinyl radicals (**24**) decay with a bimolecular rate constant of 6×10^7 M^{-1} s^{-1}. If a solution in which a significant concentration of **24** had decayed was heated from −140 to −30 °C, no evidence for radical regeneration was observed. This suggests that a head-to-tail combination of **24** to give *OS*-sulfenyl sulfinate (**25**) is favored over oxygen–oxygen (**26**), or sulfur–sulfur coupling (**27**), which would be expected to be reversible. Thus, dimerization of **24** via oxygen–sulfur coupling, gives *OS*-sulfenyl sulfinate **25**, which is unstable and rearranges to *S*-(2-methyl-2-propyl) 2-methyl-2-propanesulfonothioate [*S*-(2-methyl-2-propyl) 2-methyl-2-propanethiosulfonate, **28**].[40]



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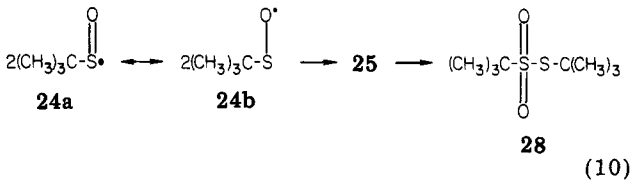

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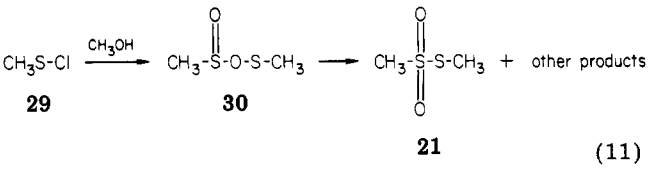
2. Decomposition of Sulfenyl Nitrates

The near quantitative conversion of sulfenyl nitrates ($RSONO_2$) to thiosulfonates involves sulfinyl radicals, *vic*-disulfoxides, and/or *OS*-sulfenyl sulfinates.[39]

3. Sulfenyl Halides and Alcohols

The complex reaction of methanesulfenyl chloride (**29**) and methanol, which is believed to yield seven products, may involve *OS*-methyl methanesulfino(thioperoxoate) (*OS*-methyl thioperoxymethanesulfinate; *OS*-sulfenyl sulfinate, **30**).[42]



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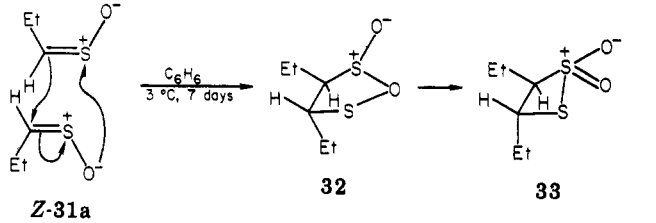
C. Sulfines

1. Cyclodimerization

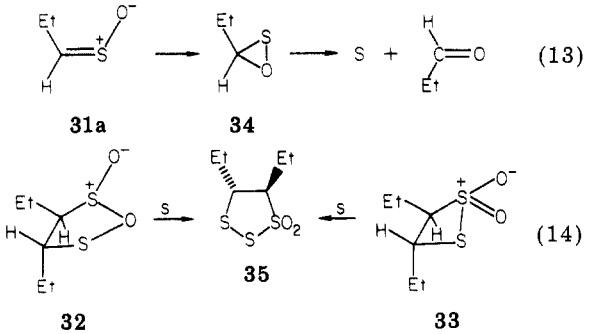
The lachrymatory factor (LF) of the onion (*Allium cepa*) has been characterized as *Z*-propanethial *S*-oxide (**31a**).[48-52] Sulfine **31a** undergoes a [4 + 2] cycloaddition reaction in which it functions as both a 1,3-dipole and a dipolarophile to give the unstable cyclic *OS*-sulfenyl sulfinate ester **32**. Rearrangement of **32** leads to the



(12)

stereospecific formation of (*E*)-3,4-diethyl-1,2-dithietane 1,1-dioxide (**33**).[53] Although various 1,2-dithietes are known,[55-57] compound **33** is the first example of an isolable 1,2-dithietane derivative.[53,58,59]

Also detected in the cyclodimerization of sulfine **31a** was a minor (ca. 5%) component of molecular formula $C_6H_{12}O_2S_3$, to which the (*E*)-4,5-diethyl-1,2,3-trithiolane 1,1-dioxide structure (**35**) was tentatively assigned.[53] Compound **35** may arise via insertion of sulfur (from



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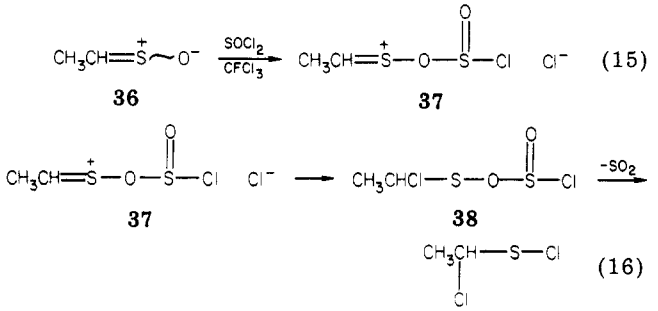
(14)

decomposition of **31a** via oxathiirane **34**)[54] into *OS*-sulfenyl sulfinate **32** or the 1,2-dithietane derivative (**33**).

2. Sulfines and Thionyl Chloride

The strong exothermic reaction of ethanethial *S*-oxide (**36**) with thionyl chloride may involve a chloro *OS*-sulfenyl sulfinate derivative (**37** or **38**).[49,60] Low-tem-



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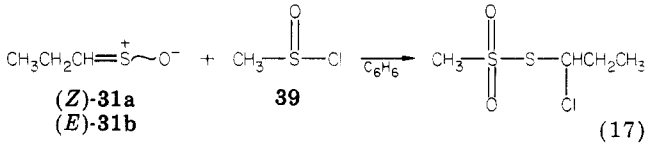
perature ^{1}H NMR, ^{13}C NMR, ^{17}O NMR, and ^{33}S NMR studies may demonstrate the transient existence of **8**, **32**, **37**, and/or **38**.

D. Sulfinyl Halides

1. Alkanesulfinyl Chlorides and Base

An unusual exothermic reaction, which occurred between sulfines[48-50] and alkanesulfinyl chlorides (sulfine precursors) to yield S-(1-chloroalkyl) alkanesulfonothioates,[11] has been observed by Block and Bazzi.[49,60] For example, addition of methanesulfinyl chloride (**39**) to a benzene solution of propanethial *S*-oxides (**31**) afforded *S*-(1-chloropropyl) methanesulfonothioate (**40**, 64%). Similarly, treating 2 equiv of alkanesulfinyl



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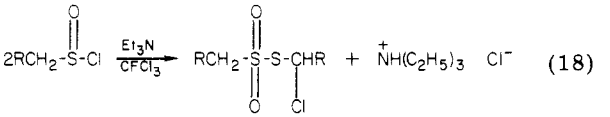
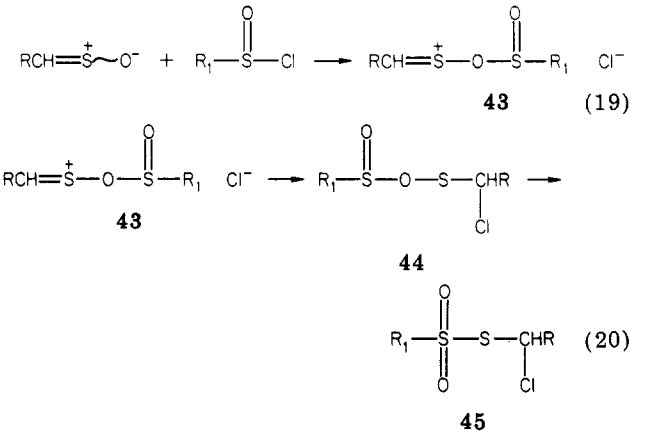
chloride with 1 equiv of triethylamine lead cleanly and in high yield directly to the α-chloroalkyl thiosulfonate esters (**41**, **42**).[49,60]



(18)

41, R = CH_3 (82%)
42, R = C_2H_5 (79%)

Chloro derivatives of *OS*-sulfenyl sulfinates (**44**) have been proposed as transient intermediates in the interesting transformations shown in eq 17 and 18 (cf. eq 15, 16).[49] The key step involves nucleophilic attack by the sulfine oxygen atom on the sulfinyl chloride to give **43**, which rearranges to the *OS*-sulfenyl sulfinate **44**.



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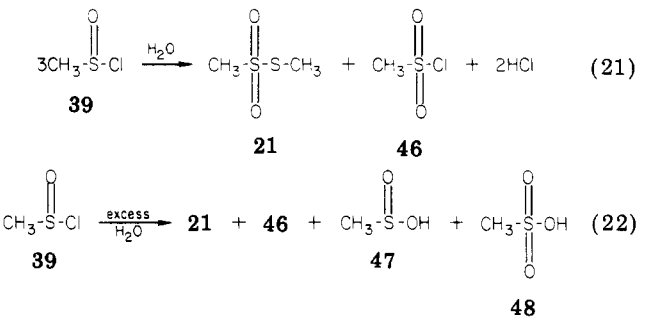
Isomerization of **44** gives α-haloalkyl thiosulfonates (**45**), which are of interest as antibacterial and antifungal agents.[49,60,61]

2. Hydrolysis of Methanesulfinyl Chloride

Methanesulfinyl chloride (**39**) reacts with a limited amount of water (mole ratio 3:1) or deuterium oxide yielding *S*-methyl methanesulfonothioate (**21**) and methanesulfonyl chloride (**46**).[62] Although initially

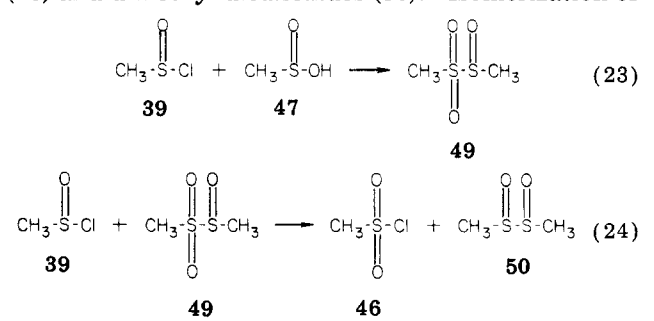


(21)

(22)

large amounts of methanesulfinic acid (**47**) are formed with greater quantities of water (up to **39**:H_2O = 0.33), the final products are thiosulfonate **21**, methanesulfonyl chloride (**46**), and methanesulfonic acid (**48**). As long as the mole ratio of water to **39** does not exceed 4:1, there is methanesulfinyl chloride (**39**) in the reaction mixture.[42,62,63]

Dimethyl disulfoxides (**50**) have been proposed as transient intermediates in the hydrolysis of methanesulfinyl chloride (**39**, eq 21, 22).[62] Presumably, methanesulfinyl chloride (**39**) reacts with methanesulfinic acid (**47**) to afford methylsulfinyl methyl sulfone (**49**), which reacts with **39** to give methanesulfonyl chloride (**46**) and dimethyl disulfoxides (**50**). Isomerization of

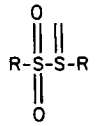


(23)

(24)

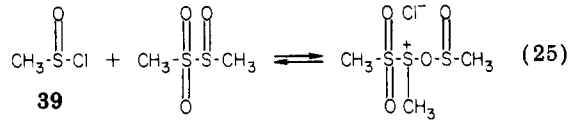
50 leads to thiosulfonate **21** or *OS*-sulfenyl sulfinate **30** (eq 3, 5, 10 and Scheme I). An alternate mechanism

TABLE III. Yields of Symmetrical Linear Alkanesulfonothioic *S*-Alkyl Esters (Alkanethiosulfonates)[10,71]

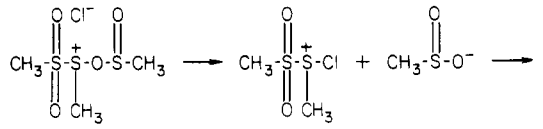


R	yield, % Et_2O	yield, % CCl_4
CH_3	55	54
C_2H_5	49	68
C_3H_7	63	73
C_4H_9	79	78
C_5H_{11}	72	78
C_6H_{13}	68	77
C_8H_{17}	61	78
$C_{12}H_{25}$	40	46

involving an *OS*-sulfenyl sulfinate salt (**51**) has been suggested (eq 25, 26).[64,65]



39 **49** **51** (25)



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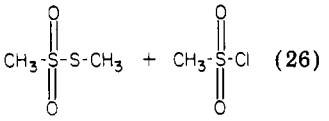
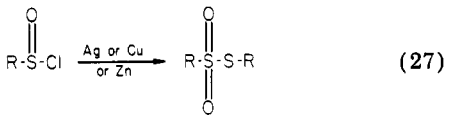


21 **46** (26)

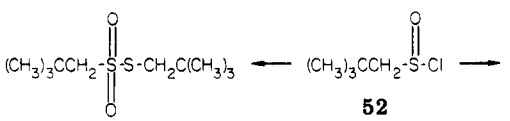
3. Alkane- and Arenesulfinyl Chlorides and Activated Zerovalent Metals

Alkanesulfinyl chlorides react with activated zerovalent zinc in diethyl ether or tetrachloromethane to give the corresponding symmetrical linear alkanesulfonothioic *S*-alkyl esters in good to excellent yields (eq 27, Table III, Scheme II).[3,10,66-71]

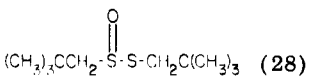


4 (27)

The reaction of alkanesulfinyl chlorides and activated zinc appears to be very sensitive to solvent and structural effects.[3,70,71] For example, 2,2-dimethylpropanesulfinyl chloride (**52**) reacted with activated zerovalent zinc powder in benzene or tetrachloromethane solvent to give *S*-(2,2-dimethylpropyl) 2,2-dimethylpropanesulfonothioate (**53**) in 79 and 78% yield, respectively.



53 **52**



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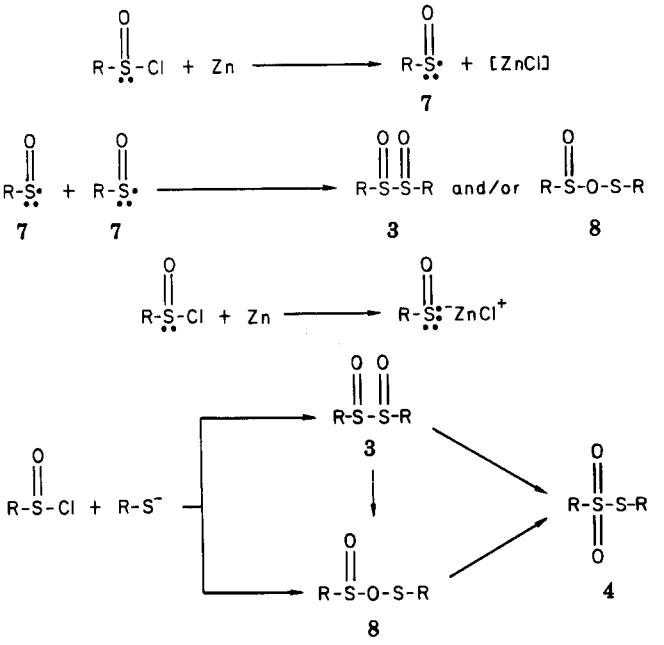
SCHEME II



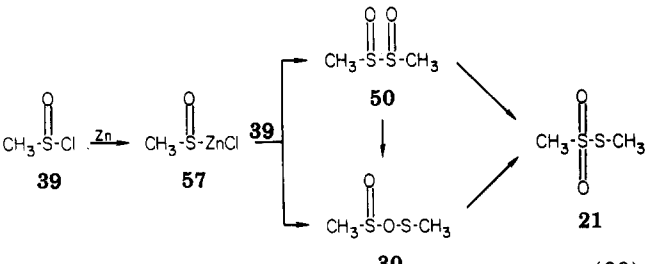
The reaction of **52** with activated zerovalent zinc in ether or deuterated ethanenitrile gave *S*-(2,2-dimethylpropyl) 2,2-dimethylpropanesulfinothioate (**54**) as the major product.[70]

Arenesulfinyl chlorides react with activated zerovalent zinc to give the corresponding symmetrical arenethiosulfonates in near quantitative yields (eq 27).[26,72]

Zerovalent copper converts alkane-[70] and arenesulfinyl[72-74] chlorides to the corresponding symmetrical thiosulfonates. Zerovalent silver also transforms arenesulfinyl chlorides to symmetrical thiosulfonates (eq 27).[75,76]

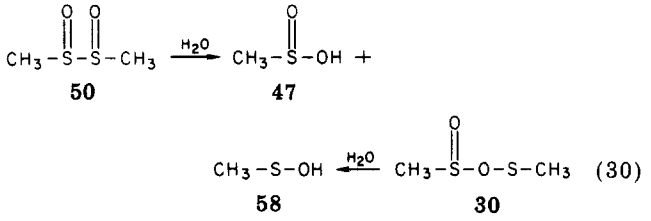
The mechanisms shown in Scheme II may account for the formation of thiosulfonates from the reaction of sulfinyl chlorides and activated zerovalent metals. However, Freeman, Angeletakis, and Keindl[10,70,71] have shown that the reaction mechanisms may be more complicated. The reduction of methanesulfinyl chloride (**39**) with activated zerovalent zinc under nitrogen in anhydrous ether at −30, −20, and 0 °C was investigated via ^1H NMR and ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of the −30 °C reaction mixture showed the presence of thiosulfonate **21**, **39**, methanesulfonyl chloride (**46**), methanesulfinic acid (**47**) or its zinc salt (**55**), methylsulfinyl methyl sulfone (**49**), and dimethyl sulfide (**56**).[69]

As shown in Scheme II, methanesulfinyl chloride (**39**) can react with methanesulfinyl zinc chloride (**57**) to give dimethyl disulfoxide (**50**) and/or *OS*-methyl thioperoxymethanesulfinate (**30**). Isomerization of **30** or **50** affords thiosulfonate **21** (eq 29).



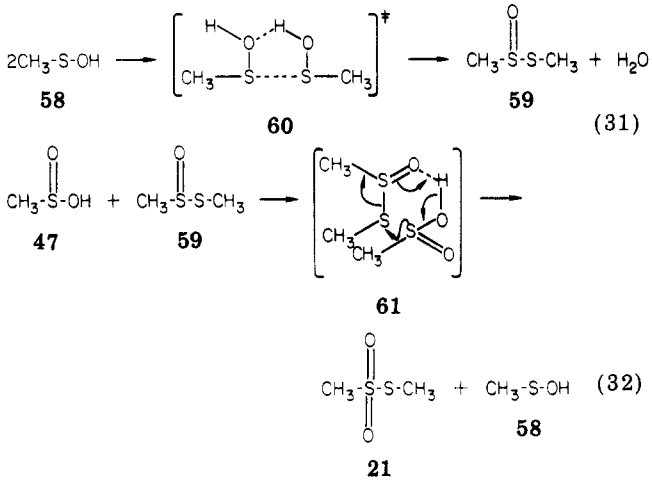
39 **57** **50** **30** **21** (29)

vic-Disulfoxide **50** or *OS*-sulfenyl sulfinate **30** can react with traces of water to give methanesulfinic acid (**47**) and methanesulfenic acid (**58**).[4-6,77]

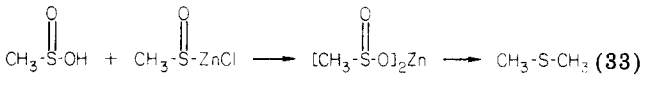


Methanesulfenic acid (**58**) can undergo cyclodehydration[78,79] to yield *S*-methyl methanesulfinothioate (*S*-methyl methanethiosulfinate, **59**). The water generated in the reaction can react with **30**, **39**, and/or **50** (eq 21, 22, 30).[4-6,10]

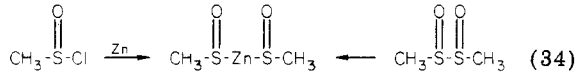
Warming the reaction mixture to 0 °C leads to the reaction of **47** with **59** to afford **21** and **58**.[4-6,80-82] The absence of **47**, **58**, and **59** in the final product mixture is consistent with eq 31 and 32.[10]



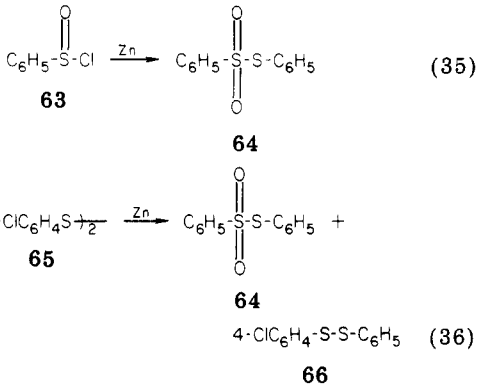
Equilibration of **47** with **57** in the presence of zinc chloride yields zinc methanesulfinate (**55**), which may be the precursor for dimethyl sulfide (**56**).[69,83]

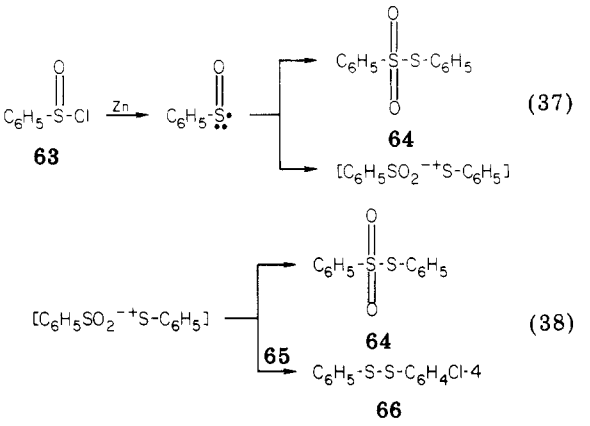


Although other plausible mechanisms are available[66,67] and no direct evidence was found for *OS*-sulfenyl sulfinate **30**, dimethyl disulfoxide (**50**), or **62**, it appears that *vic*-disulfoxides and *OS*-sulfenyl sulfinates are transient intermediates in the reaction of alkanesulfinyl chlorides and activated zerovalent metals.[10]



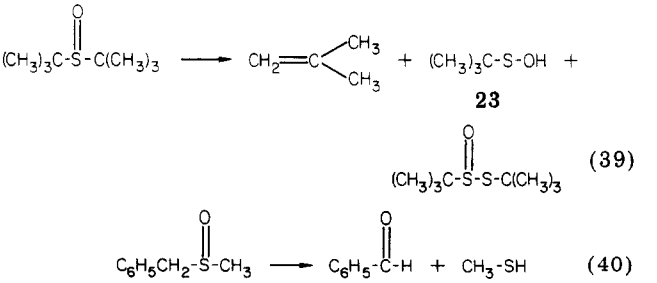
Benzenesulfinyl chloride (**63**) reacts with zerovalent zinc in ether to give *S*-phenyl benzenesulfonothioate (*S*-phenyl benzenethiosulfonate, **64**) in 96% yield.[26] In the presence of 4-chlorophenyl disulfide (**65**), the reaction of **63** and zerovalent zinc gave 4-chlorophenyl phenyl disulfide (**66**) in addition to **64**. The mechanisms involving *vic*-disulfoxides and *OS*-sulfenyl sulfinates shown in Scheme II may account for the formation of thiosulfonate **64**. Although formation of sulfinyl radicals with subsequent transfer of negatively charged oxygen has been proposed to account for the exchange of sulfenyl groups (eq 37, 38), this mechanism does not account for the absence of mixed thiosulfonates or diphenyl disulfide in the product mixture.





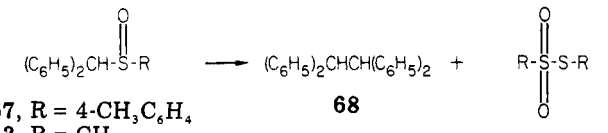
E. Photolysis and Thermolysis of Sulfoxides

The products formed from the thermolysis of sulfoxides depend upon the structure of the sulfoxide and on whether or not there is a β-hydrogen atom.[84,85] Sulfoxides with β-hydrogen atoms undergo predominantly syn elimination to form alkenes, sulfenic acids, and thiosulfinates (eq 39).[86] In contrast, benzyl methyl



sulfoxide gives phenylmethanal and methanethiol on pyrolysis.[87]

When benzhydryl *p*-tolyl sulfoxide (BTSO, **67**) in benzene-d_6 was thermally decomposed at 120 °C for 26 h, tetraphenylethane (**68**, 14%), *p*-tolyl *p*-toluenethiosulfonate (**69**, 18%), benzhydryl *p*-tolyl sulfone (**70**, 16%), bis(diphenylmethyl) ether (**71**, 24%), *p*-tolyl disulfide (**72**, 26%), and benzhydryl *p*-tolyl sulfide (**73**, 5%) were formed (Scheme III).[84] However, when the decomposition was carried out in the presence of a small amount of pyridine, only tetraphenylethane (**68**, 43%) and thiosulfonate **69** (46%) were obtained. The acti-



67, R = 4-$CH_3C_6H_4$
73, R = CH_3

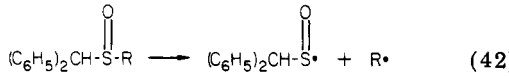
68

21, R = CH_3
69, R = 4-CH_3-C_6H_4

(41)

vation parameters in the presence of pyridine were E_a = 28.9 ± 1.9 kcal/mol and ΔS^* = −3.1 ± 5.0 eu. Similar results were obtained with benzhydryl methyl sulfoxide (**73**) in the presence of pyridine.[84]

Electron spin resonance (ESR) and CINDP studies showed that both sulfoxides, **67** and **73**, gave *p*-toluenesulfinyl and methanesulfinyl radicals, respectively, by the scission of carbon–sulfur bonds (eq 42).

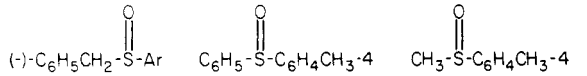


(42)

The sulfinyl radicals can form *vic*-disulfoxides and/or *OS*-sulfenyl sulfinates which then rearrange to thiosulfonates **21** and **69** (eq 41; cf. Scheme II).

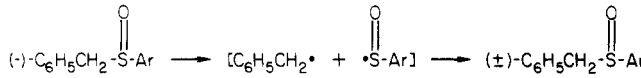
Electron spin resonance spectroscopy (ESR) has been employed to characterize radical pathways in the thermal and photolytic decomposition of a variety of diaryl sulfoxides.[85] Cleavage of the C–S bond led to the formation of delocalized and relatively unreactive sulfinyl radicals (ArS(O)·) which combined to generate *OS*-sulfenyl sulfinates (ArSOS(O)Ar). Decomposition of these *OS*-sulfenyl sulfinates generates sulfenyl (RS·) and sulfonyl ($RS(O_2\cdot)$) radicals which may recombine to form thiosulfonates (Scheme IV; cf. eq 2 and Scheme II).[85,88]

OS-Sulfenyl sulfinates are also probable intermediates in the thermal racemization of optically active benzyl *p*-tolyl sulfoxide (**74**).[89] It was found that **74**

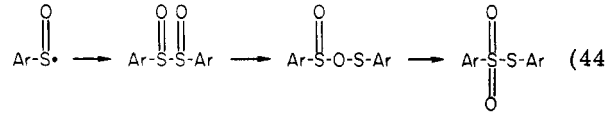


74 **75** **76**

racemized in benzene at a rate of 10^3–10^4 faster than either phenyl *p*-tolyl sulfoxide (**75**) or methyl *p*-tolyl sulfoxide (**76**). Among the products from the decomposition of **74** were *p*-tolyl *p*-toluenethiosulfonate and 1,2-diphenylethane, which arose from the coupling of *p*-toluenesulfinyl and benzyl radicals, respectively (eq 43, 44; cf. eq 41, 42).



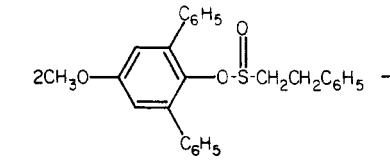
(43)



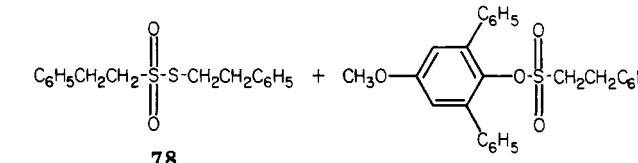
(44)

F. Thermolysis of Sulfinate *O*-Esters

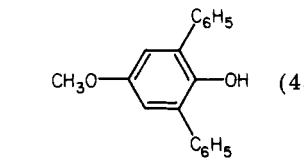
On heating sulfinate *O*-ester **77** in 1,2-dichlorobenzene at 150 °C gave thiosulfonate **78**, sulfonate **79**, and 4-methoxy-2,6-diphenylphenol (**80**).[33,34] Dissociation of the oxygen–sulfur bond generates 4-methoxy-2,6-diphenylphenoxy and 2-phenylethanesulfinyl radicals.



77



78 **79**



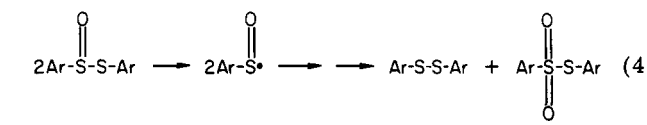
(45)

80

Thiosulfonate **78** results from the sulfinyl radical via *vic*-disulfoxide and/or *OS*-sulfenyl sulfinate. Sulfonate **79** results from the interaction of thiosulfonate **78** and 4-methoxy-2,6-diphenylphenoxy radical.

G. Thermolysis of Sulfinothioic Acid *S*-Esters

Although it is generally agreed that thiosulfinates disproportionate into disulfides and thiosulfonates via sulfinyl radicals, *vic*-disulfoxides, and/or *OS*-sulfenyl sulfinates (Scheme IV; cf. eq 44, 45), there are data that

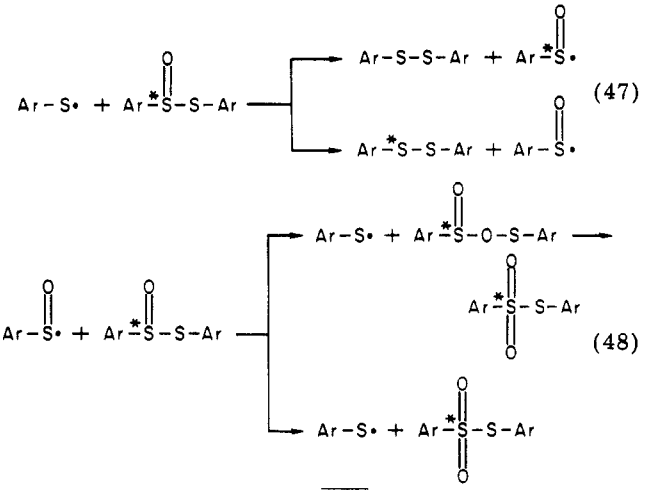


(46)

suggest that the actual mechanism may be more complicated.[90–96] The partial thermal decomposition of an aryl thiosulfinate that was labeled with ^{35}S at the sulfinyl sulfur atom led to a thiosulfonate with greater activity in the sulfonyl sulfur atom than in the sulfenyl sulfur atom and to a disulfide with a substantial amount of labeled sulfur.[92]

If the formation of thiosulfonate from two arenesulfinyl radicals occurred *only* as shown in eq 44 and 45 (cf. Scheme IV), both sulfur atoms of the thiosulfonate should have the same specific activity and one equal to the specific activity of the sulfinyl sulfur atom in the starting thiosulfinate (Scheme V). Thus, in order to explain the experimental results, it was suggested that the *OS*-sulfenyl sulfinate rearranged to thiosulfonate and also decomposed into sulfenyl and sulfonyl radicals (eq 2). The sulfonyl radicals combined in part with the unlabeled sulfenyl radicals from the initial dissociation of the starting thiosulfinate. This postulate also conforms with the observed substantial amount of labeled sulfur in the disulfide (Scheme V). The mechanism proposed in Scheme V assumes that no or minor induced decomposition occurs (eq 47, 48).[92]

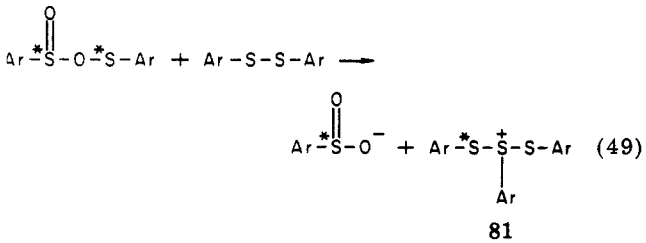
Kice[95] has proposed an alternate mechanism, which involves *OS*-sulfenyl sulfinates, in order to explain the results of the sulfur-35 experiments.[92] Since the *OS*-sulfenyl sulfinate is expected to be a potent sulfeny-



(47)

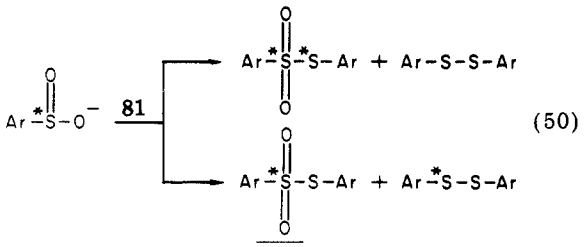
(48)

lating agent, it can react with the disulfide to give cation **81** (eq 49). Reaction of cation **81** with the arene-



(49)

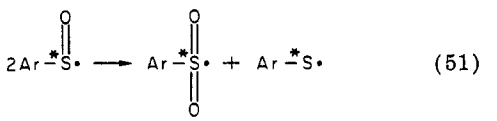
81



(50)

sulfinate anion generated in eq 49 would give a mixture of mono- and dilabeled thiosulfonate (eq 50).

Care must be exercised when interpreting the ^{35}S results since the sulfinyl radical may undergo disproportionation to some extent to yield sulfenyl and sulfonyl radicals (eq 51; cf. eq 47, 48).[85,88]

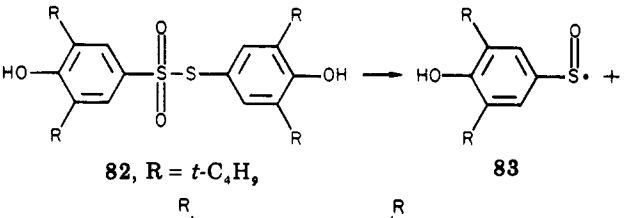


(51)

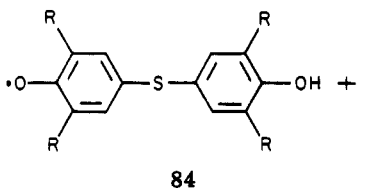
H. Photolysis and Thermolysis of *S*-Aryl Arenesulfonothioates

Photolysis of thiosulfonate **82** led to the detection of ESR signals for **83**, **84**, and **85**.[85,88,97] Photolysis of the thiosulfonate $C_6H_5CH_2SO_2SCH_2C_6H_5$ led to the detection of phenylmethanesulfinyl radical and HOS(O)·. Photolysis of *S*-aryl arenethiosulfonates in the presence of spin traps led to the detection of sulfenyl and sulfonyl adducts.[85,88]

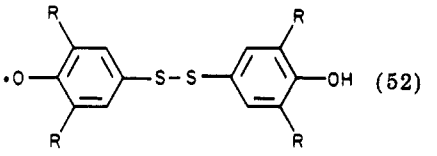
One possible mechanism for the formation of sulfinyl radicals in the photolysis of thiosulfonates is shown in eq 53.[85] Recombination of the first-formed sulfenyl and



82, R = *t*-C_4H_9 **83**

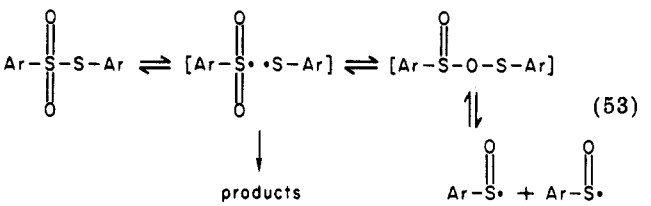


84



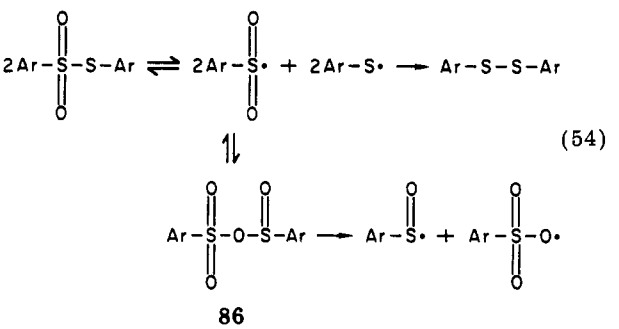
(52)

85



(53)

sulfonyl radicals leads to an *OS*-sulfenyl sulfinate, which undergoes S–O bond homolysis to yield sulfinyl radicals. Another mechanism (eq 54) involves the dimerization of initially formed arenesulfonyl radicals, without the mediation of sulfenyl radicals, to yield an intermediate sulfinyl sulfonyl anhydride (**86**).[73,85,98] Decomposition



(54)

86

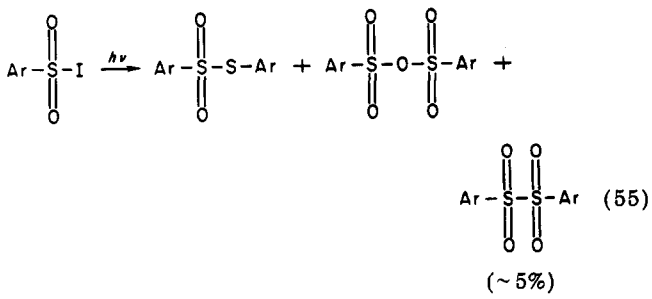
of **86** under photochemical or thermal conditions might be expected to yield sulfinyl radicals and the oxygen-centered radical $ArSO_3$·. This mechanism also predicts the formation of *vic*-disulfone, thiosulfonate, and sulfonic anhydride as products (Scheme VI).[73]

I. Photolysis of Sulfonyl Halides

Arenesulfonyl radicals, generated photochemically from arenesulfonyl iodides, appear to prefer to couple in a head-to-tail fashion to give sulfinyl sulfones (**86**, eq 54; Scheme VI). Sulfinyl radicals, and presumable *vic*-disulfoxides and/or *OS*-sulfenyl sulfinates are involved in the formation of thiosulfonates in this reaction (Scheme VI).[73]

J. Peroxidation of Disulfides and Sulfinothioic Acid *S*-Esters

The oxidation of symmetrical disulfides is considered to proceed via various intermediates, including *vic*-di-

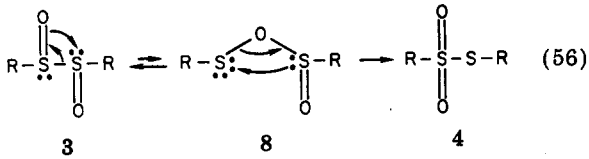


(55)

(~5%)

sulfoxides (3) and *OS*-sulfenyl sulfinates (8) to ultimately give a wide variety of products (Scheme VII).

There is disagreement as to just what role the transient *vic*-disulfoxide (3) intermediate plays in the oxidation of a thiosulfinate. Modena and co-workers[28,29]

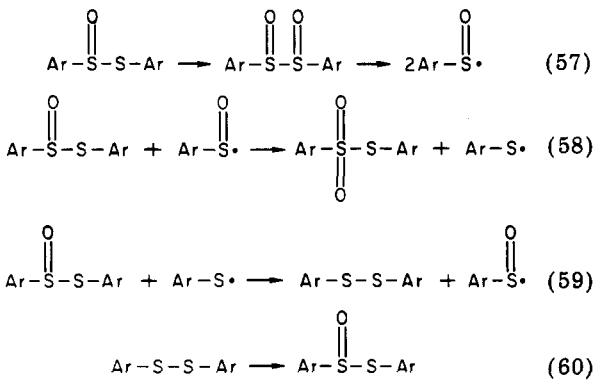


(56)

3 8 4

suggested that the *vic*-disulfoxides formed during the peroxybenzoic acid oxidation of *S*-aryl arenethiosulfinates in dioxane solution undergo rapid isomerization to thiosulfonates without cleavage of the S–S bond (eq 3–5, 56). Modena and Todesco[28] claimed that no disulfide could be detected in the oxidation of *S*-aryl arenethiosulfinates and that disulfides and thiosulfinates were oxidized at comparable rates with peroxybenzoic acid in dioxane.

Barnard and Percy[27] proposed that the role of *vic*-disulfoxides was to generate sulfinyl radicals which serve as initiators for the disproportionation of thiosulfinate to disulfide and thiosulfonate. The disulfide



(57)

(58)

(59)

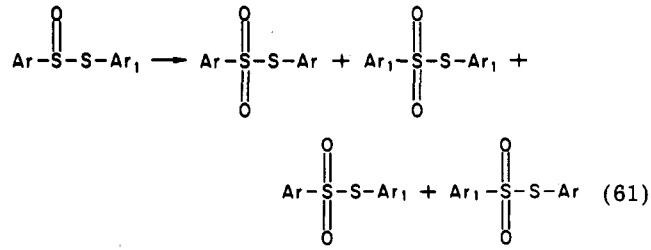
(60)

is subsequently oxidized to thiosulfinate by the oxidizing agent. The following evidence was presented in support of the mechanism proposed in eq 57–60.[27]

(1) In contrast to the results of Modena and Todesco,[28] phenyl disulfide was detected as a transient product in amounts up to 30% of the original concentration of the thiosulfinate when *S*-phenyl benzenesulfinothioate (87) was oxidized by hydrogen peroxide in enthanoic acid, by organic hydroperoxides or by peroxy acids.[27]

(2) The oxidation of unsymmetrical thiosulfinates with hydrogen peroxide or peroxy acids gave a mixture of the four possible thiosulfonates (eq 61).[12,15,16,27]

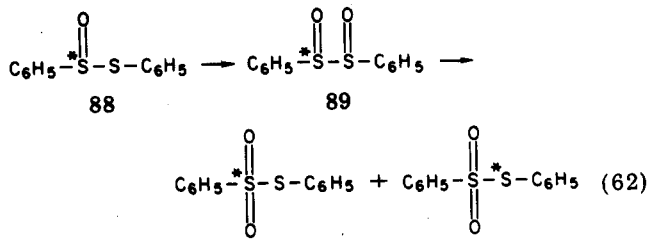
(3) Thiosulfinate was consumed more rapidly than oxidant to give initially less than the theoretical yield of thiosulfonate.[27]



(61)

(4) One equivalent of oxidant appeared to cause the disappearance of several equivalents of thiosulfinate to yield equimolar amounts of disulfide and thiosulfonate.

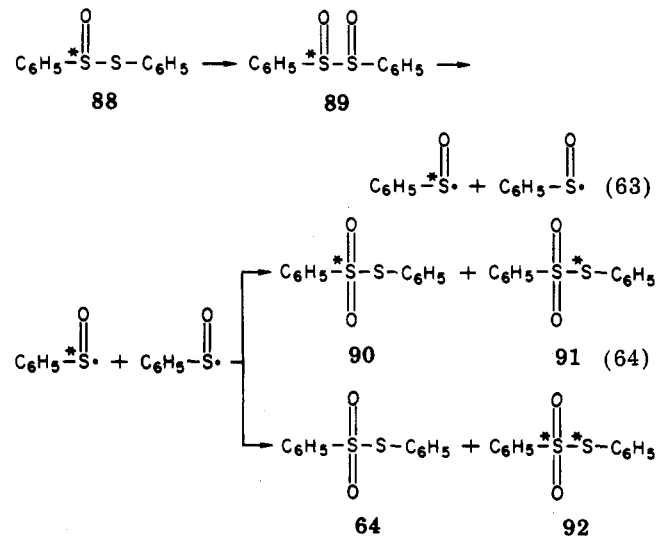
Interestingly, the mechanism shown in eq 57–60 appears to be inconsistent with the ^{35}S study by the same investigators.[27] The peroxybenzoic acid oxidation of ^{35}S-labeled 88 gave an 80% yield of thiosulfonate 90 with 66% of the activity retained in the original position. Thiosulfonate 90 could be formed via oxidation



(62)

88 89 90 91

at the labeled sulfinyl sulfur atom in 88 and/or via *vic*-disulfoxide 89. Thiosulfonate 91 could be produced from *vic*-disulfoxide 89 and/or some other intermediate. If sulfinyl radicals were involved (eq 57–60), one would predict the formation of unlabeled thiosulfonate 64 and randomly labeled thiosulfonates 90–92 (eq 63, 64; cf. Scheme V).

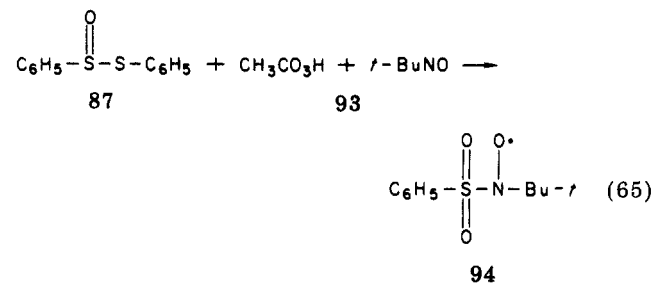


(63)

(64)

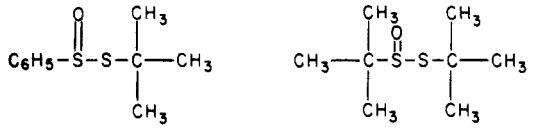
88 89 90 91 64 92

No radicals were detected directly by ESR when 87 was oxidized with peroxyethanoic acid in dichloromethane or trichloromethane at 22–24 °C, even under flow conditions. However, evidence for participation of radicals in the peroxidation was obtained from radical scavenging experiments. Thus, oxidation of 87 with peroxyethanoic acid in toluene in the presence of *tert*-butyl nitroxide (93) gave an ESR signal which was attributed to the sulfonyl adduct (94). Sulfonyl adducts with 93 were also detected in the peroxidation of *S*-(2-methyl-2-propyl) benzenethiosulfinate (95) and *S*-(2-methyl-2-propyl) 2-methyl-2-propanethiosulfinate



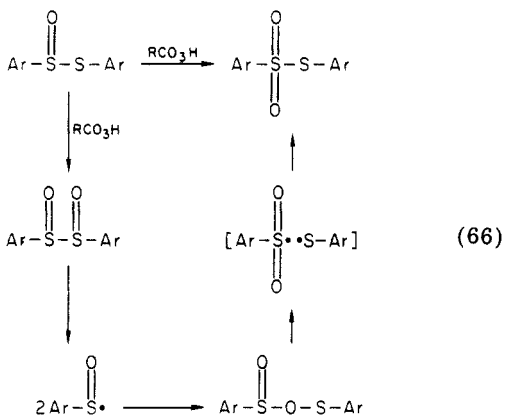
87 93 94 (65)

(96). Thus, it was concluded that the peroxidation of



95 96

thiosulfinates involves *vic*-disulfoxides, sulfinyl radicals, sulfenyl sulfinates, sulfonyl radicals, and sulfenyl radicals (eq 66; cf. eq 12, 13, 20, 23, 24, 30).[40]

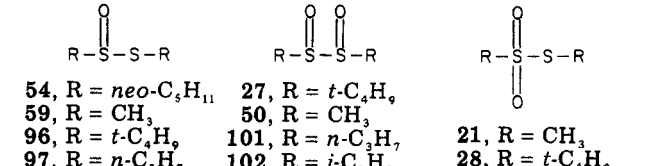


(66)

Owing to numerous conflicting reports (vide supra), the absence of systematic studies, the sensitivity of disulfides and thiosulfinates to peroxidation conditions, the significant structural effects, and the apparent pronounced differences among the behavior of symmetrical and unsymmetrical alkyl or aryl thiosulfinates, this discussion of the peroxidation of disulfides and thiosulfinates will be classified according to structures.

1. Symmetrical S-Alkyl Alkanesulfinothioates

Freeman and Angeletakis[4-6] detected diastereomeric *vic*-disulfoxides (**27**, **50**, **101–105**) for the first time during ^1H NMR and ^{13}C NMR studies of the low-temperature *m*-chloroperoxybenzoic acid (MCPBA) oxidation of symmetrical *S*-alkyl alkanethiosulfinates (**54**, **59**, **96–100**) to *S*-alkyl alkanethiosulfonates (**21**, **28**, **53**, **106–109**). Diastereomeric *vic*-disulfoxides (**27**, **50**, **101–105**) were observed at −40 °C during the MCPBA oxidation of the corresponding thiosulfinate.[6,99]

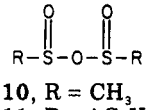


54, R = *neo*-C_5H_{11}
59, R = CH_3
96, R = *t*-C_4H_9
97, R = *n*-C_3H_7
98, R = *i*-C_3H_7
99, R = *n*-C_4H_9
100, R = $C_6H_5CH_2$

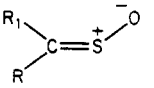
27, R = *t*-C_4H_9
50, R = CH_3
101, R = *n*-C_3H_7
102, R = *i*-C_3H_7
103, R = *n*-C_4H_9
104, R = *neo*-C_5H_{11}
105, R = $C_6H_5CH_2$

21, R = CH_3
28, R = *t*-C_4H_9
53, R = *neo*-C_5H_{11}
106, R = *n*-C_3H_7
107, R = *i*-C_3H_7
108, R = *n*-C_4H_9
109, R = $C_6H_5CH_2$

Sulfinic anhydrides **110–113** were observed at −40 °C in the reaction products from the peroxidation of thiosulfinates **59**, **96**, **98**, and **99**, respectively. No evidence was obtained for sulfinic anhydride **114**.



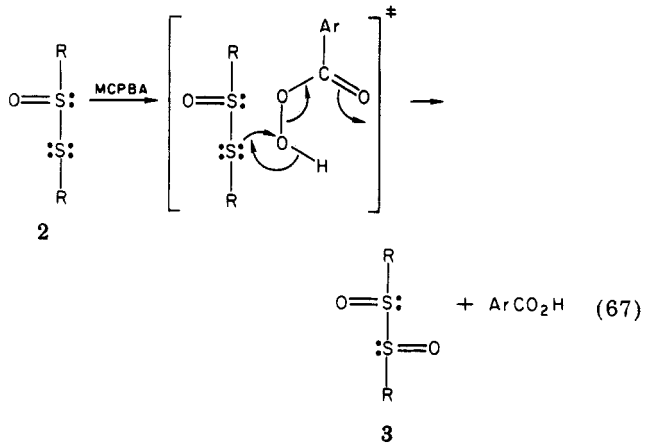
110, R = CH_3
111, R = *i*-C_3H_7
112, R = *n*-C_4H_9
113, R = *t*-C_4H_9
114, R = $C_6H_5CH_2$



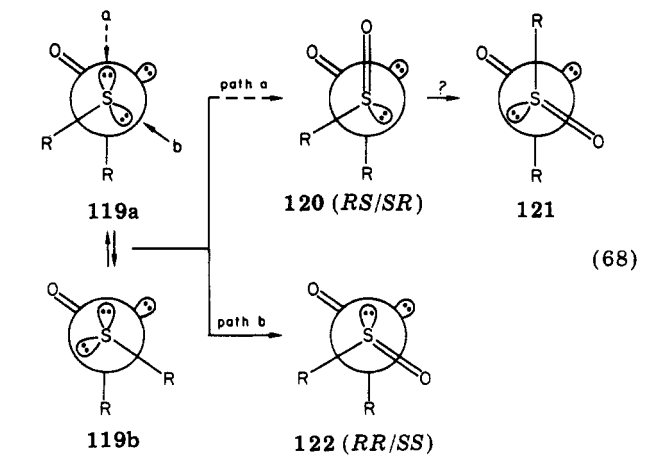
31a, R = H; R_1 = C_2H_5 (*Z*)
115, R = H; R_1 = *n*-C_3H_7 (*Z*)
116, R = H; R_1 = *t*-C_4H_9 (*E* and *Z*)
117, R = R_1 = CH_3
118, R = $C_6H_5CH_2$

Sulfines (**31a**, **115–117**), including the lachrymatory factor (LF, **31a**) of the onion *Alluim cepa* were detected on warming the oxidation product mixtures from **99**, **97**, **54**, and **98**, respectively, from −40 °C to −20 °C. Interestingly, sulfine **116** was a mixture of *E* and *Z* isomers (*E*:*Z* = 1.6:1)[6,8,48-50] and no evidence was obtained for sulfines **118**.

Another interesting aspect of the low-temperature MCPBA oxidation of thiosulfinates **54**, **59**, **96–99**, and **100** was the *absence* of thiosulfonates in the initial product mixture.[4-6] The absence of thiosulfonates, and their inertness under the experimental conditions,[4-6,100-102] are consistent with the formation of *vic*-disulfoxides (**3**), probably via eq 67. Since kinetic studies have shown that sulfenyl sulfur is more reactive toward peroxybenzoic acid,[103] the proposed electrophilic attack by MCPBA at the sulfenyl sulfur atom of **2** is reasonable. Thus, oxidation of thiosulfinate **2** can occur via attack of peroxy acid at two sites (**119**, eq 68).

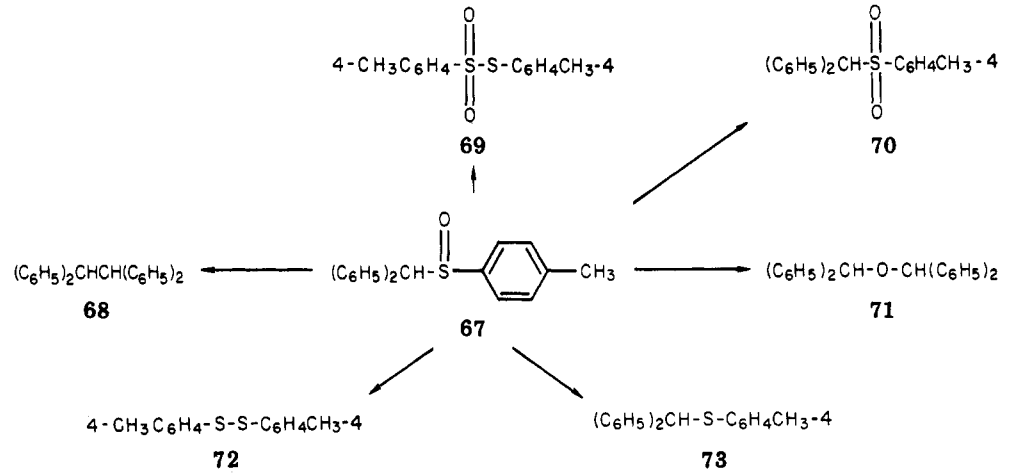


2 **3** (67)

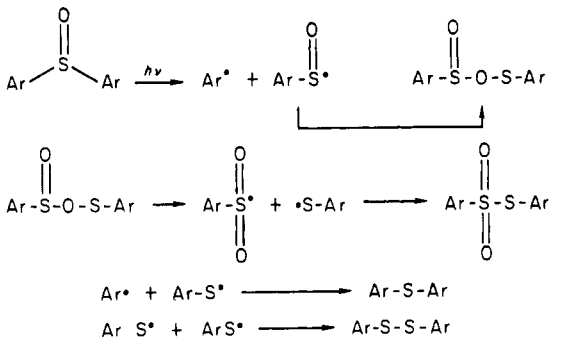


119a **119b** **120** (*RS*/*SR*) **121** **122** (*RR*/*SS*) (68)

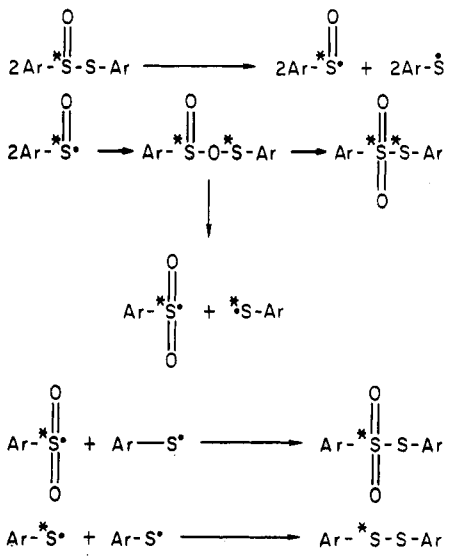
SCHEME III



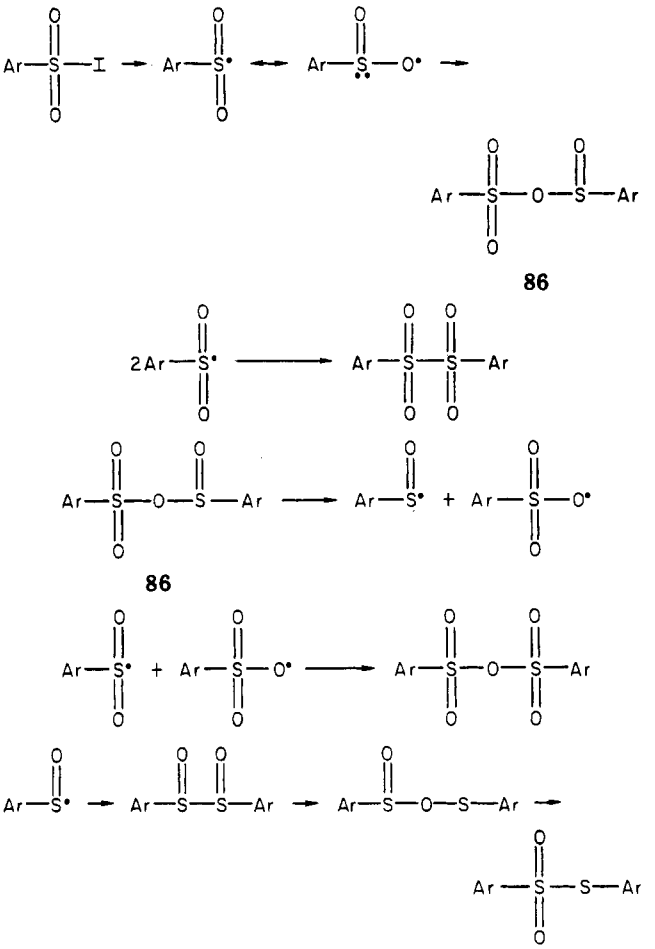
SCHEME IV



SCHEME V



SCHEME VI

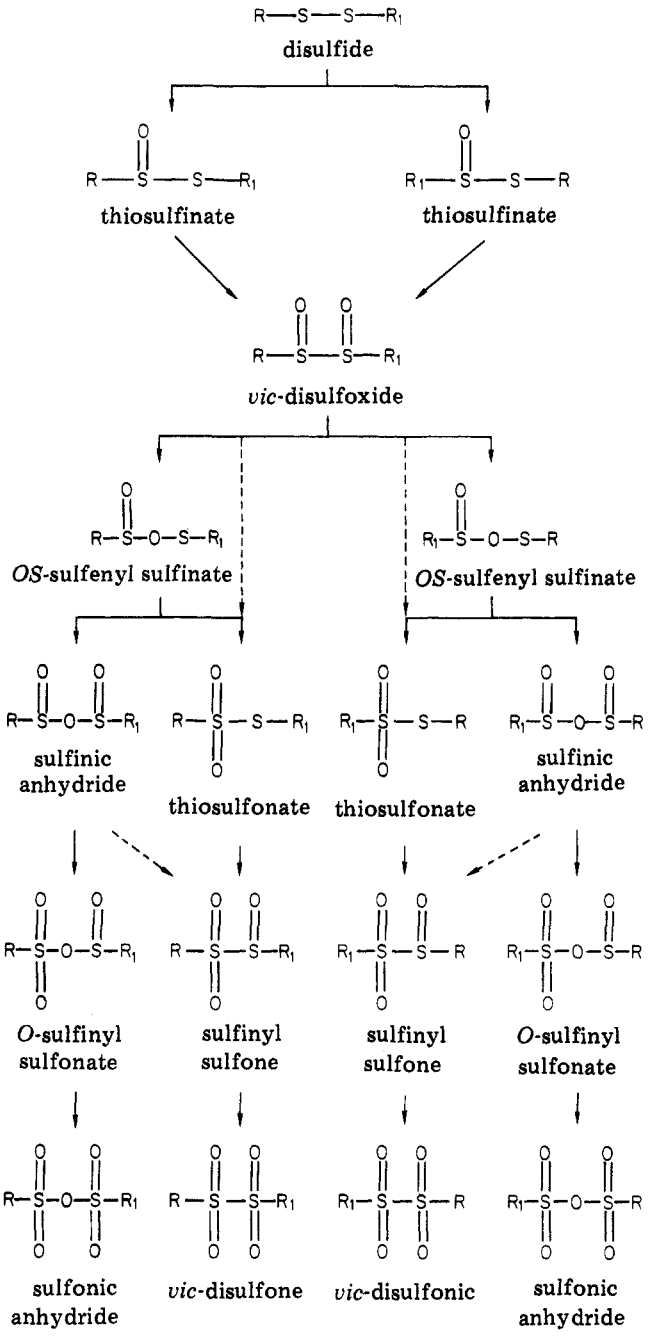


vic-Disulfoxides (**3**) contain two chiral sulfur atoms and can exist as diastereomers **120** (*RS/SR, meso*) and **122** (*RR/SS, d, l*). Although the chemical-shift data on *vic*-disulfoxides (**3**) were not sufficient to definitively assign the resonances of the respective diastereomers, several observations concerning their stereochemistry and structures were made from a study of molecular models.

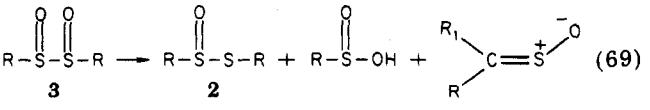
The chemical shifts of the α-carbon atoms of *vic*-disulfoxides are consistent with the ^{13}C NMR trends of oxidized derivatives of disulfides.[104-108] The difference between the chemical shifts of the α-carbon atoms of *vic*-disulfoxides (**3**) and the α-carbon atoms in the corresponding thiosulfinates may be due mostly to the α'_{SO} effect [$\alpha'_{SO} = \Delta\delta = \delta_C$(C–S(O)–S–C) – δ_C(C–S–S–C)]. The calculated value of the chemical shift of the α-carbon atom of a *vic*-disulfoxide is δ_C(C–S(O)–S–C) + α'_{SO}. The deviations of the observed chemical shifts of the α-carbon atoms of straight chain alkyl *vic*-disulfoxides from the expected values are less than 2 ppm and they reach a maximum of –4.54 ppm for the *tert*-butyl-substituted *vic*-disulfoxides **27** (Table IV).[6]

The low-temperature ^1H NMR and ^{13}C NMR spectral data of the product mixtures obtained from the MCPBA oxidation of alkanethiosulfinates **54**,[5,8] **96**,[4] **59**, and **97–100** show that the *initial* products of the decomposition and/or rearrangement of alkyl *vic*-disulf-

SCHEME VII Oxidation of Disulfides



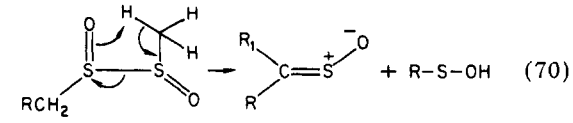
oxides (3) are sulfines, sulfinic acids, and thiosulfinates (eq 69).[6] Therefore, it seems reasonable to assume that



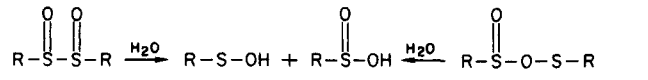
(69)

sulfinyl radicals do not play a major role in the decomposition and/or rearrangement of alkyl *vic*-disulfoxides (3).[4-6]

The disappearance of the ^{13}C NMR signals assigned to *vic*-disulfoxides (3) on warming the product mixtures led to regeneration of sizable amounts of the *starting* thiosulfinates. Two pathways have been suggested to account for this.[6] Namely, a *vic*-disulfoxide (3) can give 1 mol of sulfenic acid and 1 mol of sulfine (eq 70) or sulfinic acid (eq 71; cf. eq 30), and 2 mol of sulfenic acid can eliminate water to give 1 mol of thiosulfinate (eq 31). However, the amount of thiosulfinate produced



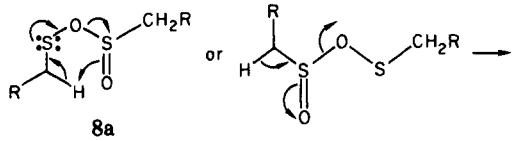
(70)

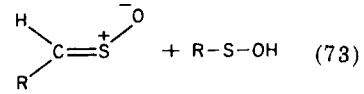


(71, 72)

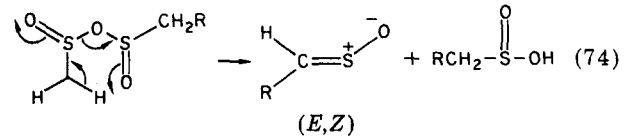
upon warming of the reaction mixtures relative to the amount of sulfine and sulfinic acid produced is much more than what is predicted from the stoichiometry outlined above.[6]

Although *vic*-disulfoxides (3) may undergo cycloelimination to afford sulfines and sulfenic acids (eq 70, 71) which dimerize to thiosulfinates (eq 31), the formation of sulfines from sulfinyl radicals (unlikely ?), sulfenyl sulfinates (8, eq 73), or sulfinic anhydrides (eq 74) must also be considered since these species can be



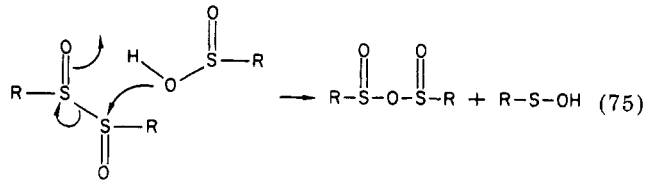


(73)



(74)

formed from the corresponding *vic*-disulfoxides (eq 56, 75). Although peaks that can be assigned to *OS*-

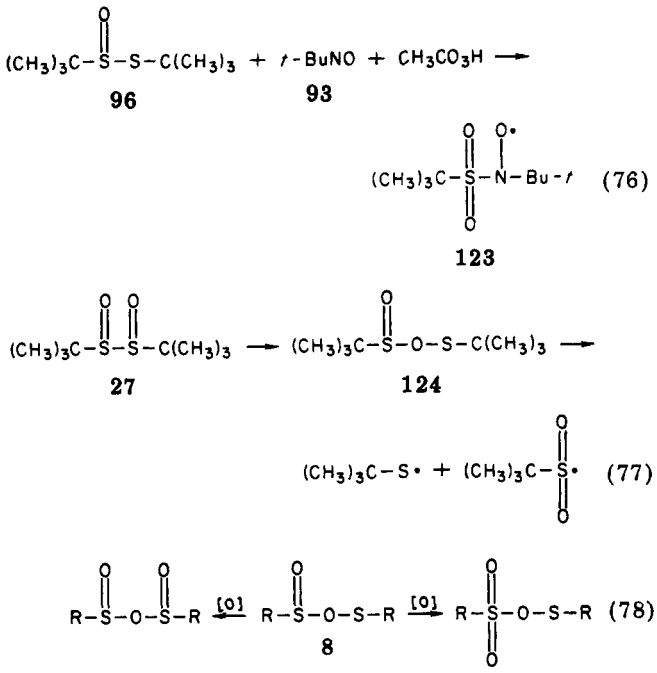


(75)

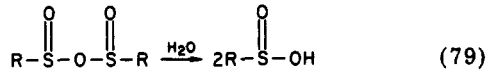
sulfenyl sulfinates (8) are absent from the low-temperature ^1H NMR and ^{13}C NMR spectra, they are still possible intermediates. The low concentration of *OS*-sulfenyl sulfinate 8 may be due to an unfavorable equilibrium between it and *vic*-disulfoxide 3.

Indirect evidence for *vic*-disulfoxides (3) and *OS*-sulfenyl sulfinates (8) has been derived from spin-trapping experiments by Gilbert and co-workers.[41] Oxidation of thiosulfinate **96** with peracetic acid in toluene in the presence of *tert*-butyl nitroxide (**93**; eq 76; cf. eq 65, 66) gave an ESR signal for sulfonyl adduct **123**.[40] Thus, it was concluded that **96** was oxidized to *vic*-disulfoxide **27** which rearranged to *OS*-sulfenyl sulfinate **124**. Decomposition of **124** gave sulfenyl and sulfonyl radicals. The sulfonyl radical then reacted with **93** to give **123** (cf. eq 1, 2, 65, 66).

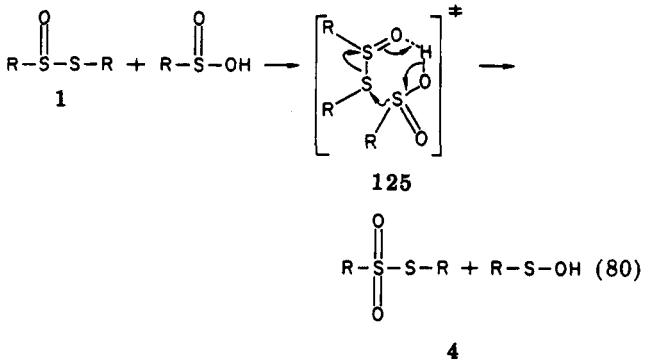
OS-Sulfenyl sulfinate (8), once formed, can compete with thiosulfinate (1) for oxidant to give sulfinic anhydrides or, less likely, sulfenyl sulfonates (eq 78).



vic-Disulfoxides (3) or *OS*-sulfenyl sulfinates (8) are expected to be easily hydrolyzed to sulfenic and sulfinic acids (eq 71, 72) while sulfinic anhydrides may be hydrolyzed to sulfinic acids (eq 79).



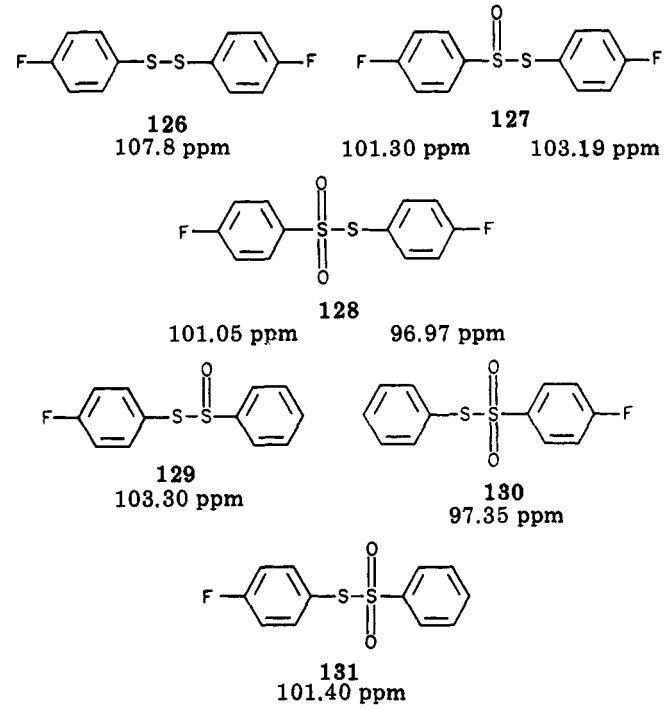
On warming the product mixtures from −40 °C to 0 °C, the sulfinic acids react readily with thiosulfinates (1) to give thiosulfonates (4, eq 80), except possibly for



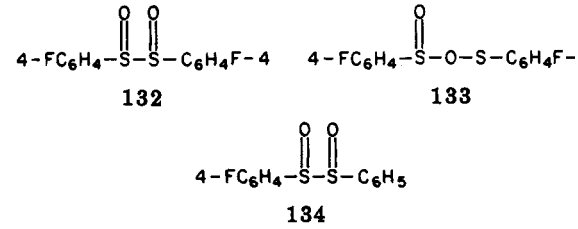
sterically hindered **54**. This is probably the major pathway by which thiosulfonates (4) form in the peroxidation of alkanethiosulfinates. A concerted mechanism with an activated complex (**125**) involving a front-side nucleophilic displacement at the sulfenyl sulfur atom of 1, which is assisted by a "push–pull" weakening of the S–S bond, has been proposed to describe the reaction of alkanethiosulfinates (1) with alkanesulfinic acids (eq 32, 80).[81]

2. Symmetrical S-Aryl Arenesulfinothioates

Chau and Kice[12] obtained the ^{19}F NMR spectra of 4-fluorophenyl disulfide (**126**), *S*-(4-fluorophenyl) 4-fluorobenzenethiosulfinate (**127**), *S*-(4-fluorophenyl) 4-fluorobenzenethiosulfonate (**128**), *S*-(4-fluorophenyl) benzenethiosulfinate (**129**), *S*-phenyl 4-fluorobenzenethiosulfonate (**130**), and *S*-(4-fluorophenyl) benzenethiosulfonate (**131**) in trichloromethane at −20 °C. The chemical shifts (δ) for **126–131** are expressed as ppm upfield from Freon 11.



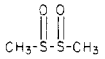
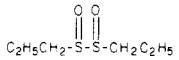
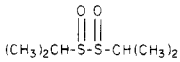
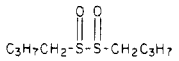
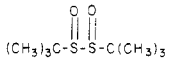
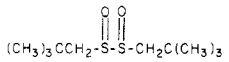
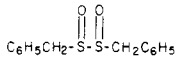
The oxidation of **127** by peroxyethanoic acid at −20 °C in trichloromethane showed that the resonances at δ 101.30 and 103.19 ppm, due to the fluorines of **127**, decreased in intensity with time with the concurrent appearance of resonances at δ 96.97 and 101.05 ppm for **128**. No resonances for disulfide **126** was observed in the 107–108 ppm region. Thus, under these reaction conditions, and in agreement with the report of Modena and Todesco,[28] the disulfide **126** is not produced in detectable (<5%) amounts during the course of the oxidation of **127** to **128**. No ^{19}F NMR evidence was observed for *vic*-disulfoxide **132** or *OS*-sulfenyl sulfinate **133**.



Peroxidation of thiosulfinate **129** under similar conditions for the oxidation of **127** gave **128**, **130**, **131**, and presumably **64**.[12] This result clearly demonstrates that the oxidation of **129** (or **127**) cannot occur exclusively at the sulfinyl sulfur atom. Thus, oxidation of **127** or **129** at the sulfenyl sulfur atom could involve *vic*-disulfoxides **132** or **134**, respectively.

Although no direct evidence has been observed for *vic*-disulfoxides (3) in the peroxidation of *S*-aryl arenethiosulfinates (2), sulfinyl radicals and/or *OS*-sulfenyl sulfinates may still be involved since the major peroxidation products are thiosulfonates. The greater tendency of aryl *vic*-disulfoxides to form sulfinyl radicals may be due to the mesomeric effect of the aryl groups. Thus, with alkyl *vic*-disulfoxides, ionic mechanisms are expected to compete effectively with radical mechanisms initiated by homolytic scission of the S–S bond in **3**. Moreover, dialkyl thiosulfinates have stronger S–S bonds than diaryl aralkanethiosulfinates.[78]

TABLE IV. Comparison of ^{13}C NMR Chemical Shifts (δ_C, ppm) of Alkyl *vic*-Disulfoxides with Those of the Corresponding Alkyl Thiosulfinates[6]

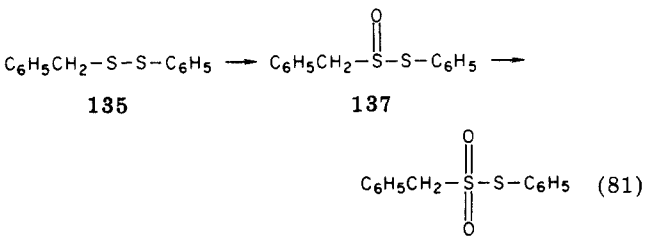
vic-disulfoxide	no.	obsd δ_C of C-α of disulfoxide *RS/SR*	obsd δ_C of C-α of disulfoxide *RR/SS*	obsd δ_C of C-α of RS(=O)SR	α'_{SO}, ppm[a]	calcd δ_C, ppm[b]	obsd δ_C − calcd δ_C, ppm	
	50	36.07	36.17	42.02	−7.60	34.42	1.74	1.65
	102	51.13	51.45	57.02	−6.35	50.67	0.77	0.46
	103	49.56	50.00	55.12	−2.87[c]	52.25	−2.25	−2.69
	104	49.20	49.53	55.09	−6.06	49.03	0.50	0.17
	27	57.20		59.44	2.30[c]	61.74	−4.54	
	105	64.00	64.35	70.44	−9.03	61.41	2.60	2.94
	106	55.38		60.71	−7.23	53.48	1.91	

[a] The α'_{SO} substituent effect was calculated from δ_C(-S(=O)-S-C-) − δ_C(C-S-S-C); see ref 104-108. [b] Calculated $\delta_C = \delta_C$ of the α-carbon atom of the thiosulfinate at −40 °C + α'_{SO}. [c] Reference 107.

If this is also true for *vic*-disulfoxides, the diaryl disulfoxides would be more likely than dialkyl disulfoxides to undergo homolysis of the S–S bond to form sulfinyl radicals. Indirect evidence for *vic*-disulfoxides and *OS*-sulfenyl sulfinates has been obtained from the peracetic acid oxidation of **64** in the presence of *tert*-butyl nitroxide (**93**), which afforded the sulfonyl adduct **94** (eq 65, 66; cf. eq 76, 77).[40]

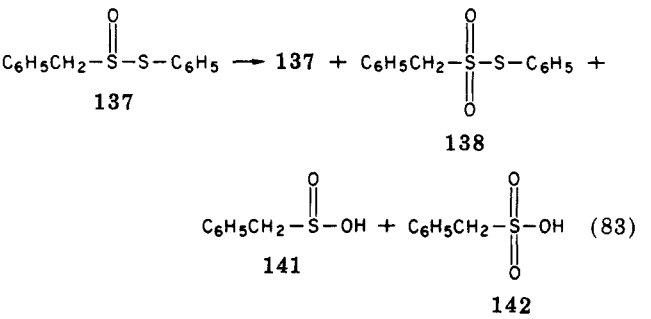
3. Disulfides, S-Alkyl Arenesulfinothioates, and S-Aryl Alkanesulfinothioates

It was reported that the oxidation of either benzyl phenyl disulfide (**135**) or ethyl phenyl disulfide (**136**) with 2.3 molar equiv of MCPBA gave only *one* of the expected thiosulfonates in each case. Thus, *S*-phenyl

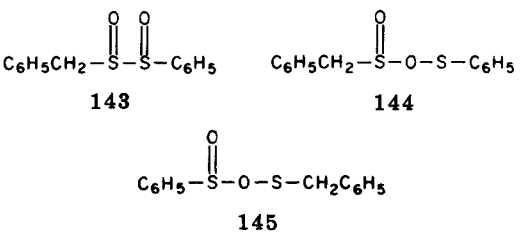


phenylmethanethiosulfonate (**138**) and *S*-phenyl ethanethiosulfonate (**140**) were obtained in 65–75% yield from **135** and **136**, respectively. Considerable amounts of difficultly separable products were also formed during the reaction. These results suggest that the first oxidation occurs at the sulfur atoms of **135** and **136** which are attached to the electron-releasing alkyl groups to give *S*-phenyl phenylmethanethiosulfinate (**137**) and *S*-phenyl ethanethiosulfinate (**139**), respectively.[109-112] The formation of only **138** and **140** and the absence of other thiosulfonates suggest that the second oxidation occurred *exclusively* at the sulfinyl sulfur atoms of **137** and **139**.

Freeman and Angeletakis[7] observed that the MCPBA oxidation of **137** at −30 °C in deuteriotrichloromethane under nitrogen gave **137**, **138**, phenylmethanesulfinic acid (**141**), and phenylmethanesulfonic acid (**142**) during the early stages of the oxidation. Although **138** may

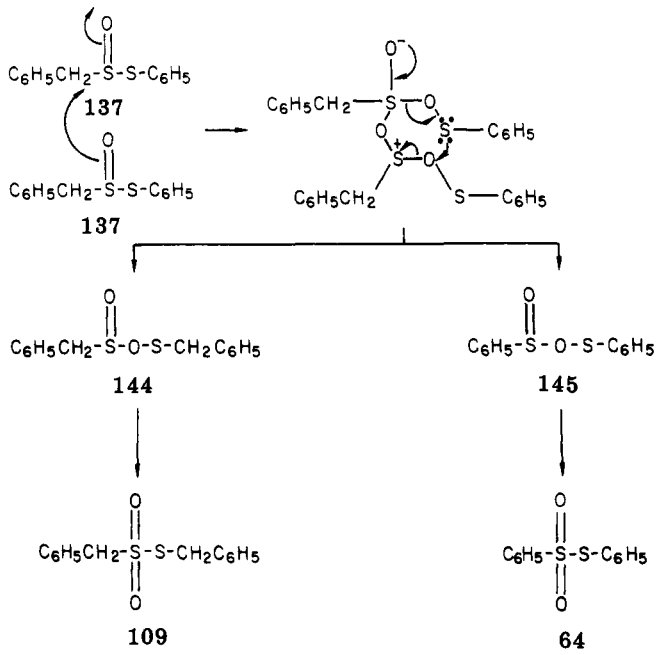


be formed via direct attack of MCPBA at the sulfinyl sulfur atom of **137**, the presence of **137**, **141**, and **142** is explicable in terms of formation and rearrangement of metastable *vic*-disulfoxides **143** and *OS*-sulfenyl sulfinates **144** and **145**.

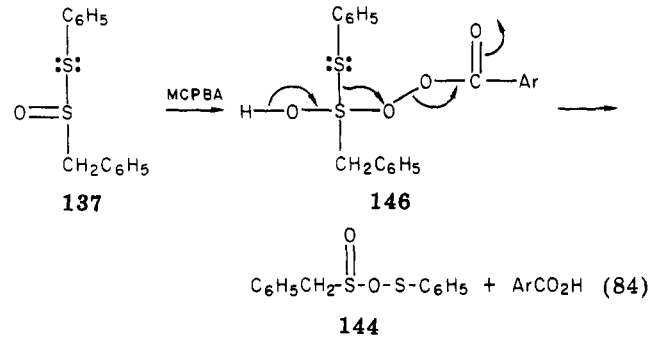


In addition to the mechanisms shown in eq 1, 2, 4, 9, and 56 for *OS*-sulfenyl sulfinate formation, an alternate pathway whereby MCPBA adds to the sulfinyl

SCHEME VIII

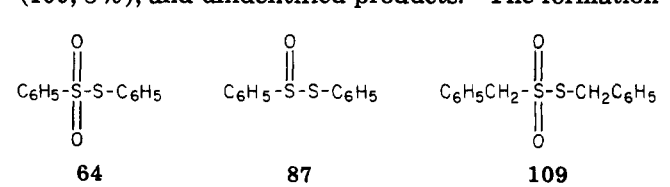


sulfur atom of thiosulfinate **137** to give *OS*-sulfenyl sulfinate intermediate **146** which undergoes a Baeyer–Villiger rearrangement must also be considered (eq 84).[7,12,103,113] Although this mechanism may be con-

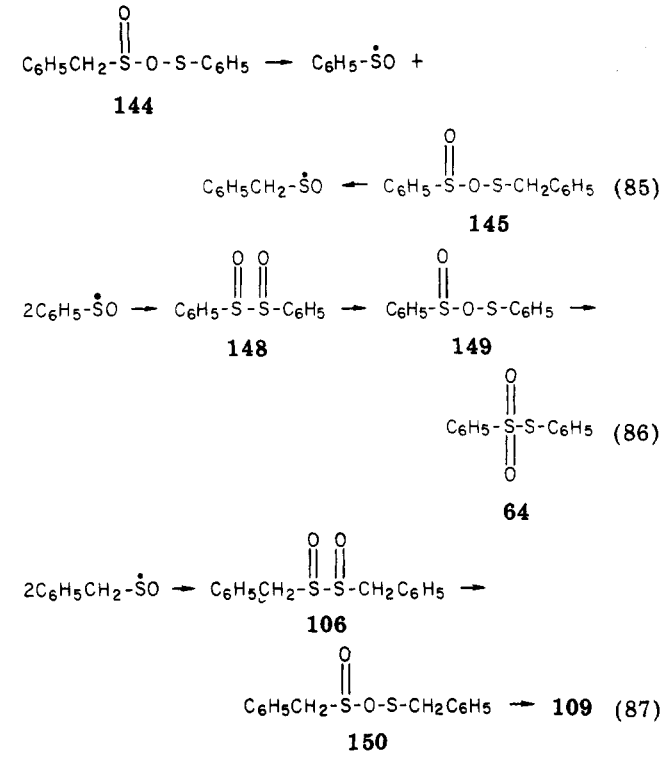


sidered unlikely owing to the low dissociation of MCPBA in trichloromethane, it cannot be completely dismissed.

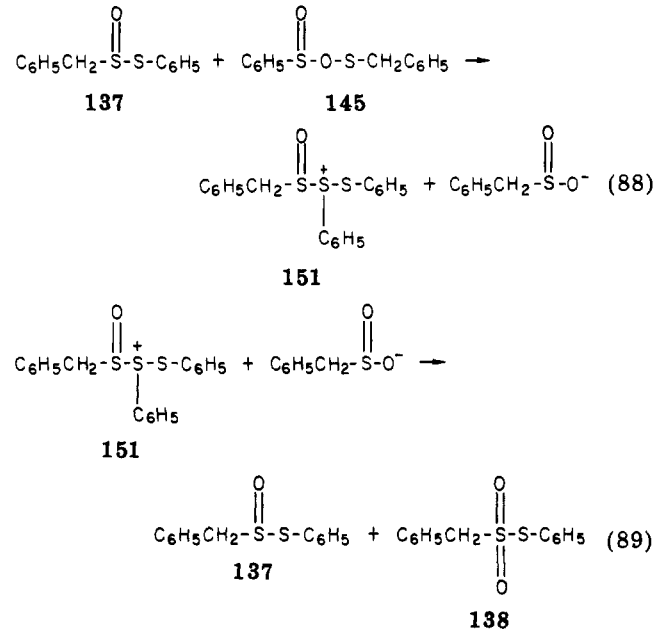
In order to intercept the easily hydrolyzable intermediates produced in the MCPBA oxidation of **137** at −30 °C, the reaction mixture from **137** was warmed to 0 °C in the presence of 10% sodium hydrogen carbonate solution.[7] Analysis of the organic phase via ^{1}H NMR and HPLC showed the presence of **64** (15–18%), **87** (0–5%), **137** (25–30%), **138** (50–60%), **141** (11%), **142** (9%), *S*-(phenylmethyl) phenylmethanethiosulfonate (**109**, 3%), and unidentified products. The formation



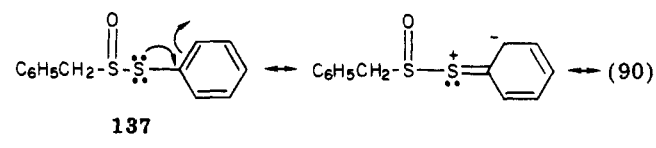
of thiosulfonates **64** and **109** can also occur via the mechanisms shown in eq 85–88. Mechanisms involving phenylmethanesulfonyl radicals (C_6H_5–SO_2·, **147**; cf. eq 1, 2) are considered to be less likely owing to the ease with which they lose sulfur dioxide.[95,114–116] Concerted mechanisms (eq 56) and ionic mechanisms (eq 88, 89;



Scheme VIII) can be imagined for the conversion of *OS*-sulfenyl sulfinates to thiosulfonates (cf. eq 4, 5).



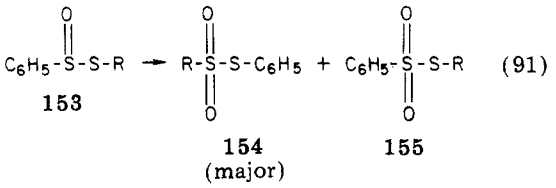
In the peroxidation of symmetrical alkanethiosulfinates (**2**), electrophilic attack by peroxy acid is expected to occur predominantly at the electron-rich sulfenyl sulfur atom (eq 67). However, one cannot unequivocally expect that electrophilic oxidation of aryl alkanethiosulfinates, i.e., **137**, to occur preferentially at sulfenyl sulfur owing to conjugation of the nonbonded electrons on sulfur with the benzene ring (eq 90). This



decreased electron density distribution around sulfenyl

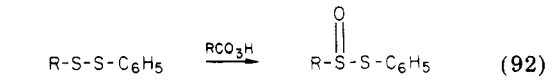
sulfur may make it less nucleophilic than the sulfinyl sulfur atom.[7] Attack by peroxy acid at the sulfinyl sulfur atom of **137** will lead directly to thiosulfonate **138** (eq 81) while attack at sulfenyl sulfur will lead to diastereomeric *vic*-disulfoxides (**143**), which may isomerize to *OS*-sulfenyl sulfinates **144** and **145**. Thus, in principle, one would predict four thiosulfonates [**64**, **109**, **138**, and $C_6H_5SO_2SCH_2C_6H_5$ (**152**)] from the peroxidation of **137**.[7,17]

In contrast to the peroxidation of **137**, the MCPBA oxidation of *S*-alkyl benzenethiosulfinates (**153**, R = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *t*-C_4H_9) gave *S*-phenyl alkanethiosulfonates (**154**, R = R in **153**) as major products (65–79%).[35] *S*-Alkyl benzenethiosulfonates (**155**, R = R in **153**) are formed in only trace amounts or, in some cases, no detectable amounts. The striking predominance of the *S*-phenyl alkanethiosulfonates (**154**) is explicable in terms of *vic*-disulfoxides and/or *OS*-sulfenyl sulfinates.



(91)

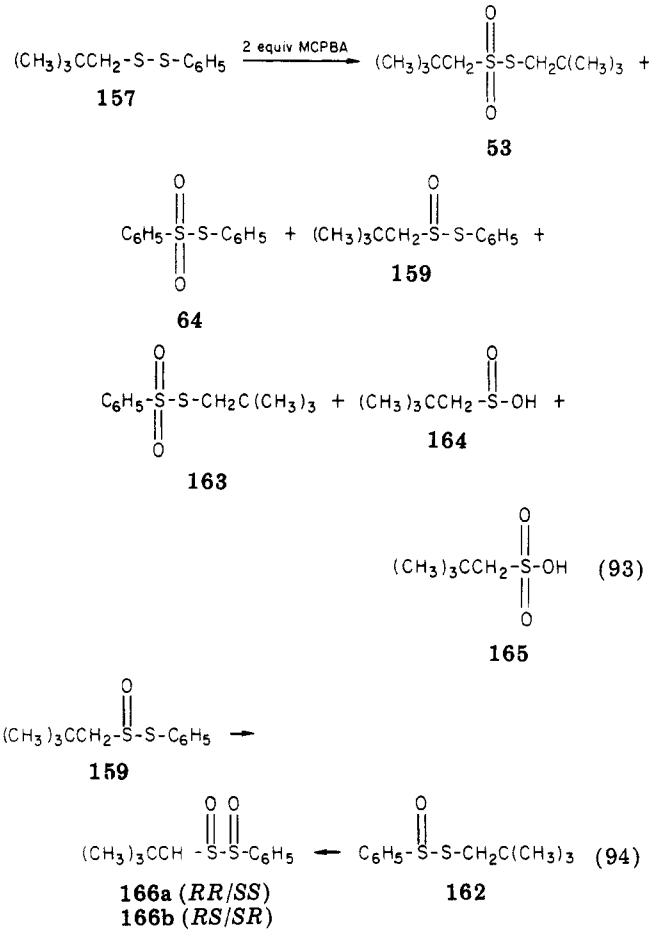
Peroxidation of unsymmetrical disulfides phenylmethyl phenyl disulfide (**156**),[117-119] 2,2-dimethylpropyl phenyl disulfide (**157**),[117] and methyl phenyl disulfide (**158**),[16] with 1 equiv of peroxy acid takes place mainly at the more electron-rich alkyl-bonded sulfur atom to give *S*-phenyl alkanethiosulfinates **137**, **159**, and **160**, respectively.



(92)

In order to obtain additional information concerning the peroxidation mechanism and for comparison purposes, Freeman and Angeletakis[117-119] oxidized unsymmetrical disulfide **156** with 2 equiv of MCPBA under the same experimental conditions used for the 1-equiv MCPBA oxidation of **137**. The product mixture from **156** was similar to that obtained from the peroxidation of **137** (cf. eq 83).

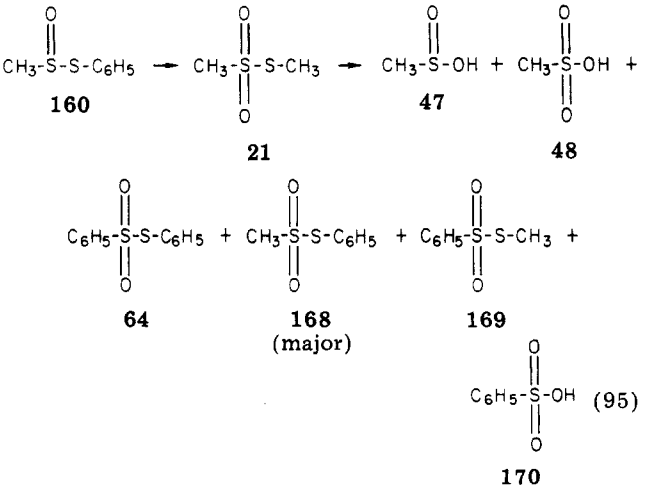
The MCPBA oxidation of unsymmetrical disulfide **157** and its regioisomeric thiosulfinates [**159** and *S*-(2,2-dimethylpropyl) benzenethiosulfinate (**162**)] were studied via low-temperature ^1H NMR and ^{13}C NMR in order to better understand the mechanisms of peroxidation.[117] Peroxidation of **157** gave **53** (7%), **64** (15%), **159** (48%), *S*-(2,2-dimethylpropyl) benzenethiosulfonate (**163**, 5%), 2,2-dimethylpropanesulfinic acid (**164**, 6%), and 2,2-dimethylpropanesulfonic acid (**165**, 8%). Peroxidation of **159** and **162** with 1 equiv of MCPBA gave respective product distributions similar to those from the oxidation of **157** (cf. eq 93). The two thiosulfinates **159** and **162** gave higher yields of sulfinic acid **164** than did **157**.[117] Thus, it appears that peroxidation of **159** or **162** leads to diastereomeric 2,2-dimethylpropyl phenyl disulfoxides (**166**).



(93)

(94)

Additional evidence for the intermediacy of *vic*-disulfoxides during the peroxidation of an unsymmetrical disulfide (**158**) and unsymmetrical thiosulfinates [**160** and *S*-methyl benzenethiosulfinate (**167**)] has been obtained from the elegant oxygen-18 studies of Oae and co-workers.[16] Oxidation of **160** with hydrogen peroxide in ethanoic acid or MCPBA in dichloromethane gave thiosulfonate **168** as the major product along with thiosulfonates, **21** and **169**, and acids, **47**, **48**, and **170**.



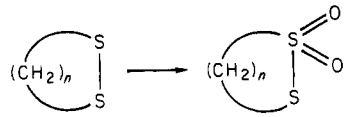
(95)

Most of the ^{18}O label in **160** was found to be incorporated into **168** and lesser amounts were found in **64** and **170**. The ^{18}O label in thiosulfinate **167** was found to be incorporated to some extent in thiosulfonates **21**, **64**, **168**, and **169**.[16] Although no resonances were observed

directly in the NMR spectra taken during oxidation, these data suggest the formation of *vic*-disulfoxides as intermediates during the oxidation.

4. Cyclic Disulfides and Cycloalkanesulfinothioates

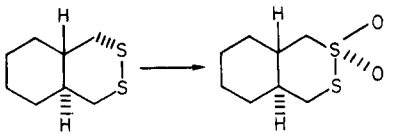
1,2-Dithiolane (171), 1,2-dithiane (172), and 1,2-dithiepane (173) were oxidized to the corresponding 1,1-dioxides (174, 175, and 176) with hydrogen peroxide in ethanoic acid.[120-124] MCPBA in trichloromethane ox-



(96)

171, n = 3
172, n = 4
173, n = 5

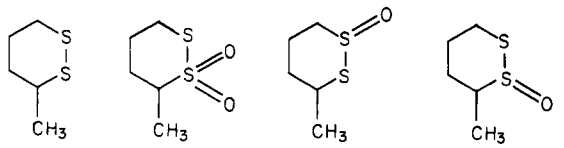
174, n = 3
175, n = 4
176, n = 5



(97)

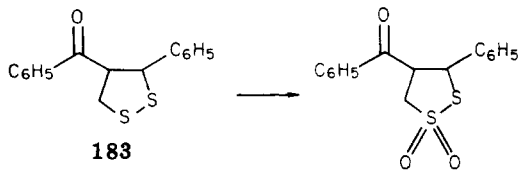
177 178

idizes 177 to thiosulfonate 178.[107] Oxidation of 3-methyl-1,2-dithiane (179) gives thiosulfonate 180.[108] It would be of interest to compare the peroxidation products from isomeric thiosulfinates 181 and 182.



179 180 181 182

MCPBA oxidized 3-phenyl-4-benzoyl-1,2-dithiolane (183) to sulfonate 184 in excellent yield.[112,125] The



(98)

183 184

formation of intermediate *vic*-disulfoxides and/or *OS*-sulfenyl sulfinates during the peroxidation of cyclic disulfides and cycloalkanesulfinothioates is under active investigation.[3,59,72]

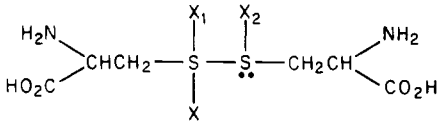
K. Biological Systems

1. Cystine and Cystine Derivatives

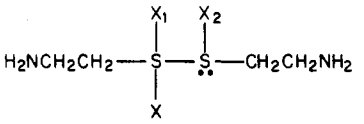
Cystine (185) is difficult to study since it is appreciably soluble only in aqueous solutions of strong acids or alkali, in anhydrous methanoic, or in trifluoroethanoic acid. Cystine perchlorate is soluble in anhydrous ethanenitrile or glacial acetic acid. An excellent summary of the oxidation of 185 has been published.[32]

Diastereomeric cystine monoxides (cystine thiosulfinate, L-cystine monoxide, 186) can be isolated in 80% yield by oxidizing cystine (185) in dilute sulfuric or perchloric acid with peracetic or performic acid.[18,32,126]

Although it was claimed that cystine *vic*-disulfoxide (187) and cystamine *vic*-disulfoxide (191) were obtained,[19,23,25,127-129] subsequent studies showed the alleged dioxides (187 and 191) to have the respective thiosulfonate structures (188 and 192).[32,126,130,131]



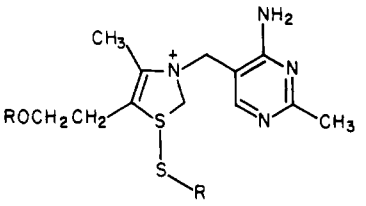
185, X = X_1 = X_2 = lone pair electrons
186, X = oxygen atom; X_1 = X_2 = lone pair electrons
187, X_1 = X_2 = oxygen atom; X = lone pair electrons
188, X = X_1 = oxygen atom; X_2 = lone pair electrons



189, X = X_1 = X_2 = lone pair electrons
190, X = oxygen atom; X_1 = X_2 = lone pair electrons
191, X_1 = X_2 = oxygen atom; X = lone pair electrons
192, X = X_1 = oxygen atom; X_2 = lone pair electrons

2. Thiamine Derivatives

vic-Disulfoxides may be involved in the hydrogen peroxide oxidation of thiamine derivatives (193).[30,31,124,132] The initially formed thiosulfinate resists further oxidation to the thiosulfonate, but is oxidized to the corresponding sulfonic acid with excess oxidant.[30,31]



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IV. Summary

The work reviewed in this manuscript shows that transient *vic*-disulfoxides (3) and *OS*-sulfenyl sulfinates (8) are reasonable intermediates in a wide variety of complex reactions involving organosulfur compounds. The products of many of the reactions clearly show that *vic*-disulfoxides (3) and *OS*-sulfenyl sulfinates (8) can undergo intramolecular rearrangements and intermolecular reactions. Modern techniques, including two-dimensional NMR, ^{13}C NMR, ^{17}O NMR, and ^{33}S NMR will be useful in solving the hundred-year-old controversy of *vic*-disulfoxides (3) and *OS*-sulfenyl sulfinates (8). Additional research will indubitably lead to the preparation and isolation of relatively stable *vic*-disulfoxides (3) and *OS*-sulfenyl sulfinates (8). Thus, the chemistry of these intermediates can be critically explored.

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